AMENDED CLINICAL TRIAL PROTOCOL 11

Protocol title:	**A Phase 3, randomized, double-blind efficacy and safety study comparing SAR442168 to teriflunomide (Aubagio®) in participants with relapsing forms of multiple sclerosis (GEMINI 2)**
Protocol number:	**EFC16034**
Amendment number:	**11**
Compound number (INN/Trademark):	**SAR442168 (Tolebrutinib/not applicable)**
Study phase:	**Phase 3**
Short title:	**RMS study of BTK inhibitor tolebrutinib (SAR442168) (GEMINI 2)**
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:	2020-000644-55
NCT:	NCT04410991
WHO:	U1111-1238-1373
Other:	Not applicable

Approval Date: 20-Dec-2023 Total number of pages: 133

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PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, version
Amended Clinical Trial Protocol 11	All	20 December 2023, version 1 (electronic 15.0)
Amended Clinical Trial Protocol 10	All	17 November 2023, version 1 (electronic 14.0)
Amended Clinical Trial Protocol 09	France	12 July 2023, version 1 (electronic 13.0)
Amended Clinical Trial Protocol 08	All	12 December 2022, version 1 (electronic 11.0)
Amended Clinical Trial Protocol 07	All	13 September 2022, version 1 (electronic 10.0)
Amended Clinical Trial Protocol 06	All	23 May 2022, version 1 (electronic 9.0)
Amended Clinical Trial Protocol 05	All	18 November 2021, version 1 (electronic 8.0)
Amended Clinical Trial Protocol 04	All	14 April 2021, version 1 (electronic 6.0)
Amended Clinical Trial Protocol 03	All	28 September 2020, version 1 (electronic 5.0)
Amended Clinical Trial Protocol 02	Belgium, Czech Republic, Greece, Hungary, Latvia, Netherlands, Norway, Portugal, Slovakia, Spain	24 August 2020, version 1 (electronic 4.0)
Amended Clinical Trial Protocol 01	All	07 May 2020, version 1 (electronic 1.0)
Original Protocol		28 February 2020, version 1 (electronic 1.0)

Amended protocol 11 (20 December 2023)

This amended protocol (amendment 11) 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 include liver function test monitoring guidance previously in the study manual and update the co-medication guidance 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.
10.6 Appendix 6: Liver and other safety: actions and follow-up assessments	Liver function test monitoring guidance provided.	Update.
10.8 Appendix 8A: Examples of drugs with a potential to change SAR442168 metabolism	Removed the reference to www.druginteractioninfo.org	Only keeping the recommendation for the sites to refer to the drug label for metabolic interactions.
	Removed 'modafinil' from the list of moderate CYP3A inducers.	Correction of error as, according to the label, modafinil is a weak CYP3A inducer, and therefore not prohibited.
	Removed 'deferasirox' from the list of potent CYP2C8 inhibitors. Table 7: removed 'rifabutin' from the list of potent CYP3A inducers. Table 8: 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.
	Updated to provide guidance to the US, Brazil, Israel, and any other sites that may be following FDA partial clinical hold.	Update to provide guidance.
10.11.4 Country-specific provisions for the US, Brazil, Israel, and sites following 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.
10.14 Appendix 12: 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.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Protocol title: A Phase 3, randomized, double-blind efficacy and safety study comparing SAR442168 to teriflunomide (Aubagio®) in participants with relapsing forms of multiple sclerosis (GEMINI 2)

Short title: RMS study of BTK inhibitor tolebrutinib (SAR442168) (GEMINI 2)

Rationale:

Despite a number of disease-modifying therapies (DMTs) approved for relapsing multiple sclerosis (RMS), there is still a need for additional efficacious treatments, especially treatments that target disease mechanisms in the central nervous system (CNS) behind a closed or partially closed blood-brain barrier. Current treatments cannot ensure long-term suppression of multiple sclerosis (MS) inflammatory activity including relapse and new magnetic resonance imaging (MRI) lesion control. Some medications delay RMS progression, but the disease may still not be completely controlled, and it affects life activities and wellbeing. Even the most recent high-efficacy DMTs mainly act on adaptive immunity in the periphery with only modest ability to slow neuroinflammatory and neurodegenerative processes, as demonstrated by recent studies in progressive MS (1, 2). Therefore, development of MS treatments with new modes of action is of interest.

In addition to the current focus on suppressing B- or T-cell mediated immunity in MS treatments, there is mounting evidence that innate immunity, including myeloid lineage bone-marrow-derived monocytes, macrophages, and CNS-resident microglial cells, is responsible for many of the neurodegenerative aspects of MS (3, 4). Modulation of innate immunity could therefore provide additional benefit in treatment of MS. SAR442168 shows in vitro capacity to inhibit Bruton's tyrosine kinase (BTK), which is responsible for downstream signaling in macrophages and microglial cells and is expected to act on these targets in the brain due to its ability to penetrate the blood-brain barrier.

Based on this knowledge of the mode of action of SAR442168, its ability to penetrate the blood-brain barrier, and available evidence from nonclinical and healthy volunteer studies, SAR442168 is expected to prove itself as a high-efficacy disease-modifying treatment for MS.

The ability of SAR442168 to reduce formation of new, active brain lesions in MS was assessed in a Phase 2b dose-finding trial in participants with RMS (DRI15928). This radiographic outcome has been established as a highly reliable predictive biomarker for clinical efficacy in pivotal studies in MS including Phase 3 RMS studies (5). The dose selected on the basis of the SAR442168 effect on gadolinium- (Gd-) enhancing T1-hyperintense lesions on MRI in the Phase 2b trial will be used for this and other Phase 3 trials with SAR442168 in MS.

The goal of this Phase 3 study is to assess SAR442168 in the RMS population. Efficacy will be assessed by adjudicated relapse rate, disability progression, and MRI findings of disease activity (Gd-enhancing lesions and new/enlarging T2-hyperintense lesions). Together with evaluation of other secondary and exploratory endpoints, this study will provide a comprehensive evaluation of the efficacy and safety of SAR442168 in the RMS population.

Objectives and endpoints

Objectives	Endpoints
Primary	
• To assess efficacy of daily SAR442168 compared to a daily dose of 14 mg teriflunomide (Aubagio) measured by annualized adjudicated relapse rate (ARR) in participants with relapsing forms of MS	• ARR during the study period assessed by confirmed protocol-defined adjudicated relapses
Secondary	
• To assess efficacy of SAR442168 compared to teriflunomide (Aubagio) on disability progression, magnetic resonance imaging (MRI) lesions, cognitive performance and quality of life	• Time to onset of confirmed disability worsening (CDW), confirmed over at least 6 months, defined as follows: - increase of ≥1.5 points from the baseline Expanded Disability Status Scale (EDSS) score when the baseline score is 0, OR - increase of ≥1.0 point from the baseline EDSS score when the baseline score is 0.5 to ≤5.5, OR - increase of ≥0.5 point from the baseline EDSS score when the baseline score is >5.5 • Time to onset of CDW, assessed by the EDSS score and confirmed over at least 3 months • 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 End-of-Study (EOS) visit and number of new and/or enlarging T2-hyperintense lesions by visit over time • Total number of new gadolinium- (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 • Time to confirmed disability improvement (CDI), defined as a ≥1.0 point decrease on the EDSS from the baseline EDSS score confirmed over at least 6 months • Percent change in brain volume loss as detected by brain MRI scans at the EOS compared to Month 6 • Change in cognitive function at the EOS compared to baseline as assessed by the Symbol Digit Modalities Test (SDMT) • Change in cognitive function at the EOS compared to baseline as assessed by the CVLT-II, where available • Change in Multiple Sclerosis Quality of Life 54 (MSQoL-54) questionnaire score at the EOS compared to baseline

Objectives	Endpoints
• To evaluate the safety and tolerability of daily 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 pharmacodynamics (PD) of SAR442168	• Change in plasma neurofilament light chain (NfL) levels at the EOS compared to baseline, where available • Changes in serum immunoglobulin level at the EOS compared to baseline • Change in serum Chi3L1 levels at the EOS compared to baseline

Overall design:

This is a Phase 3, randomized, double-blind, double-dummy, 2-arm, active-controlled, parallel group, multicenter, event-driven (6-month confirmed disability worsening [CDW]) trial with a variable treatment duration ranging from approximately 18 to 36 months.

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

Number of participants:

Approximately 1200 people will be screened to achieve approximately 900 (±10%) participants randomly assigned to the study intervention with a total sample size of at least 1800 patients across the 2 RMS studies of identical design (EFC16033 and EFC16034).

Intervention groups and duration:

Participants will be randomly assigned at a 1:1 ratio to receive the 60 mg selected dose (established from dose-finding Study DRI15928) of oral SAR442168 daily as well as a placebo to match the teriflunomide tablet or 14 mg oral teriflunomide as well as a placebo to match the SAR442168 tablet daily. Randomization will be stratified by the Expanded Disability Status Scale (EDSS) score at screening (<4 versus ≥4) and geographic region (US versus non-US).

Study intervention(s)

Investigational medicinal product

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

Investigational medicinal product

- Formulation: teriflunomide tablet
- Route of administration: oral
- Dose regimen: 14 mg once daily

Investigational medicinal product

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

Investigational medicinal product

- Formulation: placebo to match teriflunomide tablet
- Route of administration: oral
- Dose regimen: once daily

Noninvestigational medicinal products

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

Noninvestigational medicinal products

- Formulation: cholestyramine
- Route(s) of administration: oral
- Dose regimen: 8 g 3 times daily for 11 days for accelerated elimination procedure (4 g 3 times daily for 11 days in case of intolerance). The teriflunomide local label should be followed.

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 depending upon the type of surgery and the risk of bleeding.

Devices

Not applicable.

Post-trial access to study medication

After the end of this study, participants who successfully complete the trial and are taking the IMP until the end of the trial will be offered the opportunity to participate in a long-term safety (LTS) study for an additional 2 years, or until the drug is approved in their respective country, whichever comes first. Details of the LTS study will be described in a separate protocol. Post-trial access for more than 2 years may be considered if mandated by local regulations.

Statistical considerations:

- **Primary analysis:**

The purpose of the primary analysis of annualized adjudicated relapse rate (ARR) is to assess the efficacy of SAR442168 in an intent to treat (ITT) setting. In this primary approach, off-treatment events of participants who prematurely discontinue study intervention will be included for analysis per the ITT principle. Participants who permanently discontinue study intervention will be asked and encouraged to return to the clinic for all remaining study visits. In this case, all events during the planned treatment period will be included and the observation duration will be from randomization to EOS. If a participant withdraws from the study prior to the common study end date, all observed events up to the last contact date will be included in the analysis, and the observation duration will be from randomization to the last contact date. No imputation will be performed for the unobserved events that may happen after study discontinuation. This estimand compares the rate of ARR for the participants randomized to SAR442168 versus teriflunomide, regardless of what treatment participants actually received. It assesses the benefits of the treatment policy or strategy relative to teriflunomide.

Annualized adjudicated relapse rate will be analyzed using a negative binomial regression model. The model will include the total number of adjudicated relapses occurring during the observation period as the response variable, with treatment group, EDSS score at screening (<4, ≥4), and geographic region (US, non-US) as covariates. Log transformed observation duration will be the offset variable. The estimated ARR for each treatment group and corresponding 2-sided 95% confidence interval will be derived from the negative binomial model. The relative reduction in ARR with SAR442168 compared to teriflunomide, its 2-sided 95% confidence interval and p-value will be provided.

- **Analysis of secondary endpoints:**

The primary analysis of time to onset of 6-month CDW will be based on the pooled data across Studies EFC16033 and EFC16034 in the ITT population. The time to onset of 6-month CDW will be analyzed by a Cox proportional hazards model with terms for treatment, EDSS score at screening (<4, ≥4), geographic region (US, non-US) and study. A log-rank test stratified by EDSS score at screening (<4, ≥4), geographic region (US, non-US), and study to compare SAR442168 to teriflunomide 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 CDW over time. The proportion of participants with events at given time points (eg, Month 24) will be calculated using the Kaplan-Meier estimates.

In this primary ITT analysis:

- For participants who complete the study without an initial disability worsening or prematurely discontinue the study before 6-month confirmation of an onset of disability worsening, the participant's event time will be censored at the date of last EDSS assessment.

- For participants who have an initial onset of disability worsening but reach the common study end date prior to 6-month confirmation, the event status of the participant will be determined by an imputation approach. 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 EDSS score at screening (<4, ≥4) and geographic region (US, non-US) will be used as the imputation model within each treatment of each study population. A multiple imputation approach will be used to summarize the results. Details will be provided in the Statistical Analysis Plan (SAP).

All EDSS assessments (with or without relapse) will be used to determine onset of disability worsening. However, for the purpose of confirmation, only EDSS score(s) measured more than 30 days after the onset of a confirmed relapse and in the absence of an ongoing relapse will be used. In case of such MS relapse, the next quarterly EDSS assessment will be used for CDW confirmation. The minimum increase in score required for worsening must also be maintained for any non-confirmatory (ie, intervening) EDSS assessment(s) between the initial (onset) and confirmation EDSS scores.

Multiplicity consideration

To control the overall type 1 error rate, a hierarchical testing procedure will be applied to the primary and secondary efficacy endpoints (Section 3). If the primary endpoint has met significance, a selective set of secondary efficacy endpoints will be tested in a hierarchical order at $\alpha = 0.05$ (2-sided) that will be prespecified in the SAP. For the time to onset of the CDW endpoint, the main analysis will be based on pooled data from this study and Study EFC16033.

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, safety scales, electrocardiograms (ECGs), and vital signs). TEAEs are defined as 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.

Interim analysis:

No formal efficacy interim analysis is planned.

Data Monitoring Committee: Yes

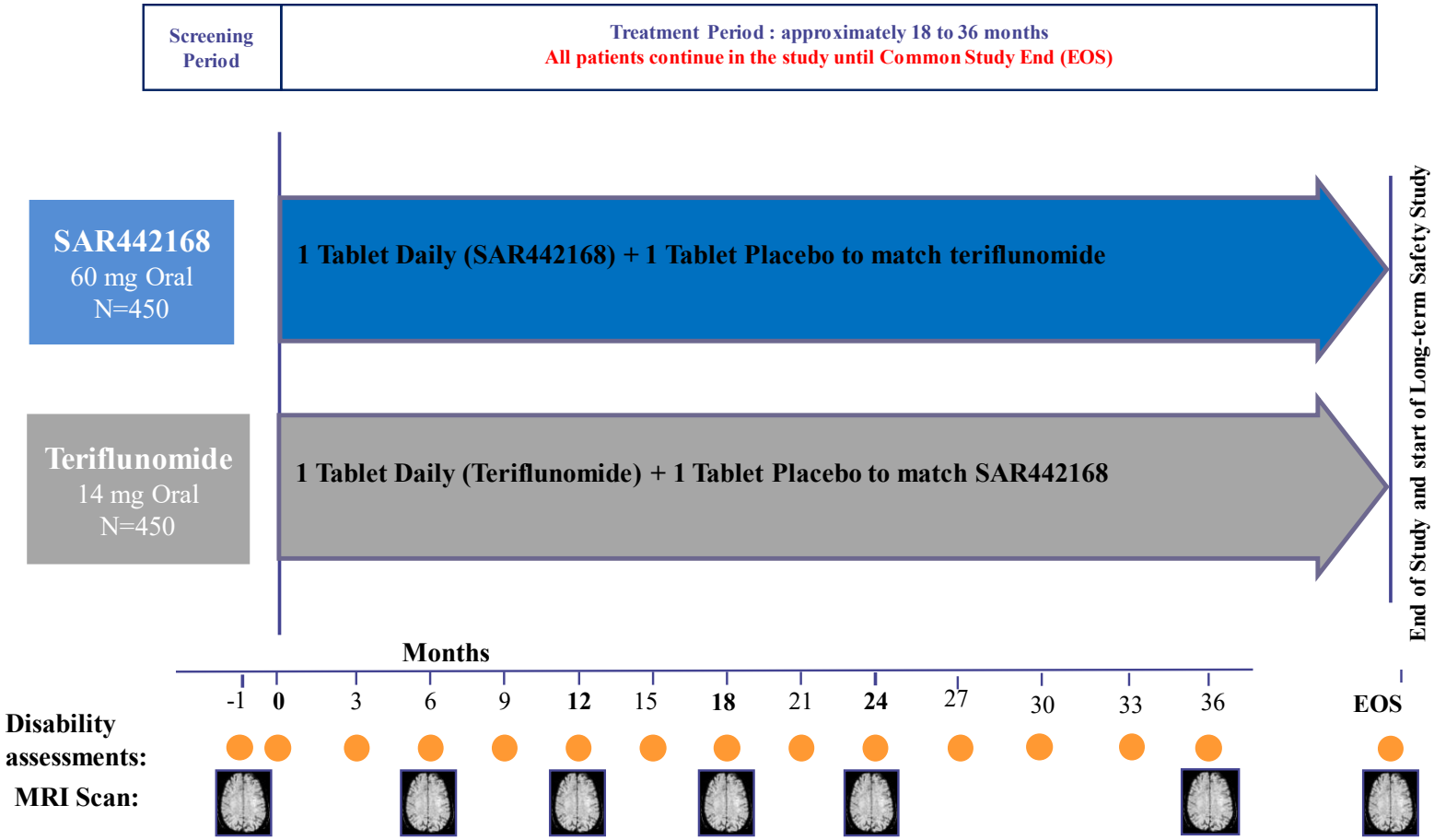
Scientific Advisory Committee: Yes

Relapse Adjudication Committee: Yes

Independent Hepatology Assessment Committee: Yes

1.2 SCHEMA

Figure 1 - Graphical study design



Abbreviations: 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	Year 1 (M12)[b]												From M15 to EOS[b]		Only for participants who prematurely discontinue IMP	For all participants	Only for participants who completed treatment to 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	Quarterly visits (M15, M18, M21, M24, M27, M30, M33, M36…)	Semi-annual visits (M18, M24, M30, M36…)	pEOT[e]	EOS[f] "Common study end date" visit	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…	V12, V14, V16, V18…	pEOT[e]	EOS	FUV
Informed consent	X																		
Demography	X																		
Inclusion/ exclusion criteria	X	X																	
Medical/ surgical history	X																		
Prior/ concomitant medications[g]	←==========→																		

Procedure	Screening[a]	Randomization /Start of IMP	Year 1 (M12)[b]												From M15 to EOS[b]		Only for participants who prematurely discontinue IMP	For all participants	Only for participants who completed treatment to 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…	V12, V14, V16, V18…	pEOT[e]	EOS	FUV
Randomization		X																	
IRT contact	X	X						X		X		X		X	X	X	X	X	X
IMP dispensation[e]		X						X		X		X		X	X	X			
IMP compliance								X		X		X		X	X	X	X[e]	X	
Paper diary dispensation/collection		X						X		X		X		X	X	X	X	X	
Safety[h]																			
Physical examination[i] and vital signs	X	X						X		X		X		X	X	X	X	X	X

Procedure	Screening[a]	Randomization /Start of IMP	Year 1 (M12)[b]												From M15 to EOS[b]		Only for participants who prematurely discontinue IMP	For all participants	Only for participants who completed treatment to 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…	V12, V14, V16, V18…	pEOT[e]	EOS	FUV
Height	X																		
Body weight	X	X						X		X				X		X	X	X	X
Serology tests for hepatitis B, C (HIV and other infectious diseases, if required locally)	X																		

Procedure	Screening[a]	Randomization /Start of IMP	Year 1 (M12)[b]												From M15 to EOS[b]		Only for participants who prematurely discontinue IMP	For all participants	Only for participants who completed treatment to 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…	V12, V14, V16, V18…	pEOT[e]	EOS	FUV
TB/ QuantiFERON® TB Gold test or equivalent[i]	X																		
Body temperature	X	X						X		X		X		X	X	X	X	X	X
12-lead ECG	X							X		X		X		X		yearly	X	X	
Hematology, biochemistry[k]	X	X[w]		X		X		X	X	X		X		X	X	X	X	X	X
Liver function tests[l]			X		X		X				X		X						

Procedure	Screening[a]	Randomization /Start of IMP	Year 1 (M12)[b]												From M15 to EOS[b]		Only for participants who prematurely discontinue IMP	For all participants	Only for participants who completed treatment to 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…	V12, V14, V16, V18…	pEOT[e]	EOS	FUV
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	

Procedure	Screening[a]	Randomization /Start of IMP	Year 1 (M12)[b]												From M15 to EOS[b]		Only for participants who prematurely discontinue IMP	For all participants	Only for participants who completed treatment to 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…	V12, V14, V16, V18…	pEOT[e]	EOS	FUV
Pregnancy test (if applicable)[m, n]	X	X		X[n]				X	X[n]	X		X		X	X	X[n]	X	X	X
Serum FSH[o]	X																		
Suicidality assessment by C-SSRS	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	
Timed 25-foot walk test		X						X		X		X		X	X	X	X	X	

Procedure	Screening[a]	Randomization /Start of IMP	Year 1 (M12)[b]												From M15 to EOS[b]		Only for participants who prematurely discontinue IMP	For all participants	Only for participants who completed treatment to 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	Quarterly visits (M15, M18, M21, M24, M27, M30, M33, M36…)	Semi-annual visits (M18, M24, M30, M36…)	pEOT[e]	EOS[f] "Common study end date" visit	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…	V12, V14, V16, V18…	pEOT[e]	EOS	FUV
9-hole peg test		X						X		X		X		X	X	X	X	X	
SDMT and CVLT-II, where available[p]		X						X		X		X		X	X	X	X	X	
Basic or expanded MRI scan[q]	X[q]									X				X		M18, M24, M36	X	X	
Clinical outcome assessment[r]																			
MSQoL-54		X								X				X		X	X	X	
EQ-5D-5L		X								X				X		X	X	X	

Procedure	Screening[a]	Randomization /Start of IMP	Year 1 (M12)[b]												From M15 to EOS[b]		Only for participants who prematurely discontinue IMP	For all participants	Only for participants who completed treatment to 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	Quarterly visits (M15, M18, M21, M24, M27, M30, M33, M36…)	Semi-annual visits (M18, M24, M30, M36…)	pEOT[e]	EOS[f] "Common study end date" visit	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…**	**V12, V14, V16, V18…**	**pEOT[e]**	**EOS**	**FUV**
Pharmacogenetics[s]																			
DNA sample[u]		X																	
Pharmacodynamics/biomarkers[s]																			
Blood sample for archiving[v]	X																		
Plasma samples (NfL), serum samples (Chi3L1)[t]		X						X		X				X		yearly	X	X	
Serum samples (Ig levels)[t]		X								X				X		yearly	X	X	

aPTT: activated partial thromboplastin time; β-HCG: β-human chorionic gonadotropin; AST: aspartate aminotransferase; ALT: alanine aminotransferase; Chi3L1: chitinase-3 like protein-1; CRF: case report form; 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 questionnaire; FSH: follicle-stimulating hormone; FU: follow-up; Ig: immunoglobulin; HIV: human immunodeficiency virus; ICF: informed consent form; IMP: investigational medicinal product; INR: international normalized ratio; IRT: interactive response technology; LTS: long-term safety study; M: month (28 days); MRI: magnetic resonance imaging; MS: multiple sclerosis; MSQoL-54: Multiple Sclerosis Quality of Life-54; NfL: neurofilament light chain; pEOT: premature end of treatment; PT: prothrombin time; SDMT: Symbol Digit Modalities Test; SWI: susceptibility-weighted imaging; TB: tuberculosis; TIBC: total iron-binding capacity; V: visit; WBC: white blood cell.

Note: All assessments shall 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 the screening MRI must be rescheduled (eg, technical issues) or repeated, an additional 1 week (7 days) 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 as needed to evaluate the participant in accordance with the Investigator's best judgment 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 the study and remain on IMP will be offered participation in a long-term safety study. Follow-up visit assessment only performed for those participants who are not willing to take part in the long-term safety 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 (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 a premature EOT visit as soon as possible. Participants will then be asked to continue with the study visits as scheduled, until global EOS visit is reached. During these visits, all study procedures/assessments will be performed except IMP administration and blood sampling for 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).

f Common EOS visit will be done when the prespecified number of events for 6-month CDW 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 need to be reported in the CRF; other prior medications will be reported for the period of 6 months prior to signing the ICF.

h Additional safety assessments can be performed if required by local regulations; such testing may be performed locally. Additional visits may be added if required by local regulations.

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

j To be performed at screening for all participants. To be repeated based on clinical judgment, borderline results, or clinical suspicion of TB infection. Screening tests for TB are described in Appendix 2 (Section 10.2).

k Hematology (platelet count, red blood cell count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, reticulocytes, white blood cell count with differential: neutrophils, lymphocytes, monocytes, eosinophils, basophils).

Biochemistry (blood urea nitrogen [BUN], creatinine, glucose, potassium, sodium, chloride, bicarbonate, calcium; liver function tests [AST, ALT, albumin, alkaline phosphatase, total and direct bilirubin, total protein; creatine phosphokinase], lipase at Screening Visit, then quarterly). Monthly visits (M1, M2, M4, 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 an abnormal laboratory test value is considered temporary. 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.

m Serum ß-HCG pregnancy test at central laboratory at screening and urine pregnancy tests within 24 hours before the first dose of IMP and at scheduled times during study. 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 Pregnancy tests will be performed monthly in all concerned EU countries (See Appendix 9, [Section 10.11.2]).

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

p 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.

q A subset of sites that have 3T MRI capacity will perform additional sequences (eg, SWI). Further details will be defined in a separate central MRI manual. For systemic corticosteroids and adrenocorticotropic hormone, 1 month washout is required prior to the MRI scans. A visit window of ±21 days is acceptable for MRIs performed after D1. 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 after it has been established that the participant meets all inclusion and no exclusion criteria.

r 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.

s Where available per local regulations.

t Pharmacodynamics/biomarkers samples collected are not timed samples.

u The DNA testing may be done, if locally applicable, at any time after signature of consent (in case it could not be done for some reason at Day 1).

v 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.

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

2 INTRODUCTION

SAR442168 is a brain penetrant inhibitor of Bruton's tyrosine kinase (BTK). SAR442168 is being developed for the treatment of MS. This study is designed to collect evidence of its efficacy and safety in a relapsing multiple sclerosis (RMS) population.

2.1 STUDY RATIONALE

Despite a number of disease-modifying therapies (DMTs) approved for RMS, there is still a need for additional efficacious treatments, especially treatments that target disease mechanisms in the central nervous system (CNS) behind a closed or partially closed blood-brain barrier. Current treatments cannot ensure long-term suppression of multiple sclerosis (MS) inflammatory activity including relapse and new magnetic resonance imaging (MRI) lesion control. Some medications delay RMS progression, but the disease may still not be completely controlled, and it affects life activities and wellbeing. Even the most recent high-efficacy DMTs mainly act on adaptive immunity in the periphery with only modest ability to slow neuroinflammatory and neurodegenerative processes, as demonstrated by recent studies in progressive MS (1, 2). Therefore, development of MS treatments with new modes of action is of interest.

In addition to the current focus on suppressing B- or T-cell mediated immunity in MS treatments, there is mounting evidence that innate immunity, including myeloid lineage bone-marrow-derived monocytes, macrophages, and CNS-resident microglial cells, is responsible for many of the neurodegenerative aspects of MS (3, 4). Modulation of innate immunity could therefore provide additional benefit in treatment of MS. SAR442168 shows in vitro capacity to inhibit BTK, which is responsible for downstream signaling in macrophages and microglial cells and is expected to act on these targets in the brain due to its ability to penetrate the blood-brain barrier.

Based on this knowledge of the mode of action of SAR442168, its ability to penetrate the blood-brain barrier, and available evidence from nonclinical and healthy volunteer studies, SAR442168 is expected to prove itself as a high-efficacy disease-modifying treatment for MS.

The ability of SAR442168 to reduce formation of new, active brain lesions in MS was assessed in a Phase 2b dose-finding trial in participants with RMS (DRI15928). This radiographic outcome has been established as a highly reliable predictive biomarker for clinical efficacy in pivotal studies in MS including Phase 3 RMS studies (5). The dose selected on the basis of the SAR442168 effect on gadolinium- (Gd-) enhancing T1-hyperintense lesions on MRI in the Phase 2b trial will be used for this and other Phase 3 trials with SAR442168 in MS.

The goal of this Phase 3 study is to assess SAR442168 in the RMS population. Efficacy will be assessed by adjudicated relapse rate, disability progression, and MRI findings of disease activity (Gd-enhancing lesions and new/enlarging T2-hyperintense lesions). Together with evaluation of other secondary and exploratory endpoints, this study will provide a comprehensive evaluation of the efficacy and safety of SAR442168 in the RMS population.

Adjudicated relapse rate is the primary endpoint in this trial, being a standard endpoint used in pivotal RMS clinical studies and in clinical practice. Six-month confirmed disability worsening (CDW) is selected as the key secondary endpoint. Confirmed disability worsening is widely used as an endpoint in clinical trials (6). Six-month CDW is considered both clinically more meaningful and statistically more robust than 3-month CDW.

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

Exploratory assessments are expected to provide additional evidence for SAR442168 activity on neuroinflammation and neurodegeneration and the impact of SAR442168 on participants' daily living functionality and quality of life.

2.2 BACKGROUND

Immunomodulatory drugs have been 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) (7). Targeting B cells represents 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 (7). However, the importance of immune cells residing in the CNS is also well known (8) and needs to be considered in MS pathogenesis.

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, primary progressive MS [PPMS] and secondary progressive MS [SPMS]) (9). Even the most recent high-efficacy DMTs act mainly on adaptive immunity in the periphery with only modest or temporary ability to slow neuroinflammatory and neurodegenerative processes and stop disease progression (1, 10). Therefore, development of MS treatments with new modes of action is of interest.

Beyond the existing strategy to modulate cellular elements of adaptive immunity, there is mounting evidence that innate immunity, mediated by cells of a myeloid lineage (bone-marrow-derived monocytes, macrophages, and CNS-resident microglial cells), is responsible for many of the neurodegenerative aspects of MS that persist in spite of the effectiveness of approved DMTs in preventing acute relapses (3, 4). Modulation of innate immunity has the potential to curtail "smoldering neuroinflammation" and other manifestations of disease progression that remain unaddressed by current, approved therapies.

BTK is an important intracellular signaling mediator in adaptive and innate immune cells. Accordingly, an inhibitor of BTK signaling represents a dual mechanism targeting both aspects of the immune system. BTK inhibitors block a signaling pathway in B lymphocytes and myeloid cells, including CNS microglia. Each of these cell types has been implicated in the pathophysiology of MS. Further, as BTK signaling is vital for maturation of B cells into antibody-secreting plasma cells, BTK inhibition can modulate both cellular and humoral immunity. BTK inhibition is reversible, since new protein is constantly synthesized, and B cells

are not depleted. Finally, because SAR442168 is brain penetrant, it has the potential to address "outside-in and inside-out" pathological mechanisms by inhibiting antigen-induced B-cell activation in the periphery and by modulating maladaptive microglial cells linked to neuroinflammation in the brain and spinal cord. Thus, SAR442168 has the potential to provide a superior benefit/risk ratio when compared to currently available MS therapies.

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.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of SAR442168 may be found in the Investigator's Brochure.

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:

<u>Potential benefits</u>

- Decrease of annualized relapse rate (ARR).
- Reduction in the risk of loss of mobility.
- Reduction in the accumulation of confirmed disability worsening (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 [SEL], T2 phase rims) 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) were reported in the ongoing Phase 3 trials; all cases occurred between Months 1 to 3, with potential confounders identified for some of the cases.

Risks associated with use of teriflunomide as a comparator:

Teriflunomide is approved for RMS treatment in many countries and there are extensive safety data collected in clinical trials and postmarketing use. The key safety information from the Aubagio (teriflunomide) United States prescribing information (USPI), 09/2019 is summarized as follows:

- In clinical trials, the most frequent adverse reactions for teriflunomide (incidence ≥10% and ≥2% greater than placebo) in placebo-controlled studies were headache, diarrhea, nausea, alopecia, and increase in ALT.
- Warnings and Precautions:
  - Hepatotoxicity
  - Embryofetal toxicity
  - Procedure for accelerated elimination of teriflunomide
  - Bone marrow effects/immunosuppression potential/infections
  - Hypersensitivity and serious skin reactions
  - Peripheral neuropathy
  - Increased blood pressure
  - Respiratory effects
  - Concomitant use with immunosuppressive or immunomodulating therapies

Detailed safety monitoring measures and risk mitigations measures for SAR442168 are provided in the study protocol.

For details on safety monitoring measures and risk mitigations measure for the comparator drug Aubagio (teriflunomide), please refer to the approved local labels in respective countries and the study protocol.

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 (11, 12). 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. 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 COVID-19, without discernable toxicity, over a 10- to 14-day treatment course (13). Infections are an important potential risk for SAR442168, and severe infections are being monitored as an adverse event of special interest (AESI) in all ongoing and future clinical trials. In the completed Phase 2b trial in 130 patients 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. 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 (11).

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.

Lastly, 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 RMS patients, 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 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 to mitigate risk of hepatic injury.

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 assess efficacy of daily SAR442168 compared to a daily dose of 14 mg teriflunomide (Aubagio) measured by annualized adjudicated relapse rate (ARR) in participants with relapsing forms of MS	• ARR during the study period assessed by confirmed protocol-defined adjudicated relapses
Secondary	
• To assess efficacy of SAR442168 compared to teriflunomide (Aubagio) on disability progression, magnetic resonance imaging (MRI) lesions, cognitive performance and quality of life	• Time to onset of confirmed disability worsening (CDW), confirmed over at least 6 months, defined as follows: - increase of ≥1.5 points from the baseline Expanded Disability Status Scale (EDSS) score when the baseline score is 0, OR - increase of ≥1.0 point from the baseline EDSS score when the baseline score is 0.5 to ≤5.5, OR - increase of ≥0.5 point from the baseline EDSS score when the baseline score is >5.5 • Time to onset of CDW, assessed by the EDSS score and confirmed over at least 3 months • 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 and number of new and/or enlarging T2-hyperintense lesions by visit over time • Total number of new gadolinium- (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 • Time to confirmed disability improvement (CDI), defined as a ≥1.0 point decrease on the EDSS from the baseline EDSS score confirmed over at least 6 months • Percent change in brain volume loss as detected by brain MRI scans at the EOS compared to Month 6 • Change in cognitive function at the EOS compared to baseline as assessed by the SDMT • Change in cognitive function at the EOS compared to baseline as assessed by the CVLT-II, where available • Change in Multiple Sclerosis Quality of Life 54 (MSQoL-54) questionnaire score at the EOS compared to baseline

Objectives	Endpoints
• To evaluate the safety and tolerability of daily 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 pharmacodynamics (PD) of SAR442168	• Change in plasma neurofilament light chain (NfL) levels at the EOS compared to baseline, where available • Changes in serum immunoglobulin level at the EOS compared to baseline • Change in serum Chi3L1 levels at the EOS compared to baseline
Tertiary/exploratory	
• To evaluate the efficacy of SAR442168 on disease activity as measured by additional clinical, brain MRI, and composite measurements	• EDSS score change from baseline at scheduled visits starting after baseline and including the EOS visit • Proportion of adjudicated relapse-free participants from randomization until the EOS visit • Time to onset of 20% worsening in the 9-hole peg test (9-HPT) confirmed over at least 3 and 6 months • Time to onset of 20% worsening in the timed 25-foot walk (T25-FW) test confirmed over at least 3 and 6 months • Time to onset of 4-point decrease in Symbol Digit Modalities Test (SDMT) confirmed over at least 3 and 6 months • Change from baseline of total volume of T2-hyperintense lesions as detected by brain MRI at Months 18, 24, and the EOS • Magnetization transfer ratio recovery at the EOS in new magnetization transfer ratio lesions detected at Months 6 and 12 • Change in number of phase rim lesions in susceptibility-weighted imaging (SWI) MRI from baseline by visit over time (subset of centers with capacity of 3T MRI) • Proportion of participants with no evidence of disease activity (NEDA-3) at Months 18, 24, and the EOS • Change from baseline to Months 12, 18, and 24 and to the EOS in modified Multiple Sclerosis Functional Composite 3 (MSFC-3), assessed as the composite of the T25-FW test, 9-HPT, and SDMT • Change from baseline by visit over time in volume of T1-hypointense lesions, and cumulative number of new T1-hypointense lesions • Number and volume of slowly evolving lesions (SELs) • Normalized T1 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 EuroQol 5-dimension 5-level questionnaire (EQ-5D-5L) from baseline by visit over time

3.1 APPROPRIATENESS OF MEASUREMENTS

Clinical relapse is the main clinical manifestation of RMS. Relapse-related endpoints (ARR and proportion of relapse-free participants) are accepted and widely used as primary endpoints in clinical trials for RMS.

The EDSS is widely used to measure neurological disability in clinical trials and routine settings (14). Due to known fluctuation in EDSS scores, CDW confirmed after 3 or 6 months is used as an endpoint in clinical trials of MS (2, 14). Confirmed disability worsening lasting for at least 6 months is considered to be more clinically relevant and superior in ruling out EDSS score fluctuations, and therefore was chosen as a supportive efficacy endpoint in this trial.

The total number of Gd-enhancing T1-hyperintense lesions as detected by MRI will be used as a secondary endpoint to assess the efficacy of SAR442168 on inflammation. This radiographic outcome has been established as a highly reliable predictive biomarker for clinical efficacy in pivotal studies in MS (5).

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

In addition, MRI measurements will include analysis of brain volume loss rate. Brain atrophy, as measured by brain volume loss rate, is known to occur early in RMS and to worsen with disease progression. Several MS drugs, including teriflunomide used as a comparator in this study (15), are known for their capacity to slow down brain volume loss; therefore, brain volume loss will be assessed in search of a possible signal. Magnetic resonance imaging at Month 6 will serve as the baseline for analyses of magnetization transfer ratio (MTR) and brain atrophy, the latter to exclude the potential confounding effect of transient changes in brain volume associated with resolution of inflammation after introduction of treatment (so-called pseudoatrophy) (16).

4 STUDY DESIGN

4.1 OVERALL DESIGN

This trial is a Phase 3, randomized, double-blind, double-dummy, 2-arm, active-controlled, parallel-group, multicenter, event-driven (6-month CDW) trial with a variable treatment duration ranging from approximately 18 to 36 months. 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 1:1 ratio to receive the 60 mg selected dose (established from dose-finding Study DRI15928) of oral SAR442168 daily as well as placebo to match the teriflunomide tablet daily or 14 mg oral teriflunomide as well as placebo to match the SAR442168 tablet daily.

Intervention Period: double-blind, double-dummy, treatment period for assessment of efficacy and safety up to the end of study (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 double-blind treatment and not entering the LTS study) to collect safety data. 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.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Duration of the study

The treatment period duration will vary for individual participants, depending on the time of recruitment and trial end as described in Section 4.4. All recruited participants will be followed in the trial until the common EFC16033 and EFC16034 trial end, which will be estimated and announced by the Sponsor to ensure that approximately 162 events of 6-month CDW are observed from the pooled data of both trials and the power related to the primary objective of each individual trial is preserved (≥90%). With an estimated recruitment period of approximately 18 months and an assumed event rate discussed in Section 9.2, the duration of the trial is expected to be approximately 36 months, with an estimated mean treatment duration of 24 to 27 months. Mean exposure duration corresponds to data generated in many MS pivotal trials and is considered sufficient to provide solid evidence of efficacy and safety of SAR442168 in the RMS population.

Choice of Control Group

Teriflunomide is considered an appropriate comparator in RMS trials for the following reasons:

- Since its initial approval, teriflunomide has been rapidly adopted for treatment of RMS and is considered a standard of care, comparable to other approved therapies in terms of safety and efficacy. This is further supported by the fact that other development candidates in MS (eg, ponesimod, ofatumumab, and ublituximab) are being compared to teriflunomide in pivotal trials.
- Double blinding will be more feasible with teriflunomide compared with other oral products, as the AE profile for teriflunomide is relatively benign, minimizing the risk of unblinding physicians and participants.
- Both treatments (SAR442168 and teriflunomide) will be taken once daily.
- As a once daily oral therapy, teriflunomide is more conveniently administered than injectable or infused therapies, potentially enhancing adherence.

Other disease-modifying treatments that are approved for treatment of RMS were considered but not chosen due to higher risk of unblinding due to safety profile (eg, flushing due to dimethylfumarate) or to sample size requirements (eg, ocrelizumab).

Gadolinium contrast-enhancing preparations for MRI (noninvestigational medicinal product [NIMP]) will be used for routine T1 contrast-enhanced sequences. These sequences are part of standard MRI controls in MS and are used in clinical practice as well as in routine management of RMS. Local recommendations and labeling of the Gd preparations used will need to be followed.

Cholestyramine will be used in the study as a NIMP for an accelerated elimination procedure for teriflunomide. It is approved for teriflunomide accelerated elimination and will be used for early IMP termination in some situations (see Appendix 4 [Section 10.4]).

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 pharmacokinetics (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. Approximately 35% of all study visits from Phase 2b were well documented as being under fed conditions. Among these documented visits, 78 participants were under fed conditions. At the 60 mg dose, most participants (19 of 32) were under a fed condition. No safety or tolerability issues were apparent under fed conditions. 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 in multiple dose groups. Overall, no new risks were identified in this trial.

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 the EOS visit, whether remaining on IMP or not.

The end of the study is defined as the date announced in advance by the Sponsor to ensure that approximately 162 events of 6-month CDW are observed from pooled data of this study and the parallel EFC16033. With an estimated recruitment period of approximately 18 months and an assumed event rate as discussed in Section 9.2, duration of the study is expected to be approximately 36 months, with an estimated mean treatment duration of 24 to 27 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. The participant must be 18 to 55 years of age, inclusive, at the time of signing the informed consent.

Type of participant and disease characteristics

I 02. The participant must have been diagnosed with RMS according to the 2017 revision of the McDonald diagnostic criteria (17).

I 03. The participant has an EDSS score ≤5.5 at the first visit (Screening Visit)

I 04. The participant must have at least 1 of the following prior to screening:

- ≥1 documented relapse within the previous year OR
- ≥2 documented relapses within the previous 2 years, OR
- ≥1 documented Gd-enhancing lesion on an MRI scan within the previous year.

Note: The initial clinical demyelinating episode of MS should be counted as a relapse for the first 2 criteria.

Weight

I 05. Not applicable.

Sex

I 06. Male or Female

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

Male participants wishing to conceive a child and female participants becoming pregnant or wishing to become pregnant must permanently discontinue the study intervention (Section 7.1.1) and follow the local teriflunomide label recommendation.

Male participants

Male participants are eligible to participate if they agree to the following during the intervention period and until the accelerated elimination procedure (when appropriate, see Section 6.1.1) is performed.

- Refrain from donating sperm

Plus either:

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

OR

- Must agree to use contraception/barrier method as detailed below
  - Agree to use a male condom and should also be advised of the benefit for a female partner to use a highly effective method of contraception as a condom may break or leak when having sexual intercourse with a woman of childbearing potential (WOCBP) who is not currently pregnant

Female participants

- A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions apply:
  - Is not a WOCBP

  OR

  - Is a WOCBP and agrees to use a contraceptive method that is highly effective (with a failure rate of <1% per year), preferably with low user dependency, as described in Appendix 4 (Section 10.4) during the intervention period and until the accelerated elimination procedure is completed after the last dose of study intervention (when appropriate, see Section 6.1.1).
  - A WOCBP must have a negative highly sensitive pregnancy test at screening and within 24 hours 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.
- Additional requirements for pregnancy testing during the study and after study intervention are located in the schedule of activities (SoA) (Section 1.3).
- 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.
- See Appendix 9 (Section 10.11) for country-specific contraception requirements.

Informed consent

I 07. The participant must have given written informed consent prior to undertaking any study-related procedure. This includes consent to comply with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol. In countries where the legal age of maturity is greater than 18 years, a specific ICF for such legally minor participants 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 been diagnosed with PPMS according to the 2017 revision of the McDonald diagnostic criteria (17) or with nonrelapsing SPMS (18).

E 02. 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) (eg, any known positive HIV test or information from participant interview).
- A history of active or latent tuberculosis (TB); TB testing should be performed at screening and again during the study, if clinically indicated, and may be repeated based on clinical judgment, borderline results, or clinical suspicion of TB infection. Screening tests for TB are described in Appendix 2 (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 source data and may then randomize the participant.
- Persistent chronic or active recurring infection requiring treatment with antibiotics, antivirals, or antifungals.

- 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, ie, results at screening for serological markers for hepatitis B and C viruses indicating acute or chronic infection. See the Study Manual for further details.
- Any other active infections that would adversely affect participation or IMP administration in this study, as judged by the Investigator.

E 03. 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 04. The following findings obtained during the Screening Visit considered in the Investigator's judgment to be clinically significant in the context of this clinical trial:

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

E 05. 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 06. Conditions that would adversely affect participation in the study or make the primary efficacy endpoint non-evaluable:

- 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.
- 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 (eg, interstitial pneumonia or pulmonary fibrosis), 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 AST >1.5 × ULN OR alkaline phosphatase >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 non-evaluable for the primary efficacy endpoint or that would adversely affect participation in this study, as judged by the Investigator.

Prior/concomitant therapy

E 07. The participant has received any of the following medications/treatments within the specified time frame before any baseline assessment (no washout is required for dimethyl fumarate, interferon beta, or glatiramer acetate treatments):

Medication	Washout period duration
Systemic corticosteroids, adrenocorticotropic hormone	1 month prior to screening MRI scan
Siponimod	1 week before randomization with MRI and clinical assessment for PML prior to randomization
Plasma exchange	1 month prior to randomization
Intravenous immunoglobulin	2 months prior to randomization
Fingolimod, ozanimod	6 weeks before randomization with MRI and clinical assessment for PML
Mildly to moderately immunosuppressive/chemotherapeutic medications such as azathioprine and methotrexate, mycophenolate	3 months prior to randomization
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	A participant who has received any of these treatments at any time is not eligible.

Medication	Washout period duration
Teriflunomide	
• <3 months treatment	3 months prior to randomization*
• ≥3 months treatment	A participant who has received this treatment at any time is not eligible.
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 prior to randomization
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 treatments	5 half-lives or until end of pharmacodynamics activity, whichever is longer

Abbreviations: MRI: magnetic resonance imaging, MS: multiple sclerosis, PML: progressive multifocal leukoencephalopathy
* No time restriction if accelerated elimination procedure is done

E 08. The participant is receiving potent and moderate inducers of cytochrome P450 (CYP) 3A or potent inhibitors of CYP2C8 hepatic enzymes as listed in Appendix 8A (Section 10.8).

E 09. The participant is receiving anticoagulant/antiplatelet therapies, including:

- 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 enrollment.

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

E 10. A history of a hypersensitivity reaction to teriflunomide, leflunomide, or to any of the inactive ingredients in Aubagio (this includes anaphylaxis, angioedema, and serious skin reactions).

Prior/concurrent clinical study experience

E 11. The participant was previously exposed to any BTK inhibitor, including SAR442168.

E 12. The participant has taken other investigational drugs within 3 months or 5 half-lives, whichever is longer, before the Screening Visit.

Diagnostic assessments

E 13. The participant has had a relapse in the 30 days prior to randomization.

E 14. The participant has 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 scans.

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

Other exclusions

E 15. Individuals accommodated in an institution because of regulatory or legal order; prisoners or participants who are legally institutionalized.

E 16. Any country-related specific regulation that would prevent the participant from entering the study (see Appendix 9 [Section 10.11]).

E 17. Participant not suitable for participation, whatever the reason, as judged by the Investigator, including medical or clinical conditions, or participants potentially at risk of noncompliance to study procedures or not able to follow the schedule of protocol assessments due to other reasons.

E 18. Participants are dependent on the Sponsor or Investigator (in conjunction with Section 1.61 of the International Council for Harmonisation [ICH] Good Clinical Practice [GCP] Ordinance E6).

E 19. 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.

E 20. 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 for IMP administration needs to be changed, a gap of a minimum of 12 hours between 2 doses should be maintained.

5.3.2 Caffeine, alcohol, and tobacco

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 the 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 details, 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 individuals 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 (Section 10.12): Contingency measures for a regional or national emergency that is declared by a governmental agency should be considered for 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 STUDY INTERVENTION(S) ADMINISTERED

Table 2 - Overview of study interventions administered

ARM name	SAR442168	Teriflunomide
Intervention name	SAR442168 60 mg Placebo matched to teriflunomide	Teriflunomide 14 mg Placebo matched to SAR442168
Type	Drug	Drug
Dose formulation	SAR442168: Film-coated tablet Placebo matched to teriflunomide: Tablet	Teriflunomide: Tablet Placebo matched to SAR442168: Film-coated tablet
Unit dose strength(s)	60 mg	14 mg
Dosage level(s)	Once daily	Once daily
Route of administration	Oral	Oral
IMP and NIMP	IMP	IMP
Packaging and labeling	Study intervention will be provided in wallet blister packaging. The content of the labeling is in accordance with the local regulatory specifications and requirements.	Study intervention will be provided in wallet blister packaging. The content of the labeling is in accordance with the local regulatory specifications and requirements.
Current/Former name(s) or alias(es)	Not applicable	Aubagio

The details of this table are specific to IMP; information of non-IMP is described separately in Section 6.1.1.
IMP: investigational medicinal product, NIMP: noninvestigational medicinal product

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

For a regional or national emergency declared by a governmental agency that results in travel restrictions, confinement, or restricted site access, contingency measures are included in Appendix 10 (Section 10.12): Contingency Measures for a regional or national emergency that is declared by a governmental agency.

6.1.1 Noninvestigational medicinal product

MRI contrast-enhancing preparations

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

Cholestyramine

- Route(s) of administration: oral
- Dose regimen: 8 g 3 times daily for 11 days for accelerated elimination procedure (4 g 3 times daily for 11 days in case of intolerance). The teriflunomide local label should be followed.

6.2 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/NIMP (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 8.3.9).

A potential defect in the quality of IMP/NIMP 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/NIMP and eliminate potential hazards.

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

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

All participants will be centrally assigned to randomized study intervention using an interactive response technology (IRT). The randomized intervention kit number will be stratified for EDSS score at screening (<4, ≥4) and geographic region (US, 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 treatment group allocation (SAR442168 or teriflunomide). Tablets of placebo to match SAR442168 and placebo to match teriflunomide will be used in a double-dummy fashion to assure blinding. Participants will receive 2 tablets daily which will be identical between treatment groups (SAR442168 60 mg and placebo matching teriflunomide or teriflunomide 14 mg and placebo matching SAR442168).

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 (blinded rater). The study site personnel designated to conduct efficacy assessments (Examining Investigators/raters or other qualified site staff) must be different from 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 an Examining Investigator/rater during the study.

The Treating Investigator is the physician responsible for participant 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. The Treating Investigator will have access to the participant's other collected data and will follow the participant, collect safety events data, and make treatment decisions based on the participant's clinical response and laboratory test findings. Once the participant has been randomly assigned to treatment, the Treating Investigator will use 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 with 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 results of prior EDSS assessments. Whenever possible, the same individual should perform the assessments and 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 comedication used or symptoms unless requested by the Examining Investigator/rater for efficacy evaluation.

An independent Data Monitoring Committee (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.

6.4 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 onsite visits).
- Measures taken to ensure study intervention accountability include:
  - 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. At each visit when study medication will be dispensed, a new paper diary should be provided to the study participant. In case of direct-to-patient 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.

6.5 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

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, the medication will not interfere with the study.

Live (attenuated) vaccines should not be administered during the intervention period.

Therapies for MS noted in the exclusion criterion E07 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.

For some prohibited concomitant medications (eg, aspirin >81 mg/day for headache), if use is not chronic, temporary discontinuation of IMP can be considered prior to a decision to permanently stop the IMP.

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:

- 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. A short course (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 Inhibitor/inducer:

Potent and moderate inducers of CYP3A or potent inhibitors of CYP2C8 hepatic enzymes are not permitted throughout the study (see Appendix 8A [Section 10.8]).

- **SAR442168**: SAR442168 is a substrate of the CYP3A4 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 (INT16385 study) and potent CYP2C8 inhibitor (gemfibrozil 600 mg twice daily for 6 days) increased SAR442168 (AUC) exposure 8.4-fold (INT16726 study). 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 once daily for 14 days under fed conditions (TDR16862 study), 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 (INT16726 study). 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 8A (Section 10.8) for the list of drugs not to be used.
- **Teriflunomide**: Other potent CYP and transporter inducers should be avoided due to their potential to decrease teriflunomide exposure. Rifampicin and other known potent CYP and transporter inducers such as carbamazepine, phenobarbital, phenytoin, avasimibe, lumacaftor, rifapentine, rifabutin, and St John's wort, should be avoided. Leflunomide is prohibited, because teriflunomide is a metabolite of leflunomide.

Cholestyramine (and other bile acid sequestrants) and activated charcoal use should be avoided because these may lead to significant decrease in plasma concentration of teriflunomide. Cholestyramine can be used only when an accelerated elimination procedure is needed. In exceptional situations (eg, when cholestyramine is not tolerated, or cholestyramine is not available) use of activated charcoal (as per the current Aubagio SmPC) can be considered.

Breast cancer resistance protein (BCRP) inhibitors (eg, eltrombopag and gefitinib) should be avoided. Based on in vitro studies, teriflunomide is a substrate of the efflux transporter BCRP, so these drugs may increase exposure of teriflunomide (Appendix 8B [Section 10.9]).

A number of drugs need to be used with caution as their exposure may be altered by teriflunomide (Appendix 8C [Section 10.10]). Adequate arrangements need to be made to monitor their effects and to ensure timely decision for change of medication.

- Medicinal products metabolized by CYP2C8 (eg, repaglinide, pioglitazone, and rosiglitazone) should be used with caution during treatment with the IMP due to potential of increase of concentrations of these drugs following CYP2C8 inhibition by teriflunomide.
- Increase in ethinylestradiol and levonorgestrel exposure following repeated doses of teriflunomide has been observed (19). While this interaction of teriflunomide is not expected to adversely impact the efficacy of oral contraceptives, it should be considered when selecting or adjusting oral contraceptive treatment used during this trial.
- Medicinal products metabolized by CYP1A2 (eg, duloxetine, alosetron, theophylline, and tizanidine) should be used with caution during treatment with IMP due to the capacity of teriflunomide to induce CYP1A2 and to reduce efficacy of these products.
- Administration of substrates of organic anion transporter 3 (OAT3) (eg, cefaclor, benzylpenicillin, ciprofloxacin, indomethacin, ketoprofen, furosemide, and cimetidine) should be performed with caution during the study due to the potential of teriflunomide to increase exposure to these medications through inhibition of OAT3.
- For substrates of BCRP (eg, sulfasalazine) and the organic anion transporter polypeptide (OATP) family (eg, rosuvastatin, simvastatin, atorvastatin, pravastatin, nateglinide, repaglinide, and rifampicin), concomitant administration with teriflunomide should be used with caution during the study due to the potential of teriflunomide to increase exposure to these products. Participants should be closely monitored for signs and symptoms of excessive exposure to the medicinal products, and reduction of the dose should be considered. If used together with the IMP, the dose of rosuvastatin should not exceed 10 mg once daily.

6.5.1 Rescue medicine

There is no rescue medication planned for this study.

Multiple sclerosis relapse treatments are allowed as per local routine practice (eg, high dose IV methylprednisolone for 3 to 5 days). These and all other concomitant medications must be reported in the eCRF.

6.6 DOSE MODIFICATION

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

6.7 INTERVENTION AFTER THE END OF THE STUDY

After the end of this study, participants who successfully complete the trial and are taking the IMP until the end of the trial will be offered the option to participate in the LTS study for an additional 2 years, or until the drug is approved in their respective country, whichever comes first. Details of the LTS study will be described in a separate protocol. Post-trial access for more than 2 years may be considered if mandated by local regulations.

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 from 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 shall be asked to remain in the study to be evaluated until the EOS visit. This will be important to continue to evaluate for safety. 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 study 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 guidance for the follow up of laboratory abnormalities in Appendix 6 (Section 10.6).
- The participant is no longer deriving a therapeutic/clinical benefit in the opinion of the Investigator.
- At participant's request, ie, withdrawal of the consent for treatment.
- If a female participant becomes pregnant or wishes to become pregnant during the study.
- If a male participant wishes to conceive a child during the study.
- Any serious opportunistic infections (eg, PML [see Appendix 6, Section 10.6], HIV).
- Continued need for/chronic use of a prohibited concomitant medication (see Section 6.5, Appendix 8A [Section 10.8], Appendix 8B [Section 10.9], and Appendix 8C [Section 10.10]).

Discontinuation of the study intervention for abnormal liver function should be considered 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 the best interest of the participant.

Any clinically significant abnormal laboratory value or ECG parameter will be immediately 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 (QTc) using Fridericia's formula [QTcF] after enrollment), the Investigator or a 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 findings recorded at the time of collection must be documented. Any new clinically relevant ECG 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 up according to the study procedures specified in this protocol up to the scheduled date of study completion or up to recovery or stabilization of any AE to be followed up as specified in this protocol, whichever comes last. 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.

Participants will be asked to continue in the study, attending all scheduled visits as 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 EOT, 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 EOS.

For participants with definitive discontinuation of study drug who do not agree to remain in the study after the premature EOT visit, if the premature EOT 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.

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 10.12]: 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, consider the benefit/risk of withholding the IMP for at least 3 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.

The following shall lead to temporary treatment discontinuation:

- Cytopenia: follow the safety algorithm for neutropenia and thrombocytopenia as per Appendix 6 (Section 10.6)
- Serum creatinine, creatine phosphokinase (CPK), and liver enzyme increase: follow corresponding safety 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

7.1.2.1 Rechallenge

Reinitiation of 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, that there are no safety concerns, and if the criteria for permanent treatment discontinuation have not been met (refer to Section 5.1 and Section 5.2).

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 10 (Section 10.12): Contingency measures for a regional or national emergency that is declared by a governmental agency.

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 (Section 1.3). See the SoA for data to be collected at the time of study discontinuation and follow up and for any further evaluations that need to be completed.
- If the participant withdraws consent 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 common study end (EOS).

The Investigators should discuss with participants 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 randomly assigned again 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/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 contacted again at the time of the EOS 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 10.1.9).

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, 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 shall be recorded on the designated field in the case report form (CRF).
- 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 Appendix 10 (Section 10.12): 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 an Examining Investigator/rater or a blinded imaging rater who is not otherwise involved in the management of participants in this study.

Key assessments of disability (eg, EDSS) will be performed by a blinded Examining Investigator/rater who will have no access to laboratory and AE reports. The MRI 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 evaluation (14). All Examining Investigators/raters will be trained and certified to perform the EDSS 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 have access to previous EDSS scores and will be blinded to all data that could unblind the participant's treatment assignment (see Section 6.3).

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

The EDSS scores, with the exception of screening EDSS scores, will not be communicated to any study staff including the Treating Investigator. Participants will not be informed of their EDSS scores.

Additional details on the EDSS score reporting will be provided in the Study Manual.

8.1.1.1 Confirmed disability worsening

Confirmed disability worsening at 3 or 6 months is a confirmed, sustained increase from baseline in EDSS score (of ≥1.5 points when the baseline score is 0, of ≥1.0 point when the baseline score is 0.5 to ≤5.5, of ≥0.5 points when the baseline EDSS score is >5.5) over at least the specified number of months and is not attributable to another etiology (eg, fever, concurrent illness, or concomitant medication).

- The initial onset increase from baseline EDSS score can be from a scheduled or unscheduled assessment.
- All intermediate EDSS scores (EDSS scores obtained after onset of disability and before the confirmatory assessment), if any, must maintain at least the minimum increase.
- Confirmatory EDSS assessments must be obtained over at least the specified number of months (3 or 6 months) after onset, at a routine quarterly visit, at least 30 days after any confirmed clinical relapse, and not be associated with an ongoing relapse.

Confirmed disability worsening at 6 months will serve as the basis of conclusion for the key secondary endpoint.

8.1.1.2 Confirmed disability improvement

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

8.1.2 Multiple sclerosis relapse assessment

8.1.2.1 Definition of multiple sclerosis relapse

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

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

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

Confirmation of MS relapse will be done by the Relapse Adjudication Committee and will be based on the EDSS score (14) (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).

Refer to Section 8.3.7 for details regarding MS relapse reporting.

8.1.2.2 Unscheduled assessment visits

Participants must be instructed to immediately report new neurological symptoms and recurring or worsening of previous symptoms to the Treating Investigator. Any reported symptoms will be recorded. If a participant reports symptoms that may be consistent with relapse, an unscheduled assessment visit to the Treating Investigator and the Examining Investigator (blinded rater) 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, per protocol. If it is consistent with the definition of MS relapse or if there is any doubt and the possibility of relapse cannot be ruled out, the standard neurological examination (for the EDSS score) will be performed by the Examining Investigator/rater. If the participant is not referred for neurological examination, this will be documented with an explanation of the reason. Whenever possible, the Examining Investigator/rater should perform the EDSS rating the same day as 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 are to 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, medically unexpected, or matches definition of 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 apply.

8.1.3 Magnetic resonance imaging

Cranial (brain) MRI before and after administering 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 MTR (all centers) and susceptibility-weighted imaging (SWI) (subset of centers with capacity of 3T MRI).
- Basic MRI sequences will be used to evaluate MRI-related endpoints of change in T2-hyperintense lesion volume, new and enlarging T2-hyperintense lesion count, number and volume of T1-hypointense lesions, brain volume loss rate, volume, number, and intensity (T1) of SELs, and Gd-enhancing T1-hyperintense lesion count (see Section 3). The expanded MRI protocol will be used to evaluate gadolinium enhancement recovery (MTR) and phase rim lesions (SWI). Additional details about MRI assessments will be provided in the central MRI manual.

Due to a potential safety risk related to deposition of certain IV Gd contrast agents in the brain, these agents should be used in accordance with local recommendations/regulations (20).

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, during the blinded intervention period, the Treating Investigator can access MRI reports 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.

8.1.4 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 (21, 22). The mean walk time will be used for assessment of the participant's walking ability. An increase of >20% from the baseline score in the T25-FW test is considered as meaningful worsening (23). 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 (22). The mean time to test completion will serve for assessment of the participant's hand dexterity. An increase of >20% from the baseline score in the 9-HPT is considered meaningful worsening (23). 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 (24) 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 (25).

The CVLT-II (26) measures verbal learning and memory by using a 16-item word list. The list is read by the examiner, and participants listen to the list and report as many of the items as possible. Five successive trials are scored.

8.1.7 Composite analyses

Data from the clinical assessments described under Section 8.1.1 to Section 8.1.6 will be utilized in various composite analyses and endpoints to assess effects of SAR442168 on 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 Multiple Sclerosis Functional Composite-3 (MSFC-3) tool is the composite of the T25-FW test, 9-HPT, and SDMT (22, 27). 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 (28):

- 6-month CDW
- Active MRI lesions (both new or enlarged T2-hyperintense lesions and Gd-enhancing T1-hyperintense lesions)
- MS relapses

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

Participants will use a handheld electronic device to record clinical outcome assessment and health-related quality-of-life parameters during onsite visits. Prior to the first attempt to complete the clinical outcome assessment, the study coordinator will train the participant in the use of the device and how to answer the questions. Participants must record clinical outcome assessment 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 (29, 30) 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 DMTs (eg, teriflunomide). This 54-item instrument generates 12 subscales and 2 single-item measures. The 12 subscales are: physical health (10 items), emotional wellbeing (5 items), cognitive function (4 items), role limit 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 and change in health. A linguistically validated MSQoL-54 is available in multiple languages.

- **EuroQoL 5-Dimension Questionnaire, 5-Level Version (EQ-5D-5L)**: The EQ-5D-5L is a generic quality of life instrument used for measuring utility (31). It consists of 2 parts: a descriptive part (5 questions) and a visual assessment scale. It is routinely used in the majority of MS (32), (eg, daclizumab NCT01797965) and non-MS clinical studies. The EQ-5D-5L is available in multiple languages.

8.2 SAFETY ASSESSMENTS

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

8.2.1 Physical examinations

The 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. A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, neurological examination, and abdomen (liver and spleen). Further details will be provided in the Study Manual.

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.

- Investigators should pay special attention to clinical signs related to previous serious illnesses.
- Any clinically significant new finding or worsening of a previous finding should be reported as an AE, per Investigator's judgment.

8.2.2 Vital signs

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

Further details will be provided in the Study Manual.

8.2.3 Electrocardiograms

- 12-lead ECGs will be performed using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals. Refer to Section 7.1.1 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.
- ECGs and (longer) 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.

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 test values do not return to normal or 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/treatment-emergent suicidal ideation and behavior will be monitored during Study EFC16034 using the C-SSRS. For safety reasons, C-SSRS will be administered throughout the study by the Treating Investigator or delegated to an individual that is certified 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 mental health professional will be consulted and will decide whether the study drugs 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

Adverse events of special interest

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

    Of note, asymptomatic overdose must be reported as a standard AE.
- **Increase in ALT**
  - Any increase of ALT >3 × ULN confirmed by retest within 72 hours or in the absence of a retest within 72 hours.
- **Project-specific AESI(s) are:**
  - ECG observation of atrial fibrillation or atrial flutter.
  - Severe infection (NCI CTCAE Grade 3 or above), 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 × 10^9/L (see Appendix 6 [Section 10.6] for management flow chart).

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

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

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study 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 throughout the study at the time points specified in the SoA (Section 1.3).

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

All SAEs and AESIs 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 AESI or SAE data to the Sponsor within 24 hours of it being available.

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

8.3.2 Method of detecting AEs and SAEs

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

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading 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 prespecified study end date, all SAEs, and nonserious AESIs (as defined in Section 8.3), 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 given in Appendix 3 (Section 10.3).

8.3.4 Regulatory reporting requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of a 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 (IRBs)/Independent Ethics Committees (IECs), and Investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary. Reporting of SUSARs will be in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.
- Adverse events that are considered expected will be specified in the reference safety information.
- An Investigator who receives an Investigator safety report describing an SAE or 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.

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 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 (Section 7.1).
- If a female participant becomes pregnant (or wishes to become pregnant) during the study and confirms plans to continue the pregnancy, the Investigator can arrange with the Sponsor unblinding so that a SAR442168-treated female participant need not be exposed to the accelerated elimination procedure.
- 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, 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).

Note: pregnancy tests will be performed monthly in all concerned EU countries (see Appendix 9, Section 10.11.2).

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 the DMC).

Death events will be reported per standard SAE reporting rules. Every effort will be done 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 8.1.2, as with all efficacy endpoints, will be exempt from being reported as AEs except when they meet the definition of a SAE or are unusually severe or medically unexpected. Hospitalization for MS relapse, if done routinely at the site (eg, for high dose IV methylprednisolone administration), will not be considered as a seriousness criterion for this study.

Data for MS relapses will be collected on the 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 from MRI scans do not need to be reported unless they are deemed unusual and thus a distinct safety finding.

8.3.9 Guidelines for reporting product complaints

Any defect in the IMP/NIMP 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 Treating 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.

Decisions regarding dose interruptions will be made by the Investigator in consultation with the Sponsor based on the clinical evaluation of the participant.

8.5 PHARMACOKINETICS

Pharmacokinetics of SAR442168 will not be systematically/routinely evaluated throughout this study.

8.6 PHARMACODYNAMICS

Pharmacodynamics (PD) evaluations will include assessment of neurofilament light chain (NfL) levels in plasma, Chi3L1, and Ig levels in serum.

8.7 GENETICS

A 6 mL blood sample will be collected for deoxyribonucleic acid (DNA) isolation from participants who have consented to participate in the genetic analysis component of the study. Participants who do not wish to participate in the genetic research may still participate in the study. The 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.

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

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

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 serum and plasma samples for biomarker research is also part of this study.
- Samples will be tested to evaluate 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, serum or plasma analytes to evaluate their association with observed clinical responses to SAR442168 (in accordance with local regulations).

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.

8.9 MEDICAL RESOURCE UTILIZATION AND HEALTH ECONOMICS

Clinical outcome assessment will be evaluated in this study through health-related quality-of-life parameters (see Section 8.1.8). The parameters will be evaluated as specified in the SoA (Section 1.3).

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

The null hypothesis for the primary efficacy endpoint of ARR is that there is no treatment difference between SAR442168 and teriflunomide and the alternative 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. The study will be declared positive if the null hypothesis for ARR for SAR442168 versus teriflunomide is rejected.

9.2 SAMPLE SIZE DETERMINATION

Approximately 1200 people will be screened to achieve approximately 900 (±10%) participants to be randomly assigned to the study intervention: approximately half to each intervention group, SAR442168 and teriflunomide. A total sample size of at least 1800 participants will be included across the 2 studies of identical design (EFC16033 and EFC16034). The study sample size of approximately 900 provides greater than 90% power to detect a 45% relative reduction of ARR (primary endpoint) with SAR442168 compared to teriflunomide, based on a negative binomial distribution for the number of relapses with the following assumptions:

- ARR of 0.29 for teriflunomide
- 1:1 randomization
- variance inflation factor (defined as variance divided by mean) of 1.5 for each arm
- 20% study discontinuation by Month 24

These calculations are based on 2-sided $\alpha = 0.05$. For the primary ITT analysis, study duration will be variable (approximately 18 to 36 months) given the event-driven trial design based on the key secondary efficacy endpoint. All randomized participants are expected to have at least an 18-month study duration, with more than 60% (approximately 550 participants) having at least 24 months. In this subset of participants, the study will also have 90% power to detect a 45% reduction for the analysis of 24-month ARR (ie, ARR during a fixed 24-month period from randomization).

This study, along with RMS study EFC16033, is planned as an event-driven trial in order to have 90% power, by pooling the two studies, for assessing the key secondary efficacy endpoint of time to onset of 6-month CDW. Each study will continue until 162 events are projected to have occurred in the pooled data, to ensure approximately 90% power to detect a 40% risk reduction in 6-month CDW with SAR442168 compared to teriflunomide, based on an assumed 24-month event rate of 12% in the teriflunomide arm. Without pooling (ie, approximately 81 events), the

study will have more than 60% power to detect a 40% risk reduction in 6-month CDW. These calculations are based on 2-sided testing and $\alpha = 0.05$.

Event rates in the SAR442168 arm are assumed to be similar to those observed in the ocrelizumab arms of RMS trials (7). The forecast of CDW risk reduction by 40% is based on current knowledge of SAR442168, including a new mode of action and brain penetration, which permit an expectation of high efficacy, similar to that of ocrelizumab (7). The forecast of the event rates in the teriflunomide group is based on observations in previous teriflunomide trials, taking into account tendencies of event rate decrease in recent trials of other MS DMTs such as those that have been observed in beta-interferon groups in ocrelizumab pivotal trials (7, 33).

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 analyses

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.

ICF: informed consent form; ITT: intent to treat

9.4 STATISTICAL ANALYSES

The SAP will be developed and finalized before database lock 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 consideration

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, 2-sided p-values and 95% confidence intervals will be provided for assessment of treatment differences.

9.4.2 Primary endpoint(s)

The purpose of the primary analysis of ARR is to assess the efficacy of SAR442168 in an ITT setting. In this primary approach, off-treatment events of participants who prematurely discontinue study intervention will be included for analysis per the ITT principle. Participants who permanently discontinue study intervention will be asked and encouraged to return to the clinic for all remaining study visits. In this case, all events during the planned treatment period will be included and the observation duration will be from randomization to the EOS. If a participant withdraws from the study prior to the common study end date, all observed events up to the last contact date will be included in the analysis, and the observation duration will be from randomization to the last contact date. No imputation will be performed for the unobserved events that may happen after study discontinuation. This estimand compares the rate of ARR for the participants randomized to SAR442168 versus teriflunomide, regardless of what treatment participants actually received. It assesses the benefits of the treatment policy or strategy relative to teriflunomide.

Annualized adjudicated relapse rate will be analyzed using a negative binomial regression model. The model will include the total number of adjudicated relapses occurring during the observation period as the response variable, with treatment group, EDSS score at screening (<4, ≥ 4), and geographic region (US, non-US) as covariates. Log transformed observation duration will be the offset variable. The estimated ARR for each treatment group and corresponding 2-sided 95% confidence interval will be derived from the negative binomial model. The relative reduction in ARR with SAR442168 compared to teriflunomide, its 2-sided 95% confidence interval and p-value will be provided.

Multiple sensitivity analyses to assess the robustness of the conclusion of the main model will be performed, including, but not limited to, an analysis of annualized relapse rate based on relapses reported by the Investigator, an analysis of ARR based on a fixed 24-month treatment duration (for the subset of participants completing at least 24 months) and an analysis to assess the efficacy of SAR442168 if participants adhere to the study intervention as directed. For the last analysis, off-treatment events of participants who prematurely discontinue study intervention will be excluded from the analysis. A negative binomial model with the same set of covariates as specified in the primary analysis will be used. This model will include relapses (or adjudicated relapses) occurring during the treatment epoch (first administration of IMP to last administration inclusive) as the response variable and the log transformed duration of the treatment epoch will be the offset variable. This approach defines the estimand to be the efficacy of SAR442168 with treatment adherence. Details of all sensitivity analyses will be included in the SAP.

Additionally, subgroup analyses will be explored to assess consistency of treatment effect. The subgroup factors include disease burden (baseline EDSS <4, ≥4), EDSS stratification factor, EDSS score at screening (<4, ≥4), geographic region (US, non-US), MRI activity at baseline, age at screening (>40, ≤40 years), sex (male, female) and highly active disease at baseline, including rapidly evolving severe RMS (34, 35, 36, 37). Participants with highly active disease are defined as having 1 relapse in the previous year AND one of the following: at least 1 Gd enhancing T1-hyperintense lesion; or 9 or more T2-hyperintense lesions at baseline for participants who were already treated with DMT (any treatment with DMTs would be considered, if documented, during the prior year) or who had 2 or more relapses in the previous year, whether treated with DMTs or not. The detailed list of subgroups and additional details of the subgroup analyses will be provided in the SAP.

9.4.3 Secondary endpoint(s)

Key Secondary Endpoint

Time to 6-month CDW, pooled across EFC16033+EFC16034

The primary analysis of time to onset of 6-month CDW will be based on the pooled data across Studies EFC16033 and EFC16034 in the ITT population. The time to onset of 6-month CDW will be analyzed by a Cox proportional hazards model with terms for treatment, EDSS score at screening (<4, ≥4), geographic region (US, non-US) and study. A log-rank test stratified by EDSS score at screening (<4, ≥4), geographic region (US, non-US), and study to compare SAR442168 to teriflunomide 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 CDW 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 worsening or prematurely discontinue the study before 6-month confirmation of an onset of disability worsening, the participant's event time will be censored at the date of last EDSS assessment.
- For participants who have an initial onset of disability worsening but reach the common study end date prior to 6-month confirmation, the event status of the participant will be determined by an imputation approach. 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 EDSS score at screening (<4, ≥4) and geographic region (US, non-US) will be used as the imputation model within each treatment of each study population. A multiple imputation approach will be used to summarize the results. Details will be provided in the SAP.

Confirmation of onset of disability worsening and 6-month CDW are defined in Section 8.1.1.1.

Time to onset of 6-month CDW will also be analyzed based on data from the current study only using similar statistical methods as for the primary analysis, but without study included in the model.

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, the same subgroup analyses as for the primary endpoint will be explored to assess consistency of treatment effect.

Other secondary efficacy endpoints

For other time-to-event endpoints (time to onset of 3-month CDW, time to CDI), similar analysis as for the primary analysis of the key secondary efficacy endpoint will be performed in the ITT population.

Continuous endpoints (percent change in brain volume loss, change in cognitive function, change in physical function, and change in MSQoL-54 at the EOS) will be analyzed using a mixed-effect model with repeated measures (MMRM) approach in the ITT population. The model will include change/percent change values for the respective endpoint at each visit as response variables, and treatment, EDSS score at screening (<4, ≥4), 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 least squares means, the corresponding 95% CI, and p-value will be provided for the comparison of SAR442168 versus teriflunomide. Participants who discontinue study intervention before the common study end date will be asked and encouraged to return for all remaining study visits and the additional off-treatment values measured up through EOS will be included in the primary analysis. For participants who withdraw from the study before EOS, values will be missing after study discontinuation.
No imputation will be performed for missing values in the primary analysis. For endpoints for which a normality assumption may not hold (eg, change in brain volume), MMRM analysis of log transformed data will be conducted for estimating treatment effects; p-values, when appropriate, will be provided using the ranked ANCOVA when a normality assumption is violated.

For categorical efficacy endpoints with count data (eg, new and/or enlarging T2 hyperintense and new Gd-enhancing T1-hyperintense lesion counts), similar analysis as for the primary analysis of the primary efficacy endpoint will be performed in the ITT population.

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.

All 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 3 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.
- If applicable, the post-treatment epoch is defined as the time from the day after the end of treatment epoch 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 • AE • TEAE • SAE • AE leading to treatment discontinuation • AE leading to death • AESI	• The number and percentage of participants with at least one TEAE, serious TEAE, 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 and 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; IMP, investigational medicinal product; SAE: serious adverse event; TEAE: treatment-emergent adverse event

9.4.6 Other analyses

Pharmacodynamic and biomarker exploratory analyses will be described in the SAP finalized before database lock. The PD analyses will be presented in a separate document from the main clinical study report (CSR).

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 10 (Section 10.12): Contingency measures for a regional or national emergency that is declared by a governmental agency.

9.5 INTERIM ANALYSES

No formal efficacy interim analysis is planned.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1 Regulatory and ethical considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and the applicable amendments and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations
- 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
  - 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 Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2 Financial disclosure

Investigators and subinvestigators 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.
- A participant who is rescreened is required to sign another ICF.
- The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The Investigator or authorized designee will explain to each participant the objectives of the exploratory 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. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for exploratory research. Participants who decline to participate in this optional research will not provide this separate signature.

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 10 (Section 10.12): Contingency measures for a regional or national emergency that is declared by a governmental agency.

10.1.4 Data protection

All personal data collected related to participants, Investigators, or any person involved in the study, which may be included in the Sponsor's databases, shall be treated in compliance with all applicable laws and regulations including the GDPR (Global Data Protection Regulation).

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 several regulatory authorities (eg, on Afro American population for FDA, or on Chinese population for the National Medicinal Product Administration, China).

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 (38, 39).

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.

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.

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 shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

10.1.5 Committees structure

10.1.5.1 Independent 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 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 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 will be trained on study procedures. Relapses, as adjudicated by the committee, need to meet protocol criteria (Section 8.1.2.1).

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.

10.1.5.4 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, European Union Clinical Trial Register (eu.ctr), euclinicaltrials.eu, and sanofi.com, as well as some national registries.

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

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

Professionals involved in the study or in the drug development program

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

10.1.7 Data quality assurance

All participant data relating to the study will be recorded on printed or eCRFs 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 onsite 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 CSR 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 closure

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:

- For study termination:
  - Information about 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

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 if the central laboratory results are not available in time for 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.

Table 5 - Protocol-required laboratory assessments

Laboratory assessments	Parameters		
Hematology	Platelet count	RBC indices:	WBC count with differential:
	RBC count	MCV	Neutrophils
	Hemoglobin	MCH	Lymphocytes
	Hematocrit	% Reticulocytes	Monocytes
			Eosinophils
			Basophils
Clinical chemistry[a]	BUN	Sodium	AST
	Creatinine[b]	Calcium	ALT
	Glucose (fasting not required)	Total and direct bilirubin	Alkaline phosphatase
	Potassium	Total protein	Creatine phosphokinase
		Chloride	Albumin
		Bicarbonate	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)		
Other screening tests	• FSH and estradiol (if needed, only in female participants to confirm postmenopausal state) • Highly sensitive serum or urine β-hCG pregnancy test (as needed for women of childbearing potential)[c] • Coagulation: PT/INR, aPTT • Serology tests for hepatitis B virus (HBsAg, anti-HBc IgM and total, anti-HBs) and C virus (anti-HCV); in case these results are inconclusive (eg anti-HBs negative and anti-HBc positive or anti-HCV IgG positive), HBV-DNA and/or HCV-RNA testing, respectively, should be performed for confirmation. HIV and other infectious diseases if required locally. • 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 a T-SPOT can also be performed, if available. • Iron panel (serum): iron, ferritin, transferrin saturation, TIBC.		

ALT, alanine aminotransferase; anti-HBc, antibody to hepatitis B core antigen; anti-HBs, hepatitis B surface antibody; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; BUN, blood urea nitrogen; β-hCG, human chorionic gonadotrophin; CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate; FSH; follicle-stimulating hormone; EC, 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; 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 after 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, may suggest severe liver injury and must be reported as SAEs.

b Other renal function parameters, creatinine clearance (CrCl) will be calculated.

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

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 blinded personnel until the study has been unblinded. This includes any post-baseline biomarker or PD assessments.

10.3 APPENDIX 3: ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

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:
  - 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.

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.

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 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 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 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: Activities of Daily Living (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 Grade 4 and 5 event must be reported as a SAE. Grade 1-3 event is defined as serious when it meets at least 1 of the predefined outcomes as described in the definition of an SAE.

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 a 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.

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 next section) 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 next section) or to the Sponsor's representative by telephone.
- Contacts for SAE reporting can be found in the Study Manual.

Back-up SAE reporting to the Sponsor's representative via paper CRF

- In case of failure of electronic reporting of SAE via the electronic data capture system, facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the Sponsor's representative.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- 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 laboratory reference range) in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone 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 highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

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[c]
- 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.)

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.

Note: Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), condoms only (male or female) spermicides only, and lactational amenorrhea method (LAM) are not acceptable sole methods of contraception. Male condom and female condom should not be used together (due to risk of failure with friction).

PARTICULAR SITUATIONS:

In case of premature EOT or after EOS:

- A WOCBP must follow the local teriflunomide label.
- A male participant must undergo the accelerated elimination procedure if planned per local teriflunomide labeling.
- Participants must be advised that if they wish to conceive a child at any point after the study is completed, they should refer to teriflunomide label recommendations.

In the situation where the participant rolls over to the proposed LTS study:

- Refer to the LTS study protocol recommendation.

If a female participant becomes pregnant during the study (if a female participant confirms plans to continue the pregnancy):

- The Investigator can arrange with the Sponsor unblinding so that a SAR442168-treated female participant need not be exposed to the accelerated elimination procedure.

In the situation where the participant leaves the study (ie, does not participate in the LTS study and cannot remain in the study to be evaluated until the EOS visit):

- The treating neurologist following the participant after the study will refer to local teriflunomide labeling.

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 1 day 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 1 day 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 will be reported as an AE or SAE. A spontaneous abortion 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 of the protocol. While the Investigator is not obligated to actively seek this information in former study participants, he/she may learn of an SAE through spontaneous reporting.

- The participant will be invited to remain in the study in any case. The pregnancy outcome and data of the newborn will be reported to the Sponsor as per usual pharmacovigilance reporting practice.

10.5 APPENDIX 5: GENETICS

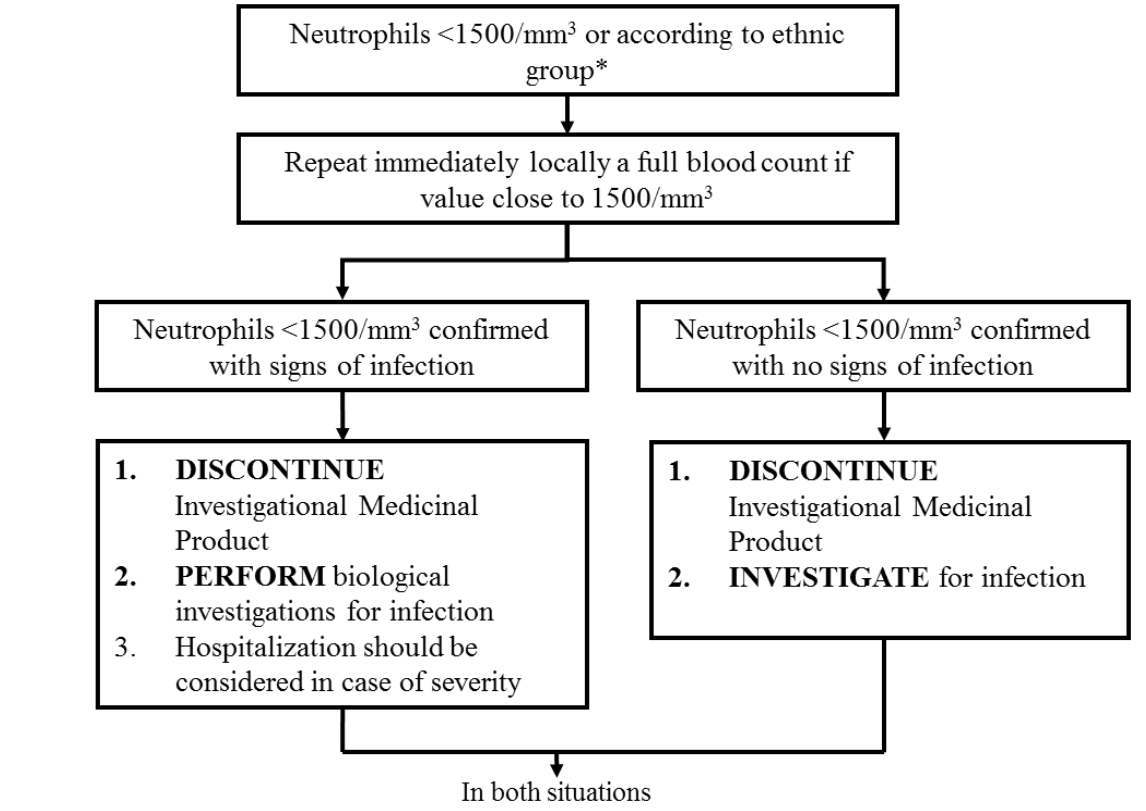
Use/Analysis of DNA

- 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 RMS and related diseases. They may also be used to develop tests/assays including diagnostic tests related to SAR442168 and RMS patients. 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 in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on SAR442168 for MS continues but for no longer than 15 years, 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.

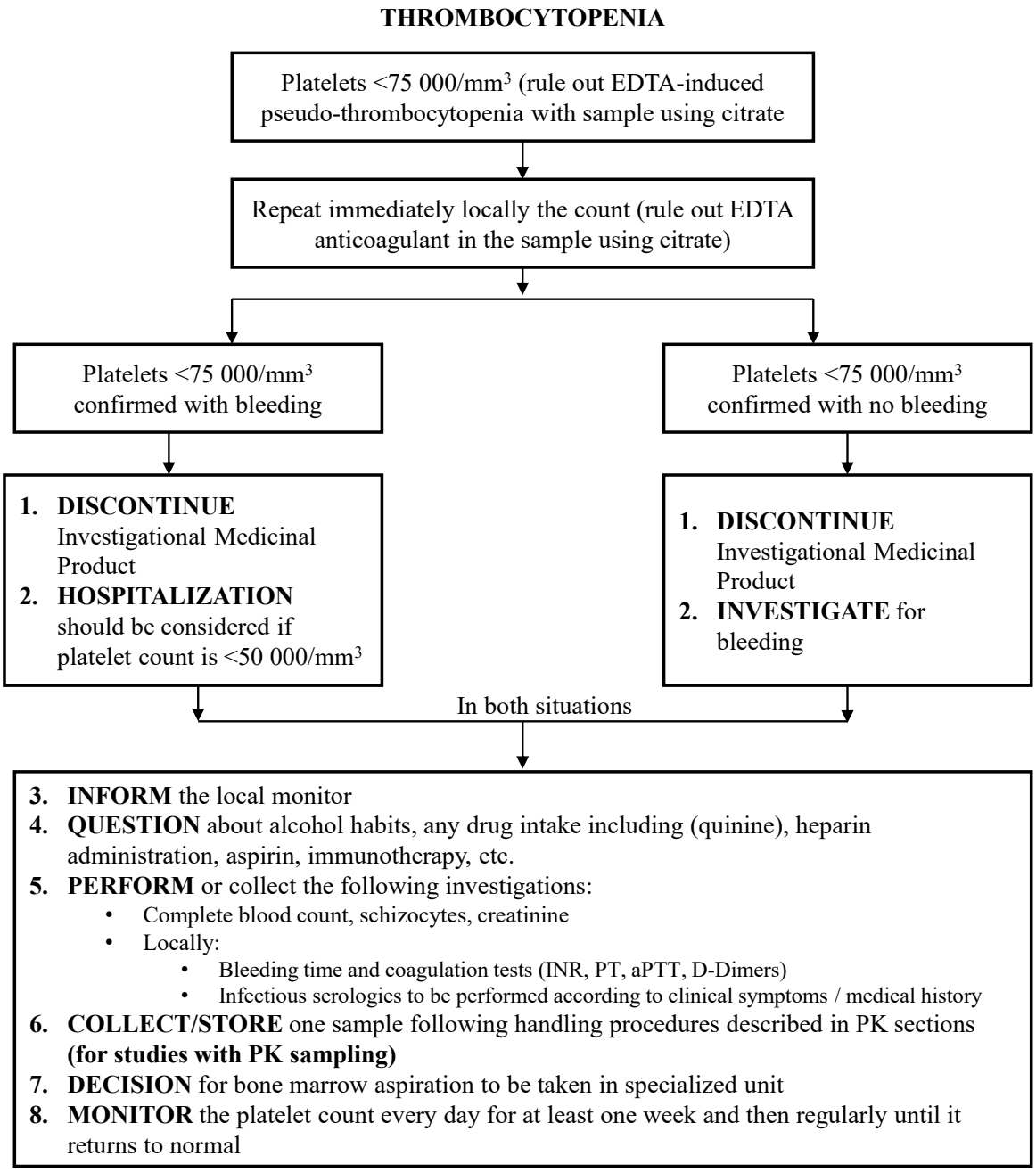
NEUTROPENIA



3. **INFORM** the local monitor
4. **INVESTIGATE** previous treatments particularly long-term, even a long time ago, exposure to toxic agents, e.g., benzene, X-rays, etc.
5. **PERFORM** and collect the following investigations (results):
   - RBC and platelet counts, Absolute Neutrophil Count (ANC)
   - Infectious serologies to be performed locally, according to clinical symptoms / medical history
6. **DECISION** for bone marrow aspiration: to be taken in specialized unit
7. **COLLECT/STORE** one sample following handling procedures described in PK sections **(for studies with PK sampling)**
8. **MONITOR** the leukocyte count 3 times per week for at least one week, then twice a month until it returns to normal

***** 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.



aPTT, activated partial thromboplastin time; EDTA, Ethylenediaminetetraacetic acid; INR, international normalized ratio; PK, pharmacokinetic(s); PT, prothrombin time.

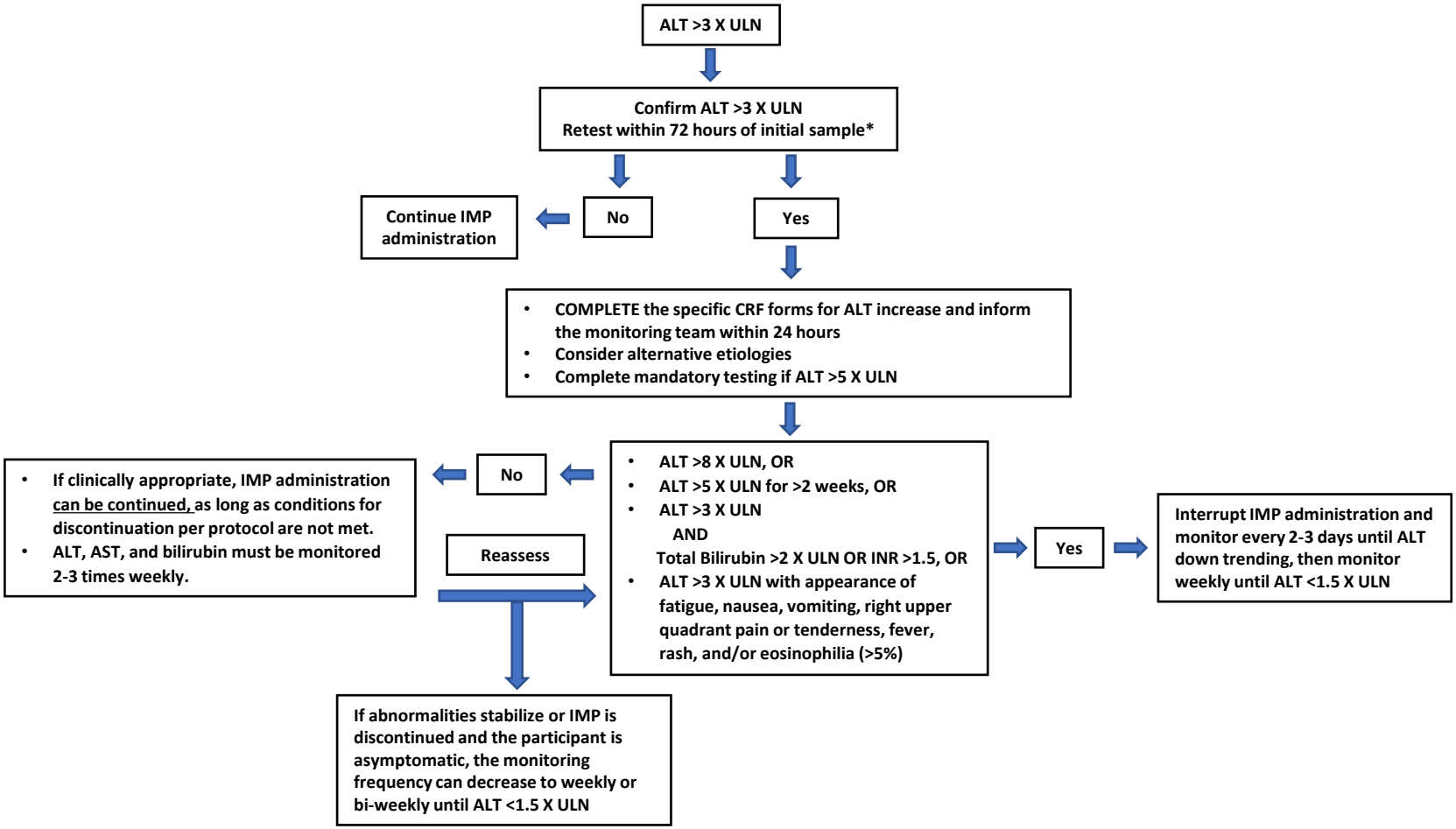
Thrombocytopenia is to be recorded as an AE only if at least 1 of the criteria listed in the general guidelines for reporting AEs in Appendix 3 (Section 10.3) is met.

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



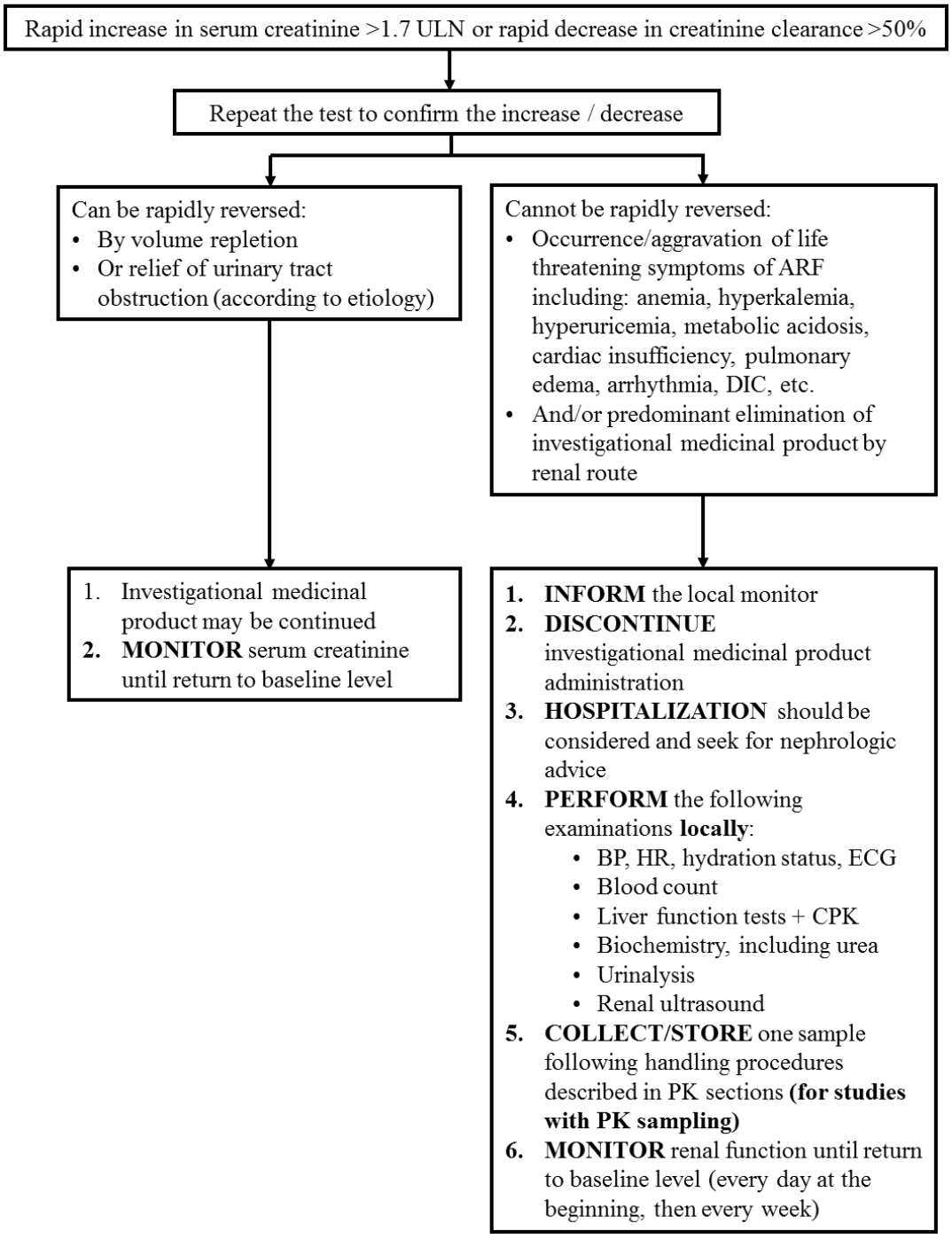
*If unable to retest in 72 hours, use original laboratory results to decide on further reporting/monitoring/discontinuation.
Note: "Baseline" refers to ALT sampled at baseline visit; or if baseline value unavailable, to the latest ALT sampled before the baseline visit. The algorithm does not apply to 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; IgM, IgG, immunoglobulin G; 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.

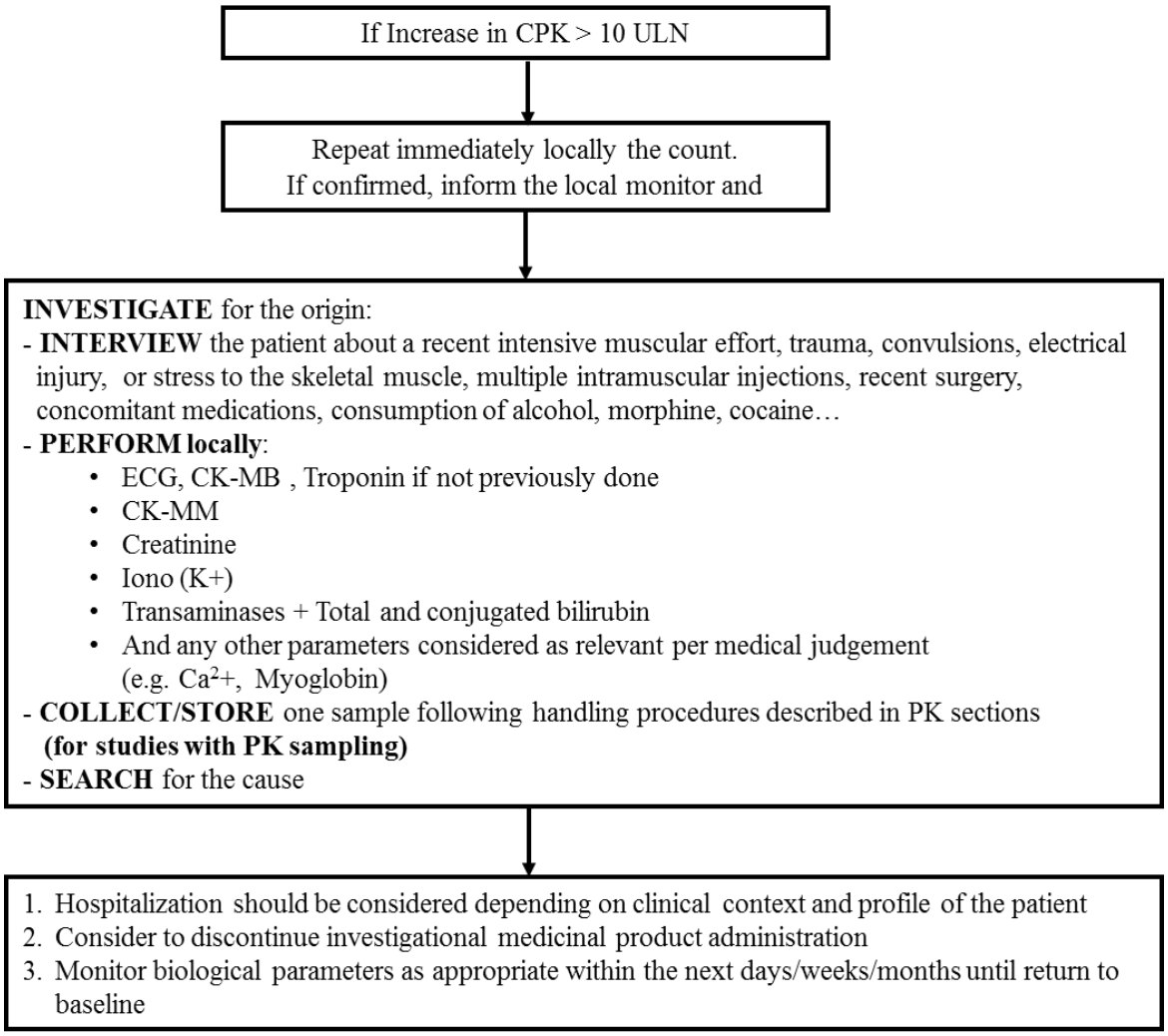
INCREASE IN SERUM CREATININE in patients with normal baseline (creatininemia between 45 µmol/L and 84 µmol/L)



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

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

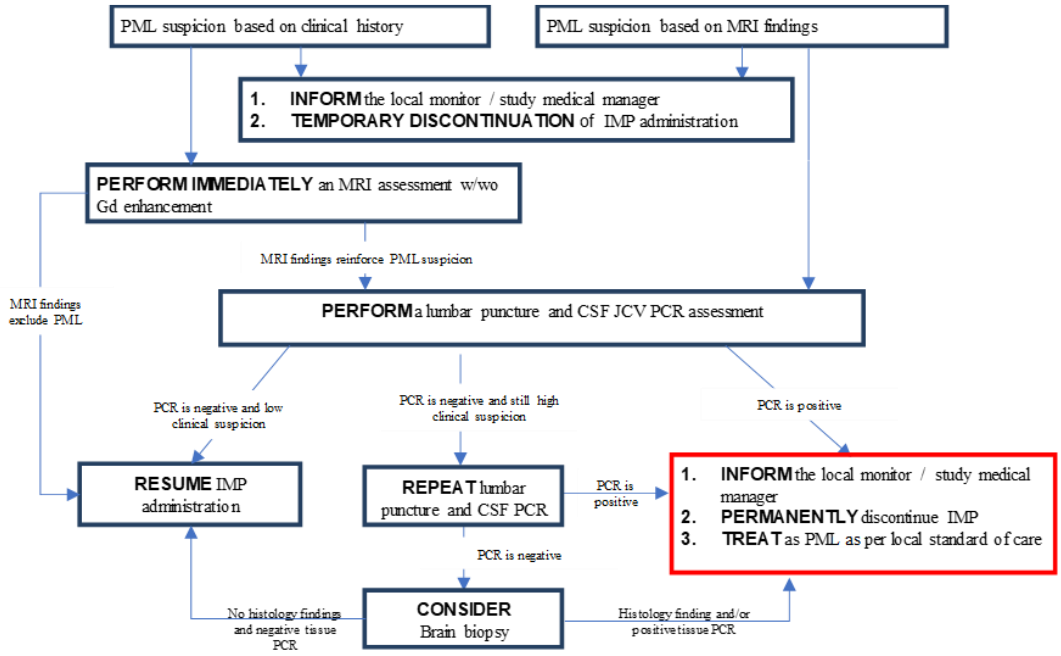


CK-MB, creatine kinase-MB; CK-MM, creatine kinase-MM; ECG, electrocardiogram; PK, pharmacokinetic(s); ULN, upper limit of normal.

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 product; 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 40 and 1).

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

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

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

10.7 APPENDIX 7: MEDICAL DEVICE INCIDENTS: DEFINITION AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

Not applicable.

10.8 APPENDIX 8A: EXAMPLES OF DRUGS WITH A POTENTIAL TO CHANGE SAR442168 METABOLISM

The following drugs should not be taken during the study concomitantly with the 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 7).

Additionally, participants in the US, Brazil, 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 8).

Please note that the lists provided in Table 7 and Table 8 are not exhaustive and that the product information of drugs intended for concomitant use should be consulted.

Table 7 - 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 8 - 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

10.9 APPENDIX 8B: EXAMPLES OF DRUGS WITH A POTENTIAL TO CHANGE TERIFLUNOMIDE DISPOSITION

BCRP Inhibitors
Cyclosporine
Eltrombopag
Gefitinib

10.10 APPENDIX 8C: EXAMPLES OF DRUGS WHICH CAN BE POTENTIALLY AFFECTED BY TERIFLUNOMIDE

Please note that the lists provided are not exhaustive and that the local product information of drugs intended for concomitant use should be consulted. If coadministration with the IMP is needed, caution needs to be exercised to detect decreased or increased exposure of these drugs and participants need to be monitored to detect this in a timely fashion.

Coadministration of teriflunomide and warfarin may lead to decreased exposure of warfarin. Therefore, when warfarin is coadministered with IMP, close INR follow up and monitoring are recommended.

Exposure of drug substances listed below may be increased by teriflunomide:

CYP2C8 substrates	
Repaglinide	Pioglitazone
	Rosiglitazone
Oral contraceptives	
Ethinylestradiol	Levonorgestrel
Organic anion transporter 3 (OAT3) substrates	
Cefaclor	
Penicillin G	
Ciprofloxacin	
Indomethacin	
Ketoprofen	
Furosemide	
Cimetidine	
BCRP substrates	
Rosuvastatin	
Sulfasalazine	
Organic anion transporting polypeptide B1 and B3 (OATP1B1/B3) substrates	
Simvastatin	
Atorvastatin	
Pravastatin	
Repaglinide	
Rifampin	
Nateglinide	

NOTE: exposure may be increased by teriflunomide

Exposure of drug substances listed below may be decreased by teriflunomide.

CYP1A2 substrates	
Duloxetine	Theophylline
Alosetron	Tizanidine
Caffeine	

10.11 APPENDIX 9: COUNTRY-SPECIFIC REQUIREMENTS

10.11.1 Contraception requirements in UK, Germany, and Denmark

For Inclusion criterion I06, 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, postovulation methods] and withdrawal are not acceptable methods of contraception).
- *For Denmark only: Acceptable methods of effective contraception include the following:*
  - IUDs;
  - Hormonal contraceptives (contraceptive pills, implants, transdermal patches, hormonal vaginal devices, or injections with prolonged release).

10.11.2 Pregnancy tests in Belgium, Czech Republic, France, Germany, Greece, Hungary, Latvia, Netherlands, Norway, Portugal, Slovakia, Spain, and United Kingdom

In Belgium, Czech Republic, France, Germany, Greece, Hungary, Latvia, Netherlands, Norway, Portugal, Slovakia, Spain, and United Kingdom, pregnancy tests will be performed monthly.

10.11.3 Country-specific provisions for France

Temporary IMP interruption will occur for all ALT >5 x ULN events regardless of 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.

For participants starting IMP, 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 (41, 42) 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 9, 43). Please note that the lists provided are not exhaustive and that the product information of drugs intended for concomitant use should be consulted.

Table 9 - Examples of herbal and dietary supplements involved in hepatotoxicity

Herbal and dietary supplements	Type of liver injury
Herbal preparations	
Pyrrolizidine alkaloids, e.g. 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
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

Herbal and dietary supplements	Type of liver injury
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.

10.11.4 Country-specific provisions for the US, Brazil, 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 8A, Section 10.8).

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.

10.12 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 participants, 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.

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 participants and those important to preserving the main scientific value of the study.

10.12.1 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 participant's medical record.

10.12.2 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 participant'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), other safety assessment (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 participant's medical record and the study CRF.

For all assessments which will not be performed remotely, the assessment windows will be extended until participants 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.

10.12.3 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.

10.12.4 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.

10.13 APPENDIX 11: ABBREVIATIONS

ADL:	activities of daily living
AE:	adverse event
AESI:	adverse event of special interest
ALT:	alanine aminotransferase
ARR:	annualized adjudicated relapse rate
AUC:	area under the curve
BCRP:	breast cancer resistance protein
BTK:	Bruton's tyrosine kinase
CDW:	confirmed disability worsening
CFR:	Code of Federal Regulations
Chi3L1:	chitinase-3 like protein-1
CNS:	central nervous system
CPK:	creatine phosphokinase
CRF:	case report form

CSR:	clinical study report
C-SSRS:	Columbia Suicide Severity Rating Scale
CYP:	cytochrome P450
DILI:	drug-induced liver injury
DMC:	Data Monitoring Committee
DMT:	disease-modifying therapy
DNA:	deoxyribonucleic acid
ECG:	electrocardiogram
eCRF:	electronic case report form
EDSS:	Expanded Disability Status Scale
EOS:	end of study
EQ-5D-5L:	EuroQol 5-dimension 5-level questionnaire
EU:	European Union
FSH:	follicle-stimulating hormone
GCP:	Good Clinical Practice
Gd:	gadolinium
HRT:	hormone replacement therapy
ICF:	informed consent form
ICH:	International Council for Harmonisation
IEC:	Independent Ethics Committee
IMP:	investigational medicinal product
INR:	international normalized ratio
IRB:	Institutional Review Board
IRT:	interactive response technology
ITT:	intent to treat
IUD:	intrauterine device
IUS:	intrauterine hormone-releasing system
IV:	intravenous
JCV:	John Cunningham virus
LTS:	long-term safety
MedDRA:	Medical Dictionary for Regulatory Activities
MRI:	magnetic resonance imaging
MS:	multiple sclerosis
MSFC-3:	Multiple Sclerosis Functional Composite-3
MSQol-54:	Multiple Sclerosis Quality of Life-54
MTR:	magnetization transfer ratio
NCI CTCAE:	National Cancer Institute Common Terminology Criteria for Adverse Events
NEDA:	no evidence of disease activity-3
NfL:	neurofilament light chain
NIMP:	noninvestigational medicinal product
NSAID:	nonsteroidal anti-inflammatory drug
OAT3:	organic anion transporter3
PD:	pharmacodynamic(s)
PK:	pharmacokinetic(s)
PML:	progressive multifocal leukoencephalopathy
PPMS:	primary progressive multiple sclerosis

QTcF:	QT interval corrected using Fridericia's formula
RMS:	relapsing multiple sclerosis
SAE:	serious adverse event
SAP:	Statistical Analysis Plan
SEL:	slowly evolving lesions
SmPC:	summary of product characteristics
SoA:	schedule of activities
SPMS:	secondary progressive multiple sclerosis
Study Manual:	Study Reference Manual
SWI:	susceptibility-weighted imaging
TEAE:	treatment-emergent adverse event
ULN:	upper limit of normal
US:	United States
USPI:	United States prescribing information
WOCBP:	woman of childbearing potential

10.14 APPENDIX 12: 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 (07 May 2020)

This amended protocol (amendment 01) 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 drivers for this amended protocol were to add exclusion criteria that were previously omitted and the regulatory requirement of a benefit/risk evaluation of the study in the context of the COVID-19 pandemic.

Protocol amendment 01 summary of changes table

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis	PD endpoint of change in lymphocyte subsets removed. Stratification by age at baseline changed to stratification by EDSS score at screening. Statistical details clarified. Adjudication added to relapse objectives, endpoints. If locally available added to Nfl secondary endpoint. Annualized relapse rate changed to annualized adjudicated relapse rate. Relapse Adjudication Committee added. Post-trial access to study medication clarified.	Correction of error. Clarity. Health Authority request.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of activities	Timing of MRI scans clarified. Timing of plasma and serum samples clarified. Participants who will enter long-term extension study and those who need to have the follow-up visit clarified. Parameters of physical exam clarified. Potential uses of archival samples clarified. Follow-up visit clarified. TB testing option clarified. IMP compliance removed from randomization visit. Urinalysis corrected to semi-annually. Beta-HCG corrected to quarterly. If locally available added to Nfl and Chi3L1 sampling. Quarterly lipase testing added. IMP compliance removed at M3 and M4, added to EOS. Visit window for MRIs performed after D1 expanded.	Clarity. Correction of errors. Flexibility because of COVID-19. Health Authority request.
2.1 Study rationale	Notion of adjudication of relapses added.	Health Authority request.
2.3 Benefit/risk assessment	Safety related events clarified: no cardiac arrhythmia clarified to no clinically significant cardiac arrhythmia. Investigator assessment of relatedness of one AE of temporary ALT increase changed to “related” to reflect update in data. Text added to address regulatory requirements for COVID-19 risk and mitigation.	Clarity. Regulatory requirement.
3 Objectives and endpoints	PD endpoint of change in lymphocyte subsets removed. Adjudication added to relapse objectives, endpoints. Annualized relapse rate changed to annualized adjudicated relapse rate. EDSS-plus endpoint removed. If locally available added to Nfl secondary endpoint.	Correction of error. Health Authority request.
3.1 Appropriateness of measurements	Justification for EDSS-plus removed.	Removal of EDSS-plus endpoint.
4.1 Overall design	Safety follow-up period clarified.	Clarity.
4.2 Scientific rationale for study design	Cholestyramine use for early IMP termination clarified.	Clarity.
4.3 Justification for dose	Details added to the description of fed versus fasted participants.	Clarity.
5.2 Exclusion criteria	Addition of exclusion criterion for history of infection or risk of infection. Combination of former E02 with E06 and deletion of duplicate text. Addition of text for sensitivity to study interventions, drug, allergies that contraindicate participation in the study. Addition of washout period for natalizumab.	Addition of erroneously omitted exclusion criteria. Simplification.
5.3.1 Meals and dietary restrictions	Time of day of IMP administration will be collected clarified.	Clarity.
6.1 Study intervention(s) administered	DTP dispensation of IMP added as a possibility.	Flexibility for COVID-19.
6.5.1 Rescue medication	Instructions for recording discussion of rescue medication removed, as no rescue medication is planned.	Clarity.
7.1.1 Definitive discontinuation	Review of ECG findings by a cardiologist clarified. Handling of participants after definitive intervention discontinuation clarified.	Clarity.

Section # and Name	Description of Change	Brief Rationale
8.0 Study assessments and procedures	Phone visits modified to include remote visits to allow for web-based visits/potential off-site visits.	Ease of continuation of study during COVID-19 pandemic.
8.1.1.1 Confirmed disability worsening	Determination of CDW clarified.	Clarity.
8.1.3 Magnetic resonance imaging	Details of MRI assessments added.	Clarity.
8.1.2.1 Definition of MS relapse	Rewording of MS relapse definition	Simplification-matching of wording to relapse definition in parallel protocols likely to be run at the same clinical site.
8.1.7.1 EDSS-Plus	Section removed.	Health Authority request.
8.2.2 Vital signs	Removal of 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	Removal of reference to additional information.	Consistency within the protocol.
8.3 Adverse events and serious adverse events	Clarified that for the project-specific AESI for ECG of clinically significant arrythmia, this pertains to only atrial fibrillation and atrial flutter 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 NCI CTCAE criteria. NIMP removed from definition of AESI of overdose.	Clarity.
8.3.5 Pregnancy	Option for unblinding for participants who wish to become pregnant.	Consistency with mirror protocol EFC16033.
8.3.6 Cardiovascular and death events	Clarification of atrial fibrillation.	Clarity.
8.3.7 MS relapse reporting	MS relapse reporting clarified.	Clarity.
9.2 Sample size determination	Approximate number of people to be screened added. Discontinuation clarified as study discontinuation.	Clarity.
9.4.2 Primary endpoint	Subgroup analysis by screening EDSS score clarified as subgroup analysis by baseline EDSS score. and sex added. Geographic origin corrected to geographic region. Age replaced by EDSS score at screening as covariate.	Clarity. Correction. Health Authority request.
9.4.3 Secondary endpoints	Onset of CDW and 6-month CDW clarified. Geographic origin corrected to geographic region.	Clarity. Correction.
10.1.5 Committees structures	Relapse Adjudication Committee added.	Health Authority request.
10.2 Appendix 2: Clinical laboratory tests	Removal of requirement of replicate testing by local and central labs. Removal of requirement for central lab testing, if infeasible.	Simplification.

10.14.2 Amended protocol 02 (24 August 2020)

This amended protocol (amendment 02) 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 driver for this amended protocol was to respond to European Health Authorities' requests.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis	Correction of dosage of cholestyramine for cases of intolerance	Correction of error
1.2 Schedule of activities	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: COVID-19
	Washout period for systemic corticosteroids added.	Inadvertent omission
1.2 Schedule of activities 10.11.3 Liver function monitoring in Belgium, Czech Republic, France, Germany, Greece, Hungary, Lithuania, Netherlands, Norway, Portugal, Slovakia, Spain, and United Kingdom	Modification of the liver function monitoring with additional tests for all concerned EU countries	Health Authorities' request
1.2 Schedule of activities 8.3.5 Pregnancy 10.11.2 Pregnancy tests in Belgium, Czech Republic, France, Germany, Greece, Hungary, Lithuania, Netherlands, Norway, Portugal, Slovakia, Spain, and United Kingdom	Monthly pregnancy testing added for all concerned EU countries.	Health Authorities' request
1.3 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.	Clarity
	MRI visit at M0 moved to M-1	Correction of error
2.3 Benefit/risk assessment	Adverse event (AE) details updated.	Clarity
	Recent information on Bruton's tyrosine kinase (BTK) inhibitors and COVID-19 added.	Health Authorities: COVID-19
5.2 Exclusion criteria	E05: Conditions that may predispose a participant to excessive bleeding clarified.	Health Authorities' request

Section # and Name	Description of Change	Brief Rationale
	E09: Investigator role in stopping anticoagulant/antiplatelet therapies clarified.	
5.3.1 Meals and dietary restriction	Meals and dietary restrictions clarified.	Clarity
5.3.2 Caffeine, alcohol, and tobacco	Amount of alcohol permitted to use for the participants added.	Health Authorities' request
6.1.1 Non-investigational medicinal product	Correction of dosage of cholestyramine for cases of intolerance	Correction of error
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
6.3 Measures to minimize bias: randomization and blinding 8.1.3 Magnetic resonance imaging	Update of the disclosure of MRI reports to the Treating Investigator.	Health Authorities' request
6.5 Concomitant therapy	Live (attenuated) vaccines prohibited during the intervention period.	Safety
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	Suicidal risk as per C-SSRS added.	Clarity
8 Study assessments and procedures	Expansion of visit window allowed.	Health Authorities: COVID-19
	Clarification added: "A study reference manual will be made available and will include additional details of study assessments".	Clarity
8.2.5 Suicidal ideation and behavior risk monitoring	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
8.6 Pharmacodynamics	Lymphocyte phenotyping and flow cytometry information deleted.	Update
10.1.9 Study and site closures	The study and site termination have been divided as two separate points. 'Information about the product leads to doubt as to the benefit/risk ratio' added to reasons for study termination. 'Total number of participants included earlier than expected' added to reasons for site termination.	Health Authorities' request
10.4 Appendix 4: Contraceptive guidance and collection of pregnancy information	Telephone reporting of home pregnancy tests allowed.	Health Authorities: COVID-19
10.6 Liver and other safety: suggested actions and follow-up assessments	Diagnostic workup for suspected PML added.	Health Authorities' request
10.13 Appendix 11: Protocol amendment history	Information regarding amended protocol 01 added.	Update
11 References	References updated	Update

Section # and Name	Description of Change	Brief Rationale
Throughout	Substitution of “long-term extension” for “long-term safety” to describe the study that participants will be allowed to roll over; substitution of “covid” for “COVID-19”; for SAR442168 and matching placebo the word "film coated" has been added; correction of small errors (eg, comma errors, duplication of words); slight rewordings for clarity.	Correction of errors, clarity

10.14.3 Amended protocol 03 (28 September 2020)

This amended protocol (amendment 03) 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 driver for this amended protocol is to update the protocol for COVID-19-related contingencies.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of activities	Duplicated exam (vital signs) removed. Additional safety tests and visits where required locally added. Timing of visit assessments clarified.	Correction of error. Clarification.
2.3 Benefit/risk assessment	Reference to Investigator’s Brochure added.	Compliance with original template.
3 Objectives and endpoints	Clarification of tertiary/exploratory endpoints.	Clarification.
5.1 Inclusion criteria	I06: Addition of “preferably” to requiring contraception with low user dependency.	Correction of error.
5.2 Exclusion criteria	E02: Clarification of history of infection with HIV; clarification of repetition of TB testing. E07: Clarification of timing of teriflunomide washout. Removal of requirement for ascertainment of B-cell levels after washout. E17: Potential participants unable to complete electronic clinical outcome assessments excluded.	Clarification. Clarification. Advancement in literature shows this to be unnecessary. Copyright issue with paper clinical outcome assessment forms.
5.3.2 Caffeine, alcohol, and tobacco	Clarification of alcohol recommendations.	Clarification.
5.5 Criteria for temporarily delaying administration of study intervention	Section added for contingency measures in the case of a regional or national emergency.	Contingency measures for COVID-19.

Section # and Name	Description of Change	Brief Rationale
6.1 Study intervention(s) administered	Reference to contingency measures in the case of a regional or national emergency added.	Contingency measures for COVID-19.
6.5 Concomitant therapy	Clarification of therapies allowed after randomization added.	Clarification.
7.1.2 Temporary discontinuation	Reference to contingency measures in the case of a regional or national emergency added.	Contingency measures for COVID-19.
7.1.2.1 Rechallenge	Reference to contingency measures in the case of a regional or national emergency added.	Contingency measures for COVID-19.
8 Study assessments and procedures	Reference to contingency measures in the case of a regional or national emergency added.	Contingency measures for COVID-19.
8.1.1.1 Confirmed disability worsening	MS relapse clarified as adjudicated MS relapse.	Clarification.
8.1.3 Magnetic resonance imaging	Rescheduling of MRI because of corticosteroid use clarified.	Clarification.
8.2.5 Suicidal ideation and behavior risk monitoring	“Mental health professional” substituted for “psychiatrist” for consultation around restarting treatment. Alerting families to monitor participants for unusual behavior removed.	Removal of unnecessary constraint.
8.3 Adverse events and serious adverse events	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.
8.3.10 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 epoch, post-treatment epoch.	Clarification
9.4.6 Other analyses	Reference to contingency measures in the case of a regional or national emergency added.	Contingency measures for COVID-19.
10.1.3 Informed consent process	Reference to contingency measures in the case of a regional or national emergency added.	Contingency measures for COVID-19.
10.1.6 Dissemination of clinical study data	Text on disclosure of information added.	Change in company policy.
10.2 Clinical laboratory tests	Exclusion of studies of hepatic impairment or cirrhosis from SAE reporting reversed. Calculation of eGFR removed.	Potential participants with hepatic impairment or cirrhosis are excluded from this trial. Cockroft-Gault formula will be used instead of eGFR.

Section # and Name	Description of Change	Brief Rationale
10.6 Liver and other safety: suggested actions and follow-up assessments	PML assessment clarified.	Clarification.
10.11.2 Pregnancy tests in Austria, Czech Republic, Denmark, Finland, Germany, Italy, Lithuania, Poland, Romania, Spain, and Sweden	Latvia substituted for Lithuania.	Correction of error.
10.11.2 Liver function monitoring in Austria, Czech Republic, Denmark, Finland, Germany, Italy, Lithuania, Poland, Romania, Spain, and Sweden	Latvia substituted for Lithuania.	Correction of error.
10.12 Appendix 10: Contingency measures for a regional or national emergency that is declared by a governmental agency	Section added.	Contingency measures for COVID-19.

10.14.4 Amended protocol 04 (14 April 2021)

This amended protocol (amendment 04) 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 driver for this amended protocol was to update the liver function test frequency in the European Union (EU) countries in accordance with the updated teriflunomide (Aubagio) summary of product characteristics (SmPC). Alanine aminotransferase exclusion criterion was also updated to align with the Aubagio label.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities 6.4 Study intervention compliance	Added the details about the paper diary.	Use of the diary was added after the release of the initial protocol.
1.3 Schedule of Activities	The footnotes were updated as follows:	
	• Footnote a: To allow a window of 1 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.
	• Footnote e: To clarify the study procedures/assessments to be performed if a participant prematurely permanently discontinues treatment with IMP	Clarity

Section # and Name	Description of Change	Brief Rationale
	• Footnote k: To correct the lipase assessment timing. Lipase levels will be assessed at screening and then quarterly along with other biochemistry parameters.	Correction of error.
	• Footnote k: To remove the cross-reference to the liver function monitoring with additional tests for all concerned EU countries.	As per updated Aubagio SmPC, biweekly liver function tests are no longer required in EU countries.
	• Footnote l: Text added: Serum ß-HCG pregnancy test at central laboratory at screening and urine pregnancy tests within 24 hours before the first dose of investigational medicinal product (IMP) and at scheduled times during study.	Clarification of pregnancy tests required during study.
	• Footnote u: To clarify the details of pharmacodynamic/biomarker samples for NfL, Chi3L1, and Ig levels; these are not timed samples.	No pharmacokinetic sample will be collected in this study so timed PD/BM sampling is not needed.
	• New footnote w: 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.
1.3 Schedule of Activities, footnote 10.2 Appendix 2: Clinical laboratory tests	Footnote k: To clarify that for glucose level measurement, fasting is not needed.	Clarity.
3. Endpoints and objectives	Removed tertiary/exploratory endpoint “total number of combined unique active lesions (CUAL*) as detected by brain MRI at Months 18, 24, and the EOS”. The associated footnote was also deleted.	MRI-related endpoints have been reassessed for the BTKi program.
	Updated the language of a tertiary/exploratory endpoint to add the assessment of cumulative number of new T1-hypointense lesions.	Clarify analysis of T1-hypointense lesions.
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 04: Removed the requirement of only brain lesion (≥1 documented Gd enhancing) on an MRI scan within the previous year.	Spine lesions are also accepted for eligibility criteria in accordance with clinical practice and similar clinical trials in the same indication.
	Inclusion criterion 06: Clarified that a woman of childbearing potential must have a negative highly sensitive pregnancy test at screening and within 24 hours before the first dose of study intervention.	Clarity.

Section # and Name	Description of Change	Brief Rationale
5.2 Exclusion criteria	Exclusion criterion 02: 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.
	Exclusion criterion 03: Clarified that the Columbia Suicide Severity Rating Scale baseline/screening version will be used for assessment of suicidal ideation.	Clarity.
	Exclusion criterion 06: Removed standalone albumin criterion. Changed screening alanine aminotransferase (ALT) exclusion threshold to >2 x upper limit of normal (ULN) and added criterion that confirmed screening ALT>2 x ULN is required.	Align ALT exclusion criteria with the Aubagio United States prescribing information (USPI) and SmPC.
	Exclusion criterion 07: Added plasma exchange with 1 month washout period required prior to randomization.	Previously omitted in error.
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 of IMP administration needs to be changed.	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 studies, investigating concomitant use of SAR442168 with drugs such as itraconazole
6. Study intervention 6.2 Preparation/handling/storage/accountability 8.3.9 Guidelines for reporting product complaints	Updated the language to remove device from the details.	Correction as no device for study intervention.
6.3 Measures to minimize bias: randomization and blinding	Added the details about randomization.	Mandatory information as per protocol template, previously omitted in error.
6.5 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.
	Guidance added to allow the use of activated charcoal in exceptional situations when cholestyramine is not tolerated or if cholestyramine is not available.	To align with the current Aubagio SmPC, (previously omitted in error).
	Updated the language related to use of NSAIDs.	Clarity

Section # and Name	Description of Change	Brief Rationale
5.2 Exclusion criterion 8 6.5 Concomitant therapy 10.8 Appendix 8A: 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), H_2 receptor antagonists, and antacids is allowed. 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. Clarified concomitant use of potent CYP3A inhibitors 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.
7.1.1 Definitive discontinuation	Updated guidance for the participant discontinuation related to laboratory abnormalities. Removed the Data Monitoring Committee (DMC) review of data to determine whether AEs should preclude continued treatment with study intervention.	Clarity The DMC has no responsibility to review individual data and advice for IMP discontinuation of a participant.
8.1.1.1 Confirmed disability worsening	Rephrased the details of the section for clarification.	Clarity.
8.1.2.1 Definition of multiple sclerosis relapse	Clarified that MS relapse confirmation will be done by the Relapse Adjudication Committee.	Clarity.
8.1.3 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.
8.2.2 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) and removed the request for 30 seconds of the rhythm strips.	To allow some flexibility as some automated electrocardiograms do not provide these parameters. All other electrocardiogram parameters will be automatically provided.
8.3 Adverse events of special interest	Definition of overdose was clarified. Definition of project-specific adverse events of special interest related to infection and hemorrhagic events was updated.	Clarity. Clarity for the infection and hemorrhagic events to be reported as adverse events of special interest.
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.

Section # and Name	Description of Change	Brief Rationale
10.2 Appendix 2: clinical laboratory test	Added details of the serology tests for hepatitis B and C and tuberculosis.	To harmonize with the other protocols in the Phase 3 MS program.
	Table 5, footnote a was updated to clarify the clinical laboratory abnormalities for liver injury.	Clarity.
	Table 5, footnote c was updated to include serum pregnancy test at screening.	Clarification of pregnancy test.
	Removed the cross-reference to unblinding section (Section 6.3).	Correction of error.
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.
10.5 Appendix 5: Genetics	Added the sample retention period.	Previously omitted in error.
10.6 Appendix 6: Liver and other safety: suggested actions and follow up assessments	Updated the figure related to suspected PML. Table 6 was updated for clinical history manifestations.	Updated figure to be easier to follow. Simplification.
10.11.3 Liver function monitoring in Belgium, Czech Republic, France, Germany, Greece, Hungary, Latvia, Netherlands, Norway, Portugal, Slovakia, Spain, and United Kingdom.	Section removed.	Biweekly liver function monitoring is no longer required per the current Aubagio SmPC.
Appendix 10, 10.12.2 Study procedures	Updated the wording associated with serum creatinine test from “efficacy assessment” to “other safety assessment”.	Correction of error.

10.14.5 Amended protocol 05 (18 November 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 driver for this amended protocol was to update the safety follow-up algorithms for ALT increase and thrombocytopenia and the platelet level threshold for definition of an AESI in order to harmonize them with the other studies in the Phase 3 program.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Document History	Correction of countries that Amended protocol 02 impacted.	Correction of error.
1.1 Synopsis 9.2 Sample size determination	Clarification of the total number of participants across the 2 RMS studies.	Clarification.
1.3 Schedule of activities	References to Section 7.1 and the Study Manual added to footnote c.	Clarification of the follow up after pEOT.
5.2 Exclusion criteria	E 07: Update of prior DMTs washout periods and addition of DMTs that are newly marketed.	Clarification to ensure washout requirement is based on the 5 half-life rule for drug elimination in participants. Update to reflect currently marketed DMTs.
	E 09: Acetylsalicylic acid (aspirin) ≤81 mg/day allowed.	Update for consistency within protocol.
6.3 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	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.
6.4 Study intervention compliance	Proper placement of tear-off label removed.	Correction of error. The study intervention has no tear-off label.
6.5 Concomitant therapy	Updated the language related to use of NSAIDs and symptomatic treatment of MS.	Clarification.
	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.
	Deleted “HMG CoA reductase inhibitors”.	Correction of error.
	Clarified use of substrates of BCRP and members of the OATP family.	Clarification.
	Added avasimibe, lumacaftor, rifapentine, and rifabutin to list of CYP and transporter inducers that should be avoided due to their potential to decrease teriflunomide exposure.	Clarification.
	Added “other bile acid sequestrants” to the list of drugs to be avoided	Clarification.
8.1.3 Magnetic resonance imaging	Clarification that full MRI report viewing restriction to one/year is applicable during the intervention period.	Clarification.

Section # and Name	Description of Change	Brief Rationale
8.3 Adverse events and serious adverse events	AESI thrombocytopenia: platelet count updated from <100 x 10^9/L to <75 x 10^9/L.	Modified to align with CTCAE guidelines for thrombocytopenia.
9.2 Sample size determination	Clarification of 24-month ARR.	Clarification.
10.4 Appendix 4: Contraceptive guidance and collection of pregnancy information	Use of male or female condoms only is not considered a highly effective contraceptive method and so not permitted as a sole method of contraception in this study.	Clarification.
10.6 Appendix 6: Liver and other safety: actions and follow-up assessments	Clarification of the mandatory and suggested flowcharts.	Clarification.
	Update of "Increase in ALT" flowchart.	To provide clear guidelines for safety of participants in case of elevated ALT or reduced platelet counts.
	Update of algorithm for thrombocytopenia.	Modified to align with CTCAE guidelines for thrombocytopenia.
10.10 Appendix 8C: Examples of drugs which can be potentially affected by teriflunomide	Added drugs for which concentration can be decreased by teriflunomide. Deleted same drugs from drugs for which concentration can be increased by teriflunomide.	Correction of error.
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) 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 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.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of activities (SoA) 5.2 Exclusion criteria (E 06)	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 03) 5.3.2 Caffeine, alcohol, and tobacco	Exclusion criteria for alcohol consumption added. Related recommendation for alcohol consumption during study updated.	To mitigate the risk of DILI.
1.3 Schedule of activities (SoA) 5.2 Exclusion criteria (E 06) 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 12: 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.	To reduce the risk of DILI.
5.2 Exclusion criteria (E 07)	"Plasma exchange" deleted under 'medication' column in the table of prior/concomitant therapy as it appeared twice.	Correction of error.
10.6 Appendix 6: Liver and other safety: actions and follow-up assessments	Increase in ALT algorithm flowchart and related instructions updated.	Update.

Section # and Name	Description of Change	Brief Rationale
10.14 Appendix 12: 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 (12 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
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 12: 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
10.11.3 Country-specific provisions for France	Section created.	HA 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 (17 November 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 update the testing requirements in the "Increase in ALT algorithm" 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) 4.1 Overall Design	Safety follow-up visit period changed from '4 to 8 weeks' to '4 weeks'.	Update.
10.6 Appendix 6: Liver and other safety: actions and follow-up assessments	Increase in ALT algorithm related assessments and rechallenge restrictions updated.	Update.
10.14 Appendix 12: 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, abbreviations as necessary.	Update in accordance with Sponsor's standards.

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