AMENDED CLINICAL TRIAL PROTOCOL 12

Protocol title:	**A Phase 3, randomized, double-blind, efficacy and safety study comparing SAR442168 to placebo in participants with nonrelapsing secondary progressive multiple sclerosis (HERCULES)**
Protocol number:	**EFC16645**
Amendment number:	**12**
Compound number (INN/Trademark):	**SAR442168 (tolebrutinib/not applicable)**
Study phase:	**Phase 3**
Short title:	**NRSPMS study of BTK inhibitor tolebrutinib (SAR442168) HERCULES**
Sponsor name:	**Genzyme Corporation*** ***Sanofi corporation organized and existing under the laws of France is the ultimate parent of a worldwide group of affiliates including Sanofi US Services Inc., Sanofi Genzyme, and Genzyme Corporation**
Legal registered address:	**450 Water Street, Cambridge, MA, 02141, USA**
Monitoring Team's Representative Name and Contact Information	

Regulatory agency identifier number(s):

IND:	140884
EudraCT:	2020-000647-30
NCT:	NCT04411641
WHO:	U1111-1246-7768
EUDAMED:	Not applicable
Other:	Not applicable

Date: 20-Dec-2023 Total number of pages: 149

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, version
Amended Clinical Trial Protocol 12	All	20 December 2023, version 1 (electronic 21.0)
Amended Clinical Trial Protocol 11	All	20 November 2023, version 1 (electronic 20.0)
Amended Clinical Trial Protocol 10	All	28 September 2023, version 1 (electronic 17.0)
Amended Clinical Trial Protocol 09	France	12 July 2023, version 1 (electronic 16.0)
Amended Clinical Trial Protocol 08	All	14 December 2022, version 1 (electronic 14.0)
Amended Clinical Trial Protocol 07	All	13 September 2022, version 1 (electronic 13.0)
Amended Clinical Trial Protocol 06	All	23 May 2022, version 1 (electronic 12.0)
Amended Clinical Trial Protocol 05	All	21 December 2021, version 1 (electronic 11.0)
Amended Clinical Trial Protocol 04	All	26 July 2021, version 1 (electronic 10.0)
Amended Clinical Trial Protocol 03	All	03 November 2020, version 1 (electronic 7.0)
Amended Clinical Trial Protocol 02	Austria, Czech Republic, Denmark, Finland, Germany, Greece, Hungary, Italy, Lithuania, Netherlands, Norway, Poland, Portugal, Romania, Spain, United Kingdom, Belgium, France, Bulgaria	28 August 2020, version 1 (electronic 5.0)
Amended Clinical Trial Protocol 01	All	15 May 2020, version 1 (electronic 2.0)
Original Clinical Trial Protocol		28 February 2020, version 1 (electronic 1.0)

Amended protocol 12 (20 December 2023)

This amended protocol (amendment 12) 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

The rationale for this protocol amendment is to update the liver function test monitoring as per Health Authority request.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of activities (SoA)	Week 3 added in the visit header and in footnote 'l'.	Update.
10.9 Appendix 9: Example of drugs with a potential to change SAR442168 metabolism or absorption	Table 8: removed 'rifabutin' from the list of potent CYP3A inducers. Table 9: moved 'rifabutin' from the list of potent CYP3A inducers to the list of moderate CYP3A inducers.	Correction of error as per updated guidance for CYP inhibitors/inducers based on information from DDI study.
10.14 Appendix 14: Protocol amendment history	Updated.	Update.
Throughout the document	Reformatted existing content when necessary. Minor, editorial, stylistic changes as necessary. Updated table of contents, section numbers, abbreviations as necessary.	Update in accordance with Sponsor's standards.

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Protocol title: A Phase 3, randomized, double-blind, efficacy and safety study comparing SAR442168 to placebo in participants with nonrelapsing secondary progressive multiple sclerosis (HERCULES)

Short title: NRSPMS study of BTK inhibitor tolebrutinib (SAR442168) (HERCULES)

Rationale:

The advent of disease-modifying therapies for relapsing forms of multiple sclerosis (MS) has led to significant strides in reducing relapse frequency and the attendant morbidity. However, chronic disability accumulation remains a significant unmet need for people living with MS. Individuals with progressive disease, including secondary progressive MS (SPMS), need therapies to reduce the accumulation of disability. The recent approval of siponimod has led to a broad relabeling of existing disease-modifying therapies, with an indication "for the treatment of relapsing forms of MS, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults". This label reflects the perception that drugs like ocrelizumab and siponimod that were tested in patients with progressive disease benefits patients with "active disease", ie, they reduced acute inflammatory activity rather than directly reducing "Progression Independent of Relapse Activity" or PIRA.

Data from the Phase 3 EXPAND trial of siponimod, a S1P receptor modulator, in a SPMS population demonstrated reduced risk (hazard ratio [HR]=0.79) of 3-month confirmed disability progression (CDP) (1). However, in the subgroup without activity at baseline (defined by the occurrence of relapses in the 24-month period prior to enrollment), the effect on 3-month CDP was limited (HR=0.87). Likewise, data from ORATORIO, the pivotal Phase 3 trial of ocrelizumab in a primary progressive MS (PPMS) population, demonstrated that this anti-CD20 monoclonal antibody that depletes B lymphocytes provided a small but statistically significant (HR=0.76) benefit in reducing the risk of disability progression (2). As with EXPAND, analysis of a subgroup defined by activity (in this case, the presence or absence of gadolinium (Gd) contrast-enhancing lesions at baseline, which amounted to 199 or 533 of 732 participants, respectively) revealed a smaller, non-significant effect size (HR=0.84) in patients without this inflammatory magnetic resonance imaging (MRI) activity at enrollment. According to these data, and to our working hypothesis, effective management of MS disease activity will require additional interventions beyond immunomodulation of peripheral immunity. Our focus is on targeting innate immunity, including monocytes and macrophages peripherally, as well as B cells in the central nervous system (CNS) and microglial cells that represent the resident innate immune system within the CNS.

BTK inhibitors do not result in chronic B-cell depletion; SAR442168 (tolebrutinib) inhibits B-cell-receptor signaling by blocking Bruton's tyrosine kinase (BTK) activity. Furthermore, abundant evidence suggests that innate immunity, and specifically CNS-resident microglial cell activity, is a significant driver of disability accumulation in all forms of MS. The dual working

hypothesis driving development of SAR442168 is based on the following: 1) modulating B cells to render them inert to antigenic stimulation will have an effect similar to B-cell depletion on progressive MS disability accumulation, and 2) CNS penetrance will provide a potential added benefit of modulating innate immunity mediated by macrophages and microglial cells to suppress maladaptive neuroinflammatory processes associated with chronic disability progression.

The ability of SAR442168 to reduce the formation of acute brain lesions in MS was assessed in a Phase 2b dose-finding trial in participants with relapsing MS (RMS) (DRI15928). Patients with progressive forms of MS may also present with acute focal inflammatory activity in the CNS. This activity manifests on MRI as T1 hyperintense Gd+ lesions and new or enlarging T2 lesions. SAR442168 has proven to be effective in reducing both types of CNS lesions. The SAR442168 Phase 2b results showed that SAR442168 reduced the number of new T1 hyperintense Gd+ lesions by 85% and the number of new or enlarged T2 lesions by 89% in the 60 mg group (the dose to be used in the Phase 3 program) compared to placebo.

Reduction in number of T1-hyperintense (gadolinium-enhanced) lesions has been established as a highly reliable predictive biomarker for clinical efficacy in pivotal studies in MS including Phase 3 RMS studies (3). While there is no comparable radiographic biomarker to predict clinical efficacy on disability progression, the assumption has been that doses effective at preventing relapses can be used to assess disability progression in PPMS or SPMS (2, 4, 5, 6, 7). SAR442168 was shown to achieve pharmacologically relevant concentrations in cerebrospinal fluid (CSF) after a single oral administration, with the potential to inhibit microglia and infiltrating bone-marrow-derived macrophages that are believed to drive neuroinflammation linked to disease progression.

The goal of this Phase 3 clinical trial is to demonstrate the efficacy and safety of SAR442168 compared to placebo in participants with nonrelapsing secondary progressive multiple sclerosis (NRSPMS). The primary endpoint is time to onset of 6-month CDP assessed via the Expanded Disability Status Scale (EDSS) score.

The EDSS is widely used to measure neurological disability in clinical trials and routine settings (8). It will be used to assess 6-month CDP, as is standard practice in many clinical trials and as is recommended by guidelines (2, 4) and considered as more stable than 3-month CDP. Electronic EDSS score collection will be employed to ensure completeness and consistency of measurement. Magnetic resonance imaging outcomes will include change in brain volume, which is considered as a marker of the CNS degenerative process and therefore recommended for use in progressive MS trials (9).

Together with additional evaluation of secondary and exploratory endpoints, this study will provide a comprehensive evaluation of the efficacy and safety of SAR442168 in people with NRSPMS.

Objectives and endpoints

Objectives	Endpoints
Primary	
• To determine the efficacy of SAR442168 compared to placebo in delaying disability progression in NRSPMS	• Time to onset of 6-month CDP defined as follows: - Increase of ≥1.0 point from the baseline EDSS score when the baseline score is ≤5.0, OR - Increase of ≥0.5 point when the baseline EDSS score is >5.0
Secondary	
• To evaluate efficacy of SAR442168 compared to placebo on clinical endpoints, MRI lesions, cognitive performance, physical function, and quality of life	• Time to onset of sustained 20% increase in the 9-HPT for at least 3 months • Time to onset of sustained 20% increase in the T25-FW for at least 3 months • Time to onset of 3-month CDP as assessed by the EDSS score • Total number of new and/or enlarging T2-hyperintense lesions as detected by MRI, defined as the sum of the individual number of new and/or enlarging T2 lesions at all scheduled visits starting after baseline up to and including the EOS visit • Time to onset of CDI defined as a ≥1.0 point decrease on the EDSS score from baseline confirmed over at least 6 months • Percent change in brain volume loss (BVL) as detected by MRI scans at the EOS compared to Month 6 • Change in cognitive function at the EOS compared to baseline as assessed by SDMT • Change in cognitive function at the EOS compared to baseline as assessed by CVLT-II, where available • Change in MSQoL-54 questionnaire score from baseline through the EOS
• To evaluate safety and tolerability of SAR442168	• Adverse events (AEs), serious AEs, AEs leading to permanent study intervention discontinuation, AEs of special interest, and potentially clinically significant abnormalities in laboratory tests, safety scales, ECG, and vital signs during the study period
• To evaluate population pharmacokinetics of SAR442168 and relevant metabolite(s) in NRSPMS and its relationship to efficacy and safety	• Plasma concentration of SAR442168 and relevant metabolite(s) (population PK assessment) at Months 6, 9, and 12
• To evaluate pharmacodynamics (PD) of SAR442168	• Change in plasma NfL levels at the EOS compared to baseline • Change in lymphocyte phenotype subsets in whole blood at the EOS compared to baseline in a subset of participants • Change in serum immunoglobulin level at baseline compared to the EOS • Change in serum Chi3L1 levels at baseline compared to the EOS

Abbreviations: 9-HPT, 9-hole peg test; AE, adverse event; AESI, adverse event of special interest; CDI, confirmed disability improvement; CDP, confirmed disability progression; Chi3L1, chitinase-3-like protein 1; ECG, electrocardiogram; EDSS, Expanded Disability Status Scale; EOS, end of study; MRI, magnetic resonance imaging; MSQoL-54, Multiple Sclerosis Quality of Life-54 Questionnaire; NfL, neurofilament light chain; PD, pharmacodynamic; PK, pharmacokinetic; nrSPMS, non-relapsing secondary progressive multiple sclerosis; T25-FW, timed 25-foot walk.

Overall design:

This is a Phase 3, randomized, double-blind, 2-arm, placebo-controlled, parallel group, multicenter, event-driven (6-month CDP) trial with a variable treatment duration ranging from approximately 24 to 48 months in participants with NRSPMS.

Disclosure Statement: This is a parallel treatment study with 2 arms that is blinded/masked for participants, the Investigator, any Investigator site staff, and the Sponsor.

Number of participants:

Approximately 1700 people will be screened to achieve up to 1290 participants randomly assigned to study intervention.

Enrolled participants will be randomly assigned at a ratio of 2:1 to 60 mg (established from dose-finding Study DRI15928) of oral, daily SAR442168 or daily matching placebo. Randomization will be stratified by age at screening (>40 versus ≤40 years) and geographic region (US versus non-US).

Note: "Enrolled" means a participant's, or their legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.

Intervention groups and duration:

Study intervention(s)

Investigational medicinal product(s)

- Formulation: SAR442168 film coated tablet
- Route(s) of administration: oral
- Dose regimen: 60 mg once daily

Investigational medicinal product(s)

- Formulation: placebo to match SAR442168 film coated tablet
- Route(s) of administration: oral
- Dose regimen: once daily

Noninvestigational medicinal product(s)

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

Temporary investigational medicinal product (IMP) interruption due to surgery

If surgery is needed during the study, consider the benefit-risk of withholding the IMP for at least 3 to 7 days pre- and post-surgery and the risk of bleeding.

Devices

Not applicable.

Long-term safety study

After the end of this study, participants who complete the trial and are taking the IMP treatment until the end of the trial (double-blind or open-label SAR442168 if meeting 6-month CDP) may be offered the option to participate in a long-term safety (LTS) study for an additional 2 years, or until SAR442168 is approved in their respective country, whichever comes first. Details of the LTS study will be described in a separate protocol.

Duration of study (per participant)

The duration of treatment will vary for individual participants, depending on the time of recruitment. Considering the recruitment period of approximately 24 months and an assumed event rate (discussed below), the duration of the study should be approximately 48 months. All recruited participants will be followed in the study until the common study end, which will be estimated and announced by the Sponsor to ensure that approximately 288 events of 6-month CDP have been observed before the study end.

Statistical considerations:

- **Primary endpoint:**

The primary estimand will be the treatment difference between SAR442168 and placebo in time to onset of 6 month-CDP regardless of completion of the treatment period. This estimand corresponds to a “treatment policy strategy”. This estimand will be considered primary for supporting regulatory decision making.

The time to onset of 6-month CDP will be analyzed by a Cox proportional hazards model with terms for treatment, age at screening (>40, ≤40 years), geographic region (US, non-US), baseline EDSS score, and baseline Gd-enhancing T1 lesions (0, ≥1). A log-rank test stratified by age at screening (>40, ≤40 years) and geographic region (US, non-US) to compare SAR442168 to placebo will also be examined.

In this primary intent-to-treat (ITT) analysis:

- For participants who complete the study without an initial disability progression, the participant’s event time will be censored at the date of last EDSS assessment.
- For participants who have an initial onset of disability progression but complete the study at the common study end date without 3-month confirmation, the participant will be censored at the date of last EDSS assessment.

- For participants who prematurely discontinue the study before 6-month confirmation of an onset of disability progression, regardless of having an initial onset, the participant will be censored at the date of last EDSS assessment.
- For participants who meet 3-month CDP but complete the study at the common study end date without 6-month confirmation, the event status of the participant will be determined by an imputation approach only if all additional EDSS assessments after 3-month confirmation to participant's end of study also meet the criteria for disability progression. Since in this setting, the partial missing data can reasonably be assumed to be missing at random, this approach leverages the partial information and follows the ITT principle. A logistic model with terms for age at screening (>40, ≤40 years), geographic region (US, non-US), baseline EDSS score, and baseline Gd-enhancing T1 lesions (0, ≥1) will be used to determine the event status as the imputation model within each treatment. A multiple imputation approach will be used to summarize the results.

Only EDSS assessments measured more than 90 days after the onset of an adjudicated relapse will be used to determine onset of disability progression. In addition, for the purpose of confirmation, only EDSS scores measured more than 90 days after the onset of an adjudicated relapse will be used. In case of such MS relapse, the next quarterly EDSS assessment >90 days after relapse onset will be used for CDP confirmation. The minimum increase in score required for progression must also be maintained for any non-confirmatory (ie, intervening) EDSS assessment(s) between the initial (onset) and confirmation EDSS scores.

- **Main secondary endpoints:**

For other time-to-event endpoints (time to onset of sustained 20% increase in the 9-HPT, of sustained 20% increase in the T25-FW, of 3-month CDP, and of CDI), similar analysis as for the primary analysis of the primary efficacy endpoint will be performed in the ITT population, but without imputation.

Continuous endpoints (percent change in brain volume loss, change in cognitive function, change in physical function, and change in MSQoL-54 at EOS) will be analyzed using a mixed-effect model with repeated measures (MMRM) approach. The model will include change/percent change values for the respective endpoint at each scheduled visit as response variables, and treatment, age at screening (>40, ≤40 years), geographic region (US, non-US), visit, treatment by-visit interaction, baseline value for the endpoint being assessed and baseline value-by-visit interaction as covariates.

Categorical efficacy endpoints with count data (new and/or enlarging T2 hyperintense over the study period after baseline) will be analyzed using a negative binomial regression model. The model will include the total lesion count across all post-randomization MRI scans during the study period as the response variable, with treatment group, age at screening (>40, ≤40 years), geographic region (US, non-US), baseline EDSS score, and baseline T2 lesions as covariates. Log-transformed observation duration from screening MRI to last available MRI will be the offset variable.

Analysis of safety data:

All safety summaries will be descriptive; no statistical significance tests will be performed on safety data. This includes treatment-emergent adverse events (TEAEs) and other safety information (eg, clinical laboratory evaluations, electrocardiograms [ECGs], and vital signs). TEAEs are defined as adverse events (AEs) that developed or worsened or became serious during the treatment period. These analyses will be based on the safety population, defined as all participants randomly assigned and exposed to study intervention, regardless of the amount of exposure, analyzed according to the treatment actually received.

Data Monitoring Committee: Yes

Scientific Advisory Committee: Yes

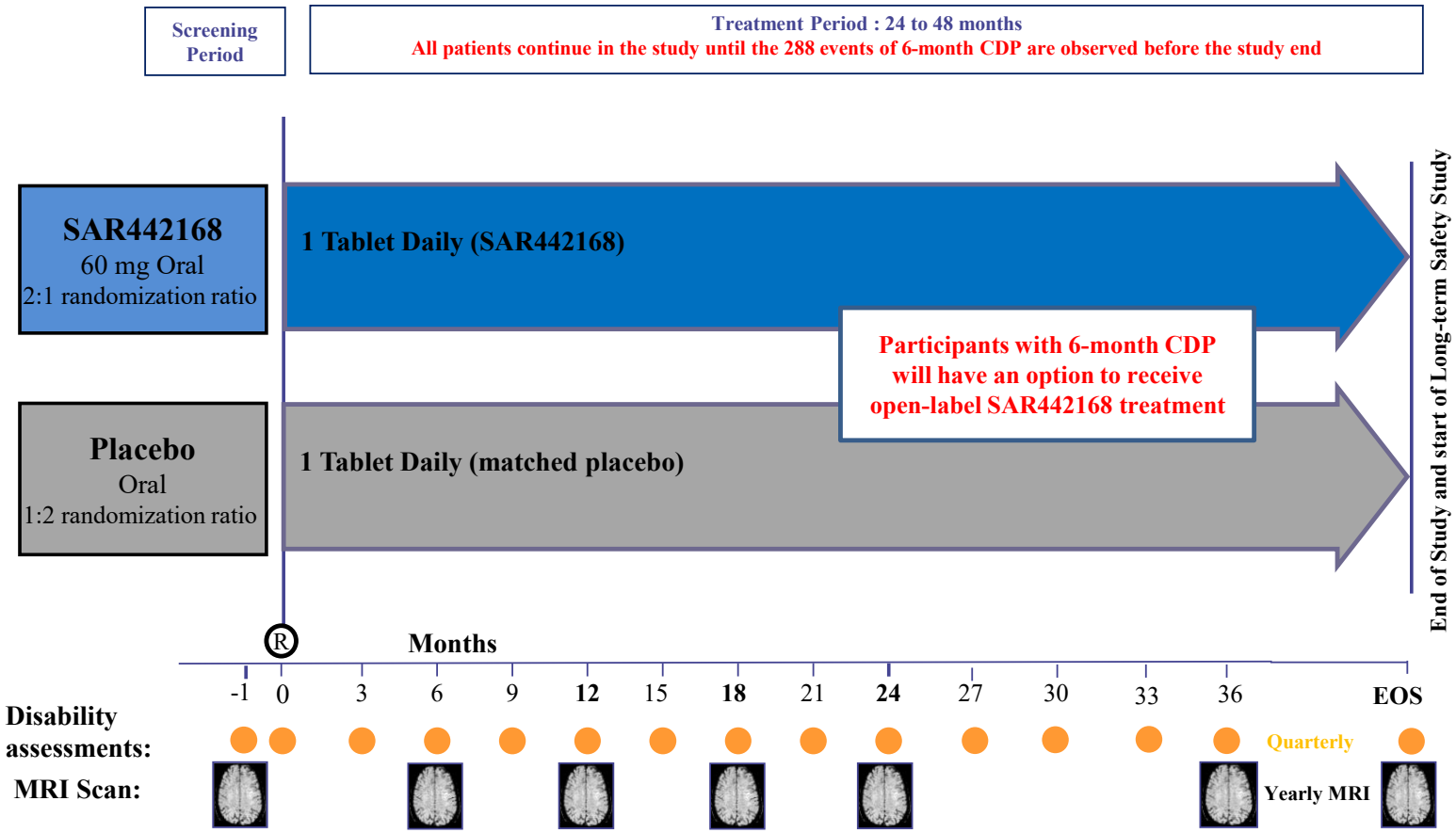
Eligibility Adjudication Committee: Yes

Relapse Adjudication Committee: Yes

Independent Hepatology Assessment Committee: Yes

1.2 SCHEMA

Figure 1 - Graphical study design



Abbreviations: CDP, confirmed disability progression; EOS, end of study; MRI, magnetic resonance imaging; R, randomization.
"Month-1 (D-28 - D-1)" refers to screening period as "Day-28 to Day-1"; "Month 0 (D1)" refers to randomization on Day 1.

1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedure	Screening[a]	Randomization/ start of IMP	To Year 2 (M24)[b]																From M27 to EOS[b]		Only for participants who prematurely discontinue IMP	For all participants	Only for participants who completed treatment EOS but do not enter LTS[c]
Visit (a window of ±7 days is allowed for all visits after D1)	D-28 to D-1	D1	M0.5 (W2) M0.75 (W3)	M1(W4)[d]	M1.25 (W5) M1.5 (W6) M1.75 (W7)	M2 (W8)[d]	M2.25 (W9) M2.5 (W10) M2.75 (W11)	M3	M4, M5[d]	M6	M7 M8	M9	M10 M11	M12	M15	M18	M21	M24	Quarterly visits (M27, M30, M33, M36, M39, M42, M45, M48…)	Semi-annual visits (M30, M36, M42, M48…)	pEOT[e]	EOS "Common study end date" visit[f]	Follow-up visit (4 weeks)
Visit Number	V1	V2		V3		V4		V5	V6, V7	V8		V9		V10	V11	V12	V13	V14	V15, V16, V17, V18, V19, V20, V21, V22	V16, V18, V20, V22	pEOT[e]	EOS	FUV
Informed consent	X																						
Demography	X																						
Inclusion/exclusion criteria	X	X																					
Medical/surgical history	X																						
Prior/concomitant medications[g]	←==========→																						
Randomization		X																					
IRT contact	X	X						X		X		X		X	X	X	X	X	X	X	X	X	X

Procedure	Screening[a]	Randomization/ start of IMP	To Year 2 (M24)[b]																From M27 to EOS[b]		Only for participants who prematurely discontinue IMP	For all participants	Only for participants who completed treatment EOS but do not enter LTS[c]
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Visit Number	V1	V2		V3		V4		V5	V6, V7	V8		V9		V10	V11	V12	V13	V14	V15, V16, V17, V18, V19, V20, V21, V22	V16, V18, V20, V22	pEOT[e]	EOS	FUV
Study treatment administration																							
IMP dispensation		X						X		X		X		X	X	X	X	X	X	X			
IMP Compliance								X		X		X		X	X	X	X	X	X	X	X[e]	X	
Paper diary dispensation/collection		X						X		X		X		X	X	X	X	X	X	X	X	X	
Safety[y]																							
Physical examination[h] and vital signs	X	X						X		X		X		X	X	X	X	X	X	X	X	X	X
Height	X																						
Body weight	X	X						X		X				X		X		X		X	X	X	X

Procedure	Screening[a]	Randomization/ start of IMP	To Year 2 (M24)[b]																From M27 to EOS[b]		Only for participants who prematurely discontinue IMP	For all participants	Only for participants who completed treatment EOS but do not enter LTS[c]
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Visit Number	V1	V2		V3		V4		V5	V6, V7	V8		V9		V10	V11	V12	V13	V14	V15, V16, V17, V18, V19, V20, V21, V22	V16, V18, V20, V22	pEOT[e]	EOS	FUV
Serology tests for hepatitis B and C	X																						
HIV and other infectious diseases, if required locally	X																						
TB/QuantiFERON® TB Gold test or equivalent[i]	X																						
Body temperature	X	X						X		X		X		X	X	X	X	X	X	X	X	X	X
12-lead ECG[j]	X							X		X		X		X				X		yearly	X	X	
Hematology, biochemistry[k]	X	X[z]		X		X		X	X	X		X		X	X	X	X	X	X	X	X	X	X

Procedure	Screening[a]	Randomization/ start of IMP	To Year 2 (M24)[b]															From M27 to EOS[b]		Only for participants who prematurely discontinue IMP	For all participants	Only for participants who completed treatment EOS but do not enter LTS[c]
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Liver function tests[l]			X		X		X				X		X										
Iron panel (serum): iron, ferritin, transferrin saturation,TIBC; to be repeated during the study if needed	X																						
Coagulation: PT/INR, aPTT (to be repeated during the study, if needed)	X																						
Urinalysis	X							X						X		X		X		X	X	X	
Pregnancy test (if applicable)[m]	X	X						X		X		X		X	X	X	X	X	X	X	X	X	X

Procedure	Screening[a]	Randomization/ start of IMP	To Year 2 (M24)[b]															From M27 to EOS[b]		Only for participants who prematurely discontinue IMP	For all participants	Only for participants who completed treatment EOS but do not enter LTS[c]
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Visit Number	V1	V2		V3		V4		V5	V6, V7	V8		V9		V10	V11	V12	V13	V14	V15, V16, V17, V18, V19, V20, V21, V22	V16, V18, V20, V22	pEOT[e]	EOS	FUV
Serum FSH[n]	X																						
Suicidality assessment by C-SSRS	X	X						X		X		X		X	X	X	X	X	X	X	X	X	X
Adverse event collection	←==========→																						
Efficacy																							
EDSS	X	X						X		X		X		X	X	X	X	X	X	X	X	X	
Timed 25-foot walk test		X						X		X		X		X	X	X	X	X	X	X	X	X	
9-hole peg test		X						X		X		X		X	X	X	X	X	X	X	X	X	
SDMT and CVLT-II, where available[o]		X						X		X		X		X	X	X	X	X	X	X	X	X	

Procedure	Screening[a]	Randomization/ start of IMP	To Year 2 (M24)[b]																From M27 to EOS[b]		Only for participants who prematurely discontinue IMP	For all participants	Only for participants who completed treatment EOS but do not enter LTS[c]
Visit (a window of ±7 days is allowed for all visits after D1)	D-28 to D-1	D1	M0.5 (W2) M0.75 (W3)	M1(W4)[d]	M1.25 (W5) M1.5 (W6) M1.75 (W7)	M2 (W8)[d]	M2.25 (W9) M2.5 (W10) M2.75 (W11)	M3	M4, M5[d]	M6	M7 M8	M9	M10 M11	M12	M15	M18	M21	M24	Quarterly visits (M27, M30, M33, M36, M39, M42, M45, M48…)	Semi-annual visits (M30, M36, M42, M48…)	pEOT[e]	EOS "Common study end date" visit[f]	Follow-up visit (4 weeks)
Visit Number	V1	V2		V3		V4		V5	V6, V7	V8		V9		V10	V11	V12	V13	V14	V15, V16, V17, V18, V19, V20, V21, V22	V16, V18, V20, V22	pEOT[e]	EOS	FUV
Basic or expanded MRI[p]	X[q]									X				X		X		X		yearly	X	X	
Actigraphy (optional for subset of participants)[r]	X																						
Clinical outcome assessments[s]																							
MSQoL-54		X								X				X		X		X		X	X	X	
EQ-5D-5L		X								X				X		X		X		X	X	X	

Procedure	Screening[a]	Randomization/ start of IMP	To Year 2 (M24)[b]															From M27 to EOS[b]		Only for participants who prematurely discontinue IMP	For all participants	Only for participants who completed treatment EOS but do not enter LTS[c]
Visit (a window of ±7 days is allowed for all visits after D1)	D-28 to D-1	D1	M0.5 (W2) M0.75 (W3)	M1(W4)[d]	M1.25 (W5) M1.5 (W6) M1.75 (W7)	M2 (W8)[d]	M2.25 (W9) M2.5 (W10) M2.75 (W11)	M3	M4, M5[d]	M6	M7 M8	M9	M10 M11	M12	M15	M18	M21	M24	Quarterly visits (M27, M30, M33, M36, M39, M42, M45, M48…)	Semi-annual visits (M30, M36, M42, M48…)	pEOT[e]	EOS "Common study end date" visit[f]	Follow-up visit (4 weeks)
Visit Number	V1	V2		V3		V4		V5	V6, V7	V8		V9		V10	V11	V12	V13	V14	V15, V16, V17, V18, V19, V20, V21, V22	V16, V18, V20, V22	pEOT[e]	EOS	FUV
Pharmacokinetics																							
SAR442168 and relevant metabolite(s) pharmacokinetic plasma samples[t]										X[u]		X[u]		X[u]							X[e]		
Pharmacogenetics																							
DNA sample (optional)[w]		X																					
Pharmacodynamics/biomarkers																							
Blood sample for archiving[x]	X																						

Procedure	Screening[a]	Randomization/ start of IMP	To Year 2 (M24)[b]															From M27 to EOS[b]		Only for participants who prematurely discontinue IMP	For all participants	Only for participants who completed treatment EOS but do not enter LTS[c]
Visit (a window of ±7 days is allowed for all visits after D1)	D-28 to D-1	D1	M0.5 (W2) M0.75 (W3)	M1(W4)[d]	M1.25 (W5) M1.5 (W6) M1.75 (W7)	M2 (W8)[d]	M2.25 (W9) M2.5 (W10) M2.75 (W11)	M3	M4, M5[d]	M6	M7 M8	M9	M10 M11	M12	M15	M18	M21	M24	Quarterly visits (M27, M30, M33, M36, M39, M42, M45, M48…)	Semi-annual visits (M30, M36, M42, M48…)	pEOT[e]	EOS "Common study end date" visit[f]	Follow-up visit (4 weeks)
Visit Number	V1	V2		V3		V4		V5	V6, V7	V8		V9		V10	V11	V12	V13	V14	V15, V16, V17, V18, V19, V20, V21, V22	V16, V18, V20, V22	pEOT[e]	EOS	FUV
Immunophenotyping/ RNA sequencing (ToleDYNAMIC/optional substudy at selected sites)[aa]		X						X						X									
Lymphocyte phenotyping by flow cytometry in whole blood (subset of participants)[bb]		X																			X	X	
Plasma samples (NfL), serum samples (Chi3L1)[v]		X						X		X				X				X		yearly	X	X	

Procedure	Screening[a]	Randomization/ start of IMP	To Year 2 (M24)[b]															From M27 to EOS[b]		Only for participants who prematurely discontinue IMP	For all participants	Only for participants who completed treatment EOS but do not enter LTS[c]
Visit (a window of ±7 days is allowed for all visits after D1)	D-28 to D-1	D1	M0.5 (W2) M0.75 (W3)	M1(W4)[d]	M1.25 (W5) M1.5 (W6) M1.75 (W7)	M2 (W8)[d]	M2.25 (W9) M2.5 (W10) M2.75 (W11)	M3	M4, M5[d]	M6	M7 M8	M9	M10 M11	M12	M15	M18	M21	M24	Quarterly visits (M27, M30, M33, M36, M39, M42, M45, M48…)	Semi-annual visits (M30, M36, M42, M48…)	pEOT[e]	EOS "Common study end date" visit[f]	Follow-up visit (4 weeks)
Visit Number	V1	V2		V3		V4		V5	V6, V7	V8		V9		V10	V11	V12	V13	V14	V15, V16, V17, V18, V19, V20, V21, V22	V16, V18, V20, V22	pEOT[e]	EOS	FUV
Serum samples (Ig levels)[v]		X								X				X				X		yearly	X	X	

aPTT, activated partial thromboplastin time; β-HCG, β-human chorionic gonadotropin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Chi3L1, chitinase-3-like protein 1; C-SSRS, Columbia Suicide Severity Rating Scale; D, day; DNA, deoxyribonucleic acid; ECG, electrocardiogram; EDSS, Expanded Disability Status Scale; EOS, end of study; EOT, end of treatment; EQ-5D-5L, EuroQol 5-dimension 5-level instrument; FSH, follicle stimulation hormone; FUV, follow-up visit; ICF, informed consent form; Ig, immunoglobulin; IRT, interactive response technology; HIV, human immunodeficiency virus; IMP, investigational medicinal product; INR, international normalized ratio; LTS, long term safety study; M, month; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MRI: magnetic resonance imaging; MS: multiple sclerosis; SDMT, Symbol Digit Modalities Test; CVLT-II, California Verbal Learning Test-II; MSQoL-54: Multiple Sclerosis Quality of Life-54; NfL: neurofilament light chain; pEOT: premature end of treatment; PK: pharmacokinetic; PT: prothrombin time; RBC, red blood cell; SWI, susceptibility weighted imaging; TB, tuberculosis; TIBC: total iron-binding capacity; V: visit; WBC, white blood cell.

Note: All assessments should be done as designated in this SoA unless not permitted according to local regulations. All visit assessments should be performed during the visit window unless otherwise specified in this protocol.

a Screening period can range from D-28 to D-1; Randomization visit can be performed only once IMPs are available at site. The interval between screening and randomization visits can range from 11 days (minimum) to 28 days (maximum). However, if required, the randomization visit can be performed earlier than 11 days upon IMP receipt at the site, assuming the participant is eligible for randomization. In case of any delay to screening (MRI rescheduling, lab retests, etc), an additional period of up to 2 weeks is allowed.

b From D1 to EOS, unscheduled visits may be performed at any time by the Investigator (eg, for evaluation of an adverse event). Assessments may be done on as needed basis to evaluate the participant in accordance with the Investigator's best judgement and in-line with the study protocol. At a minimum, a physical examination should be performed, and body temperature and vital signs should be measured.

c At the EOS, the participants who have completed treatment with IMP (double blind or open label if meeting CDP) may be offered participation in LTS study. Follow-up visit assessment only performed for those participants who completed treatment and are not willing to take part in the LTS study. For other situations where a follow-up visit is needed, please see Section 7.1 and the Study Manual.

d These visits may be done as home health visits (where applicable) or onsite visits (it is preferable that tests are performed at the central laboratory). In any situations where this is not possible (to be documented in source documents), the tests for these visits may be performed at a local laboratory.

e If a participant prematurely permanently discontinues treatment with IMP, the participant will undergo pEOT visit as soon as possible. A PK sample should also be collected if the pEOT visit can be scheduled within a maximum 24 hours after the last IMP dose. Participants will then be asked to continue with the study visits as scheduled until the common EOS Visit is reached. During these visits, all study procedures/assessments will be performed except IMP administration and blood sampling for PK and biomarkers (NfL, Chi3L1, and Ig levels). MRI scans for these participants will only be performed annually (using the next annual visit as the starting point). Additional information is provided in the Study Manual.

f For participants continuing in the study, the common EOS visit will be done when the prespecified number of events for 6-month CDP is expected to be reached. The timing and window of this visit will be communicated to sites.

g Any disease-modifying therapy for MS taken at any time prior to signing the informed consent needs to be reported in the eCRF; other prior medications will be reported for the period of 6 months prior to signing the ICF.

h Complete physical examination due at screening, baseline, yearly (M12, M24, M36, M48) and at EOS; brief physical examination is sufficient for the rest of the visits (complete and brief physical examinations will include neurological examination and collection of the following vital signs: arterial blood pressure, heart rate, temperature).

i To be performed at screening for all participants. Tuberculosis examination will be repeated based on clinical judgment, borderline results, or clinical suspicion of TB infection. For further details, refer to E 01**.** Screening tests for TB are described in Appendix 2 (Section 10.2).

j ECG and 30 second rhythm strips will be obtained locally.

k Hematology (platelet count, RBC count, hemoglobin, hematocrit, MCV, MCH, reticulocytes, WBC count with differential: neutrophils, lymphocytes, monocytes, eosinophils, basophils).
Biochemistry (blood urea nitrogen [BUN], creatinine, glucose, sodium, potassium, bicarbonate, calcium, liver function tests [AST, ALT, ALP, albumin, total and direct bilirubin], total protein; creatine phosphokinase. Lipase will be tested at the Screening Visit, then quarterly. Monthly visits (M1, M2, M4, and M5) will include hematology and full liver panel only. Additional safety assessments can be performed if required by local regulations. Such testing shall be performed at local laboratories.
Note: a one-time retest at screening may be performed if laboratory test abnormality is considered temporary. Additional safety assessments can be performed if required by local regulations; such testing shall be performed locally whenever possible. Additional visits may be added if required by local regulations.

l At intermediate timepoints (W2, W3, W5, W6, W7, W9, W10, W11, M7, M8, M10, and M11), only liver function tests will be collected (AST, ALT, albumin, alkaline phosphatase, total and direct bilirubin, total protein) and creatine phosphokinase); these can be performed at central laboratory (preferred, as on-site visits or home nursing as applicable for the site) or at local laboratory; a window of ±3 days is permitted for weekly liver function test (LFT) timepoints and ±7 days for the other timepoints. Additional information is provided in the Study Manual. For participants switching to open-label treatment, please refer to Section 6.6.1.

m At screening, perform the serum ß-hCG pregnancy test at the central laboratory. At randomization and other scheduled visits during the study, urine pregnancy tests should be performed. At randomization, a pregnancy test should be performed prior to the first dose of IMP. Additional serum or urine pregnancy tests may be performed, as determined 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. Communication by phone of the result of a pregnancy test performed at home to the site is allowed. See also Appendix 4 (Section 10.4).

n Only in female participants, if needed to establish menopausal status.

o The SDMT and CVLT-II will be performed in all participants. If for some reason, CVLT-II is not available at a given site due to reasons such as lack of translation, local certification, etc., then only the SDMT will be assessed for that participant.

p A subset of sites that have 3T MRI capacity will perform additional sequences (eg, SWI). Further details will be defined in a central MRI manual.

q A visit window of ±21 days is acceptable for MRIs performed after D1. For systemic corticosteroids and adrenocorticotropic hormone, 1-month wash-out required prior to the MRI scans. The screening MRI scan should be performed as close as possible before the start of IMP. As much as possible, the MRI scan should be performed during the screening period only after it has been established that the participant meets all inclusion and no exclusion criteria.

r A noninvasive activity monitor (actigraphy) may be optionally implemented by the Sponsor in a subset of participants during the course of the study if results from pilot assessment demonstrate feasibility.

s When available, clinical outcome assessments are to be completed by the participant prior to discussing their health status and prior to study treatment administration or other study related procedures where available per local regulations.

t On days of PK sampling, the IMP needs to be taken at the study site after a “regular meal”. In case a participant forgot IMP at home or took IMP prior to arriving at the site on the day of visits with PK sampling, he/she will be asked to have a repeat assessment within 3 days of the missed PK sampling. A PK assessment shall be done as soon as possible after an overdose or if otherwise specified per protocol (eg, investigation of abnormal laboratory test values).

u M6 and M12: Two samples: one sample between 30 to 90 minutes and one sample between 2.5 to 5 hours after IMP administration. M9: one sample 30-90 minutes after IMP.

v Pharmacodynamics and biomarkers samples will be collected only if permitted per local regulations.

w DNA testing will be allowed at any time after signature of consent (in case it could not be done for some reason at Day 1). Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study. A separate consent is required for the genetic analysis component of the study.

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

y Additional safety assessments can be performed if required by local regulations; such testing shall be performed locally whenever possible. Additional visits may be added if required by local regulations.

z Samples for hematology and biochemistry tests on Day 1 (randomization) must be collected prior to administration of the first IMP dose.

aa Samples must be shipped within 24 hours. For detailed instructions see Appendix 11 (Section 10.11) and the Study Manual.

bb Blood sample collection for lymphocyte phenotyping by flow cytometry will be performed in a subset of randomized participants. Participants who did not have a baseline sample collected, will no longer have this test performed; participants who had a baseline sample collected will have a second sample collected at EOT/pEOT.

2 INTRODUCTION

SAR442168, a brain penetrant inhibitor of Bruton's tyrosine kinase (BTK), is being developed for the indication of treatment of patients with MS. This study is designed to collect evidence of SAR442168 efficacy and safety in the nonrelapsing SPMS (NRSPMS) population.

2.1 STUDY RATIONALE

The goal of this Phase 3 clinical trial is to demonstrate the efficacy and safety of SAR442168 compared to placebo in participants with NRSPMS. SAR442168 is a small molecule administered as a once daily oral treatment that is an irreversible, covalent inhibitor of BTK. SAR442168 is a brain-penetrant compound that modulates the pro-inflammatory activity of B cells in the periphery and in the CNS as a result of the BTK inhibition. The proposed mechanism of action for SAR442168 is to inhibit the coupling of the B cell receptor to downstream signaling in B cells, thereby modulating B cells without depleting them. Additionally, it is also known that activated B cells are key players in the pathogenesis of MS, specifically in the progressive form of the disease.

The immune complex receptor FcγRII, found in macrophages and microglial cells and that also signals through BTK, will similarly be modulated. The Sponsor hypothesizes that this action will result in a decrease of inflammatory activity in the CNS, diminishing brain lesions as detected by MRI as well as reducing the accumulation of disability progression.

The advent of disease-modifying therapies for relapsing forms of MS has led to significant strides in reducing relapse frequency and the attendant morbidity for people with MS. However, chronic disability accumulation remains a significant unmet need for people living with MS. Individuals with progressive disease, including SPMS, need therapies to reduce the accumulation of disability. With several drugs approved for active secondary progressive disease, there is still no treatment available for NRSPMS.

Data from the recent pivotal trial of siponimod, a S1P receptor modulator, in SPMS patients demonstrated reduced risk of 3-month confirmed disability progression (HR=0.79) (1). Data from ORATORIO, the pivotal Phase 3 trial of ocrelizumab in a PPMS population, demonstrated that this anti-CD20 monoclonal antibody that depletes B lymphocytes could provide a small but statistically significant benefit (HR=0.76) in reducing the risk of disability progression (2).

Furthermore, abundant evidence suggests that innate immunity, and specifically CNS-resident microglial cell activity, is a significant driver of disability accumulation in all forms of MS. The dual working hypothesis driving development of SAR442168 is based on the following:
1) modulating B cells inert to antigenic stimulation will have an effect similar to B-cell depletion on progressive MS disability accumulation, and 2) CNS penetrance will provide a potential added benefit of modulating innate immunity mediated by macrophages and microglial cells to suppress maladaptive neuroinflammatory processes associated with chronic disability progression.

The ability of SAR442168 to reduce the formation of acute brain lesions in MS was assessed in a Phase 2b dose-finding trial in participants with RMS (DRI15928). Patients with progressive forms of MS may also present with acute focal inflammatory activity in the CNS. This activity manifests on MRI as T1 hyperintense Gd+ lesions and new or enlarging T2 lesions. SAR442168 has proven to be effective in reducing both types of CNS lesions. The SAR442168 Phase 2b results showed that SAR442168 reduced the number of new T1 hyperintense Gd+ lesions by 85% and the number of new or enlarged T2 lesions by 89% in the 60 mg group (the dose to be used in the Phase 3 program) compared to placebo. These data also support the use of this compound in progressive forms of MS.

Reduction in number of T1-hyperintense (Gd-enhanced) lesions has been established as a highly reliable predictive biomarker for clinical efficacy in pivotal studies in MS including Phase 3 RMS studies (3). While there is no comparable radiographic biomarker to predict clinical efficacy on disability progression, the assumption has been that doses effective at preventing relapses can be used to assess disability progression in PPMS or SPMS (2, 4, 5, 6, 7, 10, 11). SAR442168 was shown to achieve pharmacologically relevant concentrations in CSF after a single oral administration, with the potential to inhibit microglia and infiltrating bone-marrow-derived macrophages that are believed to drive neuroinflammation linked to disease progression.

The primary endpoint is time to onset of 6-month CDP assessed via EDSS score. The EDSS is widely used to measure neurological disability in clinical trials and routine settings (8). Six-month CDP is standard practice in many clinical trials and is recommended by guidelines (2, 4) and considered clinically more meaningful than 3-month CDP.

The CDI over at least 6 months measured by the EDSS score will be used as a secondary endpoint due to its clinical importance.

Magnetic resonance imaging outcomes will include change in brain volume, which is considered as a marker of the CNS degenerative process and therefore recommended for use in progressive MS trials (9).

Population pharmacokinetics (PK) will be performed in order to obtain a larger and more diverse population to evaluate the PK of SAR442168 in the NRSPMS population, to assess sources of PK variability (ethnicity, special populations), and to establish exposure correlation to clinical efficacy, biomarkers, and safety endpoints. Soft lock of the population PK data may be performed as soon as all participants have finished the Month 12 visit (a separate unblinded team will be used to preserve blinding integrity).

This study will employ other secondary outcome measures to collect additional data in an effort to assess the benefit of SAR442168 for people with NRSPMS.

Although no enrolled participants are expected to have MS relapses, their occurrence cannot be ruled out completely. Relapse data will be carefully collected and adjudicated, and their impact on the primary endpoint will be assessed (see also statistical considerations).

Exploratory assessments are expected to provide additional evidence for SAR442168 activity on neuroinflammation and neurodegeneration.

2.2 BACKGROUND

Immunomodulatory drugs are the mainstay of MS therapy. Recent clinical trials have demonstrated efficacy of agents that target B lymphocytes, especially B-cell-depleting agents like ocrelizumab (α-CD20). Targeting B cells is a departure from the prevailing dogma based on animal models that demonstrated therapeutic benefits from modulating T-cell activity. Thus, B cells have become the cellular focus of current MS drug development (12). However, the importance of immune cells residing in the CNS is also well known (13) and needs to be considered in MS pathogenesis.

Evidence of inflammation and presence of activated T and B cells in the brain have also been confirmed in PPMS and SPMS, especially in the early stages (14). Inflammatory activity in RMS has been attenuated to different degrees with a variety of immunomodulatory therapies; however, historically these therapies have shown very little effect on disease activity in people with progressive MS despite the evidence for inflammatory activity. This may relate to conditions in the CNS, especially the integrity of the blood brain barrier (BBB), but also to the potency and mechanism of action of the agents.

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 all diagnostic categories of MS (ie, RMS as well as progressive forms of the disease, PPMS and SPMS) (15). Even the most recent high-efficacy disease-modifying therapies act mainly on adaptive immunity in the periphery with only modest or temporary ability to slow neuroinflammatory and neurodegenerative processes and stop disease progression (2, 3). Therefore, development of MS treatments with new modes of action is of interest. This is particularly true for individuals with progressive disease, including SPMS, occurring in more than 50% of patients with relapsing-remitting multiple sclerosis (RRMS) within 15 to 20 years.

The disease progression for patients with PMS is not driven by relapse but by smoldering inflammation within the brain mediated by activated microglial cells. During this time, MRI signs associated with smoldering neuroinflammation and neurodegeneration mediated by resident innate immunity (maladaptive microglia) have become more prominent. In this context, brain tissue loss (atrophy), slowly evolving lesions (SEL) and paramagnetic rim lesions, are important features in progressive forms of MS (16, 17).

SAR2442168 is thought to have the potential to address “outside-in” and “inside-out” MS pathological mechanisms. In the periphery, SAR442168 inhibits antigen-induced B cell activation, while, due to its property of brain penetrance, SAR442168 modulates maladaptive microglial cells in the CNS. Microglial cells express Fc-gamma receptors that couple to BTK signaling pathways which result in the secretion of pro-inflammatory cytokines in the CNS. This pro-inflammatory activity, which is continuous, gradual, and chronic, is believed to drive neuroinflammation linked to progressive tissue damage in the brain and spinal cord that occurs in the absence of clinical relapses and MRI Gd-enhancing lesions. This smoldering neuroinflammation has, as pathophysiological consequences, axonal loss, lack of remyelination, and myelin damage, all believed to be closely related to clinical disability progression. In other words, a brain-penetrant compound that crosses the blood-brain barrier, acts directly on maladaptive reactive microglial cells, and modulates smoldering inflammatory activity may result in less tissue damage, resulting in less disability progression over time.

2.3 BENEFIT/RISK ASSESSMENT

SAR442168 is a covalent, irreversible inhibitor of BTK that has a dual mode of action. In peripheral adaptive immunity, it inhibits signaling between the B-cell receptor and downstream signaling events associated with cellular proliferation, maturation, and production of secreted immunoglobulins. BTK is also a key signaling pathway in macrophage/microglial phagocytic cells of innate immunity. By modulating both adaptive and innate immunity, SAR442168 has the potential to reduce lymphocyte-mediated acute inflammation peripherally and neuroinflammation mediated by innate immunity in the CNS.

Benefit assessment:

SAR442168 is expected to reduce MS relapse rate, disability progression, and underlying CNS damage through its dual action on adaptive immunity in the periphery and innate immunity and the inflammation process in the CNS.

The results from the Phase 2b trial (DRI15928) demonstrated a dose–response relationship for SAR442168 as evidenced by 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 85% relative reduction in lesions at 12 weeks in the 60 mg dose group as compared with placebo. This was obtained from the negative binomial regression model adjusted for baseline Gd-enhancing T1-hyperintense lesion activity.

The potential benefits of SAR442168 are as follows:

Potential benefits

- Decrease of annualized relapse rate (ARR).
- Reduction in the risk of loss of mobility.
- Reduction in the accumulation of confirmed disability progression (as expressed by an increase in the Expanded Disability Status Scale [EDSS] score).
- Reduction of disease activity as assessed by MRI (Gd-enhancing lesions and new/enlarging T2 lesions).
- Trend toward normalization of brain volume loss.
- Reduction in neuroinflammation, as assessed by modulation of chronic active lesions (slowly evolving lesions, paramagnetic rim lesions) observed by MRI.

Risk Assessment

SAR442168 has been studied in healthy participants and participants with RMS. In the completed Phase 1 clinical trials in healthy participants, oral administration of SAR442168 was generally safe and well tolerated.

The results from the Phase 2b trial (DRI15928) suggest that SAR442168 is generally safe and well tolerated in patients with RMS. No new risks were identified in this trial. The key results are summarized as follows:

- There was no death or treatment-emergent adverse event (TEAE) leading to permanent treatment discontinuation during the study. One treatment-emergent serious adverse event (SAE) (MS relapse) was reported in a participant treated with 60 mg SAR442168; the remainder of the reported TEAEs were of mild or moderate intensity.
- There was no direct correlation between the doses of SAR442168 administered and number or intensity of TEAEs. The most common events reported in participants in the SAR442168 treatment arms were headache, upper respiratory tract infection, and nasopharyngitis.
- Two participants had treatment-emergent transient alanine aminotransferase (ALT) increase >3 x upper limit of normal (ULN), 1 during the 30 mg SAR442168 treatment period (at Week 8, 105 U/L [normal range 6 to 34 U/L]) that returned to normal range within 4 days and 1 during the 60 mg SAR442168 treatment period (at Week 4, 107 U/L [normal range 6 to 34 U/L]). The participant in the 60 mg group had slightly elevated ALT at screening (48 U/L) and at baseline (50 U/L); ALT levels returned to the normal range in 8 weeks. Both participants continued study treatment during this period. All other liver enzyme levels for both participants were within normal ranges during the treatment period; one event was assessed as related and one as unrelated to the study drug by the Investigators. Both participants completed the DRI15928 study and successfully rolled over to the LTS follow-up study.
- One event of mild petechia in a female participant (at Week 8 in the SAR442168 30 mg group) and 2 events of mild microscopic hematuria in 2 male participants (1 event at Week 16 in the SAR442168 30 mg group and 1 event on Day 1 in the SAR442168 60 mg group, with occult blood noted in urine) were reported during the treatment period in the SAR442168 Phase 2b trial. The hematology results were clinically insignificant for all 3 participants from the onset of the events. The participant with mild petechia had benign pigmentary lesions noted during screening, and the event was assessed as related to the study drug by the Investigator. The 2 events of mild microscopic hematuria were assessed as unrelated to the study drug. All 3 events resolved spontaneously.
- No severe infections occurred. The most frequently reported (≥3 events total) in the SAR442168 treatment period were upper respiratory tract infection, nasopharyngitis, gastroenteritis, and respiratory tract infection.
- No clinically significant cytopenia, including thrombocytopenia and neutropenia, were reported or detected based on hematologic laboratory results, and no clinically significant cardiac arrhythmia was observed via ECG monitoring during the study.

Based on SAR442168 nonclinical safety data, Phase 1 results from healthy participants, Phase 2b results in participants with RMS, and the published data of other marketed or investigational BTK inhibitors for various indications, the potential risks of SAR442168 are as follows:

- Bleeding (hemorrhage).
- Infections.
- Cytopenia including thrombocytopenia.
- Atrial arrhythmias (atrial fibrillation and atrial flutter).

In the ongoing Phase 3 and LTS studies, tolebrutinib has been generally well tolerated to date. An identified risk for tolebrutinib has been identified as follows:

- Treatment-emergent SAEs of drug-induced liver injury (DILI), including severe DILI (risk of liver transplantation or death) as an identified risk, were reported in the ongoing Phase 3 trials; cases occurred in Months 1 to 3, with potential confounders identified for some of the cases.

Assessment of COVID-19 in trial participants:

Antiviral responses are likely to be driven mainly by T cells, in particular CD8+ cytotoxic T lymphocytes, and natural killer cells, and less so, at least initially, by B cells (18, 19). In vitro and cell-based assays indicate that SAR442168 does not deplete B lymphocytes and does not exhibit significant cellular off-target activity in human T lymphocytes. In the completed Phase 2b study in participants with RMS (DRI15928), the mean counts of CD19+ B cells, CD4 and CD8 T cells, CD16+56 natural killer cells, and the levels of IgG and IgM remained stable at the end of 12 weeks of treatment with SAR442168.

Infections are an important potential risk for SAR442168, and severe infections are being monitored as an AESI in all ongoing and future clinical trials. In the completed Phase 2b trial in 130 participants with RMS, 23.8% of participants reported only mild or moderate infections at the end of 12 weeks of treatment with SAR442168. No participant discontinued treatment due to infection or any other TEAE. In addition, the latest clinical research showed that the administration of acalabrutinib, a highly specific covalent inhibitor of BTK, was associated with reduced inflammation and improved clinical outcome in 19 patients hospitalized with severe coronavirus disease 2019 (COVID-19), without discernable toxicity, over a 10- to 14-day treatment course (20). Randomized studies with acalabrutinib and ibrutinib in COVID-19 are ongoing (21, 22, 23, 24). At present, it is unknown if people with MS are at increased risk for SARS-CoV-2 infection, acquiring COVID-19 or developing severe COVID-19 (18).

The risk of COVID-19 in participants who receive SAR442168 is unknown based on currently available data. Out of precaution, the current trial excludes people with known risk factors for severe COVID-19 including advanced age and comorbidities that may put patients at higher risk for serious illness such as chronic cardiovascular disease, liver disease, kidney disease, respiratory system compromise, and malignancies. Concomitant use of immunosuppressive or chemotherapeutic medications is excluded.

In addition, appropriate safety monitoring measures are in place including physical examination, monitoring of vital signs and clinical labs, ECG, and collection of AEs and AESIs. Every effort will be made to complete trial visits and trial assessments and to provide study drug for participants. If needed, temporary treatment discontinuation can be considered by the Investigator or by the participant for any reason, including due to any safety concerns because of COVID-19 or another illness or if there is a need for a prohibited concomitant medication. Treatment can be resumed later when it is considered safe and appropriate.

Last, the Sponsor will update the ICF to inform participants of the general risks for COVID-19 during the pandemic and the importance of appropriate behavioral modifications to reduce or ideally prevent exposure to the SARS-CoV-2 virus.

In conclusion, considering the mechanism of action of SAR442168, the lack of data on the COVID-19 course in MS patients receiving DMTs, the safety monitoring and mitigation measures already in place, and the favorable benefit-risk profile observed in the completed Phase 2b study in participants with RMS, the Sponsor maintains that the trial can be initiated and conducted as planned.

Overall benefit: risk conclusion

No safety or tolerability concerns have been identified in the completed Phase 1 studies in healthy participants or the Phase 2b trial (DRI15928) in participants with RMS. In addition, the positive Phase 2b primary endpoint results support the potential for clinical efficacy.

Drug-induced liver injury, including severe DILI (risk of liver transplantation or death) as an identified risk, has been identified in the ongoing Phase 3 trials. The reported events occurred in Months 1 to 3 after the start of the IMP. Exclusion criteria and monitoring frequency have been updated in all actively recruiting protocols.

The potential risks associated with SAR442168 are well defined and appropriate safety monitoring measures and risk mitigation strategies are in place. The overall benefit/risk balance is acceptable for further clinical development of SAR442168.

3 OBJECTIVES AND ENDPOINTS

Table 1 - Objectives and endpoints

Objectives	Endpoints
Primary	
• To determine the efficacy of SAR442168 compared to placebo in delaying disability progression in NRSPMS	• Time to onset of 6-month CDP defined as follows: - Increase of ≥1.0 point from the baseline EDSS score when the baseline score is ≤5.0, OR - Increase of ≥0.5 point when the baseline EDSS score is >5.0
Secondary	
• To evaluate efficacy of SAR442168 compared to placebo on clinical endpoints, MRI lesions, cognitive performance, physical function, and quality of life	• Time to onset of sustained 20% increase in the 9-HPT for at least 3 months • Time to onset of sustained 20% increase in the T25-FW for at least 3 months • Time to onset of 3-month CDP as assessed by the EDSS score • Total number of new and/or enlarging T2-hyperintense lesions as detected by MRI, defined as the sum of the individual number of new and/or enlarging T2 lesions at all scheduled visits starting after baseline up to and including the EOS visit • Time to onset of CDI defined as a ≥1.0 point decrease on the EDSS score from baseline confirmed over at least 6 months • Percent change in BVL as detected by MRI scans at the EOS compared to Month 6 • Change in cognitive function at the EOS compared to baseline as assessed by SDMT • Change in cognitive function at the EOS compared to baseline as assessed by CVLT-II, where available • Change in MSQoL-54 questionnaire score from baseline through the EOS
• To evaluate safety and tolerability of SAR442168	• Adverse events (AEs), serious AEs, AEs leading to permanent study intervention discontinuation, AEs of special interest, and potentially clinically significant abnormalities in laboratory tests, safety scales, ECG, and vital signs during the study period
• To evaluate population pharmacokinetics of SAR442168 and relevant metabolite(s) in NRSPMS and its relationship to efficacy and safety • To evaluate pharmacodynamics (PD) of SAR442168	• Plasma concentration of SAR442168 and relevant metabolite(s) (population PK assessment) at Months 6, 9, and 12 • Change in plasma NfL levels at the EOS compared to baseline • Change in lymphocyte phenotype subsets in whole blood at the EOS compared to baseline in a subset of participants • Change in serum immunoglobulin level at baseline compared to the EOS • Change in serum Chi3L1 levels at baseline compared to the EOS

Objectives	Endpoints
Tertiary/exploratory	
• To evaluate efficacy of SAR442168 on disease progression and activity in NRSPMS, assessed by other clinical and imaging measures and by self-reported assessment	• Time to onset of sustained 20% increase in the 9-HPT for at least 6 months • Time to onset of sustained 20% increase in the T25-FW for at least 6 months • Time to onset of a 4-point decrease in the SDMT, confirmed over at least 3 and 6 months • The proportion of participants with CDI confirmed over at least 6 months • The proportion of participants with CDI confirmed over at least 6 months and maintained until the EOS • Change from baseline to Months 12, 18, and 24 and to the EOS in the EDSS score, T25-FW test, 9-HPT, SDMT, and CVLT-II • Change from baseline to Months 12, 18, and 24 and to the EOS in modified MSFC-3, assessed as the composite of the T25-FW test, 9-HPT, and SDMT • Proportion of participants with NEDA-3 at Months 18, 24, 30, 36, and the EOS • The annualized adjudicated relapse rate (ARR) • Actigraphic analysis of activity counts and indices of change from baseline to the EOS summarized over time (in a subset of participants) • Change from baseline of total volume of T2-hyperintense lesions as detected by brain MRI at Months 18, 24, and the EOS • Total number of new Gd-enhancing T1-hyperintense lesions as detected by MRI, defined as the sum of the individual number of new Gd-enhancing T1-hyperintense lesions at all scheduled visits starting after baseline up to and including the EOS visit • Change from baseline by visit in the volume of T1-hypointense lesions and cumulative number of new T1 hypointense lesions • MTR recovery at EOS in new MTR lesions detected at months 6 and 12 • Change in number of phase rim lesions in SWI MRI from baseline through the EOS (subset of centers with capacity of 3T MRI) • Number and volume of slowly evolving lesions (SELs) • Normalized T1 (nT1) intensity evolution in SELs
• To evaluate the treatment effect of SAR442168 via changes in participants' health-related quality of life (HRQoL), and working capacity	• Change in EQ-5D-5L from baseline by visit over time

Abbreviations: 9-HPT, 9-hole peg test; AE, adverse event; AESI, adverse event of special interest; ARR, annualized adjudicated relapse rate; BVL, brain volume loss;-CDI, confirmed disability improvement; CDP, confirmed disability progression; Chi3L1, Chitinase-3 like protein-1; ECG, electrocardiogram; EDSS, Expanded Disability Status Scale; EQ-5D-5L, EuroQol 5-dimension 5-level instrument; EOS, end of study; Gd, gadolinium; HRQoL, health related quality of life; MRI, magnetic resonance imaging; MTR, magnetization transfer ratio; MSFC-3, Multiple Sclerosis Functional Composite 3; MSQoL-54, Multiple Sclerosis Quality of Life-54 Questionnaire; NEDA-3, no evidence of disease activity-3; NfL, neurofilament light chain; NRSPMS, non-relapsing secondary progressive multiple sclerosis; PD, pharmacodynamic; PK, pharmacokinetic; SAE, serious adverse event; SDMT, Symbol Digit Modalities Test; SEL, slowly evolving lesions; SWI, susceptibility weighted imaging; T25-W, timed 25-foot walk

3.1 APPROPRIATENESS OF MEASUREMENTS

Nonrelapsing SPMS is defined as an MS phenotype with progressive disability in the absence of relapse, after an initial variable period of a relapsing-remitting course. Hence, delaying the progression of disability is a clinically relevant outcome and is an aim of any disease-modifying treatment in NRSPMS. Measurement of delay of disability progression is an important clinical endpoint and is endorsed by regulatory guidance (9). The EDSS is widely used to measure neurological disability in clinical trials and routine settings (8). Due to known fluctuation in EDSS scores, CDP confirmed after 3- or 6 months is used as an endpoint in clinical trials of progressive MS (1, 2). Confirmed disability progression lasting for at least 6 months is considered to be more clinically relevant and superior in ruling out EDSS score fluctuations and is therefore chosen as the primary efficacy endpoint in this trial.

Confirmed disability improvement over at least 6 months as measured by the EDSS score will be a secondary endpoint due to its clinical importance. Magnetic resonance imaging measurements will include change in brain volume, which is considered to be a marker of the CNS degenerative process and is therefore recommended in progressive MS (9). Magnetic resonance imaging at Month 6 will serve as the baseline for analyses of MTR and brain atrophy to exclude the potential confounding effect of transient changes in brain volume associated with resolution of inflammation after introduction of treatment (so-called pseudoatrophy) (25). The MRI markers of inflammatory activity in the brain observed in previous clinical trials of progressive MS (1, 2) will also be measured. The number of active T2-hyperintense lesions and change in their volume at the EOS are selected as secondary endpoints, as they reliably reflect accumulating MS lesion load over time.

In addition, MRI measurements will include analysis of brain volume loss over time. Several MS drugs are known for their capacity to slow down brain volume loss, which will be assessed in search of a possible signal.

Clinical outcome assessments are considered important for understanding the impact of treatment on function and well-being (26). In both progressive and relapsing MS, the increasing limitation and loss of physical function are prevalent and among the most debilitating signs and symptoms of the disease (5). Physical function limitations are associated with decrements in quality of life due to diminishing productivity and ability to perform daily activities, maintain employment, and maintain social roles and emotional wellbeing. Reduction of disease impact on patient-reported physical function is therefore important to assess in addition to the clinician assessment and constitutes a direct measure of treatment effectiveness, ie, whether a treatment influences how a participant feels or functions (27). MS relapses may occur infrequently in a small part of the study population (1, 2). Relapse data will be carefully collected and adjudicated, and their impact on the primary endpoint will be assessed.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a Phase 3, randomized, double-blind, 2-arm, placebo-controlled, parallel-group, multicenter, event-driven (6-month CDP) trial with a variable treatment duration ranging from approximately 24 to 48 months in participants with NRSPMS.

The study will consist of the following study periods:

Screening period: Day -28 to Day -1.

Randomization/start of IMP: Eligible participants will be randomly assigned at a 2:1 ratio to receive oral SAR442168 (60 mg) daily or matching placebo daily.

Intervention period: Double-blind treatment period for assessment of efficacy and safety up to the EOS, as described in Section 4.4.

A month is defined as a period of 28 days by convention.

Safety follow-up period/EOS: 4 weeks after the last dose of study treatment (for participants completing IMP treatment [double blind or open-label, if initiated after 6-month CDP] and not entering the LTS study) to collect safety data.

EOS: A participant is considered to have completed the study if he/she has completed all periods of the study including the EOS Visit, whether remaining on IMP or not.

Participants with 6-month CDP are eligible for open-label active treatment (SAR442168) (Section 6.6.1).

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

This is a Phase 3 study for which a double-blind, randomized, placebo-controlled design has been selected to minimize possible biases in the study outcome.

4.2.1 Justification for participant's age and study duration

Male and female participants with a diagnosis of NRSPMS between 18 and 60 years inclusive will be selected for this study. The age range is limited to participants who are ≤60 years to reduce confounding neurological conditions prevalent in older individuals (eg, degenerative pathology of the spine, vascular disorders, other neurodegenerative processes). Besides, since the SPMS phenotype is more prevalent in an older population, it was considered appropriate to set the upper age limit to 60 years.

The duration of the treatment period will vary for individual participants, depending on the time of recruitment and study end as described below. All recruited participants will be followed in the study until approximately 288 events of 6-month CDP are observed. Considering the recruitment

period of approximately 24 months and an assumed event rate (see Section 9.2), the duration of the study should be approximately 48 months, with estimated mean treatment duration of 33 to 36 months.

Participants will be encouraged to remain in the study and comply with all study visits until the EOS in the case that they discontinue the study intervention early.

To minimize possible biases in the study outcome, the study is double blinded. The blind of initial treatment will be kept from participants, any Investigator site staff, and the Sponsor until the study end.

4.2.2 Justification for the use of placebo

This study will explore the efficacy and safety of SAR442168 in participants that are not routinely included in MS clinical trials: NRSPMS patients. This study will allow for a proper controlled data driven approach in a subset of MS patients who do not have approved therapeutic options.

Data obtained in recent MS clinical trials also support the use of placebo as a comparator in this target population. The results from the Phase 3 EXPAND study (4), that explored the efficacy and safety of siponimod in SPMS participants, did not show a significant impact of this compound on disability progression in the sub-population of participants without relapses. For this reason, EMA approved siponimod only for active SPMS, characterized by recent relapse or MRI activity. In addition, ocrelizumab, the only DMT approved for primary progressive MS, has not been studied in NRSPMS (2, 28). Despite the off-label use of other DMTs for NRSPMS patients, clinical experience has confirmed a relative lack of efficacy for patients with low or absent clinical or MRI activity.

With the current study design, participants will be allocated 2:1, SAR442168 to placebo, in order to minimize the exposure to placebo and maximize the chance of receiving active therapy. The participants who enroll in the study and achieve disease progression (6-month CDP) will be offered treatment with open-label SAR442168 or the possibility to switch to another DMT, if available for NRSPMS in their country. All participants who successfully complete the study will additionally be offered the possibility to enroll in a long-term safety study where open label SAR442168 will be provided.

4.2.3 Participant input into design

No impact to study design is anticipated.

4.3 JUSTIFICATION FOR DOSE

The choice of the dose of 60 mg SAR442168 taken with a meal is based on the results of the Phase 2b dose-finding trial for SAR442168 in participants with RMS (DRI15928).

In this study, doses of 5, 15, 30, and 60 mg SAR442168 were tested in a 12-week double-blind treatment period with the number of new Gd-enhancing T1-hyperintense lesions at the end of the

12 weeks of SAR442168 treatment as the primary endpoint. The results demonstrated a dose-response relationship for SAR442168 as evidenced by 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 85% relative reduction in lesions at 12 weeks in the 60 mg dose group as compared with placebo. This was obtained from the negative binomial regression model adjusted for baseline Gd-enhancing T1-hyperintense lesion activity. The dose-response relationship for the secondary endpoint of new or enlarging T2 lesions also supported the choice of the 60 mg dose.

Analysis of the PK data and effect of fed status on SAR442168 exposure showed a positive food effect with an increase in AUC_{0-24} of approximately 2-fold. Moreover, the correlation between the treatment response and the exposure to SAR442168 showed that higher exposure was associated with low numbers of new Gd-enhancing T1-hyperintense lesions after 12 weeks of treatment. Taken together, these data support the recommendation to take SAR442168 with a meal.

There was no correlation between the dose of SAR442168 administered and the number of TEAEs. The most common events (preferred terms) observed in participants in the SAR442168 treatment arms were headache, upper respiratory tract infection, and nasopharyngitis. There were low numbers of AESIs and PCSAs observed. Overall, no new risks were identified in this trial.

The Phase 2b trial tested efficacy and safety in a population that comprised people with RMS. One final consideration regarding dose selection is whether doses that were effective in an RMS population would also be optimal for treating progressive disease. This question has been confronted by sponsors of previous trials in progressive forms of MS. Without exception, those trials have tested the same dose as that approved to treat relapsing forms of MS, including Avonex (IMPACT), Betaseron (North American Study Group on Interferon beta-1b in Secondary Progressive MS), Copaxone (PROMiSe), Rebif (SPECTRIMS), Tysabri (ASCEND), Gilenya (INFORMS), Ocrevus (ORATORIO), and Mayzent (EXPAND). The main issue with dose selection for progressive forms of disease is that there is no clear predictive biomarker to explore doses in Phase 2b trials. The data from the Phase 2b trial support 60 mg dose as the best means to evaluate efficacy and safety in the progressive MS trials planned.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he/she has completed all periods of the study including EOS visit, whether remaining on IMP or not.

This study will end when approximately 288 primary endpoint events of 6-month CDP have been observed which is expected to provide sufficient follow up for safety and secondary efficacy endpoint evaluation. Considering the recruitment period of approximately 24 months and an assumed event rate as discussed in Section 9.2, the duration of the study should be approximately 48 months.

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 60 years of age inclusive, at the time of signing the informed consent.

Type of participant and disease characteristics

I 02. The participant must have a previous diagnosis of RRMS in accordance with the 2017 revised McDonald criteria (5).

I 03. The participant must have a current diagnosis of SPMS in accordance with the clinical course criteria (11) revised in 2013 (10) and endorsed by an Adjudication Committee.

I 04. The participant must have documented evidence of disability progression observed during the 12 months before screening. Eligibility will be analyzed by an Adjudication Committee (to evaluate source data for disability confirmation; details see Section 10.1.5.3).

I 05. Absence of clinical relapses for at least 24 months.

I 06. The participant must have an EDSS score at screening from 3.0 to 6.5 points, inclusive.

I 07. Deleted in Amended Protocol 03.

Weight

I 08. Not applicable.

Sex

I 09. Male and/or female

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

A) Male participants

Not applicable.

B) Female participants

- A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:
  - Is not a woman of childbearing potential (WOCBP).

    OR
  - Is a WOCBP and agrees to use an acceptable contraceptive method as described in Appendix 4 (Section 10.4) during the intervention period. WOCBP must use reliable means of contraception as described in Appendix 4 (Section 10.4) at a minimum. If local requirements are more stringent than what is described in Appendix 4 (Section 10.4), they should be followed.
  - A WOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) (Appendix 2 [Section 10.2]) at screening and before the first dose of study intervention.
  - 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.
  - Requirements for pregnancy testing during and after study intervention are located in the SoA (Section 1.3).
- Additional requirements for pregnancy testing during and after study intervention are located in Appendix 2 (Section 10.2).
- 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, if allowed by local regulations.

Informed consent

I 10. The participant is capable of giving signed informed consent as described in Appendix 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 the legal age of majority is above 18 years, a specific ICF must also be signed by the participant's legally authorized representative (Appendix 1, Section 10.1.3).

5.2 EXCLUSION CRITERIA

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

Medical conditions

E 01. The participant has a history of infection or may be at risk for infection:

- A history of T-lymphocyte or T-lymphocyte-receptor vaccination, transplantation (including solid organ, stem cell, and bone marrow transplantation) and/or antirejection therapy.

- The participant has received any live (attenuated) vaccine (including but not limited to varicella zoster, oral polio, and nasal influenza) within 2 months before the first treatment visit.
- The participant has a lymphocyte count less than the lower limit of normal (LLN) at the Screening Visit.
- A history of diagnosis of progressive multifocal leukoencephalopathy (PML) or evidence of findings suggestive of PML on the screening MRI.
- A history of infection with human immunodeficiency virus (HIV).
- A history of active or latent tuberculosis (TB); TB testing should be performed at screening and again during the study, if clinically indicated and maybe repeated based on clinical judgment, borderline results, or clinical suspicion of TB infection. In case of confirmed active or latent TB the patient can be re-screened after full completion of anti-tuberculosis treatment. Further details are described in the Study Manual (see Section 10.2).

NOTE: The Investigator may consult with an infectious disease expert if required, eg, test results are unclear or there is a suspicion of false-positive test results. If the infectious disease expert considers the test results as false-positive and not clinically relevant and confirms that the participant can be enrolled in the trial, the Investigator must document this in the source data and may then randomize the participant.

- Persistent chronic or active or recurring system infection that may adversely affect participation or IMP administration in this study, as judged by the Investigator.
- Fever within 4 weeks of the Screening Visit (≥38°C; however, if due to brief and mild ear, nose, throat viral infection participant may be included based on the Investigator's judgment).
- Participants at risk of developing or having reactivation of hepatitis: results at screening for serological markers for hepatitis B and C indicating acute or chronic infection. See the Study Manual for further details.

E 02. The presence of psychiatric disturbance or substance abuse as evidenced by:

- A history of any psychiatric disease, behavioral condition, or depression requiring hospitalization within 2 years prior to the Screening Visit.
- A documented history of attempted suicide or suicidal ideation of category 4 or 5 according to the Columbia Suicide Severity Rating Scale (C-SSRS) baseline/screening version over the 6 months prior to the Screening Visit, OR if in the Investigator's judgment, the participant is at risk for a suicide attempt.
- Active alcohol use disorder or a history of alcohol or drug abuse within 1 year prior to the Screening Visit.
- Current alcohol intake >2 drinks per day for men and >1 drink per day for women (1 drink = approximately 14 grams of alcohol = 350 mL beer = 140 mL wine = 40 mL of spirits).

E 03. The following findings obtained during the Screening Visit considered in the Investigator's judgment to be clinically significant in the context of this trial:

- Any screening laboratory values outside normal limits.
- Abnormal ECG.

E 04. Conditions that may predispose the participant to excessive bleeding:

- A bleeding disorder or known platelet dysfunction at any time prior to the Screening Visit.
- A platelet count <150 000/μL at the Screening Visit.
- The participant has had major surgery within 4 weeks prior to the Screening Visit, which could affect the participant's safety or affect immune response (as judged by the Investigator) or has planned any elective major surgery during the study.
- A history of significant bleeding event within 6 months prior to screening, according to the Investigator's judgment such as, but not limited to cerebral or gastrointestinal bleeding.

E 05. Conditions that would adversely affect participation in the study or make the primary efficacy endpoint non-evaluable:

- A short life expectancy due to pre-existing health condition(s) as determined by their treating neurologist.
- A history or presence of significant other concomitant illness according to the Investigator's judgment such as, but not limited to cardiovascular (including Stage III or IV cardiac failure according to New York Heart Association [NYHA] classification), or renal (ie, undergoing dialysis), neurological, endocrine, gastrointestinal, metabolic, pulmonary, or lymphatic disease that would adversely affect participation in this study.
- Acute liver disease, cirrhosis, chronic liver disease (unless considered stable for >6 months).
- Confirmed screening ALT >1.5 × ULN OR aspartate aminotransferase (AST) >1.5 × ULN OR alkaline phosphatase (ALP) >2 × ULN (unless caused by non-liver-related disorder or explained by a stable chronic liver disorder) OR total bilirubin >1.5 × ULN (unless due to Gilbert syndrome or non-liver-related disorder).
- At screening, elevated transferrin saturation (>50% in males and >40% in females) and/or with elevated ferritin levels >500 μg/L.
- Any malignancy within 5 years prior to the Screening Visit (except for effectively treated carcinoma in situ of the cervix or adequately treated non-metastatic squamous or basal cell carcinoma of the skin) will also be exclusionary.
- Any other 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.

Prior/concomitant therapy

E 06. A requirement for concomitant treatment that could bias the primary evaluation, such as any of the following medications/treatments within the specified time frame before any randomization assessment (no wash out is required for dimethyl fumarate, interferon beta or glatiramer acetate treatments although use is not permitted on or after Day 1):

Medication	Wash-out period duration
Systemic corticosteroids, adrenocorticotropic hormone	1 month prior to screening MRI scan
Siponimod, ponesimod	1 week before randomization with MRI and clinical assessment for PML prior to randomization
Plasma exchange	1 month prior to randomization
IV immunoglobulin	2 months prior to randomization
Fingolimod, ozanimod	6 weeks before randomization with MRI and clinical assessment for PML
Teriflunomide[a] mildly to moderately immunosuppressive/chemotherapeutic medications such azathioprine, mycophenolate mofetil, and methotrexate	3 months prior to randomization
Natalizumab	2 months before randomization with MRI and clinical assessments for PML
B-cell depleting therapies such as ocrelizumab and rituximab	6 months prior to randomization
Ofatumumab	4 months
Highly immunosuppressive/chemotherapeutic medications: mitoxantrone up to 120 mg/m^2 body surface area, cyclophosphamide, cladribine, cyclosporine	2 years prior to randomization
Alemtuzumab	4 years prior to randomization
Other MS-disease-modifying therapies	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	No patient who has received any of these treatments at any time is eligible.

IV: intravenous, MRI: magnetic resonance imaging, MS: multiple sclerosis, PML: progressive multifocal leukoencephalopathy
a No time restriction if accelerated elimination procedure is done.

Prior/concurrent clinical study experience

E 07. The participant is receiving potent and moderate inducers of CYP3A or potent inhibitors of CYP2C8 hepatic enzymes as listed in Appendix 9 (Section 10.9).

E 08. The participant is receiving anticoagulant/antiplatelet therapies; those that are not permitted to be taken concomitantly with the IMP, include the following:

- Acetylsalicylic acid (aspirin) >81 mg/day.
- Antiplatelet drugs (eg, clopidogrel).
- Warfarin (vitamin K antagonist).

- Heparin, including low molecular weight heparin (antithrombin agents).
- Dabigatran (direct thrombin inhibitor).
- Apixaban, edoxaban, rivaroxaban (direct factor Xa inhibitors).

Note: All the above-mentioned drugs must be stopped at least 5 half-lives before study drug administration except for aspirin, which must be stopped at least 8 days before. These washout periods are only applicable in the case that the Investigator deems it clinically appropriate to discontinue the listed medications or there is a recent history of use of these medications (as in the case when short-term treatment with anticoagulants is clinically recommended for certain thrombotic events), and therefore these washout periods will need to be followed prior to randomization.

If however the participant has a chronic underlying medical condition (stroke, coronary or carotid artery disease, valvular heart disease etc) requiring continued use of these medications, the participant cannot be enrolled in the study.

E 09. The participant has sensitivity to any of the study interventions, or components thereof, or has a drug or other allergy that, in the opinion of the Investigator, contraindicates participation in the study.

E 10. The participant was previously exposed to any BTK inhibitor, including SAR442168.

E 11. The participant has taken other investigational drugs within 3 months or 5 half-lives, whichever is longer, before the Screening Visit.

Diagnostic assessments

E 12. The participant has a 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.

Note: People with a contraindication to Gd can be enrolled into the study but cannot receive Gd contrast dyes during their MRI scan.

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 8 (Section 10.8) (country-specific requirements).

E 15. The participant is 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 or not able to follow the schedule of protocol assessments due to other reasons.

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 Council for Harmonisation [ICH] - Good Clinical Practice [GCP] Ordinance E6).

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

Note: a one-time retest at screening may be performed if an abnormal laboratory test value is considered temporary.

5.3 LIFESTYLE CONSIDERATIONS

5.3.1 Meals and dietary restrictions

SAR442168 shall be taken with a regular meal. When possible, the meal with which SAR442168 is taken (eg, breakfast, lunch, or dinner) should be consistent throughout the study. The typical meal with which the IMP is taken will be recorded at each visit. In case the mealtime needs to be changed for IMP administration, a gap of a minimum of 12 hours between 2 doses should be maintained.

5.3.2 Caffeine, alcohol, and tobacco

For each visit with PK/PD assessment (refer to Section 1.3), participants will abstain from ingesting caffeine- or xanthine-containing products (eg, coffee, tea, cola drinks, and chocolate) for 2 hours before the start of treatment until after collection of the final PK and/or PD sample later that day.

For each visit with PK/PD assessment (refer to Section 1.3), participants will abstain from alcohol for 24 hours before the start of treatment until after collection of the final PK and/or PD sample later that day.

During the entire study, participants should be warned not to consume substantial quantities of alcohol, defined as >14 grams (1 standard drink) per day in female participants or >28 grams (2 standard drinks) per day in male participants on a regular basis.

5.3.3 Activity

No special restrictions.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. 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 SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened up to 2 times. Rescreened participants should be assigned a different participant number. More information on rescreening procedures is provided in the Study Manual.

5.5 CRITERIA FOR TEMPORARILY DELAYING 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 proposed in Appendix 10 (see Section 10.10) should be considered for screening, enrollment, randomization, and administration of study intervention.

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), or placebo intended to be administered to a study participant according to the study protocol.

6.1 CRITERIA FOR TEMPORARILY DELAYING ENROLLMENT AND 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 proposed in Appendix 10 (Section 10.10) should be considered for screening, enrollment, randomization, and administration of the study intervention.

6.2 STUDY INTERVENTION(S) ADMINISTERED

Table 2 - Overview of study interventions administered

ARM name	SAR442168	Placebo
Intervention name	SAR442168	Placebo
Type	Drug	Drug
Dose formulation	Film coated tablet	Film coated tablet
Unit dose strength(s)	60 mg	0 mg
Dosage level(s)	Once daily	Once daily
Route of administration	Oral	Oral
Use	Experimental	Placebo
IMP and NIMP	IMP	IMP
Packaging and labeling	Study intervention will be provided in wallet blister packaging. Each wallet blister packaging will be labeled as per country requirements.	Study intervention will be provided in wallet blister packaging. Each wallet blister packaging will be labeled as per country requirements.
Current name	SAR442168	Not applicable

IMP: investigational medicinal product; NIMP: noninvestigational medicinal product.

Between the protocol-scheduled on-site visits, interim visits may be required for IMP dispensing. As an alternative to these visits or to replace on-site IMP dispensation, if needed, SAR442168 may be supplied from the site to the participant via a Sponsor-approved courier company (direct-to-patient [DTP]) where allowed by local regulations and approved by the Sponsor.

6.2.1 Noninvestigational medicinal product

MRI contrast-enhancing preparations

- Route(s) of administration: IV
- Dose regimen: as per respective label

6.3 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

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. In case of DTP shipment, temperature monitoring is under vendor responsibility.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions 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 IMP to a third party (except for 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.

6.4 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

All participants will be centrally assigned to randomized study intervention using an interactive response technology (IRT). Randomization will be stratified by age at screening (>40, ≤40 years) and geographic region (US versus non-US). A participant cannot be randomized more than once in the study. A participant assigned to a specific arm at randomization may be allocated, by the IRT, to several (varying) intervention numbers (and corresponding intervention kit numbers) for multiple visits despite having the same intervention arm assignment from randomization. That is, in these cases, the intervention/kit number varies but the arm assignment at randomization does not change. Before the study is initiated, the log in information and instructions for the Interactive Web Response System (IWRS) will be provided to each site.

Study intervention will be dispensed at the study visits summarized in the SoA (Section 1.3).

Returned study intervention should not be re-dispensed to the participants.

The Treating Investigator, Examining Investigator/rater, clinical site staff, and Sponsor's clinical trial team members will not have access to the randomization (treatment) codes. The IRT will be programmed with blind-breaking instructions. In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is

warranted (eg, in case of available antidote). Participant safety must always be the first consideration in making such a determination. If a participant's treatment assignment is unblinded, the Sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and electronic case report form (eCRF), as applicable. If unblinded, information pertaining to the treatment allocation should not be shared with other members of the study team or Sponsor.

Methods of blinding

This study is blinded for assignment of SAR442168 and placebo. Tablets of SAR442168 and placebo will appear identical.

In order to maintain the study blind and ensure participant safety, each site will have 2 types of Investigators: A Treating Investigator and an Examining Investigator/rater (blinded). The study site personnel designated to conduct efficacy assessments (Examining Investigators/raters or other qualified site staff) must be different than physicians responsible for participants' medical management (Treating Investigators) in order to protect against possible unblinding of the treatment assignment during regular clinical care of participants. In view of the extended duration of this study, each site will identify primary and back-up Treating and Examining Investigators/raters. A Treating Investigator cannot change roles to Examining Investigator/rater during the study.

The Treating Investigator is the physician responsible for participant's care and should be a neurologist experienced in the care of MS patients. The Treating Investigator will not have access to efficacy data including EDSS scores other than the score at screening but will receive alerts on 6-month CDP. The Treating Investigator will have access to the participant's other collected data and will follow the participant, collect safety events, and make treatment decisions based on the participant's clinical response and laboratory findings. Once the participant has been randomly assigned to treatment, the Treating Investigator will use a local laboratory if needed for additional safety assessments.

The Examining Investigator/rater should be trained and certified in administering the EDSS and other efficacy tests. Details for certification and re-certification requirements for administering the EDSS will be provided in the Study Manual. The Examining Investigator/rater will be responsible for assessment of the EDSS including the screening EDSS score assessment and other clinical efficacy tests and will have access only to data needed for these assessments. The Examining Investigator/rater can delegate assessment of T25-FW, 9-HPT, SDMT and CVLT-II to qualified study staff. The Examining Investigator/rater will not have access to scores and prior EDSS assessments. Whenever possible, the same individual should perform the examinations for the full study duration. All efforts should be made to keep the Examining Investigator/rater blinded to a participant's treatment assignment, treatment dates, and consequently to AE data, non-neurological symptoms, laboratory data, concomitant and prior medications, and any other information not related to the EDSS and other efficacy assessments. Participants will be instructed not to discuss any symptoms related to the IMP with the Examining Investigator/rater; the Examining Investigator/rater will remind the participant of this at the start of the examination and will not ask any questions that are not related to the neurological examination. Participants will be asked not to communicate any co-medication used or symptoms unless requested by the Examining Investigator/rater for efficacy evaluation.

A DMC will be used to periodically monitor safety of this study. Unblinded data will be provided for DMC review by an unblinded independent statistician. Study team members, Investigators, and study participants will not have access to unblinded data.

6.5 STUDY INTERVENTION COMPLIANCE

- Methods used by the Investigator or his/her delegate to ensure that the IMP was administered may include mouth inspection (eg, for on-site visits).
- Measures taken to ensure study intervention accountability include the following:
  - Intervention units are returned by the participant at each visit. In case of direct-to-patient process, the intervention units can be returned by the carrier (if defined in the contract).
  - The Treating Investigator or his/her delegate counts the number of tablets remaining in the returned packs and fills in the Intervention Log Form.
  - The Treating Investigator or his/her delegate records the dosing information on the appropriate page(s) of the eCRF.
  - The monitor in charge of the study then checks the eCRF data by comparing them with the IMP which he/she has retrieved and Intervention Log Form.

A paper diary, to capture the details of the use of study medication, timing of meals, change in mealtime for IMP administration, missed doses, and overdoses, will be provided to each study participant after they have received training on how to use the diary. Participants should bring the diary to each site visit for review by the Investigator and/or study staff and monitoring of compliance and exposure data. A new paper diary should be provided to the study participant at each visit when study medication will be dispensed. In case of DTP shipment, the new paper diary will be dispensed along with IMP, and the participant will return the previous completed paper diary to the study site via the carrier.

Participant compliance with study intervention will be assessed at each study site visit. Compliance will be assessed by counting returned tablets. Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF.

When participants self-administer study intervention(s) at home, compliance with study intervention will be assessed at each visit. Compliance will be assessed by counting returned tablets during the site visits and documented in the source documents and eCRF. Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF.

A record of the number of SAR442168 tablets dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded in the eCRF.

6.6 CONCOMITANT THERAPY

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) 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.

Any live (attenuated) vaccine within 2 months before the first treatment visit and during the intervention period is prohibited.

Therapies for MS noted in the exclusion criterion E 06 are not permitted after randomization while the participant is on study treatment. Short-term use (3 to 5 days) of glucocorticoids (eg, for MS relapse treatment or an acute illness) and local corticosteroids (eg, topical, nasal, ocular, otic, intra-articular) are allowed.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Participants must abstain from taking prescription or nonprescription drugs (including vitamins and dietary or herbal supplements) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) before the start of study intervention until completion of the follow-up visit, unless, in the opinion of the Investigator and Sponsor, the medication will not interfere with the study.

Medications for treatment of MS symptoms (eg, walking impairment, fatigue, spasticity, incontinence, pain) should be maintained at a stable dose prior to screening and for the duration of the treatment period, if clinically feasible.

Anticoagulant/antiplatelet therapies are not permitted to be taken concomitantly with the IMP, including the following:

- Acetylsalicylic acid (aspirin) >81 mg/day.
- Antiplatelet drugs (eg, clopidogrel).
- Warfarin (vitamin K antagonist).
- Heparin, including low molecular weight heparin (antithrombin agents).
- Dabigatran (direct thrombin inhibitor).
- Apixaban, edoxaban, rivaroxaban (direct factor Xa inhibitors).

Paracetamol/acetaminophen, at doses of ≤3 grams/day, is permitted for use at any time during the study. Short courses (up to 5 days) of nonsteroidal anti-inflammatory drugs (NSAIDs) (other than acetylsalicylic acid), preferably selective cyclooxygenase-2 inhibitors at the lowest effective dose, may be given during the study if clinically necessary for the treatment of an existing medical condition or a new event. The Investigator must record the use of NSAIDs (and any other comedication) in the eCRF.

CYP Inhibitors and Inducers:

Potent and moderate inducers of CYP3A or potent inhibitors of CYP2C8 hepatic enzymes are not permitted throughout the study (Appendix 9 [Section 10.9]).

Based on nonclinical drug metabolism studies, SAR442168 is a substrate of the CYP3A and CYP2C8 isoenzymes. In healthy participants, potent CYP3A4 inhibitor (itraconazole 200 mg once daily for 4 days) increased SAR442168 area under the curve AUC exposure 1.8-fold (Study INT16385) and potent CYP2C8 inhibitor (gemfibrozil 600 mg twice daily for 6 days) increased SAR442168 AUC exposure 8.4-fold (Study INT16726). Based on a satisfactory safety and tolerability profile and on the observed exposure in healthy participants who received SAR442168 at a dose of up to 240 mg SAR442168 once daily for 14 days under fed conditions (Study TDR16862), drugs that strongly inhibit CYP3A4 are allowed and drugs that strongly inhibit CYP2C8 are not permitted. In healthy participants, potent CYP3A4 and moderate CYP2C8 induction by rifampicin (600 mg once daily for 8 days) decreased SAR442168 exposure 6-fold (Study INT16726). Therefore, potent and also moderate (based on prediction) CYP3A inducers are not permitted due to their potential to decrease SAR442168 exposure and efficacy.

See Appendix 9 (Section 10.9) for the list of drugs to be avoided.

The Sponsor should be contacted if there are any questions regarding concomitant or prior therapy.

6.6.1 Open-label treatment

If a participant achieves the primary endpoint (6-month CDP), they may, in conjunction with the Treating Investigator, choose to receive one of the following:

1. To switch to open-label SAR442168 treatment; OR
2. To switch to a non-study treatment approved for NRSPMS in their respective country. In this case, the participant will permanently discontinue the IMP and will be encouraged to remain in the study for planned clinical visits (see Section 7.1.1) until common study end.

In case the participant switches to open-label SAR442168 treatment, he/she will need to be monitored for liver function tests after the first open-label dose at Weeks 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12, and then monthly for the next 9 months. After that, the schedule visits timepoints per SoA will be resumed (ie, every 3 months), until the common study end. Whenever a timepoint will coincide with a scheduled visit as per SoA (Section 1.3), the full scheduled visit assessments will be performed instead of the liver monitoring testing alone.

For participants achieving 6-month CDP, the Investigator must ensure that the participant does not meet any of the following criteria prior to the switch to open-label SAR442168 treatment:

- Current alcohol intake >2 drinks per day for men and >1 drink per day for women (1 drink = approximately 14 grams of alcohol = 350 mL beer = 140 mL wine = 40 mL of spirits).

- Acute liver disease, cirrhosis, chronic liver disease (unless considered stable for >6 months).
- Confirmed ALT >1.5 × ULN OR AST >1.5 × ULN OR ALP >2 × ULN (unless caused by non-liver-related disorder or explained by a stable chronic liver disorder) OR total bilirubin >1.5 × ULN (unless due to Gilbert syndrome or non-liver-related disorder).

Liver function tests will be performed for all participants prior to the start of open-label treatment.

Should the participant and Investigator opt for the provision of open-label medicine, they will remain blinded to the original treatment assignment.

All individual blinded data will be reviewed and all queries resolved, if possible, before the switch to the open-label treatment to ensure data integrity for primary assessment. Prior to initiation of open-label treatment, the Investigator shall confirm that there has been no adjudicated relapse within 90 days prior to the onset or confirmation of 6-month CDP. Based on individual symptoms and assessed risk of further progression, the Investigator and participant may choose for the participant to remain on the initial double-blind treatment after achieving 6-month CDP.

The initial treatment assignment will be kept blinded from participants, any Investigator site staff, and the Sponsor until the study end.

The supply of SAR442168 as open-label medication will be specified at the country level.

Multiple sclerosis relapses are not frequent in the NRSPMS population, but their occurrence during the study cannot be ruled out completely. In the case of MS relapse, treatments are allowed as per local routine practice (eg, high dose IV methylprednisolone for 3 to 5 days). The date and time of relapse treatment administration as well as the name and dosage regimen of the medication must be recorded.

6.7 DOSE MODIFICATION

Dose modification is not foreseen in this study. Treatment might need to be interrupted or permanently discontinued if deemed necessary due to an AE (Section 7 and Section 8.3).

6.8 INTERVENTION AFTER THE END OF THE STUDY

After the end of this study, participants who complete the IMP treatment (double-blind or open-label SAR442168 if meeting 6-month CDP) may be offered the option to participate in an LTS study for an additional 2 years, or until SAR442168 is approved in their respective country, whichever comes first. Details of the LTS study will be described in a separate protocol.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

7.1.1 Definitive discontinuation

The study intervention should be continued whenever possible.

Permanent intervention discontinuation is any treatment discontinuation associated with the definitive decision by the Investigator or the participant not to re-expose the participant to the study intervention at any time.

In rare instances, it may be necessary for a participant to permanently discontinue the study intervention. If study intervention is permanently discontinued, the participant will be asked to remain in the study to be evaluated until the EOS visit. For this set of participants (participants who discontinued the IMP and/or switched to other DMTs), no PK or biomarker samples will be collected after the pEOT visit, and MRI assessments will be performed only annually using the next annual visit as the starting point.

This will be important to continue to evaluate for safety and efficacy. See the SoA (Section 1.3) for data to be collected at the time of discontinuation of the study intervention. In the case that the study intervention is permanently discontinued, the participant should be treated for MS according to local clinical practice and the best judgment of the Investigator.

The following may be justifiable reasons for the Investigator or Sponsor to discontinue a participant from treatment:

- Adverse events that endanger the safety of the participant, or if discontinuation of study intervention is desired or considered necessary by the Investigator and/or participant.
- If IMP discontinuation criteria are met as per the guidance for the follow up of laboratory abnormalities (Appendix 2 [Section 10.2]).
- The participant is no longer deriving a therapeutic/clinical benefit in the opinion of the Investigator.
- If a female participant becomes pregnant or wishes to become pregnant during the study.
- At participant's request, ie, withdrawal of the consent for treatment.
- Any serious opportunistic infections (eg, PML [see Appendix 6 {Section 10.6}], HIV)
- Continued need for/chronic use of prohibited a concomitant medication (see Appendix 9 [Section 10.9]).
- Use of open-label SAR442168 or non-study disease modifying therapy approved for NRSPMS in their respective countries (eg, after 6-month CDP).

Discontinuation of study intervention for abnormal liver function is required by the Investigator when a participant meets one of the conditions outlined in the algorithm (Appendix 6 [Section 10.6]) or if the Investigator believes that it is in best interest of the participant.

Any clinically significant abnormal laboratory value or ECG parameter will be rechecked for confirmation after 24 hours before making a decision of definitive discontinuation of the IMP for the concerned participant.

If a clinically significant finding is identified in the ECG (including, but not limited to changes from baseline in QT interval corrected using Fridericia's formula [QTcF]) after enrollment, the Investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. Review of ECG findings by a cardiologist may be considered for a decision of a definitive discontinuation of study intervention because of ECG changes. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

See the SoA (Section 1.3) for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

Handling of participants after definitive intervention discontinuation

Participants will be followed 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 as specified in this protocol, whichever comes last.

The participant should be treated for MS according to local clinical practice and the best judgement of the Treating Investigator.

If possible, and after the definitive discontinuation of study drug, the participants will be assessed using the procedures planned for the pEOT visit, including collection of a PK sample if the pEOT visit can be scheduled within a maximum of 24 hours after the last IMP dose. Participants will be asked to continue in the study, attending all scheduled visits per SoA (Section 1.3), if possible until the end of the study. If the participant does not agree to the full visit schedule after a decision for permanent end of treatment, a reduced visit schedule may be agreed with the participant. Every effort should be made to collect endpoint information and vital status at least once a year and at the end of study.

For participants with definitive discontinuation of study drug who do not agree to remain in the study after the premature end of treatment visit, if the premature end of treatment visit is less than 3 weeks after the last dose of the study drug, an additional visit should be performed with assessments normally planned for the follow-up visit.

Participants who are treated with open label IMP who decide to prematurely and permanently discontinue the open label IMP prior to the common study end date should be assessed as soon as possible using the procedures normally planned for the premature end of treatment visit. Participants who prematurely and permanently discontinue open label IMP who do not agree to

remain in the study after performing a visit analogous to the premature end of treatment visit, should have an additional visit performed with assessments normally planned for the follow-up visit if the last study visit was less than 3 weeks after the last dose of the open label IMP.

Participants who prematurely and permanently end treatment for a reason other than 6-month CDP will not be eligible for open-label IMP.

All cases of definitive study drug discontinuation must be recorded by the Treating Investigator in the appropriate pages of the eCRF when considered as confirmed.

7.1.2 Temporary discontinuation

Temporary intervention discontinuation, because of suspected AEs or disruption of the clinical trial due to a regional or national emergency declared by a governmental agency (Appendix 10 [Section 10.10]: Contingency measures for a regional or national emergency that is declared by a governmental agency) may be considered by the Treating Investigator. For all temporary intervention discontinuations, duration should be recorded by the Investigator in the appropriate pages of the eCRF.

If surgery is needed during the study, the benefit-risk of withholding the IMP for at least 3 to 7 days pre- and post-surgery and the risk of bleeding should be considered.

The following shall lead to temporary treatment discontinuation:

- Cytopenias: algorithm for neutropenia and thrombocytopenia as per Appendix 6 (Section 10.6) should be followed.
- Serum creatinine, creatine phosphokinase (CPK) and liver enzyme increase: follow corresponding algorithms as per Appendix 6 (Section 10.6).
- Cardiac arrhythmia (Atrial fibrillation): Any Grade 3 event (symptomatic, urgent intervention indicated; device [eg, pacemaker]; ablation; new onset).
- Suicidal risk as per C-SSRS: if a participant scores “yes” on items 4 or 5 of the Suicidal Ideation Section, or “yes” on any item of the Suicidal Behavior Section.

If needed, temporary treatment discontinuation can be considered by the Investigator or by the participant for any other reason, including due to any safety concerns because of disruption of the clinical trial due to a regional or national emergency declared by a governmental agency such as COVID-19 (Appendix 10 [Section 10.10]) or another illness or if there is a need for a prohibited concomitant medication. Treatment can be resumed later when it is considered safe and appropriate.

7.1.2.1 Rechallenge

Reinitiation of intervention with the IMP will be done under close and appropriate clinical and/or laboratory monitoring once the Investigator will have considered, according to his/her best medical judgment, that the responsibility of the IMP(s) in the occurrence of the concerned event was unlikely, there are no safety concerns and if the criteria for permanent treatment discontinuation have not been met (refer to Section 5).

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 10 (see Section 10.10).

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.
- At the time of discontinuing from the study, if possible, a premature EOT visit should be conducted, as shown in the SoA. See SoA (Section 1.3) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she 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 until the EOS Visit.

The Investigators should discuss with them key visits to attend. 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 eCRF 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 (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 he or she 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 no contact can be made with 3 telephone calls, a certified letter to the participant's last known mailing address or local equivalent methods). Participants who are unable to be reached should be recontacted again at the time of the end of study visit to confirm that indeed no contact could be made. These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1 (Section 10.1).

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 (Section 1.3), 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, blood count) 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. Such assessments will be recorded on the designated field in the eCRF.
- Blood sampling details including volume for all laboratory assessments will be provided in the laboratory manual, and the informed consent form. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.
- In exceptional cases, under regional or national emergencies (eg, natural disaster, epidemic disease, terrorist attack), onsite visits may be replaced with telephone/remote visits. For example, participant interviews for medical history/prior medications could be performed by phone, local safety labs and some efficacy assessments could be performed off-site/at the participant's home (eg, home nursing) if agreed by the participant and permissible per local regulations. In such circumstances, the visit window may be expanded, if needed (eg, ±14 days for quarterly visits).

For a regional or national emergency declared by a governmental agency, contingency measures are included in Section 10.10, Appendix 10: Contingency measures for a regional or national emergency that is declared by a governmental agency.

8.1 EFFICACY ASSESSMENTS

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

Key efficacy assessments will be scored by a blinded Examining Investigator/rater or blinded imaging raters who are not otherwise involved in the management of participants in this study.

Key assessments of disability (EDSS score) will be performed by a blinded Examining Investigator/rater who will have no access to laboratory and AE reports. Magnetic resonance imaging scans for efficacy analyses will be analyzed by a blinded, independent, central MRI-reading unit.

8.1.1 Expanded disability status scale

The Examining Investigator/rater will perform the EDSS assessment (8). All Examining Investigators/raters will be trained and certified to perform the EDSS assessment in a consistent manner.

The EDSS score will be captured using an electronic EDSS tool. Quality control measures will be put in place to ensure scoring error detection and thus minimize the impact of any scoring and calculation errors.

The Examining Investigator/rater will rate functional systems in the context of a standard neurological examination and will report these ratings as per the EDSS 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) scoring will be performed by assessing neurological symptoms in each of these domains. Ambulation scoring will be done to conclude 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. The Examining Investigator/rater will not be aware of which visit a participant is completing, will not have access to previous EDSS scores, and will be blinded to all data that could unblind the participant's treatment assignment (see Section 6.4).

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

EDSS scores, except for screening EDSS scores, will not be communicated to any study staff including the Treating Investigator. The Treating Investigator will be notified if the participant meets the EDSS criteria for 6-month CDP. Participants will not be informed of their EDSS scores. They will be informed of 6-month CDP by the Treating Investigator in order to make decisions as defined in Section 6.6.1.

8.1.1.1 Confirmed disability progression

Three- and 6-month CDPs are defined as an increase in EDSS score (defined as an increase of ≥1.0 point from the baseline EDSS score when the baseline score is ≤5.0 or an increase of ≥0.5 points from the baseline EDSS score when the baseline score is >5.0) confirmed after a minimum of 3- and 6-month interval, respectively.

EDSS scores used for potential onset of disability progression may be observed by the Examining Investigator/rater during routine quarterly visits or unscheduled visits. However, confirmation of CDP (at least 3 or 6 months later) must be at a routine quarterly visit. Results of all EDSS assessments obtained during routine or unscheduled visits throughout the minimum 3- or 6-month period (for the primary endpoint) will serve as the basis for conclusion. Once confirmation is achieved, the potential onset becomes the actual onset for time to onset of CDP.

Only EDSS assessments measured more than 90 days after the onset of an adjudicated relapse will be used to determine onset of disability progression. In addition, for the purpose of confirmation, only EDSS scores measured more than 90 days after the onset of an adjudicated relapse will be used. In case of such MS relapse, the next quarterly EDSS assessment will be used for CDP confirmation. The minimum increase in score required for progression must also be maintained for any non-confirmatory (ie, intervening) EDSS assessment(s) between the initial (onset) and confirmation EDSS scores.

Confirmed disability improvement is defined as a ≥1 point decrease from baseline in the EDSS score lasting at least 6 months.

8.1.1.2 Confirmed disability improvement

Confirmed disability improvement is defined as a ≥1 point decrease from baseline in the EDSS score lasting at least 6 months.

8.1.2 Magnetic resonance imaging

Cranial (brain) MRI before and after administering the 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 administering a 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-hypoinense lesion, brain volume loss rate, volume, number and intensity (T1) of SEL, and Gd-enhancing T1-hyperintense lesion count (see Section 3). The expanded MRI protocol will be used to evaluate Gd enhancement recovery (MTR) and phase rim lesions (SWI). 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 (29).

A central MRI manual, containing instructions for brain MRI standard image acquisition requirements, MRI acquisition validation, data transfer to the central review center, archiving and shipping, and 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 central MRI 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 on MRI scanning and central review will be described in the central MRI manual. In addition, in accordance with standard clinical practice, the Treating Investigator can access MRI reports during the blinded intervention period once a year starting at Month 12 through the local radiologist.

The local radiologist needs to review MRI scans for unexpected safety-related findings, such as suspected PML. The local radiologist needs to contact the Treating Investigator in case of unexpected safety-related findings detected on the MRI scan, as per Section 8.3.8.

As use of systemic corticosteroids for treatment of MS relapse or any other medical reasons could interfere with the MRI findings, study MRI should be postponed for a minimum of 1 month following the completion of a course of systemic corticosteroids whenever possible. Alternatively, if a study MRI is planned within 7 days of the initiation of a corticosteroid treatment, the study MRI should be rescheduled to be performed earlier and prior to the initiation of corticosteroid treatment when possible.

8.1.3 Multiple sclerosis relapse assessment

8.1.3.1 Definition of multiple sclerosis relapse

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

1. Be attributable to MS,
2. Last for ≥24 hours, with or without recovery,
3. Be present at normal body temperature (ie, no infection, excessive exercise, or excessively high ambient temperature), and
4. 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 a relapse.

Confirmation of MS relapse will be done by the Relapse Adjudication Committee and will be based on the EDSS score (8) (provided by the Examining Investigator/rater), based on the following definition:

- A confirmed MS relapse is one accompanied by a clinically relevant change in the EDSS score performed by the Examining Investigator/rater, 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).

Confirmation of MS relapse for analysis and study report purposes is detailed in Section 9.4.2.

Refer to Section 8.3.7 for details regarding MS relapse reporting and Appendix 1 (Section 10.1.5.4) for details regarding the Relapse Adjudication Committee.

8.1.3.2 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 collected. If a participant reports symptoms that may be consistent with relapse, an unscheduled assessment visit to the Treating Investigator and the Examining Investigator/rater (blinded) must be scheduled as soon as possible (whenever possible within 7 days of onset of the symptoms). The assessment, management, and reporting of MS relapse is made by the Treating Investigator.

Diagnosing MS relapses during the study: The Treating Investigator will assess whether the reported episode is consistent with the definition of MS relapse. If it is consistent with the definition of MS relapse or if there is any doubt and possibility of relapse cannot be ruled out, the standard neurological examination (for the EDSS score) will be performed by the Examining Investigator/rater. If the participant is not referred for EDSS assessment, this will be documented with an explanation of the reason. Whenever possible, the Examining Investigator/rater should perform the EDSS rating the same day the examination is performed by the Treating Investigator. Subsequent EDSS assessments can still be utilized for confirmation of MS relapses but should be avoided to reduce the risk of changes in participant status in between the assessments by the Treating and Examining Investigators/raters.

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

Safety laboratory tests are optional for this 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 actively asked about possible relapse symptoms at each study visit. If relapse is suspected, the above decision-making and reporting rules will apply.

8.1.4 Timed 25-foot walk test

The T25-FW test will be used to assess a participant's walking ability. The participant is directed to one end of a clearly marked 25-foot course and is instructed to walk 25 feet as quickly as safely possible with several repetitions (30). The mean walk time will be used for assessment of the participant's walking ability. An increase of >20% from the baseline in the T25-FW test is considered meaningful worsening (31). The Examining Investigator/rater or qualified study staff will perform this test.

8.1.5 9-hole peg test

Time to complete the 9-HPT will be used to assess a participant's manual dexterity and fine motor skills. A participant will be asked to place the pegs into the holes and remove them with the dominant and nondominant hand for several repetitions (32). The mean time to test completion will serve for assessment of the participant's hand dexterity. An increase of >20% from the baseline in the 9-HPT is considered meaningful worsening (31). The Examining Investigator/rater or qualified study staff will perform this test.

8.1.6 Cognitive tests

The oral version of the SDMT, a test for cognitive function by measuring information processing speed (33) involves a simple substitution task using a reference key. The number of correct pairings made in 90 seconds is recorded. A decrease of 4 points from baseline on the SDMT is considered meaningful worsening (34). The Examining Investigator/rater or qualified study staff will perform this test.

The CVLT-II (35) measures verbal learning and memory by using a 16-item word list. The list is read by the examiner, and patients listen to the list and report as many of the items as possible. Five successive trials are scored. The Examining Investigator/rater or qualified study staff will perform this test.

8.1.7 Composite analyses

Data from the clinical assessments described above will be utilized in various composite analyses and endpoints to assess effects of SAR442168 on a range of clinical measures. The following sections provide additional details on these composite scales and related criteria for analyses.

8.1.7.1 Modified Multiple Sclerosis Functional Composite-3

The modified Multiple Sclerosis Functional Composite-3 (MSFC-3) tool is the composite of the T25-FW test, 9-HPT, and SDMT (32, 36). The MSFC-3 score will be calculated from these component tests.

8.1.7.2 Assessment of no evidence of disease activity

No evidence of disease activity-3 (NEDA-3) is defined as absence of all of the following (37):

- 6-month CDP.
- Active MRI lesions (both new or enlarged T2-hyperintense lesions and Gd-enhancing T1-hyperintense lesions).
- Adjudicated MS relapse.

8.1.8 Clinical outcome assessments and health-related quality of life parameters

Participants will be provided with a handheld electronic device to record clinical outcome assessments and health-related quality of life parameters during onsite visits. Prior to the first attempt to complete the clinical outcome assessments, the study coordinator will train the participant in the use of the device and how to answer the questions. Participants must record clinical outcome assessments at the clinic prior to any study procedures or discussion of health-related issues to ensure the objectivity of their responses. This device replaces the paper questionnaires that are normally used. Although the software is not approved as a medical device, appropriate validation of the device to ensure accurate and consistent functioning has been performed.

- **Multiple Sclerosis Quality of Life-54:** The MSQoL-54 (38, 39) is a standardized instrument comprising generic and MS-specific items. It includes the SF-36 which has been used in many MS clinical trials, especially of disease-modifying therapies (eg, teriflunomide). This 54-item instrument generates 12 subscales and 2 single-item measures. The 12 subscales are as follows: physical health (10 items), emotional well-being (5 items), cognitive function (4 items), role limitation physical (4 items), energy (5 items), health distress (4 items), overall quality of life (2 items), health perceptions (5 items), role limitations emotional (3 items), sexual function (4 items), pain (3 items), and social function (3 items) covering all aspects of MS. The single-item measures are satisfaction with sexual function (1 item) and change in health (1 item). A linguistically validated MSQoL-54 is available in multiple languages.
- **EuroQoL 5-Dimension 5-Level Instrument:** The EQ-5D-5L is a generic quality of life instrument used for measuring utility (40) and some of the regulatory bodies' requirements. It consists of 2 parts: a descriptive part (5 questions) and a visual assessment scale. It is used in the majority of MS (41), (eg, daclizumab NCT01797965) and non-MS clinical studies routinely. The EQ-5D-5L is available in multiple languages.

All clinical outcome assessments are quantitative tools; they do not collect tolerability data. No information that could be a potential safety signal is expected, so clinical outcome assessments data will be analyzed at the end of the study.

8.2 SAFETY ASSESSMENTS

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

8.2.1 Physical examinations

A physical examination will be performed at the time points specified in the SoA (Section 1.3).

- A complete physical examination will include, at a minimum, assessments of the general appearance, head and neck, abdomen, lymph nodes, skin, cardiovascular system, respiratory system, musculoskeletal system, and neurological examination by the Treating Investigator. Height (at screening) and weight will also be measured and recorded. Further details will be provided in the Study Manual.

- A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, neurological examination, and abdomen (liver and spleen).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.
- Any clinically significant new finding or worsening of previous finding should be reported as an AE, per Investigator's judgement.

The extent of the physical examination can be broadened at the discretion of the Treating Investigator in order to evaluate AEs or abnormal clinical laboratory test values.

8.2.2 Vital signs

- Body temperature, heart rate, and blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed with the participant in a supine or sitting position with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).
- Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 heart rate and 3 blood pressure measurements (3 consecutive blood pressure readings will be recorded at intervals of at least 1 minute).

8.2.3 Electrocardiograms

- 12-lead ECG will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals. Refer to Section 7 for QTcF withdrawal criteria. In case the ECG machine does not automatically calculate QTcF, manual calculation using nomogram or automatic website calculator (eg, https://reference.medscape.com/calculator/48/ecg-corrected-qt) is acceptable
- ECG and 30 second rhythm strips will be obtained locally. Further details will be included in the Study Manual.

8.2.4 Clinical safety laboratory assessments

- See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed. Per the SoA, serology tests for hepatitis B and C will be performed during screening; testing for other infectious disease should be performed during screening if required locally.
- The Treating Investigator may solicit emergency local laboratory data in case of emergent safety events to allow for appropriate treatment decisions. All clinically relevant solicited emergency local laboratory data will be recorded in the eCRF.

- The Treating Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, 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 30 days 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.
  - If abnormal laboratory 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 assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the laboratory manual and the SoA. In the event the laboratory assessments in Appendix 6 (Section 10.6) indicate discontinuation of IMP, temporary discontinuation should be considered unless otherwise specified.
  - If laboratory values from non-protocol specified laboratory assessments 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 eCRF.

8.2.5 Suicidal ideation and behavior risk monitoring

SAR442168 crosses the blood-brain barrier. Assessment of suicidal ideation and behavior as well as treatment-emergent suicidal ideation and behavior will be monitored during Study EFC16645 using the C-SSRS. For safety reasons, C-SSRS will be administered throughout the study by the Treating Investigator or delegated to an individual who is certified for to administer the scale. Study drug administration must be interrupted if a participant scores "yes" on items 4 or 5 of the Suicidal Ideation Section of the C-SSRS, or "yes" on any item of the Suicidal Behavior Section. A psychiatrist will be consulted and decide whether the study drug can be restarted and if any additional risk mitigation strategies are required (eg, increased monitoring, antidepressant administration).

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

The definitions of an AE or SAE can be found in Appendix 3 (Section 10.3).

AEs 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 intervention (see Section 7).

8.3.1 Time period and frequency for collecting AE and SAE information

All SAEs will be collected from the signing of the ICF until the follow-up visit/EOS visit at the time points specified in the SoA (Section 1.3).

All AE will be collected from the signing of the ICF at the time points specified in the SoA (Section 1.3).

All SAEs and AESI will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this 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 AE or SAE 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 AE and SAE 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 (as defined in Section 8.3.9), 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

- 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.

- Reporting of suspected unexpected serious adverse reactions (SUSARs) will be in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries. SUSARs are reported to regulatory authorities, Investigators, and IRBs/IECs as follows:
  - For SUSARs that are life-threatening or result in death, reporting is no later than 7 days after first knowledge by the Sponsor, with all relevant follow-up information subsequently reported within an additional 8 days,
  - For SUSARs, other than those that are life-threatening or result in death, reporting is no later than 15 days after first knowledge by the Sponsor.
- Adverse events that are considered expected will be specified in the reference safety information (see the Investigator's brochure [IB]).
- 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.

8.3.5 Pregnancy

Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study intervention and until the follow-up/EOS Visit (Note: A separate informed consent must be obtained for data collection from partners of male participants). The participant will be followed to determine the outcome of the pregnancy and should be followed even after the end of the study (See Appendix 4 [Section 10.4]).

- If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4 (Section 10.4).
- A negative pregnancy test is required prior to starting a treatment course. In the event that a pregnancy is confirmed during a course of treatment, the IMP should be discontinued.
- A pregnancy will qualify as an SAE only if it fulfills at least 1 of the seriousness criteria (see Appendix 3 [Section 10.3]).
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are considered SAEs.
- AEs that occur to study participants who become pregnant are to be reported according to the relevant portion of Appendix 3 (Section 10.3).

8.3.6 Cardiovascular and death events

Atrial fibrillation and atrial flutter are AESIs in this study and subject to expedited reporting to the Sponsor. All other cardiovascular events will be reported per standard safety reporting and safety oversight practices (including data review by DMC).

Death events will be reported per standard SAE reporting rules. Every effort will be made to clarify the cause of death and to report the diagnosis of the fatal event as an SAE.

8.3.7 Multiple sclerosis relapse reporting

Multiple sclerosis relapses, determined from the evaluations described in Section 8.1.3, as with all efficacy endpoints, will be exempt from being reported as AEs except when they meet the definition of an SAE or are medically severe or medically unexpected. Hospitalization for MS relapse, if done routinely at the site (eg, for high dose IV methylprednisolone), will not be considered as a seriousness criterion for this study.

Multiple sclerosis relapses will be collected on the eCRF 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.

8.3.8 Magnetic resonance imaging

Magnetic resonance imaging scans need to be reviewed locally for any pathology. In case of clinically significant findings, relevant information needs to be provided to the Treating Investigator for appropriate safety reporting and also to ensure the appropriate management of the participant's identified safety finding. 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 on MRI do not need to be reported unless they are deemed unusual and thus a distinct safety finding.

8.3.9 Adverse event of special interest

Adverse event of special interest

An 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 during a study by protocol amendment.

- 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/NIMP
  - 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, IMP 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 Appendix 4 [Section 10.4]).

- Symptomatic overdose (serious or nonserious) with IMP
  - 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 at least twice the intended dose within the intended therapeutic interval (eg, ≥2 tablets of the IMP within a 12-hour interval).
- **Increase in alanine transaminase (ALT) >3 × ULN**
  - ALT increase >3 × ULN confirmed by retest within 72 hours or in the absence of a retest within 72 hours.
- **Other project specific AESI(s)**
  - ECG observation of atrial fibrillation or atrial flutter,
  - Severe infection (NCI CTCAE Grade 3 or above) infection, that may or may not meet seriousness criteria (eg, a Grade 3 opportunistic infection),
  - Moderate or severe hemorrhagic events (NCI CTCAE Grade 2 or above), including but not limited to symptomatic bleeding, bleeding in a critical area or organ such as the CNS, or intraocular bleeding,
  - Thrombocytopenia, platelet count <75 000/mm^3 (see Appendix 6 [Section 10.6] for management flow chart).

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 TREATMENT OF OVERDOSE

The Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the Treating Investigator should do the following:

1. Contact the Sponsor immediately.
2. Closely monitor the participant for any AE/SAE and abnormal laboratory test values.
3. Obtain a plasma sample for PK analysis within 24 hours of the last documented IMP dose.
4. Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.
5. Decisions regarding dose interruptions will be made by the Investigator in consultation with the Sponsor based in the clinical evaluation of the participant.

8.5 PHARMACOKINETICS

- Blood samples of approximately 2 to 3 mL will be collected for measurement of plasma concentrations of SAR442168 and relevant metabolite(s) as specified in the SoA (Section 1.3). The 5 scheduled samples will be collected at selected timepoints during the study (for participants who discontinued IMP, no PK samples are collected after pEOT visit). If warranted and agreed upon between the Investigator and the Sponsor, additional PK samples may be collected (eg, for retesting, pEOT, or if clinically indicated). The PK sample collection/storage is strongly recommended for events of confirmed ALT increase >5 × ULN (recommended for ALT >3 × ULN) and thrombocytopenia (platelets <75 000/mm^3), and is recommended for events of neutropenia (neutrophils <1500/mm^3), serum creatinine increase (confirmed increase >1.7 × ULN or decrease clearance >50%, cannot be rapidly reversed), and CPK increase (confirmed >10 × ULN) (see Section 10.6 for more details).
- 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.
- Each plasma sample will be divided into 2 aliquots (1 each for [PK, other analyses, and a back-up]). Samples collected for analyses of SAR442168 and relevant metabolite(s) plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.
- Population PK analysis will be performed using SAR442168 and relevant metabolite(s) concentration and will be reported in a standalone report.

Drug concentration information that would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

8.6 PHARMACODYNAMICS

Blood samples for lymphocyte phenotyping will be collected during the study as detailed in the SoA (Section 1.3) for a subset of up to 200 randomized participants. Flow cytometry will be used for evaluation of change from baseline in lymphocyte count and phenotype in a subset of participants. Additional PD evaluations will include assessment of NfL levels in plasma, Chi3L1, and Ig levels in serum. For lymphocyte phenotyping, participants who did not have a baseline sample collected will no longer need to have this test performed; participants who had a baseline sample collected will have a second sample collected at EOT/pEOT. For additional PD evaluations (NfL levels and Chi3L1 and Ig levels), sample collections are no longer needed for participants who discontinued IMP or switched to other DMTs. For participants in China, see Appendix 7 (Section 10.7).

8.7 GENETICS

A 6 mL blood sample for DNA isolation will be collected from participants who have consented to participate in the genetic analysis component of the study. Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study. DNA samples will be collected during the study as detailed in the SoA (Section 1.3). Samples will be stored, and analysis may be performed on genetic variants thought to play a role in MS including, but not limited to, specific candidate genes/genome analyses to evaluate their association with observed clinical responses to SAR442168. For participants in China, see Appendix 7 (Section 10.7).

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.

8.8 BIOMARKERS

Blood samples for biomarkers research will be collected from all participants in this study as specified in the SoA (Section 1.3).

- Collection of plasma and serum samples for biomarker research is also part of this study.
- Samples will be tested to evaluate biomarkers and their association with the observed clinical responses to SAR442168.
- In addition, samples will be stored, and analysis may be performed on biomarker variants thought to play a role in MS including, but not limited to, plasma or serum analytes to evaluate their association with observed clinical responses to SAR442168.

Samples may be stored for a maximum of 2 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 biomarker responses to SAR442168. For participants in China, see Appendix 7 (Section 10.7).

8.9 IMMUNOGENICITY ASSESSMENTS

Not applicable.

8.10 MEDICAL RESOURCE UTILIZATION AND HEALTH ECONOMICS

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

8.11 USE OF BIOLOGICAL SAMPLES AND DATA FOR FUTURE RESEARCH

Future research may help further the understanding of disease and the development of new medicines. Reuse of coded data and biological samples (leftover) 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.

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.

In any case, a specific consent will be collected for the performance of genetic analyses on leftover samples.

Data protection – Processing of coded clinical data

The study participant will be provided will all mandatory details of the data processing in Part 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 for future research

Remaining leftover samples will be used only after the study ends, ie, end of study as defined in the study protocol.

The study participant will be provided with all mandatory details of the use of the human biological samples (leftover) in Section 2 of the Core ICF.

Study participant data will be stored for up to 25 years for regulatory purposes and future research. 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 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 case, samples will be destroyed and related coded data will be anonymized unless otherwise required by applicable laws.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

The null hypothesis for the primary efficacy endpoint of time to onset of 6-month CDP is that there is no treatment difference between SAR442168 and placebo, and the alternative hypothesis is that there is a between-treatment difference.

To strongly control the Type 1 error rate for the study, a hierarchical testing procedure will be applied at a 2-sided 5% significance level, ie, each hypothesis will be formally tested only if the preceding one is significant at the 5% level. If SAR442168 is significant for the primary endpoint, a selective set of secondary endpoints will be tested following the hierarchical testing procedure. The complete list of the secondary endpoints that will be adjusted for multiplicity with their testing order will be detailed in the statistical analysis plan prior to database lock or any interim analysis, if applicable. The study will be declared positive if the null hypothesis for the primary endpoint of 6-month CDP for SAR442168 versus placebo is rejected.

9.2 SAMPLE SIZE DETERMINATION

Approximately 1700 participants will be screened to achieve up to 1290 randomly assigned to study intervention (2:1 randomization ratio of SAR442168 to placebo). This study is planned as an event-driven trial based on 6-month CDP. The study will continue until approximately 288 events are projected to have occurred to provide 80% power to detect a 30% risk reduction in 6-month CDP with SAR442168 compared to placebo (2-sided α=0.05). The following assumptions were used for the calculations: 2-year placebo event rate of 23.6%; annual discontinuation rate of 10%; constant hazard rates using a log-rank test; estimated enrollment period of 24 months with last randomized participant followed for 24 months.

Actual recruitment and disability event rates may vary; therefore, it is possible to stop with a reduced sample size of around 1100 and still maintain study power by extending the duration of the trial, if needed, to reach approximately the same number of events. For example, it could be that the last randomized participant is followed for around 30 months instead of 24, if necessary. Additional recruitment of participants will not substantially reduce the trial duration. In any case, the power is based on the number of events, and the actual trial duration will be dependent on the observed placebo rate and treatment effect.

Note: “Enrolled” means a participant's, or their legally acceptable representative’s, agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.

9.3 POPULATIONS FOR ANALYSES

For purposes of analysis, the following populations are defined (Table 3):

Table 3 - Populations for analysis

Population	Description
Enrolled	All participants who sign the ICF
Randomly Assigned to Study Intervention	All participants with a treatment kit number allocated and recorded in the IRT database, regardless of whether the treatment kit was used or not. Participants treated without being randomized will not be considered randomized and will not be included in any efficacy population.
ITT	The primary efficacy population will be the ITT population, defined as all randomly assigned participants. All efficacy analyses will be conducted according to the treatment group allocated by the randomization schedule, irrespective of the treatment received.
Safety	All participants randomly assigned and exposed to study intervention, regardless of the amount of exposure, analyzed according to the treatment actually received. Randomized participants for whom it is unclear whether they took the study medication will be included in the safety population as randomized. The pharmacodynamic (PD) analyses will be performed on the safety population.
Pharmacokinetics	All participants in the safety population with at least one non- missing PK sample after first dose of the study intervention. Participants will be analyzed according to the treatment actually received.

ICF: informed consent form; ITT: intent to treat; PK: pharmacokinetic(s).

9.4 STATISTICAL ANALYSES

The SAP will be developed and finalized prior to database lock or before any interim analysis, if applicable, and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1 General considerations

The baseline value of efficacy parameters is generally defined as the last available value up to randomization but prior to the first dose of study medication unless otherwise specified. For EDSS, the baseline value will be taken as the average of the screening and randomization visit values. The baseline value of safety parameters is defined as the last available value prior to the first dose of IMP. Unless otherwise indicated, all statistical hypotheses for the primary and secondary endpoints and other treatment comparisons will be tested at the 5% significance level (α=0.05) against 2-sided alternatives.

9.4.2 Primary endpoint

The primary estimand will be the treatment difference between SAR442168 and placebo in time to onset of 6 month-CDP regardless of completion of the treatment period. This estimand corresponds to a "treatment policy strategy". This estimand will be considered primary for supporting regulatory decision making.

The time to onset of 6-month CDP will be analyzed by a Cox proportional hazards model with terms for treatment, age at screening (>40, ≤40 years), geographic region (US, non-US), baseline EDSS score, and baseline Gd-enhancing T1 lesions (0, ≥1). A log-rank test stratified by age at screening (>40, ≤40 years) and geographic region (US, non-US) to compare SAR442168 to placebo will also be examined. Kaplan-Meier plots of the cumulative incidence rate will be provided by treatment group to depict the course of onset of 6-month CDP over time. The proportion of participants with events at given time points (eg, Month 24) will be calculated using the KM estimates.

In this primary ITT analysis:

- For participants who complete the study without an initial disability progression, the participant's event time will be censored at the date of last EDSS assessment.
- For participants who have an initial onset of disability progression but complete the study at the common study end date without 3-month confirmation, the participant will be censored at the date of last EDSS assessment.
- For participants who prematurely discontinue the study before 6-month confirmation of an onset of disability progression, regardless of having an initial onset, the participant will be censored at the date of last EDSS assessment.
- For participants who meet 3-month CDP but complete the study at the common study end date without 6-month confirmation, the event status of the participant will be determined by an imputation approach only if all additional EDSS assessments after 3-month confirmation to participant's end of study also meet the criteria for disability progression. Since in this setting, the partial missing data can reasonably be assumed to be missing at random, this approach leverages the partial information and follows the ITT principle. A logistic model with terms for age at screening (>40, ≤40 years), geographic region (US, non-US), baseline EDSS score, and baseline Gd-enhancing T1 lesions (0, ≥1) will be used to determine the event status as the imputation model within each treatment. A multiple imputation approach will be used to summarize the results. Details will be provided in the SAP.

Only EDSS assessments measured more than 90 days after the onset of an adjudicated relapse will be used to determine onset of disability progression. In addition, for the purpose of confirmation, only EDSS scores measured more than 90 days after the onset of an adjudicated relapse will be used. In case of such MS relapse, the next quarterly EDSS assessment >90 days after relapse onset will be used for CDP confirmation. In order to assess robustness of the primary analysis, sensitivity analyses handling missing or incomplete data differently will be conducted. This will include an analysis that treats missing or incomplete data as censored data.

Additionally, subgroup analyses will be explored to assess consistency of treatment effect. The subgroup factors include geographic region (US, non-US; Eastern EU, Western EU, North America, Rest of the World), age strata (ie, age at screening; >40, ≤40 years), sex (male, female), baseline Gd-enhancing T1 lesions (0, ≥1), baseline EDSS score (≤4.5 versus >4.5 and ≤5.5 versus >5.5), prior disease modifying therapy use (0, 1, ≥2), duration since RRMS symptom onset (≤5, >5 to ≤10, >10 years) and adjudicated relapse during the study. The detailed list of subgroups and additional details of the subgroup analyses will be provided in the SAP.

9.4.3 Secondary endpoint(s)

For other time-to-event endpoints (time to onset of sustained 20% increase in the 9-HPT, of sustained 20% increase in the T25-FW, of 3-month CDP, and of CDI), similar analysis as for the primary analysis of the primary efficacy endpoint will be performed in the ITT population but without imputation.

Continuous endpoints (percent change in brain volume loss, change in cognitive function, change in physical function, and change in MSQoL-54 at EOS) will be analyzed using a mixed-effect model with repeated measures (MMRM) approach. The model will include change/percent change values for the respective endpoint at each scheduled visit as response variables, and treatment, age at screening (>40, ≤40 years), geographic region (US, non-US), visit, treatment by-visit interaction, baseline value for the endpoint being assessed and baseline value-by-visit interaction as covariates. Difference in LS means, the corresponding 95% CI, and p-value will be provided for the comparison of SAR442168 versus placebo. For percent change in brain volume loss, log transformation will be applied in the MMRM model. In order to assess the impact of deviation from the normality assumption, a sensitivity analysis using rank ANCOVA with the same covariates as for the MMRM analysis except visit and related interaction terms, will be performed for these continuous endpoints to provide the p-value for the comparison between the treatment groups.

Categorical efficacy endpoints with count data (new and/or enlarging T2 hyperintense over the study period after baseline) will be analyzed using a negative binomial regression model. The model will include the total lesion count across all post-randomization MRI scans during the study period as the response variable, with treatment group, age at screening (>40, ≤40 years), geographic region (US, non-US), baseline EDSS score, and baseline T2 lesions as covariates. Log-transformed observation duration from screening MRI to last available MRI will be the offset variable. In order to assess the impact of open-label therapy, sensitivity analysis excluding the data after initiation of open-label therapy will be performed for the key secondary endpoints that will be pre-specified in the SAP. Further details including details of missing data handling and subgroup analyses for secondary endpoints will also be detailed in the SAP.

9.4.4 Tertiary/exploratory endpoint(s)

Methods for analysis of tertiary/exploratory endpoints will be included in the SAP.

9.4.5 Other safety analyses

All safety analyses will be performed on the safety population.

Safety summaries will be descriptive, ie, no statistical significance tests will be performed on safety data. The summary of safety results will be presented by treatment group.

Safety analyses will be based on the reported AEs and other safety information, such as clinical laboratory data, vital signs, and ECG.

The observation period will be divided into 4 epochs:

- The screening epoch is defined as the time from the signed informed consent date up to the first administration of the study intervention.
- The treatment epoch is defined as the time from the first administration of the study intervention to:
  - The earlier of last administration of the study intervention plus 10 days or first IMP in the LTS study for participants not receiving SAR442168 open-label treatment.
  - The first administration of SAR442168 open-label treatment for participants switching to open-label therapy.
- The open-label epoch, applicable only for participants switching to SAR442168 open-label treatment, is defined as the time from first administration of SAR442168 open-label treatment to the earlier of last administration of open-label treatment plus 10 days or first IMP in the LTS study.
- If applicable, the post-treatment epoch is defined as the time from the end of treatment epoch (or end of open-label epoch, if applicable) to the participant's final study contact date.

The safety analysis of AEs will focus on TEAEs, defined as AEs that developed, worsened, or became serious during the treatment period. All AEs reported in this study will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version in effect at the time of database lock.

Table 4 - Safety analyses

Endpoint	Statistical analysis methods
Adverse Events including AEs, TEAEs, SAEs, AEs leading to treatment discontinuation, AEs leading to death and AESIs	The number and percentage of participants with at least one TEAE, treatment-emergent SAE, TEAE leading to treatment discontinuation, TEAE leading to death, and treatment-emergent AESI will be tabulated by treatment group. Multiple occurrences of the same event in the same participant will be counted only once in the tables. The denominator for computation of percentages will be the safety population within each treatment group. Serious AEs and AEs leading to study discontinuation or death that occur outside the treatment-emergent period will be summarized separately.
Vital signs, laboratory data, and ECG parameters	Descriptive statistics of values and change from baseline values for each parameter will be summarized by treatment group at each time point. The number and percentage of participants with at least one incidence of potentially clinically significant abnormality at any time during the treatment-emergent period will be summarized by treatment group.

AE: adverse event; AESI: adverse event of special interest; ECG: electrocardiography; SAE: serious adverse event; TEAE: treatment-emergent adverse event

9.4.6 Other analyses

Pharmacokinetic, pharmacodynamic (PD), and biomarker exploratory analyses that will be included in the study report will be described in the SAP. Biomarker research will not be part of statistical analysis in this study and will not be reported in the clinical study report (CSR).

For a regional or national emergency declared by a governmental agency, contingency measures are included in Section 10.10, Appendix 10: Contingency measures for a regional or national emergency that is declared by a governmental agency.

9.5 INTERIM ANALYSES

An optional, non-binding interim futility analysis may be performed when approximately 50% of the primary endpoint events are observed. The futility interim analysis will be conducted by an independent statistics group and reviewed by the DMC. Neither the Sponsor's team nor the Investigator's staff will have access to the treatment information at the individual participant level or group level before the study is formally unblinded after study completion or after the DMC recommendation/Sponsor agreement for stopping the trial.

9.6 DATA MONITORING COMMITTEE (DMC)

For details on the DMC, refer to Appendix 1 (Section 10.1.5).

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 GCP Guidelines,
  - Applicable laws and regulations (eg, data protection law as General Data Protection Regulation - GDPR).
- The protocol, protocol amendments, ICF, IB, 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.
- The Investigator will be responsible for the following:
  - 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. Determining whether an incidental finding 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.

- 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 Code of Federal Regulation (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

As applicable, according to Directive 2001/20/EC, 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.

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

- The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding 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, 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.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- Participant who is rescreened is required to sign a new ICF.
- The ICF contains a separate section that addresses the use for research of participants' data and/or samples (remaining mandatory ones). Future research is to be defined in Core

Study Informed Consent Form (CSICF) Part 2: consent for use of leftover samples and associated coded data for future research, and consent for performance of genetic analyses on biological samples. 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 Appendix 10 (see Section 10.10).

10.1.4 Data protection

All personal data collected related to participants, Investigators, or any person involved in the study will be handled in compliance with all applicable Privacy & Data Protection laws and regulations, including the General Data Protection Regulation (GDPR). 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.

- 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 these data are required by regulatory agencies (eg, on Afro American population for the FDA or on Chinese population for the China Food and Drug Administration in China) (42, 43). Participant race and ethnicity will not be collected in the countries where this is prohibited by local regulation.
- Since a participant's response to treatment may vary by factors such as race or ethnicity due to intrinsic or extrinsic factors, subgroup analyses by race and ethnicity are therefore planned for the primary endpoints and may be performed for other efficacy or safety endpoints to demonstrate the applicability of the overall trial results to a specific subgroup.
- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred to the Sponsor.
- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant as described in the informed consent.

- The participant must be informed that his/her 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.
- When archiving or processing personal data pertaining to the Investigator and/or to the participants, the Sponsor will take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.
- 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 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 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 Committee structures

10.1.5.1 Data Monitoring Committee

A DMC, operating independently of the Sponsor and clinical Investigators, will be responsible for overseeing the safety of participants throughout the study. This committee is composed of externally based individuals with expertise in the disease under study, biostatistics, or clinical research. The primary responsibilities of the DMC are to review and evaluate the safety data and to assess futility through an interim analysis during the trial and to make appropriate recommendations to the Sponsor regarding the conduct of the clinical trial.

Details describing the DMC processes and procedures are outlined in the DMC charter. To maintain continuous blinding and study integrity, the analysis will be conducted by an independent statistician who will directly transfer data to DMC members, and measures will be taken to ensure the validity of the data.

10.1.5.2 Scientific Advisory Committee

A Scientific Advisory Committee will provide advice to the Sponsor regarding scientific issues and operational conduct of the study. This committee will be composed of a Chairperson, selected by the Sponsor, field experts, and Sponsor-based scientists with clinical and methodological expertise. The Scientific Advisory Committee will also review any amendments and provide input regarding interpretation of study results. The members will remain blinded until completion of the study. Among its responsibilities, the Scientific Advisory Committee will receive blinded study status reports from the Sponsor and will review the recommendations from the DMC throughout the study.

The responsibilities of the Scientific Advisory Committee are provided in the Scientific Advisory Committee charter.

10.1.5.3 Eligibility Adjudication Committee

Before randomization, an adjudication committee of MS experts will evaluate anonymized data of participants to endorse the diagnosis of NRSPMS and disability progression during the last 12 months. Details of the workflow between the adjudication committee and Investigators will be provided in the Study Manual.

Any increase in EDSS score is sufficient to confirm disability progression. If an EDSS score is unavailable or disability progression is not confirmed by EDSS assessment, disability progression can be further explained by a functional systems assessment. In addition, objective neurologic findings can also be used to support disability progression (a validated checklist for trial eligibility will be provided to the site).

10.1.5.4 Relapse Adjudication Committee

To ensure objectivity in the assessment of relapses, a Relapse Adjudication Committee will be convened to evaluate all relapses reported during the study. This committee will consist of independent neurologists with expertise in MS clinical research who be trained on study procedures. Relapses, as adjudicated by the committee, need to meet protocol criteria (Section 8.1.3.1).

Relapse Adjudication Committee assessments will be performed using blinded data. Details of the responsibilities of the Relapse Adjudication Committee and workflow will be described in a separate charter.

10.1.5.5 Independent Hepatology Assessment Committee

An expert committee of independent hepatologists will review all cases of potential DILI and will provide guidance on case evaluation and risk mitigation. The Hepatology Assessment Committee recommendations will be made available to the DMC. Details of the responsibilities of the Independent Hepatology Assessment Committee and its workflow will be described in a separate charter.

10.1.6 Dissemination of clinical study data

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 (eu.ctr), euclinicaltrials.eu, and sanofi.com, as well as some national registries.

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, the Sponsor will continue to protect the privacy of participants in their 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 undertakes the legal obligation to disclose the full name of the Investigator and his/her affiliated institute/ hospital's name and location on the China Trial Disclosure website as required by the National Medical Products Administration (NMPA) in its guidance "Implementation of Drug Clinical Trial Information Registration and Disclosure" ("Notification No. 28"), requesting name disclosure of Chinese and foreign investigational sites and Investigators in any eligible clinical trial.

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 eCRF 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 eCRF.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

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 or designee is responsible for the data management of this study including quality checking of the data.

The Sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF 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.

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 longer 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 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 the Study Manual.

10.1.9 Study and site start and closure

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 site open and will be the study start date.

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.

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 the following:

- 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 will 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 will 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 5 will be performed by the central laboratory when feasible.

Local laboratory results are only required in the event that the central laboratory results are not available 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 entered into the eCRF.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.

Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations. Additional serum or urine pregnancy tests may be performed, as determined 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.

Table 5 - Protocol-required laboratory assessments

Laboratory assessments	Parameters
Hematology	
	Platelet count RBC count Hemoglobin Hematocrit RBC indices: MCV MCH %Reticulocytes WBC count with differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Clinical chemistry[a]	
	BUN Creatinine Glucose Potassium Sodium Calcium Chloride AST/SGOT ALT/SGPT Alkaline phosphatase Total and direct bilirubin Creatine phosphokinase Albumin Bicarbonate Total protein Lipase
Routine urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal and for signs of infection)

Laboratory assessments	Parameters
Other screening tests	• Follicle-stimulating hormone (if needed in female participants to confirm postmenopausal status) • Highly sensitive serum or urine hCG pregnancy test (as needed for women of childbearing potential)[b] • Serology test for hepatitis B (HBs Ag, anti-HBc IGM and total, anti- HBs) and C (anti HCV); in case these results are inconclusive (eg, anti-HBs negative and anti-HBc positive or anti-HC IgG positive), HBV-DNA and/or HCV-RNA should be done, respectively, for confirmation. HIV and other infectious disease, if locally required • Coagulation: PT/international normalized ratio (INR), aPTT • Tuberculosis test: 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[c] • Iron panel (serum): iron, ferritin, transferrin saturation, TIBC. The results of each test must be entered into the eCRF.

ALT: alanine aminotransferase; anti-HBc: antibody to hepatitis B core antigen; anti-HBs: hepatitis B surface antibody; AST: aspartate aminotransferase; aPTT: activated partial thromboplastin time; BUN: blood urea nitrogen; eCRF: electronic case report form; hCG: human chorionic gonadotropin; HIV: human immunodeficiency virus; IEC: independent ethics committee; INR: international normalized ratio; HBsAg: hepatitis B surface antigen; HBV: hepatitis B virus; HCV: hepatitis C virus; HIV: human immunodeficiency virus; Ig: immunoglobulin; IRB: institutional review board; MCV: mean corpuscular volume; MCH: mean corpuscular hemoglobin; PT: prothrombin time; RBC: red blood cell; SAE: serious adverse event; SGOT: serum glutamic-oxaloacetic transaminase; SGPT: serum glutamic-pyruvic transaminase; TB: tuberculosis; TIBC: total iron-binding capacity; ULN: upper limit of normal; WBC: white blood cell.

a Details of liver chemistry stopping criteria and required actions and follow-up assessments observations of ALT >3 × ULN are given in Appendix 6 (Section 10.6). Clinical laboratory findings of ALT >3 × ULN and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT >3 × ULN and INR >1.5, if INR measured that may suggest severe liver injury and must be reported as an SAE.

b Local urine testing will be standard for the protocol (except for the Screening Visit when serum pregnancy test is required) unless serum testing is required by local regulation or IRB/IEC.

c Further details are given in E 01.

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 study has been unblinded. This includes PK assessments and any post-baseline biomarker or PD assessments.

10.3 APPENDIX 3: ADVERSE EVENTS: 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 patient 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), 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.
- "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 fulfil the definition of 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

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:

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 detained (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 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 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.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

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 in the eCRF.
- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to the Sponsor representative in lieu of completion of the SAE eCRF page.
- 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 severity

The Investigator will assess the severity for each AE and SAE using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5.0, published on 27 November 2017. Listings of MedDRA terms should be consulted first in NCI CTCAE to look for severity grade description for a particular AE. For AEs not listed in the NCI CTCAE, the Investigator will be required to assess the severity of the AE using general guideline:

1. Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2. Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activity of Daily Living (ADL)*.
3. Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
4. Grade 4 Life-threatening consequences; urgent intervention indicated.
5. Grade 5 Death related to AE.

Note: ADL

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Any life-threatening AE or death must be reported as an SAE. Any other AE event can be defined as "serious" if it meets at least 1 of the predefined outcomes as described in the definition of an SAE in Section 10.3.2.

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 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's representative. 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's representative**.
- 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's representative with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed eCRF.
- 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's representative 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 Section 10.3.4) in order 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 Section 10.3.4) or to the Sponsor's representative by telephone.
- Contacts for SAE reporting can be found in the Study Manual.

10.4 APPENDIX 4: CONTRACEPTIVE GUIDANCE AND COLLECTION OF PREGNANCY INFORMATION

DEFINITIONS:

Woman of childbearing potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

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

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - 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), Investigator discretion should be applied to determining study entry.

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

3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
     - A high follicle stimulating hormone (FSH) level (eg, >30 IU/L or as per the laboratory reference range) in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required;
     - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal acceptable 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.

CONTRACEPTION GUIDANCE:

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[b]
  - Intrauterine device (IUD)
  - Intrauterine hormone-releasing system (IUS)[c]
- Bilateral tubal occlusion

Vasectomized partner

(Vasectomized partner 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. Spermatogenesis cycle is approximately 90 days.)

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
- 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.)

ACCEPTABLE METHODS[d]

1. Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action
2. Male or female condom with or without spermicide[e]
3. Cervical cap, diaphragm, or sponge with spermicide
4. A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods)[c]

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 If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.
d Considered effective, but not highly effective - failure rate of ≥1% per year. Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception.
e Male condoms and female condoms should not be used together (due to risk of failure with friction).

COLLECTION OF PREGNANCY INFORMATION:

Male participants with partners who become pregnant

- The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy.
- The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor.
- Generally, the follow up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female participants who become pregnant

- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information can be collected either during site visits or by phone (in case a pregnancy test has been performed at home by the participant) and it will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to the Sponsor. Generally, follow up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

- Any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at <22 weeks gestational age) or still birth (occurring at >22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- 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, he or she may learn of an SAE through spontaneous reporting.
- The participant will be invited to remain in the study in any case. Pregnancy outcome and data of the newborn will be reported to the Sponsor as per usual pharmacovigilance reporting practice.

10.5 APPENDIX 5: GENETICS

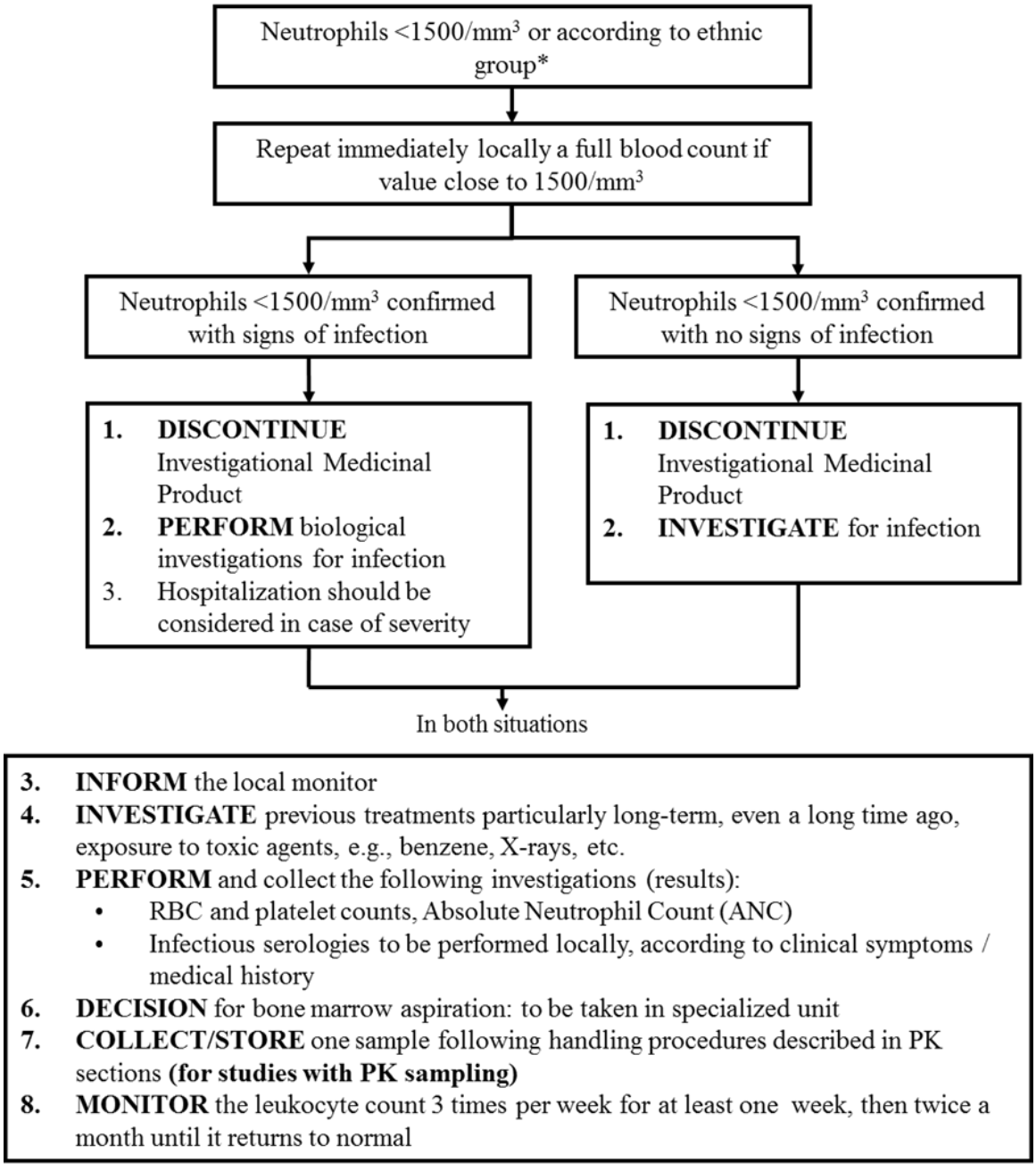
Use/Analysis of DNA

- 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 SAR442168 or NRSPMS and related diseases. They may also be used to develop tests/assays including diagnostic tests related to SAR442168 and NRSPMS. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome.
- DNA samples will be analyzed for human leukocyte antigen genotyping. Specific analysis of these samples will be determined at a later date once the blinded clinical data becomes available. These analyses 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 SAR442168 or study interventions of this class to understand study disease 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 for 15 years in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on SAR442168 for NRSPMS or other period as per local requirements.

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

These actions are required for ALT increase and thrombocytopenia events ONLY. For all other safety events described, these are suggested per the Investigator's medical judgement.

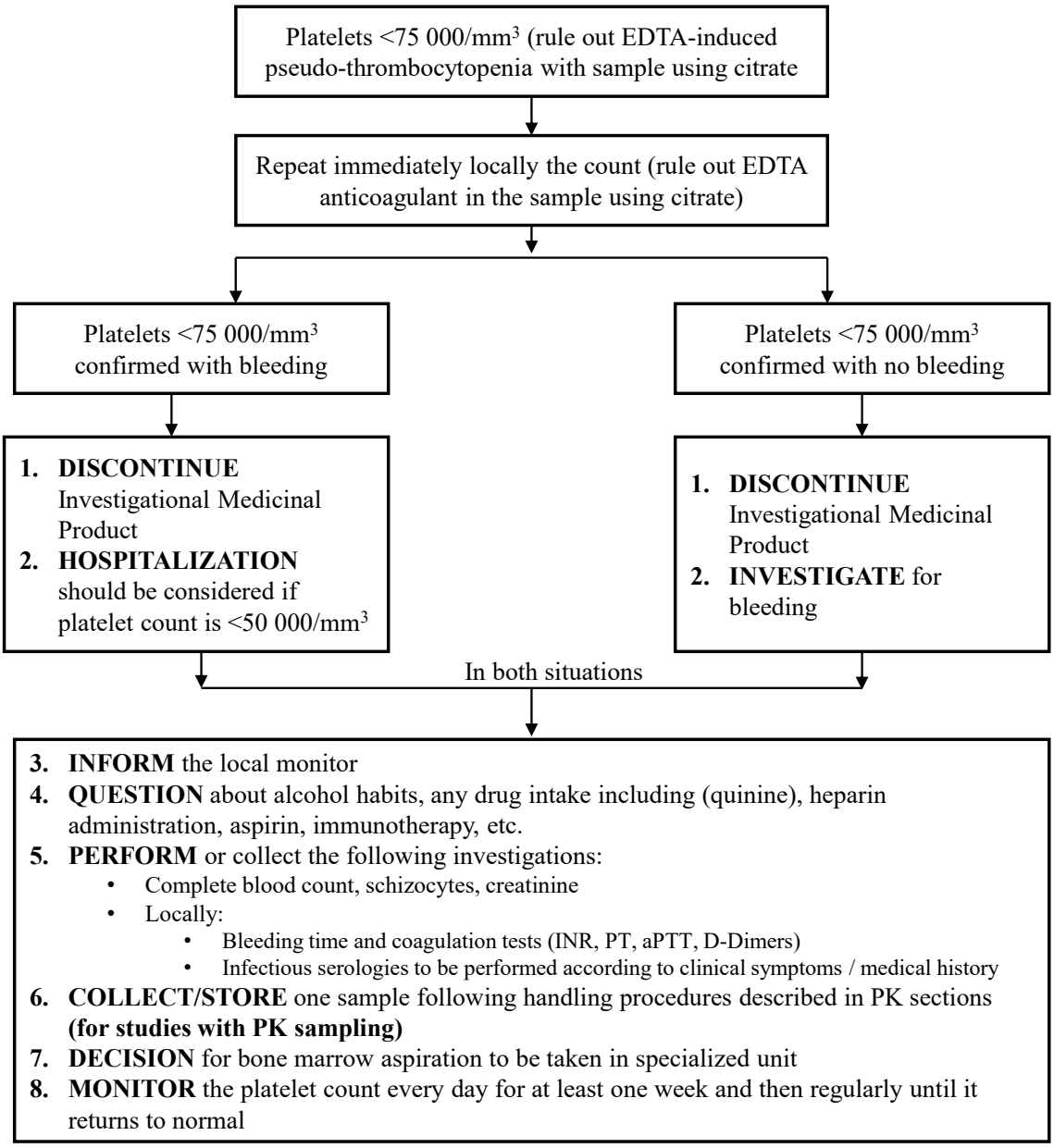
NEUTROPENIA



* 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 AEs in Appendix 3 (Section 10.3) is met.

THROMBOCYTOPENIA



Abbreviations: aPTT: activated partial thromboplastin time; EDTA: Ethylenediaminetetraacetic acid; INR: international normalized ratio; PK: pharmacokinetic; PT: prothrombin time

Thrombocytopenia is to be recorded as an AE only if at least 1 of the criteria listed in the general guidelines for reporting AEs in Appendix 3 (Section 10.3) is met.

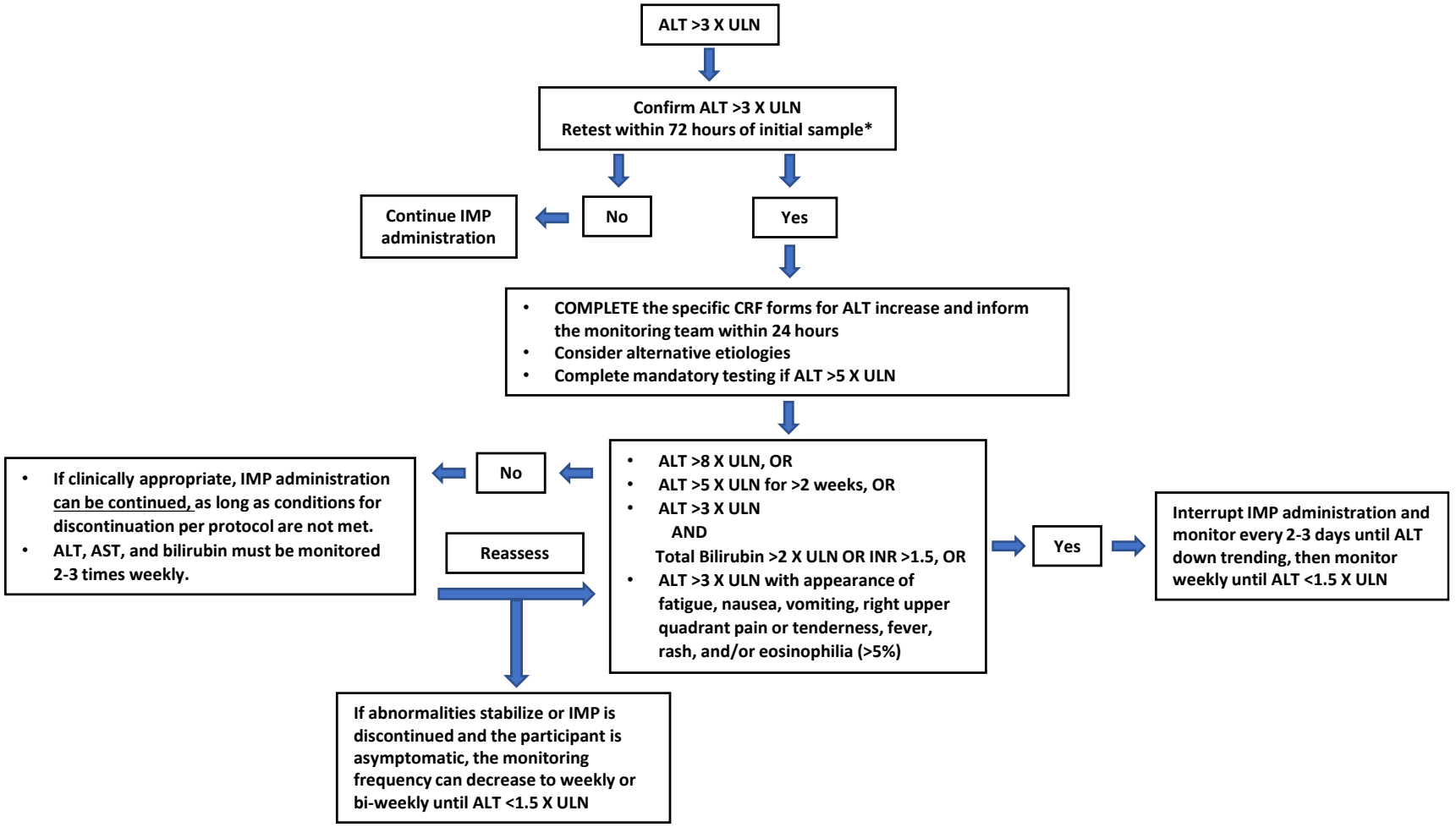
LIVER FUNCTION TEST MONITORING ADDITIONAL GUIDANCE:

To allow timely review for these data, please enter the date of collection for the central lab and the date of collection and the results for the local lab in the eCRF within 24 hours of their availability.

1. If 1 LFT monitoring timepoint is missed, the study site should:
   - Reach out to the study participant as soon as possible to schedule an alternative timepoint as soon as possible and prior to the next scheduled timepoint.
   - Retrain the study participant on the LFT monitoring rationale and requirements and inform the study participant that IMP will need to be interrupted if LFTs cannot be monitored as required.

2. If 2 consecutive LFTs timepoints are missed, the site should:
   - Call the participant immediately to reschedule the next LFTs timepoint as soon as possible and discuss with them about the underlying reasons of missing the timepoints.
   - Instruct participant to hold IMP immediately if they decline to reschedule the timepoint or miss the rescheduled timepoint.
   - Inform the participant that IMP can resume only after LFTs monitoring compliance is achieved.
   - Inform the monitoring team of any underlying reason identified for participant non-compliance and work with the monitoring team to resolve underlying issues to ensure compliance.

Increase in ALT Algorithm



*If unable to retest in 72 hours, use original laboratory results to decide on further reporting/monitoring/discontinuation.

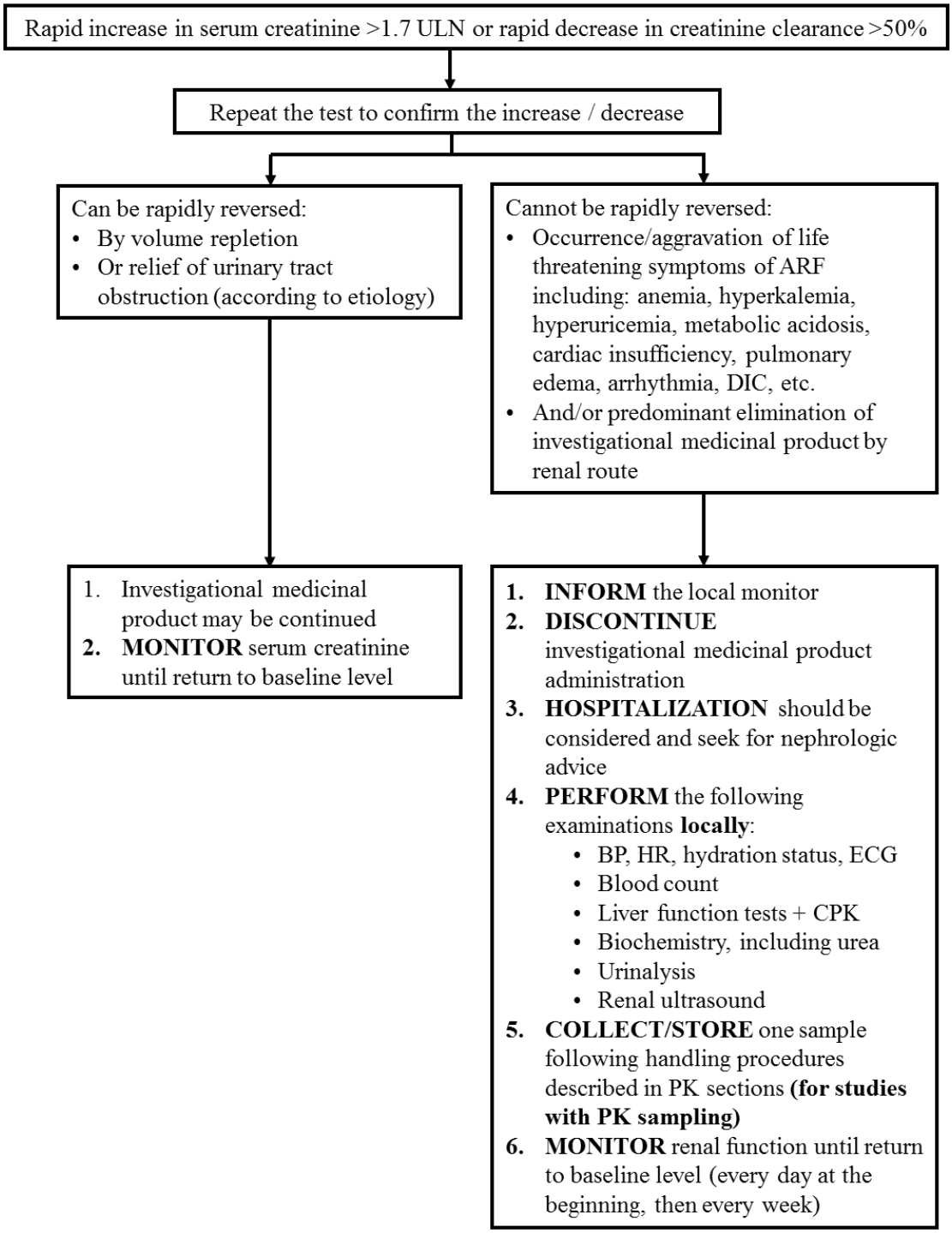
Note: "Baseline" refers to ALT sampled at baseline visit; or if baseline value unavailable, to the latest ALT sampled before the baseline visit. The algorithm does not apply to the instances of increase in ALT during screening. See Section 8.3 for guidance on safety reporting. Normalization is defined as ≤ ULN or baseline value if baseline value is > ULN.

In ANY CONFIRMED CASE of ALT >5 x ULN or ALT >3 x ULN with bilirubin >2 x ULN, the following steps are REQUIRED (recommended for ALT >3 x ULN but ALT <5 x ULN, as clinically indicated):

- **INFORM** the Site Monitor, who will forward the information to the Study Manager.
- **INVESTIGATE** specifically for malaise with or without loss of consciousness, dizziness, and/or hypotension and/or episode of arrhythmia since the last visit, particularly in the previous 72 hours; rule out muscular injury.
- **PERFORM** the following tests/actions:
  - LFTs: AST, ALT, alkaline phosphatase, GGT, total and conjugated bilirubin, and prothrombin time/INR (mandatory assessments for ALT >3 x ULN);
  - CPK, serum creatinine, complete blood count;
  - Anti-HAV IgM, anti-HBc IgM, (HBV-DNA if clinically indicated), hepatitis B surface antigen (HBsAg), anti-HCV and HCV RNA, anti-CMV IgM and anti-HEV IgM antibodies;
  - Iron, ferritin, transferrin saturation;
  - Auto-antibodies: serum IgG levels, antinuclear, anti-DNA, anti-smooth muscle, anti-LKM, anti-mitochondrial;
  - Evaluate recent infection with EBV, herpes viruses. Depending on the clinical context, consider testing for toxoplasma;
  - Collect and freeze serum sample (5 mL x 2);
  - Collect and store one PK sample following the instructions in the central laboratory manual;
  - Perform-hepatobiliary imaging (ultrasonography or other imaging investigations is required);
  - Consider DNA test for Gilbert's disease if clinically indicated;
  - Recommend consulting a hepatologist (mandatory if ALT >8 x ULN or is associated with elevated bilirubin);
    - Discuss with the hepatologist the clinical indication for potential liver biopsy (strongly recommended if the participant meets Hy's law criteria or has ALT >20 x ULN) and/or initiation of treatment with steroids;
  - Consider patient hospitalization if INR >2 (or PT <50%) and/or central nervous system disturbances suggesting hepatic encephalopathy.
- **MONITOR LFTs after discontinuation of IMP:**
  - Monitor closely (every 2-3 days) until ALT is down-trending, then weekly until <1.5 x ULN, and then at every scheduled visit;
  - This frequent LFT monitoring may be done through central or local lab, or via home visit (depending on the Investigator's assessment and/or local regulatory requirements).
- **RECHALLENGE:** Re-initiation of the study drug can only be considered after discussion with the Sponsor's Medical Monitor once the ALT/AST decreases to <1.5 x ULN, and there is no clinical contraindication. Rechallenge is not permitted for the following participants unless a clear non-DILI etiology is identified:
  - ALT >8 x ULN
  - ALT >5 x ULN for greater than two weeks
  - ALT >3 x ULN and total bilirubin >1 x ULN
  - In case it is agreed to re-start the study drug, it is recommended that ALT/AST be assessed per protocol schedule of assessments for the first 6 months of the treatment period.
  - The occurrence of new elevation to >3 x ULN for the ALT/AST values will lead to permanent discontinuation of the study drug.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CMV, cytomegalovirus; CPK, creatine phosphokinase; CRF, case report form; EBV, Epstein-Barr virus; GGT, gamma glutamyl transferase; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HEV, hepatitis E virus; IgG, immunoglobulin G; IgM, immunoglobulin M; IMP, investigational medicinal product; INR, international normalized ratio; LFT, liver function test; LKM, liver-kidney microsomal antibody; PT, prothrombin time; ULN, upper limit of normal.

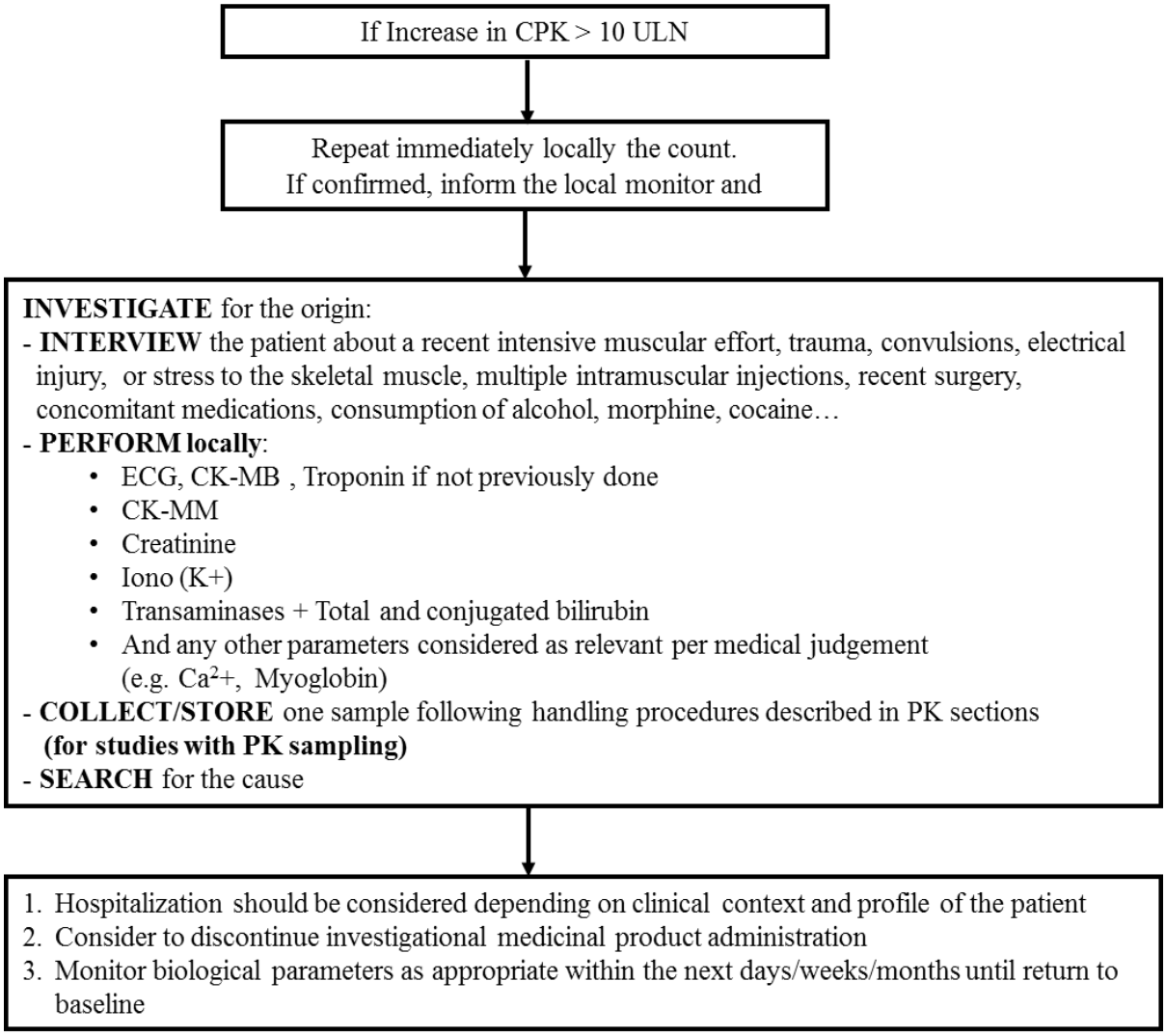
INCREASE IN SERUM CREATININE in patients with normal baseline (creatininemia between 45 µmol/L and 84 µmol/L)



ARF, acute renal failure; CPK, creatine phosphokinase; DIC, disseminated intravascular coagulation; ECG, electrocardiogram; PK, pharmacokinetic(s); ULN, upper limit of normal

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 AEs in Appendix 3 (Section 10.3) is met.

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

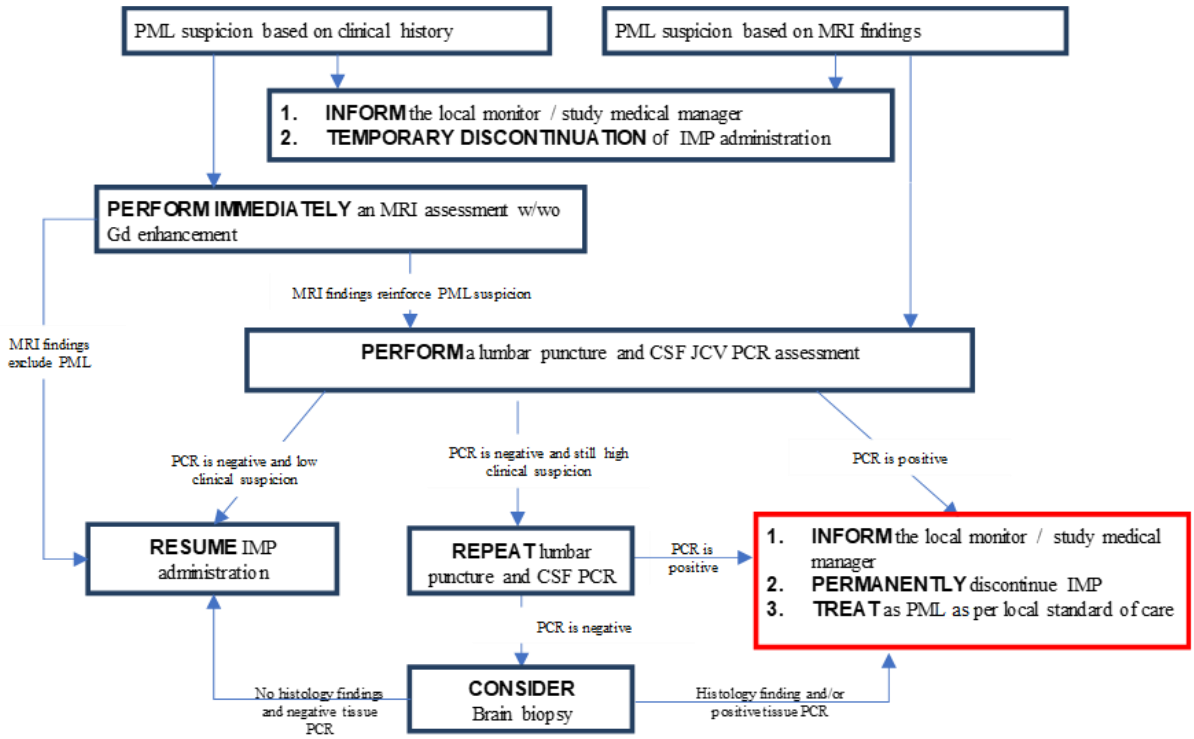


CK-MB, creatine kinase-MB; CK-MM, creatine kinase-MM; ECG, electrocardiogram; PK, pharmacokinetic(s); ULN, upper limit of normal

Increase in CPK is to be recorded as an AE only if at least 1 of the criteria in the general guidelines for reporting AEs in Appendix 3 (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.



Abbreviations: CSF, cerebrospinal fluid; Gd, Gadolinium; IMP, investigational medicinal drug; JCV, John Cunningham virus; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; PML, progressive multifocal leukoencephalopathy

Clinical manifestations or MRI lesions features suspicious for PML are proposed in Table 6 (based on [44] and [45]).

Table 6 - Clinical and MRI features suggestive of PML

Clinical history	Subacute onset of weakness, sensory deficits, cognitive or behavioral abnormalities, 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.

In the event that PML is suspected based on imaging results, the local radiologist will directly inform the Investigator and a central review of the MRI will not be required. The Investigator will obtain additional plasma, urine, and CSF samples for John Cunningham virus (JCV) analysis. Samples will be analyzed upon receipt and the results will be provided directly to the investigational site and to the Sponsor. Further management will be deferred to the Treating Investigator. However, next steps will include discontinuation of study treatment. Additional imaging will be at the discretion of the Investigator depending on the diagnostic workup and treatment plan.

- The detection of JCV DNA in the CSF of a participant with clinical and MRI features suggestive of PML establishes the diagnosis of PML.
- If JCV DNA is not detected in CSF 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: MEDICAL DEVICE ADVERSE EVENTS (AES), ADVERSE DEVICE EFFECTS (ADES), SERIOUS ADVERSE EVENTS (SAES) AND DEVICE DEFICIENCIES: DEFINITION AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

Not applicable.

10.8 APPENDIX 8: COUNTRY-SPECIFIC REQUIREMENTS

10.8.1 Contraception requirements in UK, Germany, and Denmark

For inclusion criterion I 09, the following apply:

- *For UK and Germany Only: Acceptable forms of effective contraception include the following:*
  - 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 participant (Periodic abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception).
- *For Denmark Only: Acceptable methods of effective contraception include the following:*
  - IUD;
  - Hormonal contraceptives (contraceptive pills, implants, transdermal patches, hormonal vaginal devices, or injections with prolonged release).

10.8.2 Country-specific differences for China

There will be no biological sample exportation from China in this study, and the sites in China will not participate in the following testing:

- Pharmacodynamic: Assessment of NfL levels in plasma.
- Genetics: A 6 mL blood sample will be collected for DNA isolation, then be stored. Analysis may be performed on genetic variants thought to play a role in MS including, but not limited to, specific candidate genes/genome analyses to evaluate their association with observed clinical responses to SAR442168.
- Biomarkers: Samples may be stored for a maximum of 2 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 biomarker responses to SAR442168.

10.8.3 Country-specific provisions for France and Japan

Temporary IMP interruption will occur for all ALT >5 x ULN events regardless of the duration of ALT elevation above 5 x ULN. The remaining components of the ALT algorithm (Appendix 6, Section 10.6) apply for participants in France and Japan.

For participants starting IMP/open-label tolebrutinib, liver testing will occur at Weeks 1 and 3 in addition to the frequent liver monitoring outlined in the Schedule of Activities (Section 1.3).

It is strongly recommended to avoid initiating and continuing use of hepatotoxic drugs and hepatotoxic herbs/supplements while receiving IMP, due to the risk of hepatotoxicity associated with the administration of tolebrutinib.

Large, publicly available resources such as the DILIrank reference drug list (46, 47) can be a useful guide in identifying hepatotoxic medications. Examples of hepatotoxic herbals/supplements determined by the European Association for the Study of Liver Clinical Practice Guidelines for DILI are outlined below (Table 7, 48). Please note that the lists provided are not exhaustive and that the product information of drugs intended for concomitant use should be consulted.

Table 7 - Examples of herbal and dietary supplements involved in hepatotoxicity

Herbal and dietary supplements	Type of liver injury
Herbal preparations	
Pyrrolizidine alkaloids, eg, Crotalaria,senecio, heliotrpium, Symphytum officinale (comfrey)	Acute and chronic SOS
Teucrium chamaedrys (germander)	AHH, ACH, ALF, chronic hepatitis, cirrhosis, cholangitis
Teucrium polium	AHH, ACH, ALF
Atractylis gummifera L.	AHH, ACH, ALF
Callilepis laureola L.	AHH, ALF

Herbal and dietary supplements	Type of liver injury
Mentha pulegium	AHH, ACH, ALF
Hedeoma pulegioides	AHH, ACH, ALF
Chelidonium majus (greater celandine)	AHH, ACH, chronic hepatitis, cholangitis
Piper methysticum (kava-kava)	AHH, ACH, ALF, chronic hepatitis
Camellia sinensis (green tea extracts)	AHH, ACH, ALF
Actaea racemosa (black cohosh)	AHH, ACH
Cimicifuga racemosa	AHH, ACH
Morinda citrifolia (Noni juice)	AHH, ACH, ALF
Serenoa	ACH
Azadirachta indica	Microvesicular steatosis
Catha edulis (khat)	AHH, ACH, ALF
Borago officinalis (borage)	AHH, ACH
Cassia angustifolia (senna)	AHH, ACH
Larrea tridentata (chaparral)	AHH, ACH, cholangitis, chronic hepatitis/cirrhosis
Asian herbal medicine (Chinese, Japanese, ayurvedic medicines)	
Lycopodium serratum (Jin Bu Huan)	AHH, ACH, ALF
Ephedra (Ma Huang)	AHH with autoimmunity
Sho-Saiko-To (Xiao-Chai-Hu-Tang; complex preparation)	AHH/chronic hepatitis
Dai-Saiko-To (complex preparation)	AHH with autoimmunity
Chaso and Onshido	AHH, ACH, ALF
Boh-Gol-Zhee/Bu Ku Zi	ACH
Polygonum multiflorum (Shou-Wu-Pian)	AHH, ACH
Ganoderma lucidum (Linghzi)	AHH
Brena officinalis (Chi R Yun)	AHH
Dysosma pleiantha (Boh-Gol-Zhee)	AHH
Dietary supplements	
Usnic acid with other ingredients:	
LipoKinetix®	AHH, ALF
UCP-1®	AHH, ALF
Oxy ELITE®	AHH, ALF
Hydroxycut®	AHH, ACH, ALF, AHH with autoimmunity
Linoleic acid	AHH
Plethoryl® (vitamin A, thyroid hormones)	AHH, ACH, chronic hepatitis, cirrhosis
Illicit anabolic androgenic steroids	AHH, ACH, liver adenoma, HCC, SOS

ACH, acute cholestatic hepatitis; AHH, acute hepatocellular hepatitis; ALF, acute liver failure; HCC, hepatocellular carcinoma; SOS, sinusoidal obstruction syndrome.

10.8.4 Country-specific provisions for Japan

Temporary IMP interruption will occur if ALT >3 × ULN and INR >1.3 or bilirubin >2 × ULN. Monitoring should then occur every 2 to 3 days until ALT and INR/bilirubin start downtrending, then monitoring can be decreased to weekly until ALT <1.5 × ULN.

The remaining components of the ALT algorithm (Appendix 6, Section 10.6) and Appendix 8, Section 10.8.3 apply for participants in Japan.

10.8.5 Country-specific provisions for the US

Participants who previously discontinued IMP within 60 days of trial start due to the partial clinical hold and are now restarting IMP, will require liver function test monitoring at Weeks 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12 (M3), and then monthly for the next 9 months until M12. After that, the schedule visit timepoints per SoA (Section 1.3) will be resumed (ie, every 3 months), until the study end. Whenever a timepoint will coincide with a scheduled visit as per SoA, the full scheduled visit assessments will be performed instead of the liver monitoring testing alone.

10.8.6 Country-specific provisions for the US, Israel, and sites following FDA partial clinical hold conditions

In addition to refraining from medications that are moderate and potent inducers of CYP3A, participants must not take medications that are mild, moderate, and potent inhibitors of CYP3A or CYP2C8 hepatic enzymes throughout the conduct of the trial (see Appendix 9, Section 10.9).

Participants must refrain from consumption of grapefruit or grapefruit juice (due to inhibition of CYP3A4) from 5 days prior to intervention administration and throughout the treatment phase.

If medications that are mild, moderate, or potent inhibitors of CYP3A or CYP2C8 are clinically indicated, alternative options for non-CYP3A or non-CYP2C8 inhibitors should be considered, as medically appropriate. For participants not eligible for alternative options, IMP should be temporarily discontinued for the duration of treatment on these medications.

10.9 APPENDIX 9: EXAMPLE OF DRUGS WITH A POTENTIAL TO CHANGE SAR442168 METABOLISM OR ABSORPTION

The following drugs should not be taken during the study concomitantly with IMP due to their potential to change SAR442168 kinetics due to interaction with P450-mediated metabolism, being potent and moderate inducers of CYP3A or potent inhibitors of CYP2C8 liver enzymes (Table 8).

Additionally, participants in the US, Israel, and any other sites following FDA partial clinical hold conditions must not take medications that are mild, moderate, or potent inhibitors of CYP3A or CYP2C8 (Table 9).

Please note that the lists provided in Table 8 and Table 9 are not exhaustive and that the product information of drugs intended for concomitant use should be consulted.

Table 8 - Potent and moderate CYP3A inducers and potent CYP2C8 inhibitors

Potent CYP3A Inducers:	
Rifampin	Carbamazepine
St John's Wort extract	Phenobarbital
Avasimibe	Lumacaftor
Rifapentine	
Phenytoin	
Potent CYP2C8 Inhibitors:	
Gemfibrozil	Clopidogrel
Moderate CYP3A Inducers:	
Semagacestat	Asunaprevir/beclabuvir/daclatasvir
Cenobamate	Nafcillin
Lesinurad	Telotristat ethyl
Bosentan	Elagolix
Thioridazine	Rifabutin

Table 9 - Mild, moderate, and potent inhibitors of CYP3A and CYP2C8, and moderate and potent inducers of CYP3A

CYP2C8 inhibitors	Potent	Moderate	Mild
	Clopidogrel	Trimethoprim	Sulfamethoxazole
	Gemfibrozil		trimethoprim
			Fluvoxamine
CYP3A inducers	**Potent**	**Moderate**	
	Avasimibe	Elagolix	
	Rifampin	Cenobamate	
	Carbamazepine	Nafcillin	
	Lumacaftor	Asunaprevir/beclabuvir/daclatasvir	
	Phenobarbital	Lesinurad	
	Phenytoin	Bosentan	
	Rifapentine	Thioridazine	
	St. John's Wort	Rifabutin	
CYP3A inhibitors	**Potent**	**Moderate**	**Mild**
	Clarithromycin	Ciprofloxacin	Alprazolam
	Itraconazole	Diltiazem	Atorvastatin
	Ketoconazole	Erythromycin	Amlodipine
	Nirmatrelvir and ritonavir	Fluconazole	Cimetidine
	Fluoxetine	Verapamil	Ranitidine
	Grapefruit juice	Sertraline	Roxithromycin
			Ginkgo biloba
			Isoniazid

10.10 APPENDIX 10: CONTINGENCY MEASURES FOR A REGIONAL OR NATIONAL EMERGENCY THAT IS DECLARED BY A GOVERNMENTAL AGENCY

A regional or national emergency declared by a governmental agency (eg, public health emergency, natural disaster, pandemic, terrorist attack) may prevent access to the clinical trial site.

Contingency procedures are suggested below for an emergency that prevents access to the study site, to ensure the safety of the patients, to consider continuity of the clinical study conduct, protect trial integrity, and assist in maintaining compliance with Good Clinical Practice in Conduct of Clinical Trials Guidance. Sponsor agreement MUST be obtained prior to the implementation of these procedures for the duration of the emergency; this agreement must be provided in writing by the Sponsor and will be kept in the Investigator file.

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 onsite monitoring) are provided in separate study documents.

During the emergency, if the site will be unable to adequately follow protocol mandated procedures, screening and enrollment may be temporarily delayed/halted.

Attempts should be made to perform all assessments in accordance with the approved protocol to the extent possible. In case this is not possible due to a temporary disruption caused by an emergency, focus should be given to assessments necessary to ensure the safety of patients and those important to preserving the main scientific value of the study.

10.10.1 Informed consent

For a regional or national emergency declared by a governmental agency, contingency procedures may be implemented for the duration of the emergency. The participant or their legally authorized representative should be verbally informed prior to initiating any changes that are to be implemented for the duration of the emergency (eg, study visit delays/treatment extension, use of local labs), and the verbal information given to the participant should be documented in the subject's medical record.

10.10.2 Study procedures

Procedures to be considered in the event of a regional or national emergency declared by a governmental agency:

1. New screenings during a regional or national emergency declared by a governmental agency can be performed only if allowed by local competent authorities and after Sponsor's agreement is obtained. Rescreening will be permitted when the situation normalizes and only if allowed by local competent authorities and after Sponsor's agreement is obtained.

2. If onsite visits or alternative location (out of subject's home) are not possible, all visits from Week 1 (including those planned to be done onsite) will be performed at home by a trained healthcare professional and if allowed by local competent authorities for:
   - Treatment administration
   - Blood sampling for safety (at least hematology, hepatic function panel, coagulation panel) and other safety assessments (at least serum creatinine), and pregnancy test (if applicable)
   - Measuring vital signs
   - Monitoring of injection site reactions, AEs, and SAEs

The use of a local laboratory may be allowed for safety follow up in case the central lab cannot be used.

The Investigator or delegate will perform a phone-call visit at each onsite planned visit to collect safety data and concomitant treatment. All data collected remotely will be properly documented in the subject's medical record and the study CRF.

For all assessments which will not be performed remotely, the assessment windows will be extended until subjects may access the site.

If onsite visit and home visit are not possible, a temporary treatment discontinuation may be considered. The Investigator or delegate will perform a phone-call visit at each onsite planned visit to collect safety data and concomitant treatment.

Contingencies implemented due to emergency will be documented in the participant's medical record.

10.10.3 Temporary discontinuation

A temporary IMP discontinuation may be considered by the Investigator because of suspected AEs or disruption of the clinical trial due to a regional or national emergency declared by a governmental agency.

Reinitiation of study drug can only occur once the investigator has determined, according to his/her best judgement, that the study drug did not contribute to the occurrence of the epidemic event (eg, COVID-19).

For all temporary intervention discontinuations, duration should be recorded by the Investigator in the appropriate pages of the CRF or eCRF.

10.10.4 Statistical analysis

The impact of the regional or national emergency declared by a governmental agency on study conduct will be summarized (eg, study discontinuation or discontinuation/delay/omission of the intervention due to the emergency). Any additional analyses and methods required to evaluate the impact on efficacy (eg, missing data due to the emergency) and safety will be detailed in the SAP.

10.11 APPENDIX 11: IMMUNOPHENOTYPING (TOLEDYNAMIC SUBSTUDY)

Title

An immunological substudy to better understand the mechanism of action of the BTK inhibitor tolebrutinib in participants with multiple sclerosis and to correlate immunological changes with clinical/paraclinical responses (ToleDYNAMIC).

Introduction/Study rationale

Bruton's tyrosine kinase mediates B cell receptor signaling and is also expressed in innate immune cells such as monocytes, macrophages, and microglial cells. BTK inhibitors exhibit well characterized effects in (autoreactive) B cells as one of the key target cell population in MS. However, nonclinical models also indicate indirect effects on T cell subsets due to the intricate, reciprocal B cell and T cell crosstalk, which is particularly interesting in light of their role in the pathogenesis of MS.

The second target population of BTK inhibitors is myeloid lineage cells. BTK inhibition alters macrophage phagocytic capacity and reduces secretion of proinflammatory and cytotoxic cytokines and mediators. In the context of MS pathophysiology, these effects on innate immune cells have been proposed to contribute to control of progression. This concept is supported by recent neuropathologic findings that the "mixed active-inactive" MS lesions exhibiting absence of signs of relevant remyelination depict a pronounced rim of infiltrating macrophages, implicating this cell population in this "repair-hostile" environment.

We propose to elucidate the impact of BTK inhibition via tolebrutinib on the peripheral immune regulatory network beyond B cells and to characterize its effects on functional properties and transcriptional signatures of peripheral blood monocyte populations in patients with PMS. In light of existing nonclinical data, it can be hypothesized that tolebrutinib exerts distinct effects on peripheral immune signatures exceeding its direct immune-modulatory effects on B cells and monocytes and which may restore immune-regulatory network function.

Objectives

The major advantage of the multicenter substudy is that several key immunological questions can be addressed in context with available clinical/MRI data in order to gain knowledge about the potential correlation between key immunological changes and treatment response.

In light of the limited amount of blood available and to ensure sufficient participant recruitment, we will focus on the following:

1. Highly standardized functional multiparameter (13 colors per panel) flow cytometry of peripheral blood of tolebrutinib-treated participants with PMS before and at different time points after onset of tolebrutinib treatment. We will focus on a characterization of T and B cell subsets as well as monocyte populations, ie,

- **T cells:** CD4, CD8, CD4-CD8-, CD4+CD8+, naive, central memory, effector memory, TEMRA, RTE, Treg

- **CD4 memory:** Th1, Th2, Th 17, IL, Tfh, IFNγ, TNFα, GM-CSF, IL4, IL22, IL17A, GrA, GrB, GrK, GrM, perforin, MCAM
- **CD8 memory:** Cytolytic activity, IFNγ, TNFα, GM-CSF, IL4, IL22, IL17A, GrA, GrB, GrK, GrM, perforin
- **Treg:** pTreg, tTreg, RTE Treg, CD39, DNAM-1, TIGIT
- **B cells:** naïve, class switch memory, Breg, unusual, transitional, marginal-zone-like, IgM only
- **Monocytes:** classical, intermediate, nonclassical subsets

  Classical, intermediate, nonclassical:

  - Chemokine receptor expression (CCR2, CCR5, CX3CR1)
  - Activation markers (CD80, CD86, CD116, CD39)
  - Pro-inflammatory markers (CD69, CD54, CD68, CD40, CD64, CD32)
  - Anti-inflammatory markers (S100A9, CD93, CD36, CD163, PD-1, CD106, CD206, CD124, CD121b)
  - Adhesion and migratory capacities (CCR7, CD31)

The frequency will be determined as well as activation status and functional properties such as cytokine production and cytolytic profile. Simultaneous assessment of peripheral blood cell counts within the main study will allow for quantification of each immune cell subset in peripheral blood.

2. The second set of experiments will focus on functional properties of peripheral blood monocytes. Cytokine profile of ex vivo and short-term stimulated CD14 monocytes will be determined using Luminex technology.

- **Isolated CD14 monocytes:** cytokine/chemokine production (IFNα, IFNγ, TNFα, IL6, IL1α, IL1β, IL1RA, IL2, IL4, IL6, IL8, IL10, IL15, IL33, CCL2C)
- **Isolated CD14 monocytes:** capacity to phagocytose myelin as determined by flow cytometry
- **Production of reactive oxygen species by CD14 monocytes** as determined by flow cytometry
- **Analysis of key metabolic properties of CD14 monocytes by Seahorse technology**

The effect of tolebrutinib on transcriptional profiles of peripheral blood B cells and CD14 monocytes using unbiased RNA sequencing of magnetic-bead-sorted cells will be determined. This approach will provide a detailed overview of therapy-induced changes within the T cell monocyte compartments to potentially identify immune cell subsets as well as transcriptional networks affected by tolebrutinib. This approach may identify transcriptional markers which might be used in the future as biomarkers for treatment response.

Statistical analysis will be described in a separate SAP.

Study duration

This substudy will take place during the main study. There will be 3 sampling points (baseline, Months 3 and 12) to collect approximately 40 mL of blood per sample/per visit for the 3 visits. A total of approximately 120 mL blood will be collected from each participant for this substudy.

Study design

- Inclusion/exclusion criteria are those for the main study.
- Multicenter substudy in participants with PMS sampled at baseline (before treatment) and Months 3 and 12 (after initiation of tolebrutinib).
- Clinical endpoints and MRI measures are from the main study.
- This substudy will be performed in 80 participants total (40 participants from both PERSEUS and HERCULES, respectively). RNA sequencing will be performed in a subset of participants.
- Blood sampling, handling, and shipment.
- Each blood sample is approximately 40 mL (3 samples of approximately 120 mL for the substudy).
- Special procedures for collection, storage and shipping of blood samples will be described in the operational Study Manual for handling samples.
- Shipment to the central laboratory must be within 24 hours of sampling.
- Bulk RNA-sequencing will be performed from frozen and subsequently thawed peripheral blood mononuclear cells and monocytes.

Participating centers

Selected sites.

10.12 APPENDIX 12: ACTIGRAPHY SUBSTUDY

A subset of participants may perform actigraphy (a noninvasive activity monitor) to assess disease symptoms and progression in the participant's free-living environment. The objective of this assessment is to test the hypothesis that the increased sensitivity and ecological validity of an actigraphy device will reflect changes in the participant's condition more accurately and more comprehensively than occasional in-clinic assessments. If implemented based on pilot assessment, the Sponsor will provide participants with an actigraphy device. Participants will be required to wear the device during waking hours for 14 days on and 14 days off every month from enrollment into the substudy until the end of the sub-study, as specified in the schedule of activities (Section 1.3). Additional details can be found in the Study Reference Manual.

10.13 APPENDIX 13: ABBREVIATIONS

ADL:	activity of daily living
AE:	adverse event
AESI:	adverse event of special interest
ALP:	alkaline phosphatase
ALT:	alanine transaminase
aPTT:	activated partial thromboplastin time
AST:	aspartate aminotransferase
BTK:	Bruton's tyrosine kinase
CD:	cluster of differentiation
CDP:	confirmed disability progression
CFR:	Code of Federal Regulation
Chi3L1:	chitinase-3 like protein-1
CIOMS:	Council for International Organization of Medical Sciences
CNS:	central nervous system
COVID-19:	Coronavirus Disease 2019
CPK:	creatine phosphokinase
CSF:	cerebrospinal fluid
CSR:	clinical study report
C-SSRS:	Columbia-suicide severity rating scale
DDI:	drug-drug interaction
DILI:	drug-induced liver injury
DMC:	data monitoring committee
DNA:	deoxyrebonucleic acid
DNAM-1:	DNAX accessory molecule 1
DTP:	direct-to-patient
EC:	ethics committee
eCRF:	electronic case report form
EDSS:	expanded disability status scale
EU:	European Union
FSH:	follicle stimulating hormone
GCP:	Good Clinical Practice
Gd:	gadolinium
GM-CSF:	granulocyte-macrophage-colony stimulating factor
GrA:	human granzyme A
GrB:	human granzyme B
GrK:	human granzyme K
GrM:	human granzyme M
HIV:	human immunodeficiency virus
HR:	hazard ratio
HRT:	hormonal replacement therapy
ICF:	informed consent form
ICH:	International Council for Harmonisation
IEC:	Independent Ethics Committees

IFNγ:	Interferon γ
IL:	interleukin
IMP:	investigational medicinal product
INR:	international normalized ratio
IRB:	Institutional Review Boards
IRT:	interactive response technology
ITT:	intent-to-treat
IUD:	intrauterine device
IUS:	intrauterine hormone-releasing system
IV:	intravenous
IWRS:	interactive web response system
JCV:	John Cunningham virus
LTS:	long-term safety
MCAM:	melanoma cell adhesion molecule
MedDRA:	Medical Dictionary for Regulatory Activities
MMRM:	model with repeated measures
MRI:	magnetic resonance imaging
MS:	multiple sclerosis
MSFC-3:	multiple sclerosis functional composite 3
MTR:	magnetization transfer ratio
NCI CTCAE:	National Cancer Institute Common Terminology Criteria for Adverse Event
NEDA:	no evidence of disease activity-3
NfL:	neurofilament light chain
NRSPMS:	nonrelapsing secondary progressive multiple sclerosis
NSAIDs:	nonsteroidal anti-inflammatory drugs
PCSA:	potentially clinically significant abnormality
PD:	pharmacodynamic(s)
PK:	pharmacokinetics
PML:	progressive multifocal leukoencephalopathy
PPMS:	primary progressive multiple sclerosis
pTreg:	peripheral regulatory T cells
RMS:	relapsing multiple sclerosis
RRMS:	relapsing-remitting multiple sclerosis
RTE:	recent thymic emigrant
SAP:	statistical analysis plan
SEL:	slowly evolving lesions
SoA:	schedule of activities
SPMS:	secondary progressive multiple sclerosis
SUSAR:	suspected unexpected serious adverse reaction
SWI:	susceptibility-weighted imaging
TB:	tuberculosis
TEAE:	treatment-emergent adverse event
Tfh:	T follicular helper
Th 17:	T helper 17 cells
Th1:	T helper 1 cells
Th2:	T helper 2 cells

TIGIT:	T cell immunoglobulin and immunoreceptor tyrosine-based inhibitory motif (ITIM) domain
TNFα:	tumor necrosis factor α
Treg:	regulatory T cell
tTreg:	thymically derived Foxp3(+) regulatory T cells
ULN:	upper limit of normal
WBC:	white blood cells
WOCBP:	women of childbearing potential

10.14 APPENDIX 14: PROTOCOL AMENDMENT HISTORY

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

10.14.1 Amended protocol 01 (15 May 2020)

This amended protocol (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 primary driver for this amended protocol consists of regulatory requirements including addition of a Relapse Adjudication Committee, change in stratification factor, removal of an endpoint and addition of a benefit-risk evaluation of the study in the context of the COVID-19 pandemic.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis	Expanded Disability Status Scale (EDSS)-plus endpoint removed. Time to onset of sustained 20% increase in the timed 25 foot walk (T25-FW) and the 9-hole peg test (9-HPT) for at least 3 months maintained as secondary endpoints. Stratification by absence/presence of gadolinium (Gd) enhancing T1 lesions at baseline changed to stratification by age at screening. Geographic origin corrected to geographic region. Mention that investigational medicinal products (IMPs) are film coated tablets. Relapse Adjudication Committee added. Post-trial access to study medication clarified. Statistical considerations updated for consistency with rest of document.	Accuracy. Clarity. Consistency. Health authority request.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of activities	Removal of dispensation of IMP and matching placebo from premature end of treatment (pEOT) visit. Removal of investigational medicinal product (IMP) compliance check from randomization visit. Parameters of physical examination clarified. Clarification of tuberculosis (TB) testing. Timing of plasma and serum samples clarified. Participants who will enter long-term extension study was clarified. Quarterly lipase testing added. Mention that additional safety assessments may be performed locally if required. Visit window for magnetic resonance imaging (MRI) performed after D1 expanded. Clarification of potential uses of archival sample.	Accuracy. Clarity.
2.1 Study rationale	Removal of paragraph on EDSS-Plus. Mention that relapse data will be adjudicated	EDSS-Plus is removed from secondary and tertiary/exploratory endpoints. Health authority request.
2.3 Benefit/risk assessment	In potential benefits, “reduction in the accumulation of confirmed disability worsening” changed to “reduction in the accumulation of confirmed disability progression” for clarity. Investigator assessment of relatedness of one adverse event (AE) of temporary alanine transaminase (ALT) increase changed to “related” to reflect update in data. “No cardiac arrhythmia was observed” was changed to “No clinically significant cardiac arrhythmia was observed” for clarity. Text added to address regulatory requirements for COVID-19 risk and mitigation.	Clarity. Accuracy. Response to regulatory requirement.
3 Objectives and endpoints	Adjudication added to relapse tertiary/exploratory endpoint. EDSS-plus endpoint removed. Time to onset of sustained 20% increase in the T25-FW and the 9-HPT for at least 3 months moved from tertiary/exploratory to secondary endpoints. Change from baseline to Months 12, 18, and 24 and to the end of study (EOS) in California Verbal Learning Test-II (CVLT-II) added in tertiary/exploratory endpoints.	Accuracy. Clarity. Consistency. Health authority request.
3.1 Appropriateness of measurements	Removal of paragraph on EDSS-Plus. Mention that relapse data will be adjudicated	EDSS-Plus is removed from secondary and tertiary/exploratory endpoints. Health authority request.
4.1 Overall design	Safety follow-up period clarified.	Clarity.
4.2 Scientific rationale for study design	Clarification of statistical issue.	Clarity.
4.3 Justification for dose	Text about external trials added.	Clarity. Addition of accidentally omitted text.
5.1 Inclusion criteria	Move country specificities to Appendix 8.	Clarity.
5.2 Exclusion criteria	In E01, wording “baseline” was change to “screening”. Removal of E18 as E09 is a similar criterion. In E06, timing of washout for concomitant medications changed from “before any baseline” to “before any randomization”, and table clarified.	Clarity.

Section # and Name	Description of Change	Brief Rationale
5.3.1 Meals and dietary restrictions	Timing of IMP administration clarified.	Clarity.
6.1 Study intervention(s) administered	Mention that IMPs are film coated tablets. Direct-to-patient (DTP) dispensation of IMP added as a possibility.	Accuracy. Flexibility for COVID-19.
6.2 Preparation/handling/ storage/accountability	Mention of responsibility in case of DTP shipment	Flexibility for COVID-19.
6.3 Measures to minimize bias: randomization and blinding	Stratification by absence/presence of Gd enhancing T1 lesions at baseline changed to stratification by age at screening. Geographic origin corrected to geographic region.	Clarity. Health authority request.
6.5 Concomitant therapy	Mention that live (attenuated) vaccines are prohibited.	Clarity
6.5.1 Rescue medicine	"A non-study treatment available for NRSPMS in their respective country" changed to "a non-study treatment approved for NRSPMS in their respective country". Clarification that there can be no adjudicated relapse within 90 days prior to onset or confirmation of 6-month CDP.	Clarity.
6.7 Intervention after the end of the study	Participants who will enter long-term extension study was clarified.	Clarity.
7.1.1 Definitive discontinuation	Clarification of discontinuation reason related to non-study disease modifying therapy. Recommendation for cardiologist review of electrocardiograms (ECGs) clarified. Last visit for participants with definitive discontinuation and participants who decide to discontinue open-label IMP clarified. Last visit for participants who decide to discontinue the IMP clarified. Participants who prematurely and permanently end treatment for a reason other than 6-month CDP will not be eligible for open-label IMP	Clarity.
7.1.2 Temporary discontinuation	Text added to address regulatory requirements for COVID-19 risk and mitigation.	Consistency.
8 Study assessments and procedures	"Phone visits" changed to "telephone/remote visits" to allow for web-based visits.	Ease of continuation of study during COVID-19 pandemic.
8.1.1.1 Confirmed disability progression	Definition of confirmed disability progression clarified.	Clarity.
8.1.2 Magnetic resonance imaging	Details of MRI assessments added.	Clarity.
8.1.3.1. Definition of MS relapse	Clarification of MS relapse confirmation definition. Crosslinks added.	Clarity.
8.1.7.1 EDSS plus	Section removed	EDSS-plus is not an endpoint anymore.
8.1.7.2 Assessment of no evidence of disease activity	Mention that MS relapse is adjudicated	Health Authority requirement.
8.1.8 Actigraphy	Actigraphy device must be worn for 14 days after screening for baseline assessment.	Clarity.

Section # and Name	Description of Change	Brief Rationale
8.2.2 Vital signs	Removed respiratory rate from vital signs. Oral or tympanic body temperature simplified to body temperature.	Simplification. Not necessary in an MS study.
8.2.3 Electrocardiograms	Removed reference to additional information.	Consistency within the protocol.
8.3.6 Cardiovascular and death events	Clarification that only atrial fibrillation and atrial flutter are AESIs in this study.	Clarity.
8.3.7 MS relapse reporting	MS relapse reporting criteria clarified.	Clarity.
8.3.9 Adverse events of special interest	Clarified that the project-specific adverse event of special interest (AESI) for ECG pertains to atrial fibrillation and atrial flutter only and that confirmation by a cardiologist is not required. Clarified that AESI reporting is intended for infections that are of severity Grade 3 or above by National Cancer Institute Common Terminology Criteria for Adverse Event (NCI CTCAE).	Clarity.
8.5 Pharmacokinetics	Blood samples of approximately 3 mL clarified as blood samples of approximately 2 to 3 mL.	Accuracy.
8.6 Pharmacodynamics	Clarification of the number of participants expected to participate in the pharmacodynamics part of the study.	Clarity.
9.1 Statistical hypotheses	Addition of details on hypotheses.	Clarity.
9.1 Statistical hypotheses	Details added for clarification.	Clarity.
9.4.2 Primary endpoint	Clarification of definition of confirmed disability progression. Stratification by absence/presence of Gd enhancing T1 lesions at baseline changed to stratification by age at screening. Geographic origin corrected to geographic region. Subgroup analyses clarified.	Clarity. Health Authority request.
9.4.3 Secondary endpoint(s)	Stratification by absence/presence of Gd enhancing T1 lesions at baseline changed to stratification by age at screening. Geographic origin corrected to geographic region	Clarity. Health Authority request.
9.5 Interim analyses	The futility criteria or boundary will be predefined in the data monitoring committee (DMC) charter.	Correction of error. This definition belongs in the DMC statistical analysis plan (SAP).
10.1.5.4 Relapse Adjudication Committee	Section added. All relapses are to be adjudicated.	Clarity. Health Authority request.
10.2 Appendix 2: Clinical laboratory tests	Removal of requirement of replicate sampling for local and central labs. Removal of requirement for central lab testing, if infeasible.	Simplification.
10.8 Appendix 8: Country-specific requirements	Country specificities in inclusion criteria moved here.	Clarity
Whole document	Minor format changes and typos correction.	Accuracy. Consistency.

10.14.2 Amended protocol 02 (28 August 2020)

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

The primary driver for this amended protocol is to respond to European Health Authorities' requests. The amendment also added Phase 2b results with regard to SAR442168 potential benefit for non-relapsing secondary progressive multiple sclerosis (NRSPMS).

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Title page	Added NCT number.	Administrative change
Section 1.1 Synopsis - objectives and endpoints, Section 1.3 Schedule of Activities (SoA), Section 3 Objectives and Endpoints, and Section 8.5 Pharmacokinetics	Addition of SAR442168 relevant metabolite(s) when referring to the pharmacokinetic (PK) evaluation.	Clarity
Section 1.1 Synopsis - Rationale, Section 2.1 Study rationale	Updated text in these sections.	Health Authorities' request
1.3 Schedule of Activities (SoA)	Addition of hematology, biochemistry, pregnancy test, and Columbia-suicide severity rating scale (C-SSRS) to the follow-up visit.	Health Authorities' request
	Time period for randomization visit relaxed. Additional safety assessments allowed if locally required.	Health Authorities: Coronavirus disease 2019 (COVID-19)
	Repeated vital signs assessment row and checkmark for the same deleted.	Correction
	Due to revision of footnotes, sequencing of footnotes has been updated	Updation
1.3 Schedule of Activities (SoA), 10.4 Appendix 4 Contraceptive guidance and collection of pregnancy information	Telephone reporting of home pregnancy tests allowed.	Health Authorities: COVID-19
2.3 Benefit/risk assessment	Adverse events (AEs) details updated.	Clarity
	Recent information on Bruton's tyrosine kinase (BTK) inhibitors and COVID-19 added.	Health Authorities: COVID-19
4.1 Overall design	"whether or not remaining on IMP" was added to EOS definition	Clarity
4.2.2 Justification for the use of placebo	Added a new sub-heading- Justification for the use of placebo, and relevant text.	Health Authorities' request, clarity

Section # and Name	Description of Change	Brief Rationale
5.1 Inclusion criteria	I09B was updated by adding "women of childbearing potential (WOCBP) must use reliable means of contraception as described in Appendix 4 (Section 10.4) at a minimum. If local requirements are more stringent than what is described in Section 10.4, they should be followed".	Health Authorities' request
5.2 Exclusion criteria	E04: Conditions that may predispose the patient to excessive bleeding clarified.	Health Authorities' request
	E08: Investigator's role in stopping anticoagulant therapies clarified.	
	E18: Deleted the placeholder for already deleted exclusion criteria E18	Clarity
6.3 Measures to minimize bias: randomization and blinding	Contacting of Sponsor for unblinding is removed.	Health Authorities' request
	Data access of "Treating Investigator" clarified.	Health Authorities' request
6.5 Concomitant therapy	"Therapies for MS noted in the exclusion criterion E06 (Section 5.2) are not permitted after randomization while the patient is on study treatment" was added.	Health Authorities' request. Clarity. To address the issues around use of ocrelizumab and siponimod both prior to enrolment and during the trial.
7.1.1 Definitive discontinuation	Role of Investigator in treating participant after definitive discontinuation clarified. Progressive multifocal leukoencephalopathy (PML) added to criteria for definitive discontinuation.	Health Authorities' request
7.1.2 Temporary discontinuation, 7.1.2.1 Rechallenge, 8.0 Study assessments and procedures, 10.1.3 Informed consent process, and 10.12 Appendix 12 Contingency Measures for a regional or national emergency that is declared by a governmental agency.	Contingency measures for a regional or national emergency were added.	Include flexibility and ease of continuation of study during regional or national emergency such as COVID-19.
7.1.2 Temporary discontinuation	Suicidal risk as per C-SSRS added.	Clarity
8.1.2 Magnetic resonance imaging	Added provision for study manual to be provided to all sites for MRI related procedure.	Clarity
	Update of the disclosure of MRI reports to the Treating Investigator.	Health Authorities' request
8.2.5 Suicidal ideation and behavior risk monitoring	Columbia-suicide severity rating scale (C-SSRS) criteria for interruption of study drug clarified.	Health Authorities' request
8.3.4 Regulatory reporting requirements for SAEs	Requirements for reporting of suspected unexpected serious adverse reactions (SUSARs) clarified.	Health Authorities' request

Section # and Name	Description of Change	Brief Rationale
10.6 Liver and other safety: suggested actions and follow-up assessments	Diagnostic workup for PML suspicion added.	Health Authorities' request
10.8 Appendix 8: Country-specific requirements	A new sub-heading was added "10.8.1 Contraception requirements in UK, Germany and Denmark"	Updation
10.11 Appendix 11	Protocol amendment history with the change that the section was updated with amended protocol01 history	Updation
Throughout	Substitution of "long term safety (LTS)" for "long term extension (LTE)" to describe the study that participants will be allowed to roll over to; correction of small errors (eg, comma errors, duplication of words); slight rewordings for clarity, addition of abbreviations, covid-19 changed to COVID-19. New references have been added and sequence numbering have been changed throughout the document.	Correction of errors, clarity

10.14.3 Amended protocol 03 (03 November 2020)

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 primary driver for this amended protocol is to respond to the feedback from Investigators with regard to the inclusion/exclusion criteria.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
1.2 Schema	Addition of footnote to clarify that "Month-1 (D-28 – D-1)" refers to screening period as "Day-28 to Day-1"; "Month 0 (D1)" refers to randomization on Day 1.	Clarification
	M1 corrected to M0. MRI visit at M0 moved to M-1. "Long-term extension study" changed to "Long-term safety study".	Correction of error
1.3 Schedule of activities (SoA)	Timing of visit assessments clarified. Reference to E01 added in footnote "l". Timing of MRI scans clarified (footnote "p" added and duplicated text removed from footnote "o"). Sequencing of footnotes has changed due to the addition of footnote "p".	Clarification
3 Objectives and endpoints	Tertiary/exploratory endpoints: Clarification of the MTR recovery and slowly evolving lesions (SELs) endpoints.	Clarification
5.1 Inclusion criteria	I07: Deletion of existing criteria.	Update and clarification

Section # and Name	Description of Change	Brief Rationale
5.2 Exclusion criteria	E01: Clarification of repetition of TB testing. Clarification of hepatitis testing.	Clarification.
	E06: Changes of the wash-out period header of the table. Removal of requirement for ascertainment of B-cell levels after washout.	Clarification. To allow earlier treatment that may potentially reduce the progression of disability and it is routine practice to continue certain MS treatments for participants on anti-CD20 antibody treatments with low B-cell counts.
	E15: Potential participants unable to complete electronic clinical outcome assessments excluded.	Copyright issue with paper clinical outcome assessment forms.
Section 5.5 Criteria for temporarily delaying administration of study intervention Section 6.1 Criteria for temporarily delaying enrollment and administration of study intervention	Sections added to allow flexibility in case of a regional or national emergency declared by a governmental agency.	Contingency measures for COVID-19.
Section 8 Study assessments and procedures. Section 9.4.6 Other analyses	Reference to contingency measures in the case of a regional or national emergency added.	Contingency measures for COVID-19.
8.1.2 Magnetic resonance imaging	Rescheduling of MRI because of systemic corticosteroid use clarified.	Clarification.
8.2.5 Suicidal ideation and behavior risk monitoring	Alerting families to monitor participants for unusual behavior removed.	Removal of unnecessary constraint.
8.3.9 Adverse event of special interest	Acute hypersensitivity/anaphylaxis removed from list of adverse events of special interest.	Found to be unnecessary because of lack of safety signal in previous studies.
8.3.11 Guidelines for reporting of medication errors	Section removed.	Template section that does not apply to this study was erroneously included.
9.4.5 Other safety analyses	Changes in definition of treatment and post-treatment epochs.	Clarification.
10.1.5.3 Eligibility Adjudication Committee	Clarification of the assessment of disability progression.	Clarification.
10.1.6 Dissemination of clinical study data	Text on disclosure of information added.	Change in company policy.
10.2 Appendix 2: Clinical laboratory tests	Clarification of repetition of TB testing and reference to E01 added.	Clarification.
	Template wording regarding hepatic impairment and cirrhosis removed.	Template wording not applicable to this study.
10.6 Liver and other safety: suggested actions and follow-up assessments	PML assessment clarified.	Clarification.

Section # and Name	Description of Change	Brief Rationale
10.11 Appendix 11: Protocol amendment history	Protocol amendment history updated.	Update.
10.12 Appendix 12: Contingency measures for a regional or national emergency that is declared by a governmental agency	Additional measures added.	Contingency measures for COVID-19.
Throughout the document	Correction of small errors (eg, comma errors, duplication of words); slight rewordings for clarity, addition of abbreviations. New references have been added and sequence numbering has been changed throughout the document. Table of contents has been updated. In-text references updated in relation to update of sections.	Correction of errors, clarity.

10.14.4 Amended protocol 04 (26 July 2021)

This amended protocol (amendment 04) 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 primary reason for this amendment is the availability of new information from drug-drug interaction studies.

Protocol amendment summary of changes

Section # and Name	Description of Change	Brief Rationale
Synopsis 3 Objectives and endpoints	Changed a secondary endpoint from "Change in lymphocyte phenotype subsets in whole blood at the EOS compared to baseline" to "Change in lymphocyte phenotyping subsets in whole blood at the EOS compared to baseline in a subset of participants."	Lymphocyte phenotyping will be assessed only for participants who were sampled before implementation of amended protocol 04.
1.3 Schedule of Activities, footnotes	The footnotes were updated as follows:	
	• Footnote a: To allow a window of 1 additional week (7 days) for screening magnetic resonance imaging (MRI) if required to be rescheduled or repeated (eg, in case of technical issues).	To allow more flexibility for screening MRI and safety laboratory tests.
	• Footnote d: To allow safety laboratory tests at Months 1, 2, 4, and 5 to be done locally if either onsite visit or home health visit is not possible.	To allow more flexibility for the laboratory test assessment.

Section # and Name	Description of Change	Brief Rationale
	• Footnote e: To clarify the study procedures/assessments to be performed if a participant prematurely permanently discontinues treatment with the IMP.	Clarity.
	• Footnote i: Text added: Screening tests for TB are described in Appendix 2 (Section 10.2).	Clarity.
	• Footnote k: Text added: Lipase will be tested at the Screening Visit, then quarterly. Also clarified that additional safety assessments can be performed at local laboratories, if required by local regulations.	Clarity.
	• Footnote l: Text updated as: A serum ß-hCG pregnancy test will be analyzed at a central laboratory at screening and urine pregnancy tests before the first dose of investigational medicinal product (IMP) and at scheduled times during the study.	Clarification of pregnancy tests required during the study.
	• Footnote u: Clarified the details of pharmacodynamic/biomarker samples are not timed at pEOT and EOS.	Timed pharmacodynamic/biomarker sampling is only needed at visits when pharmacokinetic (PK) samples are also collected at these same time points.
	• New footnote y added to add requirement that samples for hematology and biochemistry tests on Day 1 (randomization) must be collected prior to administration of the first IMP dose.	To ensure collection of baseline (pre-IMP) values for the safety laboratory tests.
	• New footnote z added to clarify immunophenotyping/RNA sequencing samples shipping details.	Clarity.
1.3 Schedule of activities, footnote e 8.5 Pharmacokinetics	To add the collection of a pharmacokinetic sample at premature end of treatment (pEOT) visit, if the visit can be scheduled within a maximum 24 hours from the last IMP dose.	To clarify that the PK sample should be collected in case of pEOT only if the visit can be scheduled within 24 hours due to short $t_{1/2}$ after the last IMP dose.
1.3 Schedule of Activities	Immunophenotyping/RNA sequencing (ToleDYNAMIC/optional substudy at selected sites) added.	Additional substudy to investigate immunological changes over the treatment duration.
1.3 Schedule of Activities 8.6 Pharmacodynamics	Updated footnote aa for lymphocyte phenotyping blood collection: Blood sample collection for lymphocyte phenotyping by flow cytometry will be performed in a subset of randomized participants. Participants who did not have a baseline sample collected, will no longer have this test performed; participants who had a baseline sample collected will have a second sample collected at EOT/pEOT.	Lymphocytes phenotyping by flow cytometry will be determined only in a subset of participants. Sample time points have also been reduced. Approximately up to 200 participants will be randomized to SAR442168, as deemed adequate to assess the effect at end of treatment.

Section # and Name	Description of Change	Brief Rationale
3. Objectives and endpoints	Updated the language of a tertiary/exploratory endpoint to add the assessment of cumulative number of new T1-hypointense lesions.	To clarify analysis of T1 hypointense lesions.
4.1 Overall design 4.4 End of study definition	Text was added to the definition of study completion to clarify that a participant is considered to have completed the study if he/she has completed all periods of the study including the EOS visit, whether remaining on IMP or not.	Clarity.
5.1 Inclusion criteria	Inclusion criterion 09: Clarified that a woman of childbearing potential must have a negative highly sensitive pregnancy test at screening and before the first dose of study intervention.	Clarity.
5.2 Exclusion criteria	Exclusion criterion 01: Updated the details of tuberculosis and hepatitis tests.	Clarification of these screening procedures and harmonization with the other studies in the Phase 3 multiple sclerosis (MS) program participants.
	Exclusion criterion 02: Clarified that the Columbia Suicide Severity Rating Scale baseline/screening version will be used for assessment of suicidal ideation	Clarity.
	Exclusion criterion 03: Updated language to clarify Investigator's judgement to be clinically significant in the context of this trial.	Clarity.
	Exclusion criterion 05: Removed standalone albumin criterion.	Clarity.
	Exclusion criterion 06: Added plasma exchange with a 1-month washout period required prior to randomization with MRI and clinical assessment for PML. Updated washout period for fingolimod and natalizumab and in addition provided the washout period for ofatumumab and ozanimod.	Clarification to ensure washout requirement is based on the 5 half-life rule for drug elimination in participants.
5.3.1 Meals and dietary restrictions	Clarification of IMP administration details to specify that a gap of a minimum of 12 hours between 2 doses should be maintained in case the mealtime needs to be changed for IMP administration.	Clarification of the minimum time between 2 IMP doses.
	Removed the restrictions related to consumption of grapefruit or grapefruit juice.	Update based on outcomes from PK results of drug-drug interaction (DDI) studies, investigating concomitant use of SAR442168 with drugs such as itraconazole.
6. Study intervention	Updated language to remove device from the details.	Correction as no device for study intervention.

Section # and Name	Description of Change	Brief Rationale
6.4 Measures to minimize bias: Randomization and blinding	Added text: A participant cannot be randomized more than once in the study.	Clarity.
1.3 Schedule of activities 6.5 Study intervention compliance	Added details of paper diary provision to all participants, to capture all study-related details.	Clarity.
6.6 Concomitant therapy	Added the concomitant use of short-term use (3 to 5 days) of glucocorticoids (eg, for MS relapse treatment or an acute illness) and local corticosteroids (eg, topical, nasal, ocular, otic, intra-articular).	Clarification for use of topical corticosteroids and short-term corticosteroids.
	Updated the language related to use of NSAIDs and symptomatic treatment of MS.	Clarity.
	Added allowed daily maximum dose of aspirin 81 mg/day.	With the extensive safety monitoring during the study and with no bleeding risk identified so far for Tolebrutinib, the Sponsor has relaxed this restriction to improve patient engagement.
5.2 Exclusion criterion 7 6.6 Concomitant therapy 10.9 Appendix 9: Examples of drugs with a potential to change SAR442168 metabolism or absorption	Updated for antacid drugs: Removed the restrictions related to antacid drugs as concomitant use of proton-pump inhibitors (PPI), H2 receptor antagonists, and antacids is allowed.	Update based on outcomes from PK results of drug-drug interaction studies, investigating concomitant use of SAR442168 with drugs such as itraconazole, gemfibrozil, rifampicin and pantoprazole.
	Updated guidance for CYP inhibitors/inducers: Potent and moderate inducers of CYP3A or potent inhibitors of CYP2C8 hepatic enzymes are not permitted throughout the study.	New information from DDI studies.
	Clarified concomitant use of potent CYP3A inhibitors is allowed.	New information from DDI studies.
6.6.1 Rescue medicine	Updated language to clarify options of medicines that participants may choose to receive if they achieve primary endpoint.	Clarity.
7.1.1 Definitive discontinuation	Updated guidance for the participant discontinuation related to laboratory abnormalities.	Clarification for participants who discontinued IMP will have not need PK, biomarker and will have reduced MRI schedules.
	Removed the Data Monitoring Committee (DMC) review of data to determine whether AEs should preclude continued treatment with study intervention.	The DMC has no responsibility to review individual data and advice for IMP discontinuation for a participant.
	To add collection of a pharmacokinetic sample at premature end of treatment (pEOT) visit, if the visit can be scheduled within a maximum 24 hours from the last IMP dose.	To clarify that the PK sample should be collected in case of pEOT only if the visit can be scheduled within 24 hours due to short $t_{1/2}$ after the last IMP dose.

Section # and Name	Description of Change	Brief Rationale
7.1.2 Temporary discontinuation	Text updated to clarify contingency measures in case of temporary intervention discontinuation because of AEs or regional or national emergency declared by a government agency.	Clarity.
8.1.2 Magnetic resonance imaging	Increased the MRI test time from 21 days to 1 month following last course of systemic corticosteroids.	To be consistent with screening MRI requirement and to minimize the risk of corticosteroid impact on MRI findings.
8.1.3.1 Definition of multiple sclerosis relapse	Clarified that MS relapse confirmation will be done by the Relapse Adjudication Committee.	Clarity.
8.2.2 Vital signs	Clarified that blood pressure and heart rate measurements will be assessed in a supine or sitting position	Clarity.
8.2.3 Electrocardiograms	Added allowance of manual calculation of QT interval corrected using Fridericia's formula (QTcF).	To allow some flexibility as some automated electrocardiograms do not provide these parameters. All other electrocardiogram parameters will be automatically provided.
8.3.8 reporting of safety findings from magnetic resonance imaging	Text updated to "In case of clinically relevant findings, relevant information needs to be provided to the Treating Investigator for appropriate safety reporting and also to ensure the appropriate management of the participant's identified safety finding."	Clarity.
8.3.9 Adverse events of special interest	Definition of overdose was clarified.	Clarity.
	Definition of project-specific adverse events of special interest related to infection and hemorrhagic events was updated.	Clarity for the infection and hemorrhagic events to be reported as adverse events of special interest.
	Thrombocytopenia, platelet count updated from <100 000/mm^3 to <75 000/mm^3	Modified to align with CTCAE guidelines for thrombocytopenia
8.4 Treatment of overdose	Corrected the language to clarify that plasma sample for PK analysis is to be obtained within 24 hours of the last documented IMP dose (rather than the last dose of SAR442168).	Correction of error.
8.6 Pharmacokinetics	Updated the section for number of PK samples: The five scheduled samples will be collected. Additional PK samples may be collected (eg, for retest or if clinically indicated).	Clarity; no change in number of samples.
10.2 Appendix 2: Clinical laboratory test	Added details of the serology tests for hepatitis B and C.	To harmonize with other protocols in Phase 3 MS program.
	Table 5, footnote a was updated to clarify the clinical laboratory abnormalities for liver injury.	Clarity.
	Table 5, footnote b was updated to include serum pregnancy test at screening.	Clarification of pregnancy test.
	Removed the cross-reference to unblinding section (Section 6.3).	Clarification of error.

Section # and Name	Description of Change	Brief Rationale
10.4 Appendix 4: Contraceptive guidance and collection of pregnancy Information	Clarified the definition of high follicle-stimulating hormone level: >30 IU/L or as per laboratory reference ranges.	Clarification of follicle-stimulating hormone level for postmenopausal status confirmation as not all laboratories use the threshold of 30 IU/L.
10.6 Appendix 6: Liver and other safety: required actions and follow up assessments	Table 6 was updated for clinical history manifestations.	Simplification.
	Updated 'Increase in ALT' flowchart.	To provide clear guidelines for safety of participants in case of elevated ALT or reduced platelet counts.
	Updated algorithm for thrombocytopenia.	To align with CTCAE guidelines for thrombocytopenia.
10.8.2 Country-specific differences for China	Added text to clarify that China will not participate in pharmacodynamic, genetic, and biomarker testing.	Previously omitted in error.
10.10.2 Study procedures	Updated the wording associated with serum creatinine test from "efficacy assessment" to "other safety assessments.	Correction of error.
10.11 Appendix 11 Immunophenotyping/ToleDYNAMIC substudy	Added appendix for immunophenotyping substudy.	Additional substudy to investigate immunological changes over the treatment duration
Throughout the document	Correction of small errors (eg, comma errors, duplication of words); slight rewordings for clarity, addition of abbreviations. New references have been added and sequence numbering has been changed throughout the document. Table of contents has been updated. In-text references updated in relation to update of sections.	Correction of errors, clarity.

10.14.5 Amended protocol 05 (21 December 2021)

This amended protocol (amendment 05) was 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 primary reason for this amendment was to facilitate operational feasibility and reduce complexity, without compromising study integrity.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Document History	Countries impacted by amendment changed for Amended protocol 02.	Correction of error.
1.3 Schedule of activities	PK sampling added to pEOT visit. Footnote a: additional week of flexibility allowed for broadened scheduling. Footnote c: added references to Section 7.1 and the Study Reference Manual. Footnote t updated, added to M9 PK sampling. Footnote u: clarification of pharmacodynamics and biomarkers sampling.	Correction of error. Additional flexibility in case of logistical issues. Clarification.
5.2 Exclusion criteria	E 01: Text inserted to allow for rescreening after TB treatment.	Flexibility.
6.4 Measures to minimize bias: randomization and blinding 8.1 Efficacy assessments 8.1.1 Expanded Disability Status Scale 8.1.4 Timed 25-foot walk test 8.1.5 9-hole peg test 8.1.6 Cognitive tests	Requirement for Examining Investigator/rater to perform all clinical efficacy tests removed. Blinding requirements revised for certain data such as participant visit number.	Update to facilitate operational feasibility and reduce complexity, without compromising study integrity.
6.5 Study intervention compliance	Proper placement of tear-off label removed.	Correction of error. This study has no tear-off label.
6.6 Concomitant therapy	Updated the language related to use of NSAIDs.	Clarification.
8.1.1.1 Confirmed disability progression	Clarification of timing of observation of EDSS scores used for confirmed disability progression.	Clarification.
8.1.2 Magnetic resonance imaging	Clarification that full MRI report viewing restriction to one/year is applicable during the intervention period.	Clarification.
8.1.8 Actigraphy	Section 8.1.8 moved to appendices. Reference to Study Reference Manual added. Timing of requirement for wearing device clarified.	Compliance with requirement that substudies be listed as appendices. Clarification.
8.2.1 Physical examinations	Clarification of reporting of AEs.	Clarification.
Throughout the document	Reformatting of existing content when necessary. Minor, editorial, stylistic changes as necessary. Update table of contents, section numbers, references as necessary.	Update in accordance with Sponsor's standards.

10.14.6 Amended Protocol 06 (23 May 2022)

This amended protocol (amendment 06) 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 primary driver for this amended protocol is to update liver related exclusion criteria and monitoring to mitigate risk of drug-induced liver injury.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Cover page	Sponsor's legal address updated.	Update.
1.1 Synopsis 10.1.5. Committees structure	Independent Hepatology Assessment Committee subsection added.	To evaluate on an ongoing basis cases of potential liver injury.
1.3 Schedule of activities (SoA) 5.2 Exclusion criteria (E 05)	Iron panel at screening and corresponding exclusion criteria for genetic liver diseases added.	To mitigate the risk of DILI.
10.2 Appendix 2: Clinical laboratory tests (Table 5)	Abbreviations under the SoA and Table 5 updated.	Update.
2.3 Benefit/Risk Assessment	Text related to drug-induced liver injury identified in an ongoing Phase 3 trial added.	Update.
5.2 Exclusion criteria (E 02) 5.3.2 Caffeine, alcohol, and tobacco	Exclusion criteria for alcohol consumption added. Related recommendation for alcohol consumption during study and PK/PD visits updated.	To mitigate the risk of DILI.
1.3 Schedule of activities (SoA) 5.2 Exclusion criteria (E 05) 10.6 Appendix 6: Liver and other safety: actions and follow-up assessments	Liver and safety monitoring plan updated. Hepatic monitoring and hepatic exclusion criteria added. ALT algorithm and related instructions updated	To mitigate the risk of DILI. Updated monitoring request as per new exclusion threshold for ALT level.
10.14 Appendix 14: Protocol amendment history	Updated.	Update.
Throughout the document	Reformatting of existing content when necessary. Minor, editorial, stylistic changes as necessary. Updated table of contents, section numbers, references, abbreviations as necessary.	Update in accordance with Sponsor's standards.

10.14.7 Amended protocol 07 (13 September 2022)

This amended protocol (amendment 07) 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 rationale for this protocol amendment is to further reduce the risk of drug-induced liver injury (DILI) by increasing the intensity of liver monitoring.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Cover page	Sponsor disclaimer added.	Update.
1.3 Schedule of activities (SOA)	Increased liver laboratory monitoring frequency in the first year after the start of the IMP. Footnote 'l' updated. Albumin' added in footnote 'k'. Footnote 's' next to 'Pharmacokinetics', 'Pharmacogenetics', and 'Pharmacodynamics/biomarkers' removed.	To reduce the risk of DILI. Correction of error. Correction of error.
6.6.1 Rescue medicine	Increased liver laboratory monitoring added for participants switching to open-label SAR442168 treatment after 6-month CDP confirmation.	To reduce the risk of DILI.
10.6 Appendix 6: Liver and other safety: actions and follow-up assessments	Increase in ALT algorithm flowchart and related instructions updated	Update.
10.14 Appendix 14: Protocol amendment history	Updated.	Update.
Throughout the document	Reformatting of existing content when necessary. Minor, editorial, stylistic changes as necessary. Updated table of contents, section numbers, references, abbreviations as necessary.	Update in accordance with Sponsor's standards.

10.14.8 Amended protocol 08 (14 December 2022)

This amended protocol (amendment 08) 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 rationale for this protocol amendment is to clarify information about drug-induced liver injury (DILI) and update the ALT increase algorithm in relation to the risk of DILI.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
1.2 Schema	Number of participants removed and replaced by the ratio in Figure 1 - Graphical study design.	Clarification.
9.2 Sample size determination	Updated to clarify that with a reduced sample size, study power can be maintained by extending follow-up duration.	Sample size is adjusted based on actual recruitment and event rates. The target number of events is unchanged.
1.3 Schedule of activities (SOA)	Removal of actigraphy wording from footnote 'r'.	Update.
10.12 Appendix 12: Actigraphy substudy	Updated to allow performing actigraphy in participants from enrollment into the substudy instead of screening.	
2.3 Benefit/risk assessment	Updated information about drug-induced liver injury.	Update.
10.1.6 Dissemination of clinical study data	Addition of 'euclinicaltrials.eu' in the list of websites where Sanofi shares information about clinical trials. 'Clinicalstudydatarequest.com' replaced with 'vivli.org'.	Update.
10.6 Appendix 6: Liver and other safety: actions and follow-up assessments	Related instructions of the increase in ALT algorithm updated.	Update.
10.14 Appendix 14: Protocol amendment history	Updated.	Update.
Throughout the document	Reformatting of existing content when necessary. Minor, editorial, stylistic changes as necessary. Updated table of contents, section numbers, references, abbreviations as necessary.	Update in accordance with Sponsor's standards.

10.14.9 Amended protocol 09 (12 July 2023)

This amended protocol (amendment 09) 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 rationale for this protocol amendment is to incorporate country-specific guidelines for France.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Document history	Countries impacted by amendment added for Amended protocol 02.	Correction of error.
10.8.3 Country-specific differences for France	Section created.	Health Authority request.
10.14 Appendix 14: Protocol amendment history	Updated.	Update.
11 References	Updated.	Update.
Throughout the document	Reformatted existing content when necessary. Minor, editorial, stylistic changes as necessary. Updated table of contents, section numbers, references, abbreviations as necessary.	Update in accordance with Sponsor's standards.

10.14.10 Amended protocol 10 (28 September 2023)

This amended protocol (amendment 10) 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 rationale for this protocol amendment is to clarify the language and requirements for the use of open-label SAR442168 in participants who have achieved 6-month confirmed disability progression, and to update the testing requirements in the "Increase in ALT algorithm" in accordance with the Council for International Organization of Medical Sciences (CIOMS) working group on DILI consensus report.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis	Changed the subtitle of "Post-trial access to study medication" to "Long-term safety study".	Clarification.
1.1 Synopsis, 1.3 Schedule of activities (SoA), and 6.8 Intervention after the end of the study	Revised "will be offered" to "may be offered".	Clarification.
1.1 Synopsis and 9.4.2 Primary endpoint	Added "baseline EDSS score" and "baseline Gd-enhancing T1 lesions (0, ≥1)" as a covariate of the Cox proportional hazards model.	Update.
	Updated the censoring and imputation algorithm for analyzing the time to onset of 6-month CDP.	Update primary ITT analyses based on the feedback from the health authority.
1.1 Synopsis and 9.4.3 Secondary endpoint(s)	Added "baseline EDSS score" and "baseline number of T2 lesions" as covariates and update the offset variable based on the different duration of times between MRI scans.	Update secondary endpoint analyses.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of activities (SoA)	Updated footnote 'e' to include reference to the Study Manual. Updated footnote 'l' to include permitted time window for liver function tests.	Clarification.
2.2 Background 2.3 Benefit/risk assessment	Changed "T2 phase rims" to "paramagnetic rim lesions".	Update.
2.3 Benefit/risk assessment	Removed "all" for the identified risk for tolebrutinib and removed "to mitigate risk of hepatic injury". Updated "drug-induced liver injury (DILI)" to "DILI, including severe DILI (risk of liver transplantation or death), as an identified risk".	Update to keep consistency with the Investigator's Brochure.
4.1 Overall Design	Replaced "rescued" with "initiated". Removed "as rescued".	Clarification.
6.6.1 Open-label treatment	Replaced the term 'rescue treatment' with 'open-label treatment'. Replaced the term "rescue medication" with "relapse treatment". Updated requirements related to the exclusion criteria for participants switching to open-label treatment.	Clarification. Clarification.
7.1.1 Definitive discontinuation	Replaced "should be considered" with "is required".	Clarification.
8.5 Pharmacokinetics	Clarified PK sample collection/storage requirements and recommendations for liver and other safety events. Added cross-reference to Section 10.6 for more details.	Clarification.
8.11 Use of biological samples and data for future research	Added details about the future use of participant's biological samples and data.	To keep consistency with ICF and Sponsor standards related to data privacy guidelines.
9.4.2 Primary endpoint	Updated the subgroup analyses on the primary endpoint, including geographic region, baseline EDSS score, prior disease modifying therapy use, and duration since relapsing-remitting multiple sclerosis (RRMS) symptom onset.	Clarification on the subgroup factors.
9.4.3 Secondary endpoint(s)	Updated the handling of the impact of deviation from normality. Updated the estimate as annualized rate based on the different duration of times between MRI scans.	Clarification. Update the secondary endpoint analyses.
10.1.3 Informed consent process	Clarification of informed consent process.	To keep consistency with ICF and Sponsor standards related to data privacy guidelines.

Section # and Name	Description of Change	Brief Rationale
10.1.4 Data protection	Sponsor's data privacy and protection responsibilities clarified. Data protection for professionals involved in the study clarified.	To be compliant with data privacy guidelines.
10.3.3 Recording and follow up of AE and/or SAE	Updated requirement for reporting SAEs in case of life-threatening or death events.	Clarification.
10.6 Appendix 6: Liver and other safety: actions and follow-up assessments	Increase in ALT algorithm related assessments updated.	Update, for consistency with the CIOMS consensus report.
10.8.3 Country-specific provisions for France and Japan	Added Japan to this section.	Health authority request.
10.8.4 Country-specific provisions for Japan	Section created.	Health authority request.
10.9 Appendix 9: Example of drugs with a potential to change SAR442168 metabolism or absorption	Removed "(per the lists of the Drug Interaction Database Program of the University of Washington)" and "modafinil".	Correction of error as, according to the labels, modafinil is a weak CYP3A inducer, and therefore not prohibited; also, only keeping the recommendation for the sites to refer to the drug label for metabolic interactions.
10.14 Appendix 14: Protocol amendment history	Updated.	Update.
11 References	Updated.	Update.
Throughout the document	Reformatting of existing content when necessary. Minor, editorial, stylistic changes as necessary. Updated table of contents, section numbers, references, abbreviations as necessary.	Update in accordance with Sponsor's standards.
	Replaced the word 'rescue treatment' with 'open-label treatment'.	Clarification.

10.14.11 Amended protocol 11 (20 November 2023)

This amended protocol (amendment 11) 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 rationale for this protocol amendment is to clarify the liver function monitoring requirements, update the testing requirements in the "Increase in ALT algorithm", and update the concomitant medications that are prohibited during the conduct of the study as per health authority request.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis, 9.4.3 Secondary endpoints	Clarification of statistical descriptions.	Clarification.
1.3 Schedule of activities (SOA)	Safety follow-up visit period changed from 4 to 8 weeks to 4 weeks.	Update.
6.6.1 Open-label treatment	Liver function test monitoring provided.	Update.
10.6 Appendix 6: Liver and other safety: actions and follow up assessments	Liver function test monitoring guidance provided. Increase in ALT algorithm related assessments updated. Rechallenge restrictions updated.	Update.
10.8.5 Country specific provisions for US	New section added to address liver function monitoring for participants restarting IMP after discontinuing due to partial clinical hold.	Update.
10.8.6 Country specific provisions for US, Israel, and sites under FDA partial clinical hold conditions	New section added to reflect the prohibited use of CYP3A and CYP2C8 inhibitors and the restriction of grapefruit/grapefruit juice (a CYP3A4 inhibitor).	Update.
10.9 Appendix 9: Example of drugs with a potential to change SAR442168 metabolism or absorption	Update to provide guidance to US, Israel, and any other sites that may be under FDA partial clinical hold.	Update to provide guidance.
Throughout the document	Reformatting of existing content when necessary. Minor, editorial, stylistic changes as necessary. Updated table of contents, section numbers, abbreviations as necessary.	Update in accordance with Sponsor's standards.

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