NCT03889639

AMENDED CLINICAL TRIAL PROTOCOL 02

Protocol title:	**A Phase 2b dose-finding study for SAR442168, a Bruton's tyrosine kinase inhibitor, in participants with relapsing multiple sclerosis**
Protocol number:	**DRI15928**
Amendment number:	**02**
Compound number (INN/Trademark):	**SAR442168** **Not applicable**
Short title:	**Dose-finding study for SAR442168 in relapsing multiple sclerosis**
Sponsor name:	**Genzyme Corporation**
Legal registered address:	**50 Binney Street** **Cambridge, MA 02142 USA**

Monitoring Team's Representative Name and Contact Information

Regulatory agency identifying number(s):

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DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, version
Amended Clinical Trial Protocol 02	All	09-Apr-2019, version 1 (electronic 5.0)
Amended Clinical Trial Protocol 01	All	13-Feb-2019, version 1 (electronic 3.0)
Original Protocol		15-Dec-2018, version 1 (electronic 4.0)

Amended clinical trial protocol 02: 09-Apr-2019

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

OVERALL RATIONALE FOR THE AMENDMENT

This protocol is being amended primarily in response to comments from health authorities and ethics committees during the clinical trial application process.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis	"Clinical and" removed from secondary endpoint "To evaluate efficacy … as assessed by clinical and imaging measures." "Phase 2" was changed to "Phase 2b" in "The goal of this Phase 2 study is to define a safe, optimal dose of SAR442168, a small molecule, oral, once daily, CNS-penetrant, irreversible, covalent inhibitor of BTK" and "DRI15928 is a Phase 2, randomized, double-blind, placebo-controlled, cross-over, dose-ranging study to investigate the MRI efficacy and the safety of 12 weeks administration of SAR442168." "And no exclusion" was added to "People diagnosed with RMS are eligible for enrollment as long as they meet all inclusion and no exclusion criteria."	Corrections
Section 1.3 Schedule of Activities	Clinical site visit (for hematology) added at Weeks 2 and 6; physical examination added at Week 4.	Correction of omissions
Section 2.1 Study Rationale	"Phase 2" was changed to "Phase 2b" in "The goal of this Phase 2 study is to define a safe, optimal dose of SAR442168, a small molecule, oral, once daily, CNS-penetrant, irreversible, covalent inhibitor of BTK."	Correction
Section 2.3 Benefit/Risk Assessment	"Thrombocytopenia" replaced with "decreased platelet count" in description of the event that led to an unblinding during the Phase 1 SAD/MAD study.	Typographical error
Section 3 Objectives and Endpoints	"Clinical and" removed from secondary endpoint "To evaluate efficacy … as assessed by clinical and imaging measures."	Correction
Section 3.1 Appropriateness of Measurements	"The count of new Gd-enhancing T1-hyperintense lesions" was changed to read "the total count of Gd-enhancing T1-hyperintense lesions."	Correction
Section 4.1 Overall Design	"Phase 2" was changed to "Phase 2b" in "DRI15928 is a Phase 2, randomized, double-blind, placebo-controlled, cross-over, dose-ranging study to investigate the MRI efficacy and the safety of 12 weeks administration of SAR442168."	Correction
Section 5.1 Inclusion Criteria	IO3 updated to include "OR" between the criteria	To clarify that for I03 that the participant should meet either one of the criteria.
Section 5.2 Exclusion Criteria	E10 updated to delete "if more than 81 mg/day". The notes to E10 updated from "aspirin >80 mg" to "aspirin."	Rectification of transcription error; aspirin use is prohibited in this study.
	E17 "The participant is involved with any specific situation during the study implementation/course that may raise"	More concrete criteria in the same area (E15, E16, and E18) already

Section # and Name	Description of Change	Brief Rationale
	ethical considerations" is deleted.	given make E17 redundant.
Section 6.5 Concomitant Therapy	Addition of short course of non-acetylsalicylic acid NSAIDs to permitted comedications.	To specify that only short courses of NSAIDs can be used; also prolonged use may increase the risk of bleeding
	Deleted "if >80 mg/day in "•Acetylsalicylic acid (aspirin) if >80 mg/day"	Consistency with E10
[redacted]	[redacted]	[redacted]
Section 9.2 Sample Size Determination	"12-week" removed in "The 60 participants in Cohort 2 will start with a 4-week placebo run-in that will be utilized as the 12-week placebo data." Deletion of "about" in "Assuming 15% of participants without the primary endpoint." Change of "12" to "4" in "and placebo mean number of ≥1 for new Gd-enhancing T1-hyperintense lesions at 4 weeks."	Clarification of confusing text; corrections
Section 10.1.1 Regulatory and Ethical Considerations	Submission of protocol amendments to health authorities is added.	To clarify that health authorities will be informed of protocol amendments
Section 10.4 Appendix 4: Contraceptive guidance and collection of pregnancy Information	The sentence, "As definitive reproduction toxicity studies have yet to be conducted with SAR442168, the investigator is directed to take appropriate precautions during exposure of WOCBP in this clinical trial" was added.	To align the recommendations in appendix 4 regarding contraception with the inclusion criteria
Section 10.4 Appendix 4: Contraceptive guidance and collection of pregnancy Information	The sentence "Female participants of childbearing potential are eligible to participate if they agree to use double methods of contraception, including one highly effective method consistently and correctly as described in Table 9" was added.	To align the recommendations in appendix 4 regarding contraception with I04
Section 10.7 Appendix 7: List of example drugs with a potential to change with SAR442168 metabolism	The sentence "Please note that the lists provided above are not exhaustive and that the product information of drugs intended for concomitant use should be consulted" was added.	To clarify that the list in appendix 7 is not exhaustive
[redacted]	[redacted]	[redacted]

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Protocol title: A Phase 2b dose-finding study for SAR442168, a Bruton's tyrosine kinase inhibitor, in participants with relapsing multiple sclerosis

Short title: Dose-finding study for SAR442168 in relapsing multiple sclerosis

Rationale:

The Bruton's tyrosine kinase (BTK) pathway is critical to signaling in B lymphocytes and myeloid cells including central nervous system (CNS) microglia. Each of these cell types has been implicated in the pathophysiology of multiple sclerosis (MS). Accordingly, SAR442168, a CNS-penetrant BTK inhibitor has the potential for a dual mechanism of action by inhibiting antigen-induced B-cell activation responsible for inflammation and by modulating maladaptive microglial cells linked to neuroinflammation in the brain and spinal cord. There is still a significant unmet need for therapies that target neuroinflammation in the CNS with a goal of halting long-term disability and neurodegeneration in people with relapsing multiple sclerosis (RMS), and also in progressive forms of the disease (primary progressive multiple sclerosis [PPMS] and secondary progressive multiple sclerosis [SPMS]) (1). Even the most recent high-efficacy disease-modifying therapies act mainly on adaptive immunity in the periphery with only modest or temporary ability to halt neuroinflammatory and neurodegenerative processes and stop disease progression, as also demonstrated by recent studies in progressive MS (2, 3). The goal of this Phase 2b study is to define a safe, optimal dose of SAR442168, a small molecule, oral, once daily, CNS-penetrant, irreversible, covalent inhibitor of BTK. The proposed mechanism of action for SAR442168 is inhibition of formation of new, active brain lesions in MS as measured by magnetic resonance imaging (MRI) and thus predicted to demonstrate clinical efficacy in further trials in MS patients. A dose-response curve for SAR442168 in terms of reduction of brain MRI lesion activity will be estimated. Formation of new, active brain lesions has been demonstrated to be a predictive biomarker for clinical efficacy (reduction in annualized relapse rate [ARR]) in Phase 3 registration studies (4, 5). [redacted] The study will also characterize safety and tolerability of SAR442168 in participants with RMS.

Objectives and endpoints

Objectives	Endpoints
Primary	
To determine the dose-response relationship for SAR442168 to reduce the number of new active brain lesions	• Number of new Gd-enhancing T1-hyperintense lesions at the end of 12 weeks of SAR442168 treatment as detected by brain MRI
Secondary	
To evaluate efficacy of SAR442168 on disease activity as assessed by imaging measures	• Number of new or enlarging T2 lesions at the end of 12 weeks of SAR442168 treatment • Number of Gd-enhancing T1-hyperintense lesions at the end of 12 weeks of SAR442168 treatment
To evaluate the safety and tolerability of SAR442168	• Adverse events (AEs), serious adverse events (SAEs), potentially clinically significant abnormalities in laboratory tests, electrocardiogram (ECG), or vital signs during the study period

Overall design:

DRI15928 is a Phase 2b, randomized, double-blind, placebo-controlled, cross-over, dose-ranging study to investigate the MRI efficacy and the safety of 12 weeks administration of SAR442168. People diagnosed with RMS are eligible for enrollment as long as they meet all inclusion and no exclusion criteria.

All participants will be centrally assigned to 1 of 8 arms (4 dose groups in each of 2 cohorts at equal ratio to start with SAR442168 (in Cohort 1) or placebo (in Cohort 2) period before cross-over, using an Interactive Voice/Web Response System (IVRS/IWRS).

- Within each cohort, participants will be randomly assigned equally to 1 of 4 SAR442168 doses, 5, 15, 30, or 60 mg once daily, in a blinded manner.
- Cohort 1: Participants will receive 1 of the SAR442168 doses for the first 12 weeks, then cross-over to placebo for 4 weeks.
- Cohort 2: Participants will receive placebo for the first 4 weeks, then cross over to 1 of the SAR442168 doses for 12 weeks.

Upon completing the double-blinded treatment period, participants will be given the option to enroll in a long-term safety (LTS) follow-up study to assess safety and tolerability of SAR442168. The LTS follow-up study will be described in a separate protocol.

Number of participants:

Approximately 160 people will be screened to randomize approximately 120 participants (based on a 25% screening failure rate) to the study intervention such that approximately 105 evaluable participants (based on an approximately 15% dropout rate, providing at least 26 participants for each dose level of SAR442168) complete 12 weeks of SAR442168 treatment. Participants from Cohort 2 (n = 60) will receive 4 weeks of placebo before crossing over to SAR442168, providing data that can be utilized in estimating a dose-response curve and comparison to placebo. This approach is based on the assumption of a theoretical constant rate of new Gd-enhancing

T1-hyperintense lesions over 12 weeks under placebo. The approach will minimize placebo exposure to study participants. A brief description of handling placebo data and analysis and additional details including sample size determination is provided in Section 9.

Intervention groups and duration:

The 4-week period of placebo will be introduced either after or before 12-week treatment with SAR442168 (Cohorts 1 and 2, respectively).

Participants will be randomly assigned in an equal ratio to each of 8 groups (4 dose groups within each of 2 cohorts).

Study intervention(s)

Investigational medicinal product(s):

SAR442168

- Formulation: 2.5 or 15 mg tablet
- Route(s) of administration: oral
- Dose regimen: up to 4 tablets once daily to achieve 5, 15, 30, and 60 mg daily doses

Matching placebo

- Formulation: tablet
- Route(s) of administration: oral
- Dose regimen: up to 4 tablets administered once daily (to maintain a total of 4 tablets daily for SAR442168 and/or placebo in a blinded fashion)

Post-study access to study medication:

A separate, open-label, LTS study will be offered to participants completing the Week 16 visit of this study. Details of this study will be provided in a separate protocol.

Statistical considerations:

Primary analysis:

The primary objective of dose-response relationship of SAR442168 with the primary endpoint, number of new Gd-enhancing T1-hyperintense lesions as detected by brain MRI at the end of 12 weeks of SAR442168 treatment, will be evaluated in the modified intent-to-treat (mITT) population by a 2-step multiple comparison procedure with modelling techniques (MCP-Mod). The first step of this procedure tests for an efficacy signal (compared to the null hypothesis of a flat, no dose-response curve) in a procedure that controls the type 1 error. To account for the uncertainty of the dose-response shape, 6 candidate models have been considered to cover diverse and potential dose-response profiles: 2 E_{max} models (ED_{50} = 10 mg, ED_{50} = 30 mg), a linear model, a quadratic model, a logistic model, and an exponential model. The second step is the

estimation of the dose-response curve, provided that an efficacy signal is established in the first step.

A negative binomial regression model with covariates for baseline Gd-enhancing T1-hyperintense lesion count, treatment, and cohort (Cohort 1 or Cohort 2) will be used to assess the mean count of new Gd-enhancing T1-hyperintense lesions in each of the 4 dose groups at the end of 12 weeks of SAR442168 treatment and at the end of 4 weeks of placebo. The 4-week post-randomization placebo data from Cohort 2 (ie, Week 4 data from Cohort 2) will be utilized as the placebo data at Week 12 in analysis, under the assumption of a constant rate of Gd-enhancing T1-hyperintense lesion formation if participants would be receiving placebo over 12 weeks. Participants in Cohort 2 contribute to the placebo data (at Week 4) as well as the data for 4 SAR442168 doses (at Week 16). Thus, in order to account for the potential correlation between the measurements in the 4-week placebo period and the subsequent 12-week SAR442168 treatment period in Cohort 2, a generalized estimating equation (GEE) approach is used to fit the negative binomial model accounting for the within-participant correlation via the repeated statement in SAS PROC GENMOD. A minus log transformation of the mean lesion count will be entered into the MCP-Mod procedure. The null hypothesis of a flat dose-response curve (ie, no dose–response relationship) at the end of 12 weeks of SAR442168 treatment for the primary endpoint will be jointly evaluated for each of the 6 candidate dose response models with a contrast test that controls the family wise error rate at 2-sided alpha = 0.05. If step 1 yields significant results, the best fitting model from the 6 predefined candidate models will be chosen using the generalized Akaike information criterion (AIC). The dose for the Phase 3 program will then be estimated from the final selected model.

The primary analysis will be based on pooled data of Cohorts 1 and 2 for each of the SAR442168 doses (ie, data at Week 12 for Cohort 1 and at Week 16 for Cohort 2 for the number of new Gd-enhancing T1-hyperintense lesions). Data from Cohorts 1 and 2 may also be separately explored as necessary. Sensitivity analyses will be detailed in the statistical analysis plan (SAP).

Analysis of secondary endpoints:

For the secondary endpoint of number of Gd-enhancing T1-hyperintense lesions at the end of 12 weeks of SAR442168 treatment, a similar negative binomial model and MCP-Mod procedure will be used. As it is reasonable to assume a constant rate of lesion formation over 12 weeks under placebo for total number of Gd-enhancing T1-hyperintense lesions, the same approach as that utilized for the primary endpoint will be used, by using the Week 4 data in Cohort 2 as the Week 12 placebo data while accounting for the within-participant correlation. Descriptive summary statistics over time will be provided for each of the 4 SAR442168 doses.

For the number of new or enlarging T2 lesions, descriptive summary statistics over time (4, 8, 12, and 16 weeks) will be provided for each of the 4 SAR442168 doses. Further, a similar MCP-Mod approach will be explored if it is deemed reasonable to extrapolate the Week 4 data from Cohort 2 to the Week 12 placebo data.

All safety summaries will be descriptive and will be performed on the safety population. Safety data for the first 4 weeks following randomization (where participants in Cohort 2 receive placebo) will be summarized by SAR442168 and placebo. Safety data during the 4-week placebo period (ie, 4 weeks) in Cohort 1 will be summarized separately and displayed by SAR442168 dose group and overall.

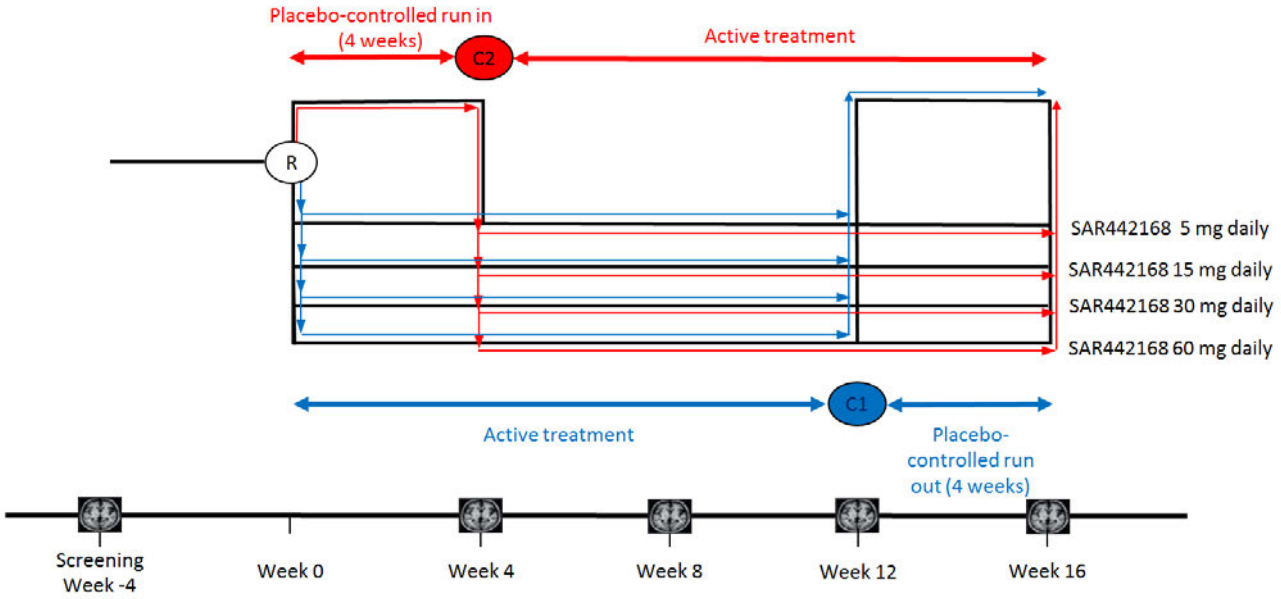
[redacted]

[redacted]

Data Monitoring Committee: Yes

1.2 SCHEMA

Figure 1 - Graphical study design



C1: Cohort 1; C2: Cohort 2; R: randomization; Schedule of Activities (SoA)

1.3 SCHEDULE OF ACTIVITIES

Table 1 - Schedule of Activities

Phase	Screening	Baseline /start of IMP		Intervention Phase					Follow-up phase	Unscheduled visit	Premature end of treatment[a]
Week (a window of ±3 days is allowed for all visits after screening)	**W-4 to D-1**[b]	**D1**	**W2**	**W4**	**W6**	**W8**	**W12**	**W16**	**Follow-up visit (W18 to W20)**[a,c]	**UNSCH**	
Informed consent	X										
Visit at clinical site	X	X	X	X	X	X	X	X	X	X	X
Inclusion/exclusion criteria	X										
Medical/surgical history	X										
Prior/concomitant medications	X	X		X		X	X	X	X	X	X
Randomization		X									
Study treatment administration											
SAR442168/placebo (dispensation and accountability)		X[l]		X[l]		X[l]	X[l]	Accountability[l]			
Treatment adherence diary[m]		X		X		X	X	X			
Safety											
Physical examination[d]	X	X[e]		X		X	X	X	X	X	X
Height	X										
Body weight	X	X		X		X	X	X	X	if needed	X
Serology tests for hepatitis B, C, other infectious disease if locally required	X										

Phase	Screening	Baseline /start of IMP		Intervention Phase					Follow-up phase	Unscheduled visit	Premature end of treatment[a]
Week (a window of ±3 days is allowed for all visits after screening)	**W-4 to D-1**[b]	**D1**	**W2**	**W4**	**W6**	**W8**	**W12**	**W16**	**Follow-up visit (W18 to W20)**[a,c]	**UNSCH**	
Vital signs	X	X[e]		X[e]		X	X	X	X	X	X
12-lead ECG	X	X[e]		X[e]		X	X	X	X	if needed	X
Body temperature	X	X[e]		X[e]		X	X	X	X	X	X
Hematology, biochemistry[f]	X	X[e]	X[g]	X[e]	X[g]	X	X	X	X	If needed	X
Coagulation[f]	X									If needed	
Urinalysis[f]	X	X[e]		X[e]		X	X	X	X	If needed	X
TB/QuantiFERON-TB Gold® test or equivalent	X										
β-HCG test (if applicable)[h]	X	X[e]		X[e]		X	X	X		If needed	
Serum FSH	X										
Suicidality assessment (C-SSRS)	X	X[e]		X		X	X	X	X	If needed	X
Adverse event collection	X	X		X		X	X	X	X	X	X
Efficacy											
EDSS	X	X[e,i]					X			If MS relapse suspected	X
MRI[j]	X			X[e]		X	X	X			X

Phase	Screening	Baseline /start of IMP		Intervention Phase					Follow-up phase	Unscheduled visit	Premature end of treatment[a]
Week (a window of ±3 days is allowed for all visits after screening)	**W-4 to D-1**[b]	**D1**	**W2**	**W4**	**W6**	**W8**	**W12**	**W16**	**Follow-up visit (W18 to W20)**[a,c]	**UNSCH**	
Pharmacokinetics											
SAR442168 pharmacokinetic plasma samples (sampling to be done as indicated ±0.5 hour)		X (1 hour post-dose)[f]		X (1 and 3 hours post-dose)[f]		X (1 ±0.5 hour post-dose)[f]	X (1 and 3 hours post-dose)[f]	X (1 hour post-dose)[f]			X (1 hour post-dose)
[redacted]											
[redacted]		[redacted]									
[redacted]											
[redacted]		[redacted]									
[redacted]		[redacted]									
[redacted]		[redacted]									

Abbreviations: β-HCG: beta human chorionic gonadotropin; BTK: Bruton's tyrosine kinase; C-SSRS: Columbia Suicide Severity Rating Scale; [redacted] D: day; DME: drug-metabolizing enzymes; [redacted] ECG: electrocardiogram; EDSS: Expanded Disability Status Scale; FSH: follicle-stimulating hormone; [redacted]; MRI: magnetic resonance imaging; [redacted] TB: tuberculosis; W: week

a The participant should return for a follow-up visit 2 to 4 weeks after premature end-of-treatment.

b Screening activities can be done any time starting from 4 weeks to Day 1 before intervention.

c Only participants who do not enroll into the LTS study should come for a Week 18 to 20 follow-up visit.

d A full physical examination must be performed at screening; a brief physical examination is sufficient thereafter. The brief physical examination needs to be extended as needed as per the judgment of the Investigator if any new findings occur.

e Sample or measurement to be taken before treatment.

f For a detailed list of laboratory tests, refer to Appendix 2 (Section 10.2). Pre-study tests may be accepted, if they are performed in the period Week -4 to Day -1.

g Hematology only
h Serum β-HCG must be tested at screening; urine β-HCG is sufficient thereafter unless a pregnancy is detected or the urine test it is inconclusive and a serum test needs to be used for verification.
i Baseline EDSS can be done in the frame of 3 days before Day 1.
j MRI can be performed within a window of ±5 days. The screening MRI should be performed as close before Day 1 as feasible.
k [redacted]
l On site visit days, participants should not take the IMP before the visit but should bring their drug wallets to the visit in order that the time of administration can be recorded in order to schedule PK sampling.
m Treatment adherence diaries will be dispensed for a 4-week period, collected, and clarified at the following visits. Treatment compliance will be reported with the help of diary data.

2 INTRODUCTION

SAR442168 is a brain-penetrant, selective, covalent inhibitor of BTK. SAR442168 exhibits activity in the experimental allergic encephalomyelitis animal model used to evaluate immunomodulatory agents in treating MS.

2.1 STUDY RATIONALE

The goal of this Phase 2b study is to define a safe, optimal dose of SAR442168, a small molecule, oral, once daily, CNS-penetrant, irreversible covalent inhibitor of BTK. The proposed mechanism of action for SAR442168 is inhibition of formation of new active brain lesions in MS as measured by MRI and thus predicted to demonstrate clinical efficacy in further trials in MS patients. This study will assess dose-response by measuring changes in the number of gadolinium (Gd)-enhancing T1-hyperintense lesions associated with inflammation. This radiographic outcome has been established as a highly-reliable predictive biomarker for clinical efficacy in pivotal studies in MS and has been demonstrated to be a predictive biomarker for clinical efficacy (reduction in ARR) in Phase 3 registration studies (4, 5). Dose-response for lesion suppression will be assessed, based on 4 dose levels and a short placebo period, with a 2-step statistical approach. SAR442468 efficacy relative to placebo will be assessed by evaluating inhibition of the formation of new active brain lesions as measured by MRI. The study will also characterize safety and tolerability of SAR442168 in participants with RMS.

The DRI15928 study will employ a number of secondary outcome measures in an effort to collect additional data on the potential benefit of SAR442168 in neuroinflammation.

[redacted]

2.2 BACKGROUND

Immunomodulatory drugs have been the mainstay of MS therapy. Recent results from clinical studies have demonstrated very good efficacy of agents that target B lymphocytes, especially B-cell-depleting agents like ocrelizumab (anti-CD20) (6). Targeting B-cells represents a departure from the prevailing dogma based on animal models that demonstrated therapeutic benefits from modulating T-cell activity and positions the B cell as the centerpiece of current MS drug development (7). 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 people with RMS and with progressive forms of the disease (PPMS and SPMS) (1). Even the most recent high-efficacy disease-modifying therapies act mainly on adaptive immunity in the periphery with only modest or temporary ability to halt neuroinflammatory and neurodegenerative processes and stop disease

progression, as also demonstrated by recent studies in progressive MS (2, 3). 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 myeloid cell lineages (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 disease-modifying therapies in preventing acute relapses (9, 10). Immunomodulation directed at innate immunity has 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 cells of both adaptive and innate immunity. Accordingly, an inhibitor of BTK signaling represents a dual mechanism targeting both aspects of the immune system. BTK inhibits 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 for a dual mechanism of action by inhibiting antigen-induced B-cell activation responsible for neuroinflammation 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.

Renal and hepatic impairment: The pharmacokinetics (PK) of SAR442168 have not been investigated in human subjects with either renal or hepatic impairment. Based on the routes of elimination, SAR442168 exposures may increase in participants with hepatic impairment; therefore, SAR442168 should not be administered to individuals with underlying hepatic impairment until evaluated in clinical studies.

Drug abuse and dependence: SAR442168 is not classified as a controlled substance. No data are available regarding the potential of SAR442168 for abuse and dependence.

Phase 1 first-in-human single-ascending-dose/multiple-ascending-dose study: Seventy-four healthy participants (30 in the single-ascending-dose, 40 in the multiple-ascending-dose, and 4 in the cerebrospinal-fluid [CSF] exposure phases) have received up to 120 mg SAR442168 in the single-ascending-dose phase, up to 90 mg once daily for 10 days in the multiple-ascending-dose phase, and 120 mg (single dose) in the CSF exposure study. No serious adverse events (SAEs) have been reported in Phase 1. One participant in the multiple-ascending-dose 60 mg cohort was unblinded due to thrombocytopenia. Because of this, platelet counts will be monitored during the DRI15928 study. There was no platelet decrease lower than 100 x 10^9/L observed during the study. SAR442168 is rapidly absorbed (t_{max} is close to 1 hour) and rapidly eliminated ($t_{1/2}$ was less than 2.5 hours). Covalent binding enables a durable pharmacodynamic (PD) effect, and steady state is achieved within 5 to 10 days. Cerebrospinal fluid exposure has been confirmed in humans with CSF concentrations of approximately 1.87 ng/mL at 2 hours, which is more than 10 times greater than the cell-based IC_{50} of 0.18 ng/mL.

Drug-drug interactions: The potential for drug-drug interactions has been investigated in vitro with SAR442168 evaluated as a substrate, inhibitor, or inducer of CYP450 metabolizing enzymes. Based on preclinical drug metabolism studies, SAR442168 is a substrate of the CYP3A and CYP2C8 isoenzymes, and therefore, it is possible that plasma exposures of SAR442168 would be altered if coadministered with other drugs that either induce or inhibit CYP3A and/or CYP2C8 metabolism. Based on estimations strong inhibitors/inducers could change SAR442168 concentrations by approximately 50% from expected. This has not been studied in humans to date, and therefore, drugs that strongly inhibit or induce CYP3A or CYP2C8 should be avoided (see the list of such drugs in Appendix 7, Section 10.7).

The results show that SAR442168 does not significantly induce nor inhibit CYP450 enzymes at therapeutically relevant concentrations. Therefore, SAR442168 is unlikely to alter the PK of other drugs that are metabolized by these enzymes.

In vitro, SAR442168 was not an inhibitor or a substrate of drug transporters including human OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, BCRP, and BSEP and was a minor substrate for P-glycoprotein. Therefore, clinically significant transporter-related drug-drug interactions with SAR442168 are considered unlikely.

No human drug-drug interaction studies have been conducted to date.

2.3 BENEFIT/RISK ASSESSMENT

SAR442168 is an oral, investigational, small molecule drug that inhibits BTK and has the potential to target inflammatory diseases including MS and other autoimmune diseases. It is anticipated that the dual proposed mechanism of action, targeting peripheral inflammation and neuroinflammation, will be of benefit to participants in the study and will potentially have efficacy superior to established MS therapies.

Expected benefits:

Suppression of neuroinflammation is expected to be observed as decreased MRI activity and will be monitored by evaluating formation and count of new Gd-enhancing T1-hyperintense lesions and volume and count of new or enlarging T2 lesions. Risk of MS relapse, the clinical manifestation of neuroinflammation, is expected to be decreased due to the anti-inflammatory activity of the compound, but due to the short duration of the treatment period, it is not expected to result in significant differences in relapse count between groups or compared to the placebo period. Nevertheless, MS relapse and Expanded Disability Status Scale (EDSS) data to monitor disability due to MS will be collected to detect any possible changes and will be used as a baseline for long-term observations in the LTS study, open to all participants of DRI15928.

To summarize, SAR442168 is expected to reduce MS relapse rate, disability progression, and underlying CNS damage through its dual action on peripheral immune cells as well as immune cells and the inflammation process in the CNS. These effects will be evaluated in this study, which will allow dose selection and later confirmation of efficacy in Phase 3 studies.

Risks and adverse drug reactions:

The safety profile of 2 approved BTK inhibitors in oncology (mantle cell lymphoma and chronic lymphatic leukemia) patients (11) is characterized. The MS population is very different from oncology patients with regards to some risks, eg, hematological risks (hemorrhage, anemia, etc). All of these potential risks will be taken into consideration in this study.

Human exposure of SAR442168 is limited to the exposure in the aforementioned Phase 1 study in healthy participants. Overall, the drug was considered generally safe and well-tolerated following both single dose administration of up to 120 mg, and multiple dose administration for 10 days at up to 90 mg daily. There were no SAEs reported in the study and no clinically significant abnormalities in vital signs, electrocardiogram (ECG) parameters, or laboratory changes in treated subjects except than dose-dependent platelet decrease. One participant who had decreased platelet count in the 60 mg multiple doses cohort discontinued treatment at Day 9 when the platelet count decreased from 145 x 10^9/L to 105 x 10^9/L. All drug-related adverse events (AEs) were classified as mild (Grade 1).

Potential risks:

BTK inhibitors, as a potential immunosuppressant class of small molecules, have been approved to treat oncology patients for chronic lymphocytic leukemia and mantle cell lymphoma.

BTK inhibitors may increase the risk of bleeding, infection, cytopenias (thrombocytopenia, neutropenia), and atrial arrhythmia (in particular atrial fibrillation and atrial flutter).

In this study, platelet counts will be followed at monthly visits to timely detect any adverse reaction. Participants will be instructed to report any bleeding signs (such as petechiae and easy bruising) to the Investigator to evaluate any underlying platelet disorder and bleeding risk. Major hemorrhagic events, including symptomatic bleeding in a critical area or organ such as the CNS, will be reported as adverse event of special interest (AESI).

Other cytopenias such as neutropenia and anemia have also occurred in the oncology setting and are a potential class risk. Monthly complete blood counts will be used to monitor for such events.

Atrial fibrillation and atrial flutter have been detected with some BTK inhibitors (12); therefore, these are also considered as a potential class risk. Frequent ECG recording is planned in the study to mitigate this. QTc ≥500 ms or clinically significant arrhythmia will be collected as AESIs in this study.

Detailed information about the known and expected benefits and risks and reasonably expected AEs of SAR442168 can be found in the Investigator's Brochure for SAR442168.

Overall, the benefit/risk profile is considered positive to develop this drug in the target population.

3 OBJECTIVES AND ENDPOINTS

Table 2 - Objectives and endpoints

Objectives	Endpoints
Primary	
To determine the dose-response relationship for SAR442168 to reduce the number of new active brain lesions	• Number of new Gd-enhancing T1-hyperintense lesions at the end of 12 weeks of SAR442168 treatment as detected by brain MRI
Secondary	
To evaluate efficacy of SAR442168 on disease activity as assessed by imaging measures	• Number of new or enlarging T2 lesions at the end of 12 weeks of SAR442168 treatment • Number of Gd-enhancing T1-hyperintense lesions at the end of 12 weeks of SAR442168 treatment
To evaluate the safety and tolerability of SAR442168	• Adverse events (AEs), serious adverse events (SAEs), potentially clinically significant abnormalities in laboratory tests, electrocardiogram (ECG), or vital signs during the study period
[redacted]	
[redacted]	[redacted]
[redacted]	[redacted]

Objectives	Endpoints
	[redacted]
To evaluate PK [redacted]	• Pharmacokinetics of SAR442168 • [redacted]

3.1 APPROPRIATENESS OF MEASUREMENTS

Magnetic resonance imaging markers of inflammatory activity in the brain will be collected as in most RMS clinical trials. Number of new Gd-enhancing T1-hyperintense lesions will be used as the primary endpoint to assess the efficacy of SAR442168. Because MS results in a leaky blood-brain barrier, accumulation of Gd contrast agent in brain tissue is related to inflammatory activity in MS patients. This radiographic outcome has been established as a highly-reliable predictive biomarker for clinical efficacy in pivotal studies in MS.

Central review will be used to identify new Gd-enhancing T1-hyperintense lesions not present at the previous MRI. 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 lesions, a marker of inflammatory activity and brain tissue destruction in RMS, will also be evaluated in central review to collect additional data with respect to the efficacy of SAR442168. The total volume of T2 lesions (MS burden) and the number of T1-hypointense lesions (black holes) will also be assessed as supportive data with respect to efficacy.

Magnetic resonance imaging measurements will include change in brain volume, which is considered to be a marker of CNS degeneration but is also related to inflammatory events in RMS patients. Several MS drugs are known for their capacity to slow down brain atrophy, which will be assessed in search of a possible signal.

Clinical relapse is the main clinical expression of RMS. Relapse-related endpoints (ARR, proportion of relapse-free participants) are widely used as endpoints in clinical trials. Although the short duration of this trial does not allow expectation of a significant difference between dose groups in occurrence of relapse and relapse is considered rare in PPMS, it will be assessed due to its clinical importance and in an attempt to collect additional efficacy data.

The EDSS is widely used to measure neurological disability in clinical trials and routine settings (13). Large changes are not expected during the period of this study, but it will be used as supportive data for efficacy.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a Phase 2b, randomized, double-blind, placebo-controlled, cross-over, dose-ranging study to investigate the MRI efficacy and the safety of 12 weeks administration of SAR442168. People diagnosed with RMS are eligible for enrollment as long as they meet all inclusion and no exclusion criteria.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

This study is blinded for dose and for administration sequence. It is focused on dose finding but also takes into account the need to minimize participant exposure to placebo. Accordingly, we will evaluate the dose range using 4 doses: 5, 15, 30, and 60 mg once daily. In addition, to minimize exposure to placebo while maintaining the blinding of Investigators and participants, each participant will be assigned to a 4-week placebo period that will occur during either the first or the last 4 weeks of the study.

The 4-week period of placebo is introduced either after or before 12-week treatment with SAR442168 (Cohorts 1 and 2, respectively). Participants are randomly assigned to 1 of 8 arms (4 dose groups at an equal ratio in each of the 2 cohorts). The duration of administration of placebo is limited to 4 weeks to minimize placebo exposure; a cross-over design allows all participants to be treated with SAR442168. This cross-over design will blind for administered intervention and will permit a more objective evaluation of safety events at the beginning of the study and of efficacy endpoints.

The duration of treatment period of SAR442168 of 12 weeks should allow to detect its effect on suppressing the formation of new Gd-enhancing T1 lesions. Recent communication on an evobrutinib study in RMS patients confirms that meaningful reduction of such lesions may be observed from the Week 12 already (14).

4.3 JUSTIFICATION FOR DOSE

The dose range chosen for this study is informed by several assessments. First, allometric modeling intended to translate BTK occupancy by SAR442168 in preclinical animals (mouse, rat, and dog) predicts an optimal dose range between 1 and 100 mg once daily in humans. Second, Phase 1 multiple-ascending-dose measurements of BTK occupancy in human peripheral blood mononuclear cells (PBMCs) show an asymptotic approach to saturation of the receptor by SAR442168 at the 7.5 mg once daily dose with a more rapid approach to saturation at higher doses. Finally, measurements of absolute CD19+ B-cell counts show a dose-dependent increase (observed maximally at Day 4) of up to 80% relative to baseline. The BTK-induced increase in circulating B-cells is predicted from the literature, as BTK inhibition alters expression of cell surface adhesion molecules leading to egress from lymph nodes (11). The dose-response

relationship for this effect is maximal at approximately 30 mg once daily. Taking all of these elements into consideration, a dose range between 5 and 60 mg once daily has been set to provide the best chance of capturing the optimal dose for SAR442168 in RMS.

4.4 END OF STUDY DEFINITION

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

The end of the study is defined as the date of the last visit of the last participant in the study.

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as a protocol waiver or exemption, 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 (15).

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

I 04. A female participant must use a double contraception method including a highly effective method of birth control from inclusion and up to 2 months after the last study dose, except if she has undergone sterilization at least 3 months earlier or is postmenopausal. Menopause is defined as being amenorrheic for ≥12 months with serum follicle-stimulating hormone (FSH) level >30 UI/L.

I 05. Male participants, whose partners are of childbearing potential (including breastfeeding women), must accept to use, during sexual intercourse, a double contraceptive method according to the following algorithm: (condom) plus (intrauterine device or hormonal contraceptive) from inclusion up to 3 months after the last dose.

I 06. Male participants whose partners are pregnant must use, during sexual intercourse, a condom from inclusion up to 3 months after the last dose.

I 07. Male participants must have agreed not to donate sperm from the inclusion up to 3 months after the last dose.

Weight

Not applicable.

Sex

I 08. Male or Female

Informed Consent

I 09. The participant must have given written informed consent prior to undertaking any study-related procedure.

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 (15) or with non-relapsing SPMS (16).

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

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

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

- A history of T-lymphocyte or T-lymphocyte-receptor vaccination, transplantation (including solid organ, stem cell, and bone marrow transplantation) and/or antirejection therapy
- A history of diagnosis of progressive multifocal leukoencephalopathy (PML) or evidence of findings suggestive of PML on the baseline MRI
- As the investigational medical product (IMP) has the potential to diminish immunocompetence, people with a history of infection with human immunodeficiency virus will be excluded

- A history of active or latent tuberculosis (unless the participant has completed a full course of anti-tuberculosis therapy or it is documented by a specialist that the participant has been adequately treated and can begin treatment with an immunosuppressive agent); screening tuberculosis testing should be performed as per local health care authority recommendations prior to study start and during the study if clinically indicated. Blood testing (eg, QuantiFERON®-TB Gold test) is preferred; skin testing (eg, tuberculin skin test) will be allowed if blood testing is not available or the blood test result is indeterminate
- Any other active infections that would adversely affect participation or IMP administration in this study, as judged by the Investigator
- A history of malignancy within 10 years prior to the first screening visit, except effectively treated carcinoma in situ of the cervix or adequately treated non-metastatic squamous or basal cell carcinoma of the skin
- A history of alcohol or drug abuse within 1 year prior to the first screening visit
- A history of any psychiatric disease, behavioral condition, or depression requiring hospitalization within 2 years prior to the first screening visit
- Presence of any screening laboratory or ECG values outside normal limits that are considered in the Investigator's judgment to be clinically significant
- Presence of liver injury defined as underlying hepatobiliary disease or screening alanine aminotransferase (ALT) >3 x upper limit of normal (ULN)

E 04. At screening, the participant is positive for hepatitis B surface antigen and/or hepatitis B core antibody and/or is positive for hepatitis C antibody.

E 05. The participant has any of the following:

- A bleeding disorder or known platelet dysfunction at any time prior to the first screening visit
- A platelet count <150 000/μL at the screening visit

E 06. The participant has a lymphocyte count less than the lower limit of normal (LLN) at the screening visit.

E 07. 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.

Prior/concomitant therapy

E 08. The participant has received any of the following medications/treatments within the specified time frame before any baseline assessment (no wash-out is required for interferons beta or glatiramer acetate treatments):

Medication	Exclusionary if used/used within required wash-out period
Systemic corticosteroids, adrenocorticotropic hormone	1 month prior to screening MRI scan
Dimethyl fumarate	1 month prior to randomization
Intravenous (IV) immunoglobulin, fingolimod, natalizumab (participants who have discontinued natalizumab in the 6 months prior to randomization should be evaluated to rule out PML)	2 months prior to randomization
Teriflunomide	2 years prior to randomization or 1 month prior to randomization if participant undergoes an accelerated elimination procedure and has documented teriflunomide plasma level below 0.02 mg/L before randomization
B-cell-depleting therapies such as ocrelizumab and rituximab	6 months prior to randomization or until return of B-cell counts to normal levels, whichever is longer
Mildly to moderately immunosuppressive/chemotherapeutic medications such azathioprine and methotrexate	6 months prior to randomization
Highly immunosuppressive/chemotherapeutic medications: mitoxantrone up to 120 mg/m^2 body surface area, cyclophosphamide, cladribine	2 years prior to randomization
Alemtuzumab	4 years prior to randomization
Lymphoid irradiation, bone marrow transplantation, mitoxantrone (with evidence of cardiotoxicity following treatment, or cumulative lifetime dose >120 mg/m^2), other strongly immunosuppressive treatments with very long-lasting effects	Any time

E 09. The participant is receiving strong inducers or inhibitors of CYP3A or CYP2C8 hepatic enzymes as listed in the Appendix 7 (Section 10.7).

E 10. The participant is receiving anticoagulant/antiplatelet therapies, including:

- Acetylsalicylic acid (aspirin)
- 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 above drugs need to be stopped at least 5 half-lives before study drug administration except for aspirin, which needs to be stopped at least 8 days before.

Prior/concurrent clinical study experience

E 11. The participant has previously participated in any clinical trial of a BTK inhibitor

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

Diagnostic assessments

E 13. The participant has an EDSS score >5.5 at the first screening visit.

E 14. The participant has had a relapse in the 30 days prior to randomization.

Other exclusions

E 15. The participant is accommodated in an institution because of a regulatory or legal order, is a prisoner, or is legally institutionalized.

E 16. The participant is 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 17. The participant has sensitivity to any of the study interventions, or components thereof or has a drug or other allergy that, in the opinion of the Investigator, contraindicates participation in the study.

E 18. The participant is pregnant or a breastfeeding woman.

E 19. The participant has any of the following within 4 weeks of the first screening visit:

- Fever (≥38°C)
- Persistent chronic or active recurring infection requiring treatment with antibiotics, antivirals, or antifungals

E 20. The participant has a documented history of attempted suicide over the 6 months prior to the screening visit, presents with suicidal ideation of category 4 or 5 on the Columbia Suicide Severity Rating Scale (C-SSRS) during the study, OR if in the Investigator's judgment, the participant is at risk for a suicide attempt.

E 21. The participant has had major surgery within 4 weeks prior to the first screening visit, which could affect participant’s safety or affect immune response (as judged by the Investigator) or has planned any elective surgery during the course of the study.

E 22. The participant has 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, neurological, endocrine, gastrointestinal, hepatic, metabolic, pulmonary, or lymphatic disease that would adversely affect participation in this study.

E 23. The participant is uncooperative or has any condition that could make the participant potentially non-compliant with the study procedures.

5.3 LIFESTYLE CONSIDERATIONS

5.3.1 Meals and dietary restrictions

Consumption of grapefruit fruits and their juices is prohibited from 5 days prior to intervention administration and during further participation in the study.

5.3.2 Caffeine, alcohol, and tobacco

For each visit session, participants will abstain from ingesting caffeine- or xanthine-containing products (eg, coffee, tea, cola drinks, and chocolate) for 2 hours before the start of treatment until after collection of the final PK[redacted].

Participants will abstain from alcohol for 24 hours before the start of treatment until after collection of the final PK [redacted]

5.3.3 Activity

Not applicable.

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 the same participant number as the initial screening. If an MRI has been performed within the 4 weeks prior to treatment, it does not need to be repeated.

6 STUDY INTERVENTION

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

6.1 STUDY INTERVENTION(S) ADMINISTERED

This study intervention includes an IMP and a noninvestigational medicinal product (NIMP).

6.1.1 Investigational medicinal product

To maintain blinding, participants will receive 4 tablets once per day of SAR442168 and/or placebo in a blinded fashion. The IMP can be taken with or without food. The time of day and whether IMP is taken with or without food should be as consistent as much as possible throughout the study. Details for the interventions are provided in Table 3.

Table 3 - Overview of study interventions administered

Study intervention name	SAR442168	Matching placebo
Dosage formulation	Film coated tablet	Film coated tablet
Unit dose strength(s)/dosage level(s)	Up to 4 tablets daily to achieve 5, 15, 30, and 60 mg doses	NA
Route of administration	Oral	Oral
Dosing instructions	Up to 4 tablets daily to achieve 5, 15, 30, and 60 mg doses	Up to 4 tablets daily to maintain double-blind
Packaging and labeling	Study intervention will be packaged in blister packs, which will further be packaged into visit box containing 4 weeks of treatment. Each wallet and box will be labeled as required per country requirements.	Matching placebo in blister packs, which will further be packaged into visit box containing 4 weeks of treatment. Each wallet and box will be labeled as required per country requirements.

Study interventions will be dispensed at regular site visits.

6.1.2 Noninvestigational medicinal product

A radiological, signal-enhancing, intravenous (IV) contrast medium will be used for T1 contrast-enhanced MRI sequences. A locally approved medium will be used.

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 (17).

Otherwise, use of these agents will be similar to their routine use and will be sourced locally. The study manual will provide more detail of their administration.

6.1.3 Devices

Not applicable.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

The Investigator or designee must confirm specified 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.

1. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.
2. 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).
3. Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.

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

Under no circumstances will the Investigator supply IMP to a third party, allow the IMP to be used other than as directed by this clinical trial protocol, or dispose of IMP in any other manner. The exception is a duties and taxes paid (DTP) shipment, for which a courier company has been approved by the Sponsor.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

All participants will be centrally assigned to 1 of 8 arms (4 dose groups in each of the 2 cohorts at equal ratio to start with SAR442168 (in Cohort 1) or placebo (in Cohort 2) period before cross-over, using an IVRS/IWRS. A participant cannot be randomly assigned more than once in the study. Before the study is initiated, the telephone number and call-in directions for the IVRS and/or the log in information and directions for the IWRS will be provided to each site. Study interventions will be dispensed at the study visits summarized in the Schedule of Activities (Section 1.3). Returned study interventions should not be re-dispensed to the participants. Investigators will remain blinded to each participant's assigned cohort (sequence) and SAR442168 dose throughout the study.

Blind Break (IVRS/IWRS)

The IVRS/IWRS 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. Participant safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, the Investigator should make every effort to contact the Sponsor prior to unblinding a participant's treatment assignment unless this could delay emergency treatment of the participant. 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 case report form, as applicable.

Methods of blinding

- This study is blinded for dose and SAR442168-placebo administration sequence. Tablets of different SAR442168 dose levels and placebo will be identical. Due to ethical considerations, placebo duration is restricted to 4 weeks, which will allow more objective evaluation of safety events at the beginning of the study period, and will also add to objectivity of evaluation of clinical endpoints
- Investigators will not have access to MRI data except for any non-MS-related findings, which will be communicated in order to evaluate the safety of the participant. The radiology service for the site will be in charge of timely reporting of any non-MS findings on MRI to the Investigator
- The Independent Data Monitoring Committee (IDMC) will be used to periodically monitor safety of this study. Unblinded data will be provided for IDMC 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

At the end of the baseline visit (Day 1), the participant will receive the study intervention for the following 4 weeks. At each following visit, a new kit will be dispensed.

It is the responsibility of the Investigator to check the participant's compliance to the study intervention. Compliance is tracked by counting dispensed and unused tablets at each on-site visit after baseline until the end-of-treatment visit. The Investigator (or authorized delegate) will complete the appropriate pages of the electronic case report form (eCRF) and IMP source document logs by recording the numbers and dates of doses taken (or not) by the participant. The monitor in charge of the clinical trial will check the case report form data by comparing the recorded data with the retrieved IMP kit and data recorded on the IMP source document logs and 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

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

Standard treatment of MS relapse with high-dose glucocorticoids is permitted. Local guidance is to be followed for such treatments.

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

- Other MS disease-modifying treatments
- Acetylsalicylic acid (aspirin)
- Anti-platelet drugs (eg, clopidogrel)
- Anticoagulants, including:
  - Warfarin
  - Heparin, including low-molecular-weight heparins
  - Dabigatran
  - Apixaban, edoxaban, rivaroxaban

Paracetamol/acetaminophen, at doses of ≤3 grams/day, is permitted for use at any time during the study. Short courses (up to 5 days) of NSAIDs (other than acetylsalicylic acid) at the recommended dose may be given during the course of 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 CRF.

[redacted] Use of proton pump inhibitors (eg, omeprazole) should be avoided. Use of antacids (eg, calcium carbonate) should be staggered with respect to SAR442168 dosing, with antacid administration occurring no less than 2 hours before or 2 hours after SAR442168 administration. Use of H2-receptor antagonists (eg, ranitidine) should also be staggered with respect to SAR442168 dosing, with H2-receptor antagonist administration occurring no less than 10 hours before or 2 hours after SAR442168 administration. See Section 10.8 for a list of example drugs with a potential to affect plasma exposure of SAR442168 via reduction of gastric acid.

Based on preclinical drug metabolism studies, SAR442168 is a substrate of the CYP3A and CYP2C8 isoenzymes, and therefore, it is possible that plasma exposures of SAR442168 would be altered if co-administered with other drugs that either induce or inhibit CYP3A and/or CYP2C8 metabolism. This has not been studied in humans to date and therefore, drugs that strongly inhibit or induce CYP3A or CYP2C8 should be avoided, if possible. See Appendix 7, Section 10.7 for the list of drugs not to be used.

6.5.1 Rescue medicine

Not applicable.

6.6 DOSE MODIFICATION

Dose reduction is not foreseen in this study. Participants, Investigators, and the Sponsor's team will be blinded with respect to assigned dose levels. Treatment might 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

A separate, open-label, LTS study will be offered to participants completing the Week 16 visit of this study. Upon completing the double-blinded treatment period, participants already enrolled in the DRI study and all subsequent participants will be given the option to enroll in a LTS follow-up study to assess safety and tolerability of SAR442168. The LTS follow-up study will be described in a separate protocol.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Withdrawal of consent for treatment should be distinguished from (additional) withdrawal of consent for follow-up visits and from withdrawal of consent for nonparticipant contact (eg, medical record checks) follow up. The site should document any case of withdrawal of consent.

7.1 DISCONTINUATION OF STUDY INTERVENTION

7.1.1 Definitive discontinuation

The IMP should be continued whenever possible.

In case the IMP is stopped, it should be determined whether the stop can be made temporarily; definitive IMP discontinuation should be a last resort. Any IMP discontinuation must be fully documented in the eCRF. In any case, the participant should remain in the study as long as possible.

Definitive intervention discontinuation is any intervention discontinuation associated with the definitive decision from the Investigator not to re-expose the participant to the IMP at any time during the study, or from the participant not to be re-exposed to the IMP, whatever the reason.

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 Section 10.6 or if the Investigator believes that it is in best interest of the participant.

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

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

Any abnormal laboratory value or ECG parameter will be immediately rechecked for confirmation after 24 hours before a decision of definitive discontinuation of the intervention for the concerned participant is made.

In case of premature discontinuation of the intervention, the end-of-treatment visit will be conducted.

Handling of participants after definitive intervention discontinuation

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

If possible, and after the definitive discontinuation of intervention, the participants will be assessed using the procedure normally planned for the last treatment day with the IMP including a PK sample. Details are provided in the SoA (Table 1). All cases of definitive intervention discontinuation must be recorded by the Investigator in the appropriate pages of the eCRF when considered as confirmed.

7.1.2 Temporary discontinuation

Temporary intervention discontinuation may be considered by the Investigator because of suspected AEs and/or laboratory abnormalities and/or ECG abnormalities. For all temporary intervention discontinuations, the duration of the discontinuation should be recorded by the Investigator in the appropriate pages of the eCRF.

Temporary intervention discontinuation decided by the Investigator corresponds to >1 dose not administered to the participant.

Analysis of missed doses will be described in the SAP.

7.1.2.1 Rechallenge

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

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.

- If a 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
- See the SoA (Section 1.3) for data to be collected at the time of study discontinuation and follow up and for any further evaluations that need to be completed
- If participants no longer wish to take the IMP, they will be encouraged to remain in the study

Investigators should discuss key visits with participants. The value of all study data should 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 consent to participate 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 nonparticipant 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 re-randomized (treated) in the study. Their participant and kit 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 necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study

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.

- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue the study intervention
- Adherence to the study design requirements, including those specified in the SoA (Section 1.3), is essential
- 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 potential participant's routine clinical management (eg, blood count) and obtained before signing of the informed consent form (ICF) may be utilized for screening or baseline purposes, provided the procedures meet the protocol-specified criteria and were performed within the time frame defined in the SoA (Section 1.3)
- In case of premature discontinuation of study intervention, the end-of-treatment visit will be conducted
- The participant will return 2 to 4 weeks after a premature end-of-treatment visit
- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 70 mL for participants of the main study [redacted] Additional repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples

8.1 EFFICACY ASSESSMENTS

8.1.1 Magnetic resonance imaging assessments

Cranial (brain) MRI with and without Gd contrast will be performed. Basic MRIs will be performed for all participants at all study sites and will consist of T2- and T1-weighted sequences without and with Gd contrast.

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 (17).

The study manual containing instructions for standard image acquisition requirements for brain MRI, data transfer to the central review center, archiving and shipping will be provided to all

participating sites. Study site personnel will undergo training regarding MRI acquisition and data handling procedures, training will be documented, and adherence to the manual will be monitored throughout the study with retraining performed as necessary.

New T1 Gd-enhancing hyperintense and new and enlarging T2 lesions will be evaluated at each visit as per the SoA (Section 1.3), comparing lesion count to that from the previous MRI scan.

Unless specified otherwise, the baseline brain MRI will be used as the reference to assess all MRI-derived endpoints. The baseline MRI will be the last MRI performed before the randomization visit. Standardized endpoint evaluation is assured by central review of brain MRI scans. Blinded central review will be performed for all MRI-derived endpoints. Magnetic resonance imaging reviewers will be blinded to treatment assignments and to other participant data. Details on MRI testing and central review will be described in the study manual.

Spinal MRIs may be required if spine MS lesions are suspected by the Investigator. Spinal MRIs will be evaluated locally and reported in the eCRF. No central review will be performed for spinal MRIs.

Magnetic resonance imaging scans need to be reviewed locally for any non-MS pathology to assure safety reporting as per Section 8.3.5. In case of detection of non-MS findings, the MRI scan report needs to be reported to the Treating Investigator. Normal MS findings on MRI should not be disclosed to Investigators or to the site team if not relevant to any safety concern.

[redacted]

8.1.2 Multiple sclerosis relapse

8.1.2.1 Unscheduled assessment visits for a suspected multiple sclerosis relapse

Participants must be instructed to immediately report new neurological symptoms and recurring or worsening of previous symptoms to the Investigator. Any reported symptoms will be collected. If a participant reports symptoms that may be consistent with relapse, an unscheduled assessment visit with the Investigator will be scheduled as soon as possible (whenever possible within 7 days of onset of the symptoms). The Investigator will assess whether the reported episode is consistent with the definition of MS relapse (see Section 8.1.2.2). If it is consistent with the definition of MS relapse or if there is any doubt and relapse cannot be ruled out, an EDSS assessment should be performed.

All MS relapses are to be reported on the MS relapse eCRF page. Multiple sclerosis relapse should not be reported as an AE/SAE unless, in the judgment of the Investigator, it is unusually severe or medically unexpected (see Section 8.3.5 for reporting rules).

Unscheduled visit activities are detailed in SoA (Section 1.3), they need to be adapted, if other pathology than MS is cause for it, and additional examinations or laboratory tests are needed for safety follow up and optimal treatment decisions.

8.1.2.2 Definition of multiple sclerosis relapse

For the purposes of this study, MS relapse is defined as acute, 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, and
- Be present at normal body temperature (ie, no infection, excessive exercise, or excessively high ambient temperature)

Note: An exacerbation or recurrence of symptoms and signs 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 injection of interferon beta), raised core body temperature (the Uhthoff phenomenon), or systemic cytokine release (such as occurs with the administration of alemtuzumab) will not be considered a relapse.

It is at the Investigator's discretion and responsibility to choose the best treatment option for any MS relapse, such as a high-dose glucocorticoid treatment course.

Analysis of relapses will be detailed in the SAP.

8.1.3 Expanded Disability Status Scale evaluation

The Investigator will perform the EDSS evaluation (13) as indicated in the SoA (Section 1.3). All Investigators will be trained and certified to perform the EDSS in a consistent manner.

EDSS scores will be captured on paper. Details will be included in the study manual.

The Investigator 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 neurological symptoms in each of 7 functional domains (visual, brainstem, pyramidal [motor], cerebellar [coordination], sensory, cerebral and bowel/bladder) will be performed. Ambulation will also be scored as part of the evaluation. Fatigue may optionally be evaluated, but it will not contribute to the EDSS score. Details of EDSS assessment and scoring will be described in the study manual.

[redacted]

[redacted]

8.2 SAFETY ASSESSMENTS

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

The definitions of AEs and SAEs can be found in Appendix 3 (Section 10.3). For the purpose of this protocol, MS relapses (Section 8.1.2) are waived from reporting as AEs except if they meet the criteria of an SAE. Nonserious MS relapses will be collected on a special eCRF page and will be analyzed as an efficacy endpoint. Following an MS relapse assessment, (Section 8.1.2), events that are concluded as not meeting the criteria of an MS relapse will be reported as AEs.

8.2.1 Physical examinations

The complete physical examination will include, at a minimum, assessments of general appearance, head and neck, abdomen, lymph nodes, skin (signs of bleeding include bruises, petechial rash), cardiovascular, respiratory, gastrointestinal, musculoskeletal, and neurological systems. Height and weight will also be measured and recorded. Details will be provided in the study manual.

- The brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen)
- Investigators should pay special attention to clinical signs related to previous serious illnesses
- Any new finding or worsening of a previous finding should be reported as a new AE
- The SoA (Table 1) provides a schedule of physical examinations. A full examination should be performed whenever the Investigator judges a need for complete evaluation of the participant

8.2.2 Vital signs

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

8.2.3 Electrocardiograms

- Twelve-lead ECG will be obtained as outlined in the SoA (Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. At least one longer rhythm monitoring recording needs to be part of each ECG testing. The ECG will be reviewed by a cardiologist for confirmation of abnormality and clinical evaluation. Refer to Section 7 for QTc withdrawal criteria and any additional QTc readings that may be necessary

8.2.4 Clinical safety laboratory assessments

See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and to the SoA (Section 1.3) for the timing and frequency.

- The Investigator must review the laboratory report, document this review, and record any clinically 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 that 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 4 weeks after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or medical monitor
  - If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified and the Sponsor notified

All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).

- If laboratory values from non-protocol specified laboratory 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 Suicide risk monitoring

SAR442168 is considered to be CNS-active, and therefore routine suicide risk monitoring will be performed.

The C-SSRS and thorough clinical evaluation of complaints will be used for suicide risk assessment. Any observations or events of clinical importance will be reported as AEs.

8.2.5.1 The Columbia Suicide Severity Rating Scale

The C-SSRS is a tool used to assess the lifetime suicidality of a participant and to track suicidal events through the study. The structured interview prompts recollection of suicidal ideation, including the intensity of the ideation, behavior and attempts with actual/potential lethality. The scale will be administered by the Investigator or a qualified designee at the time points indicated in the SoA (Section 1.3).

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 Adverse events of special interest

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

- Acute hypersensitivity/anaphylaxis
- 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;
  - Pregnancy occurring in a female participant entered in the clinical study or in a female partner of a male participant entered in the clinical study. It will be qualified as an SAE only if it fulfills one of the seriousness criteria (see Appendix 3 [Section 10.3]).
  - In the event of pregnancy in a female participant, IMP should be discontinued.
  - Follow up of the pregnancy in a female participant or in a female partner of a male participant is mandatory until the outcome has been determined (See Appendix 4 [Section 10.4])
- Symptomatic overdose (serious or nonserious) with IMP/NIMP
  - An overdose (accidental or intentional) with the IMP/NIMP 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, adjusted according to the tested drug.
  - Of note, asymptomatic overdose must be reported as a standard AE.
- Increase in ALT
  - Any increase of ALT >3 x ULN

Other project specific AESI(s)

- ECG observation of QTc ≥500 ms or of clinically significant arrhythmia (eg, atrial fibrillation, atrial flutter) confirmed by a cardiologist
  - Serious infection, particularly any opportunistic infection

- Major hemorrhagic events, including symptomatic bleeding in a critical area or organ, such as CNS or intraocular bleeding resulting in an SAE
- Thrombocytopenia platelet count <100 x 109/L (see Appendix 6, Section 10.6 for management flow chart)

The definition of an AE or 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).

8.3.2 Time period and frequency for collecting AE and SAE information

All SAEs will be collected from the signing of the ICF until the last study visit at the time points specified in the SoA (Section 1.3).

All AEs will be collected from the signing of the ICF until the last visit 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 within 24 hours, as indicated in Appendix 3 (Section 10.3). The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek 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.

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

8.3.3 Method of detecting AEs and SAEs

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

8.3.4 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 10.3), 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).

8.3.5 Regulatory reporting requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor's policy and forwarded to Investigators as necessary
- 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 Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements

8.3.6 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 last visit of the study.

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).

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are considered SAEs.

8.3.7 Cardiovascular and death events

Atrial fibrillation, atrial flutter, observation of QTc ≥500 ms, or other clinically significant arrhythmia 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 IDMC). Central ECG review will be performed to assure consistency in ECG evaluation.

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.

8.3.8 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 an SAE. Hospitalization for MS relapse, if done routinely at the site (eg, for high dose IV methylprednisolone), will not be considered as a seriousness criterion for this study. Multiple sclerosis relapses will be collected on the eCRF and be analyzed as part of the efficacy analysis.

Other worsening of neurological symptoms that do not meet the definition of MS relapse will be reported as AEs according to general safety reporting rules.

8.3.9 Reporting of safety findings from magnetic resonance imaging

Magnetic resonance imaging scans need to be reviewed locally for any non-MS pathology. In case of such findings, the MRI report needs to be provided to the Investigator for appropriate safety reporting. When available, a diagnosis of pathology as a cause of such MRI findings or the findings themselves will be reported as an AE until the diagnosis is clear.

Multiple sclerosis findings on MRI do not need to be reported unless they are deemed unusual and thus a distinct safety finding.

8.3.10 Guidelines for reporting product complaints

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

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

8.3.10.1 Medical devices

Not applicable.

8.4 TREATMENT OF OVERDOSE

Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the Investigator should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities until study intervention can no longer be detected systemically and activity is over (at least 9 days).
3. Obtain a plasma sample for PK analysis within 1 day from the date of the last dose of study intervention if possible or later if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

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

8.5 PHARMACOKINETICS

8.5.1 Sampling time

Samples for SAR442168 PK analysis will be collected 1 hour post-dose (±0.5 hour) at visits during Weeks 1, 4, 8, 12, and 16 for all participants in both cohorts. An additional PK sample will be collected 3 hours post-dose (±0.5 hour) at visits during Weeks 4 and 12 for all participants in both cohorts. Data of the most recent meal prior to PK sampling will be noted in the eCRF.

8.5.2 Pharmacokinetics handling procedure

Detailed procedures of sample preparation, storage, and shipment will be described in the specific laboratory manual. A total of 2 mL of blood is to be collected for each PK sample.

The total amount of blood for PK per participant and the total number of samples taken in the study are presented in Table 4.

Table 4 - Blood volume per participant and total number of samples

Number of pharmacokinetics samples by participant	Blood volume per participant for pharmacokinetics	Total number of samples in the study for pharmacokinetics
7	7 x 2 mL = 14 mL	7 x 120 samples = 840 samples

8.5.3 Bioanalytical method

SAR442168 and its metabolite PRN2677 will be assayed by a validated LC/MS method. The details of the bioanalytical method will be specified in the study manual.

8.5.4 Pharmacokinetics parameters

SAR442168 concentrations at selected time points after IMP intake will be reported using descriptive statistics. Additional PK parameters such as C_{max}, t_{max}, and AUC at steady state will be estimated using a population PK approach. These parameters will be presented in a separate, stand-alone report.

[redacted]

[redacted]

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

The primary objective of this study is to assess the dose-response relationship based on the primary endpoint (number of new Gd-enhancing T1-hyperintense lesions as detected by brain MRI) at the end of 12 weeks of SAR442168 treatment. The null hypothesis is a flat, no dose-response curve for the primary endpoint and the alternative is that there is a dose-response signal.

9.2 SAMPLE SIZE DETERMINATION

The study will have 120 participants equally randomly assigned to 1 of 4 SAR442168 doses in 2 cohorts (60 participants in each of Cohorts 1 and 2). Cohorts 1 and 2 represent different treatment sequences, and participants in each will cross-over to SAR442168 or placebo in a blinded manner.

The 60 participants in Cohort 2 will start with a 4-week placebo run-in that will be utilized as the placebo data in analyses for the primary endpoint based on the assumption of the constant monthly mean number of new Gd-enhancing T1-hyperintense lesions over 12 weeks of placebo treatment. Assuming 15% of participants without the primary endpoint at the end of 12 weeks of SAR442168, 105 participants (26 per SAR442168 dose) has at least 83% power to detect the maximum reduction of 85% using a 2-step MCP-Mod with 6 pre-defined dose response curves (2 E_{max} models, a quadratic model, a linear model, a logistic model, and an exponential model). This calculation assumes the dispersion parameter of 2 (estimated from Week 12 placebo data from the vatelizumab [SAR339658] DRI13839 study), within-subject correlation ranging from -0.9 to 0.9 in measurements between 4-week placebo and 12-week SAR442168 in Cohort 2, and placebo mean number of ≥1 for new Gd-enhancing T1-hyperintense lesions at 4 weeks.

This power was calculated using the package Dose Finding from the Comprehensive R Archive Network (CRAN) (18), using the 6 candidate curves considered for dose-response modelling in a negative binomial regression framework.

9.3 POPULATIONS FOR ANALYSES

For purposes of analysis, the following populations are defined (Table 5):

Table 5 - Populations for analyses

Population	Description
Enrolled	All participants who sign the ICF
Randomly assigned to study intervention	All participants who are randomly assigned to the study intervention
mITT	The primary efficacy population will be the mITT population, defined as all randomly assigned participants exposed to study intervention. The 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 to the study intervention and who take at least 1 dose of the study intervention. Participants will be analyzed according to the intervention they actually receive.

Abbreviations: ICF: informed consent form; mITT: modified intent-to-treat

9.4 STATISTICAL ANALYSES

The SAP will be developed and finalized before database lock and will describe the participant populations to be included in the analyses and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses for the primary and secondary endpoints.

9.4.1 Efficacy analyses

The primary efficacy analysis will be based on the mITT population. For the endpoints assessed by change from baseline, the baseline values are defined as the last measurements collected on or before the randomization visit (Day 1) prior to initiation of the first dose of study intervention. Data from Cohorts 1 and 2 will be combined for the primary analysis (ie, data at Week 12 for Cohort 1 and at Week 16 for Cohort 2 for the number of new Gd-enhancing T1-hyperintense lesions).

For each cohort, descriptive statistics will be summarized over time (Weeks 4, 8, 12, and 16) when appropriate. The summary from Cohort 1 will include descriptive statistics for the 4-week placebo period after 12 weeks of SAR442168 treatment. Additional efficacy analyses will be described in the SAP.

Table 6 - Efficacy analyses

Endpoint	Statistical Analysis Methods
Primary • Number of new Gd-enhancing T1-hyperintense lesions at the end of 12 weeks of SAR442168 treatment as detected by brain MRI	For the mITT population, the dose-response relationship will be evaluated by a 2-step MCP-Mod procedure. The first step of this procedure tests for an efficacy signal (compared to the null hypothesis of a flat, no dose-response curve) in a procedure that controls the type 1 error. To account for the uncertainty of the dose-response shape, 6 candidate models have been considered to cover diverse and potential dose-response profiles: 2 E_{max} models (ED_{50} = 10 mg, ED_{50} = 30 mg), a linear model, a quadratic model, a logistic model, and an exponential model. The second step is the estimation of the dose-response curve, provided that an efficacy signal is established in the first step. A negative binomial regression model with covariates for baseline Gd-enhancing T1-hyperintense lesion count, treatment, and cohort (Cohort 1 or Cohort 2) will be used to assess the mean count of new Gd-enhancing T1-hyperintense lesions in each of the 4 dose groups at the end of 12 weeks of SAR442168 treatment and at the end of 4 weeks of placebo. The 4-week post-randomization placebo data from Cohort 2 (ie, Week 4 data from Cohort 2) will be utilized as the placebo data at Week 12 in analysis, under the assumption of a constant rate of Gd-enhancing T1-hyperintense lesion formation if participants would be receiving placebo over 12 weeks. Participants in Cohort 2 contribute to the placebo data (at Week 4) as well as the data of 5 SAR442168 doses (at Week 16). Thus, in order to account for the potential correlation between the measurements in the 4-week placebo period and the subsequent 12-week SAR442168 treatment period in Cohort 2, a GEE approach is used to fit the negative binomial model accounting for the within-participant correlation via the repeated statement in SAS PROC GENMOD. A minus log transformation of the mean lesion count will be entered into the MCP-Mod procedure. The null hypothesis of a flat dose-response curve (ie, no dose–response relationship) at the end of 12 weeks of SAR442168 treatment for the primary endpoint will be jointly evaluated for each of the 6 candidate dose response models with a contrast test that controls the family wise error rate at 2-sided alpha = 0.05. If step 1 yields significant results, the best fitting model from the 6 predefined candidate models will be chosen using the generalized AIC. The dose for the Phase 3 program will then be estimated from the final selected model. Data from Cohorts 1 and 2 will be combined for the primary analysis (ie, data at Week 12 for Cohort 1 and at Week 16 for Cohort 2 for the number of new Gd-enhancing T1-hyperintese lesions). Data from each cohort may be separately explored. Descriptive statistics will also be provided for the 4 SAR442168 doses for number of new Gd-enhancing T1-hyperintense lesions over time (ie, Week 4/Week 8, Week 8/Week 12, and Week 12/Week 16 for Cohort 1/Cohort 2).
Secondary • Number of new or enlarging T2 lesions at the end of 12 weeks of SAR442168 treatment • Total number of Gd-enhancing T1-hyperintense lesions at the end of 12 weeks of SAR442168 treatment	For the secondary endpoint of number of Gd-enhancing T1-hyperintense lesions at the end of 12 weeks of SAR442168 treatment, a similar negative binomial model and MCP-Mod procedure will be used. As it is reasonable to assume a constant rate of lesion formation over 12 weeks under placebo for total number of Gd-enhancing T1-hyperintense lesions, the same approach as that utilized for the primary endpoint will be used, by using the Week 4 data in Cohort 2 as the Week 12 placebo data while accounting for the within-participant correlation. Descriptive statistics over time will also be provided for the 4 SAR442168 doses. For the secondary endpoint of number of new or enlarging T2 lesions, descriptive summary statistics over time (4, 8, 12, and 16 weeks) will be provided for each of the 4 SAR442168 doses. Further, a similar MCP-Mod approach will be explored if it is deemed reasonable to extrapolate the Week 4 data from Cohort 2 to the Week 12 placebo data.

Endpoint	Statistical Analysis Methods
[redacted]	

9.4.2 Safety analyses

All safety analyses will be performed on the safety population.

All safety summaries will be descriptive. No statistical significance tests will be performed on safety data. Safety endpoints are described in Table 7.

The baseline value is defined generally as the last available value before the first administration of randomized study intervention.

Safety data for the first 4 weeks following randomization (where participants in Cohort 2 receive placebo) will be summarized by SAR442168 and placebo. Safety data during the 4-week placebo period (ie, 4 weeks) in Cohort 1 will be summarized separately and displayed by the SAR442168 dose group and overall.

For SAR442168 treatment safety data, summaries by dose group, by time on SAR442168, and overall will be provided.

For safety variables, the following observation periods are defined and used for classification of AEs, determination of on-treatment PCSA values, and the last on-treatment value for laboratory and vital sign parameters:

- The pretreatment period is defined as the time from the signed ICF to the first administration of randomized study intervention
- For the purpose of defining ‘treatment-emergent’, the on-treatment period is defined as the time from the first administration of randomized study intervention until the last study visit. The treatment periods are further defined as:
  - The “Weeks 1 to 4 period” is defined as the time from first administration of randomized study treatment to the administration of the Week 4 study treatment. For Cohort 1 this is SAR442168 treatment for 4 weeks and for Cohort 2 is placebo treatment for 4 weeks
  - The “SAR442168 treatment period” is defined as Weeks 1 to 12 for Cohort 1 and Weeks 4 to 16 for Cohort 2

Note: participants from the Cohort 1 Weeks 1 to 4 period are also included in the 12 weeks of the SAR442168 period.

- The "placebo/post-SAR442168 dose period" is defined as Week 12 to Week 16 for Cohort 1. This is the 4 weeks of placebo treatment following 12 weeks of SAR442168 treatment

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. The analyses of AEs will focus on treatment-emergent adverse events (TEAEs).

- Pretreatment AEs are defined as AEs that developed, or worsened, or become serious during the pretreatment period
- Treatment-emergent AEs are defined as AEs that develop, worsen, or become serious during the on-treatment period

The following definitions will be applied to laboratory parameters, ECG, and vital sign results:

- Potentially clinically significant abnormality (PCSA) values are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review and are defined by the Sponsor for clinical laboratory tests and vital signs
- Potentially clinically significant abnormality criteria will determine which participants had at least 1 PCSA during the on-treatment period, taking into account all evaluations performed during the on-treatment period including unscheduled or repeated evaluations. The number of all such participants will be the numerator for the on-treatment PCSA percentage

Table 7 - Safety analyses

Safety measures	Statistical Analysis Methods
Adverse events • AEs • TEAEs • SAEs • AEs leading to IMP or study discontinuation • AEs leading to death • AESIs	• Adverse event incidence tables will be presented by system organ class (sorted by internationally agreed order), high-level group term, high□level term, and preferred term sorted in alphabetical order and will present the number (n) and percentage (%) of participants experiencing an AE, by treatment period for: the Weeks 1 to 4 period for each SAR442168 dose group or placebo, for the SAR442168 dose period, by SAR442168 dose group, and for the placebo/post-SAR442168 dose period. Multiple occurrences of the same event in the same participant will be counted only once within a treatment period in the tables. The denominator for computation of percentages will be the number of participants in the safety population (N) within each SAR442168 dose group or placebo, for the treatment period. • The incidence of TEAEs will also be summarized by severity grade/intensity, and relationship to IMP, by treatment period for: the Weeks 1 to 4 period for each SAR442168 dose group or placebo, for the SAR442168 period, by SAR442168 dose group, and for the placebo/post-SAR442168 period. • Deaths and serious TEAEs will be summarized and presented as numbers and percentages of participants, by treatment period for: the Weeks 1 to 4 period for each SAR442168 dose group or placebo, for the SAR44168 period, by SAR442168 dose group, and for the placebo/post-SAR442168 period. • The following summaries will be generated for deaths: - Numbers (%) of participants who died by the following categories and reasons for death summarized for the safety population by treatment received ▪ Death on study: deaths from any cause occurring after the randomization, and

Safety measures	Statistical Analysis Methods
	to the end of the study: eg, to the date of last protocol planned visit if participants complete the whole study period as defined in the protocol ▪ Death on treatment: deaths from any cause occurring during the on-treatment AE period ▪ Death post-study: deaths from any cause occurring after the end of study, if any, eg, after the date of last protocol planned visit if participants complete the whole study period ▪ Deaths in nonrandomized participants • Treatment-emergent AEs leading to treatment discontinuation will be summarized and presented as numbers and percentages of participants by treatment period for: the 'Weeks 1-4' period for each SAR442168 dose group or placebo, for the 'Active Dose' period, by SAR442168 dose group, and for the 'Placebo-Post Active Dose' period. • Numbers (%) of participants for each AESI will be summarized. by treatment period for: the Weeks 1 to 4 period for each SAR442168 dose group or placebo, for the SAR442168 period, by SAR442168 dose group, and for the placebo/post-SAR442168 period.
Vital signs, ECG and laboratory data	• Vital signs and ECG data will be summarized by treatment period for: the Weeks 1 to 4 period for each SAR442168 dose group or placebo, for the SAR442168 period by SAR442168 dose group, and for the placebo/post-SAR442168 period by baseline and change from baseline at scheduled visits with descriptive statistics. Numbers and percentages of participants with at least 1 PCSA by treatment period for: the Weeks 1 to 4 period for each SAR442168 dose group or placebo, for the SAR442168 period by SAR442168 dose group, and for the placebo/post-SAR442168 period will be summarized for each vital sign and ECG variable. • Clinical laboratory test results will be summarized by treatment period for: the Weeks 1 to 4 period for each SAR442168 dose group or placebo, for the SAR442168 period by SAR442168 dose group, and for the placebo/post-SAR442168 period by baseline value and change from baseline value at each scheduled visit using descriptive statistics. • Numbers and percentages of participants with at least 1 incident of PCSA during the on-treatment period will be summarized by treatment period for: the Weeks 1 to 4 period for each SAR442168 dose group or placebo, for the SAR442168 period by SAR442168 dose group, and for the placebo/post-SAR442168 period. Shift tables showing change from baseline will be provided as necessary. • Potentially clinically significant abnormality values with flags indicating out-of-range values will be provided.

9.4.3 Other analyses

The individual PK concentrations will be descriptively summarized by visit [redacted].

9.5.1 Independent Data Monitoring Committee (IDMC)

An IDMC will be used to monitor safety of the study. Unblinded IDMC reports will be prepared by an independent unblinded statistician for IDMC data reviews. Timing of such reviews as well as the specific responsibilities and mode of operation of the IDMC will be described in the IDMC charter.

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, Investigator's Brochure, and other relevant documents (eg, advertisements) must be submitted to the health authorities (competent regulatory authority) as required by local regulation and to an IRB/IEC by the Investigator and reviewed and approved by those health authorities and the IRB/IEC before the study is initiated
- Any amendments to the protocol will require health authority (as required by local regulations) and 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 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 for complete disclosure or certification to the appropriate regulatory authorities. Investigators are responsible for providing this information before participating in the study and updating this information if any relevant changes occur during the course of the study and for 1 year after its completion.

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

10.1.4 Data Protection

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

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 agencies (eg, on the African American population for the FDA or on the Japanese population for the Pharmaceuticals and Medical Devices Agency in Japan).

- 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 that 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

Independent Data Monitoring Committee

An IDMC, 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 IDMC are to review and evaluate the safety data and to assess futility through an interim analysis during the course of the trial and to make appropriate recommendations to the Sponsor regarding the conduct of the clinical trial.

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

10.1.6 Dissemination of Clinical Study Data

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

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

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

10.1.7 Data Quality Assurance

- All participant data relating to the study will be recorded on the eCRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF

- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data
- 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 end of the clinical study 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
- The 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 the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- 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 recruitment of participants by the Investigator
- Discontinuation of further study intervention development

10.1.10Publication Policy

- The results of this study will be published or presented at scientific meetings
- 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. A coordinating Investigator and other major contributors will be invited to be authors by mutual agreements. Authors agree to submit all manuscripts or abstracts to the Sponsor at least 4 weeks before submission
- 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 8 will be performed by the central or local laboratory (as mentioned in the table).

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

Table 8 - Protocol-required safety laboratory assessments

Laboratory assessments	Parameters			
Hematology (central)	Platelet count Red blood cell (RBC) count Hemoglobin Hematocrit	RBC indices: MCV MCH % reticulocytes	White blood cell (WBC) count with differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Coagulation	PT/INR	aPTT		
Clinical chemistry (central)[a]	Blood urea nitrogen (BUN)	Potassium	Aspartate aminotransferase (AST)/ serum glutamic-oxaloacetic transaminase (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	Alanine aminotransferase (ALT)/ serum glutamic-pyruvic transaminase (SGPT)	Total protein
	Lipase	Amylase	Creatine phosphokinase	

Laboratory assessments	Parameters			
	Glucose (nonfasting)	Calcium	Alkaline phosphatase	Serum FSH Serum human chorionic gonadotropin (hCG) pregnancy test
Routine urinalysis (central)	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick, urine drug screen • Microscopic examination (if blood or protein)			
Other screening tests (central)	• Hepatitis B surface antigen (HBsAg), and hepatitis C virus antibody, other infectious disease if locally required			
Other screening tests (local)	• Urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[b] • Serology (HIV antibody, or other tests)] if locally required • TB/QuantiFERON-TB Gold® test or equivalent The results of each locally done test must be entered into the eCRF.			

NOTES:
a Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Appendix 6, Section 10.6. All events of ALT ≥3 × upper limit of normal (ULN) and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international normalized ratio (INR) >1.5, if INR measured that may indicate severe liver injury (possible Hy's Law) must be reported as an SAE.
b Local urine testing will be standard for the protocol except screening, unless only serum testing is required by local regulation or IRB/IEC, or needed for inconclusive urine test.

Investigators must document their review of each laboratory safety report.

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)
- 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 fulfill the definition of an AE or SAE

Events NOT meeting the AE definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments 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 as per the definition above, then it cannot be an SAE even if seriousness 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 that 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) that 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 AEs AND/OR SAEs

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's representative instead of completion of the AE/SAE eCRF page. Medical records may need to be submitted as additional data for SAE and AESI reporting. They must be anonymized in such a case by replacing the participant's name and initials by the participant number of this study
- There may be instances when copies of medical records for certain cases are requested by the Sponsor's representative. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor representative
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE

Assessment of intensity

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

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe

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

Assessment of causality

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than 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 Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to the Sponsor's representative. However, **it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor's representative**
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment
- The causality assessment is one of the criteria used when determining regulatory reporting requirements

Follow up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor's representative to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor's representative with a copy of any post-mortem findings including histopathology
- New or updated information will be recorded in the originally completed eCRF
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information

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 for more than 24 hours, then the site will use the paper SAE data collection tool (see next section)
- 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

SAE reporting to the Sponsor's representative via case report form

- Facsimile transmission of the paper SAE 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 paper 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 case report form pages within the designated reporting time frames
- Contacts for SAE reporting can be found in 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 post-menopausal unless permanently sterile (see below).

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

   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 FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

- Females on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen 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

Male participants

- Male participants with female partners of childbearing potential are eligible to participate if they agree to ONE of the following [during the protocol-defined time frame in Section 5.1]:
- Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent
- Agree to use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year as described in Table 9 when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant

- In addition, male participants must refrain from donating sperm for the duration of the study and for 3 months after the last dose of study intervention.
- Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration for 3 months after the last dose.

Female participants

As definitive reproduction toxicity studies have yet to be conducted with SAR442168, the Investigator is directed to take appropriate precautions during exposure of WOCBP in this clinical trial. Female participants of childbearing potential are eligible to participate if they agree to use a double contraception method including a highly effective method of contraception consistently and correctly as described in Table 9 from inclusion and up to 2 months after the last study dose.

In addition, WOCBP must refrain from donating ova for the duration of the study and for 2 months after the last dose of study intervention.

Table 9 - Highly effective contraceptive methods

Highly effective contraceptive methods that are user dependent[a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation • Oral • Intravaginal • Transdermal
Progestogen only hormonal contraception associated with inhibition of ovulation • Oral • Injectable
Highly effective methods that are user independent[a]
Implantable progestogen only hormonal contraception associated with inhibition of ovulation • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • Bilateral tubal occlusion
Vasectomized partner *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
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.*
NOTES: *a* Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

PREGNANCY TESTING:

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive urine or serum pregnancy test
- Additional pregnancy testing should be performed at monthly intervals during the intervention period and at 1 month after the last dose of study intervention and as required locally
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected

COLLECTION OF PREGNANCY INFORMATION:

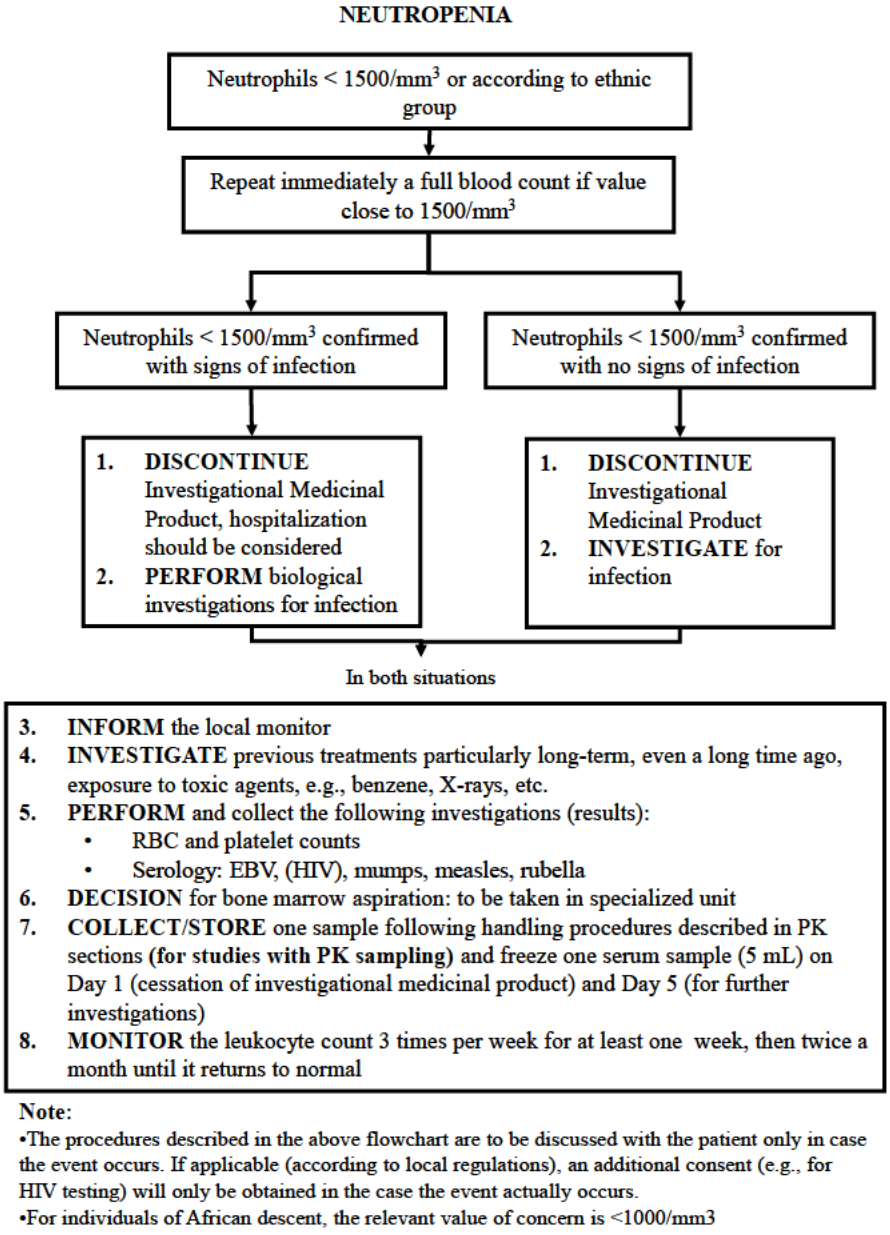
Male participants with partners who become pregnant

- 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. This applies only to male participants who receive SAR442168
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female participants who become pregnant

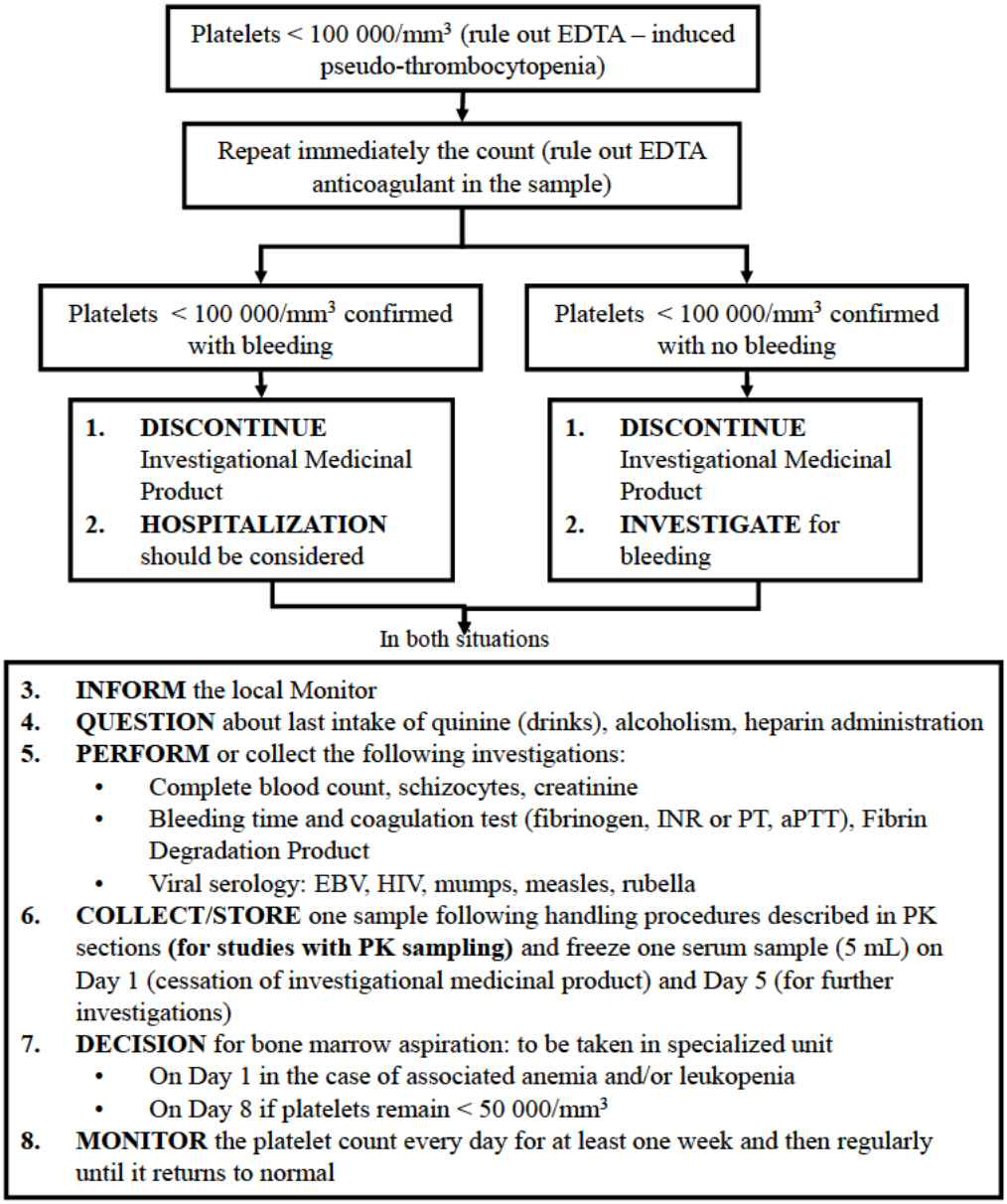
- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow up information on the participant and the neonate and the information will be forwarded to the Sponsor. Generally, follow up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure
- Any pregnancy complication or elective termination of a pregnancy 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 8.3.5 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
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study

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



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 Section 10.3 is met.

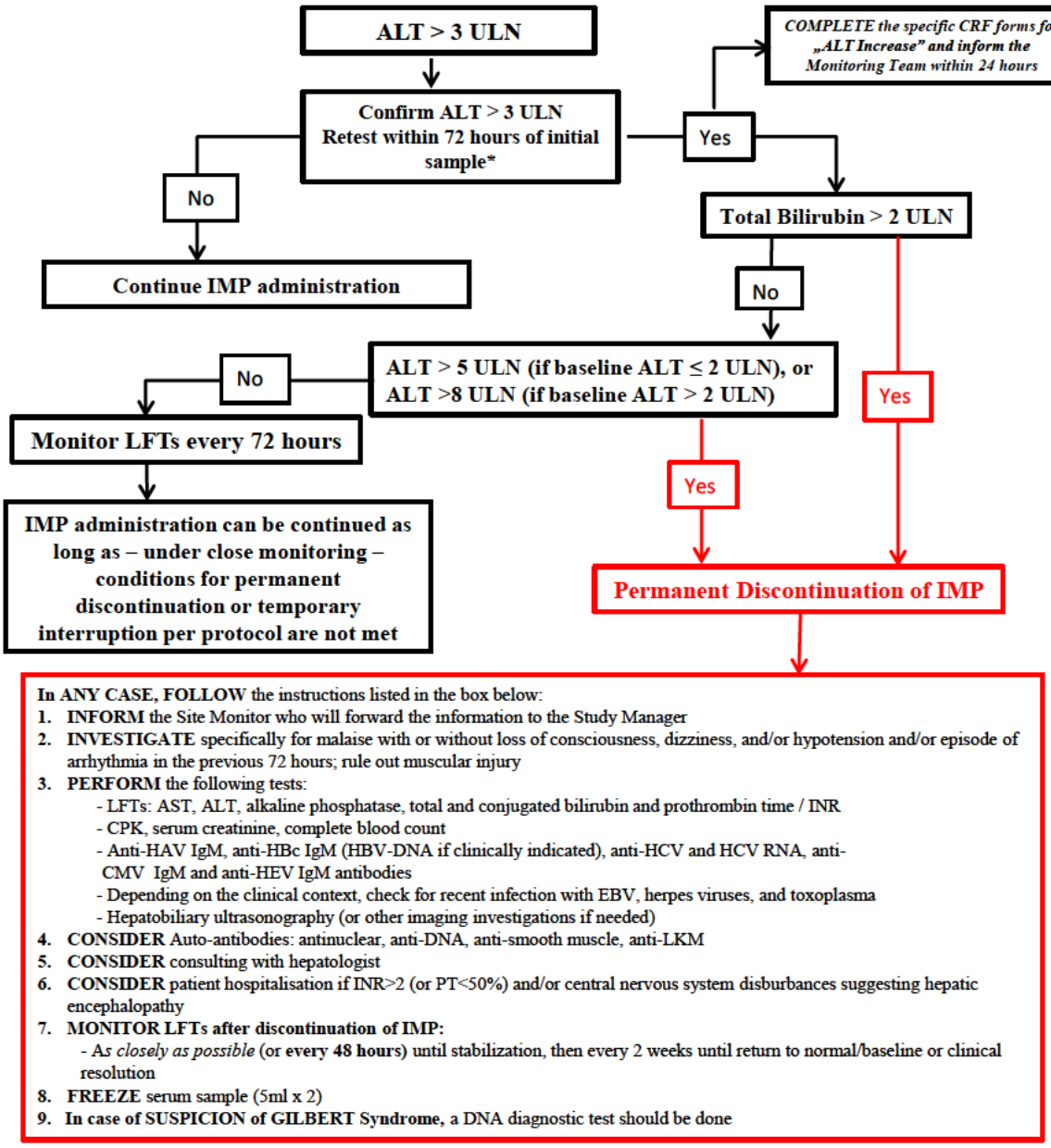
THROMBOCYTOPENIA



Note:
The procedures above flowchart are to be discussed with the patient only in case described in the the event occurs. If applicable (according to local regulations), an additional consent (e.g., for HIV testing) will only be obtained in the case the event actually occurs.

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 Section 10.3 is met.

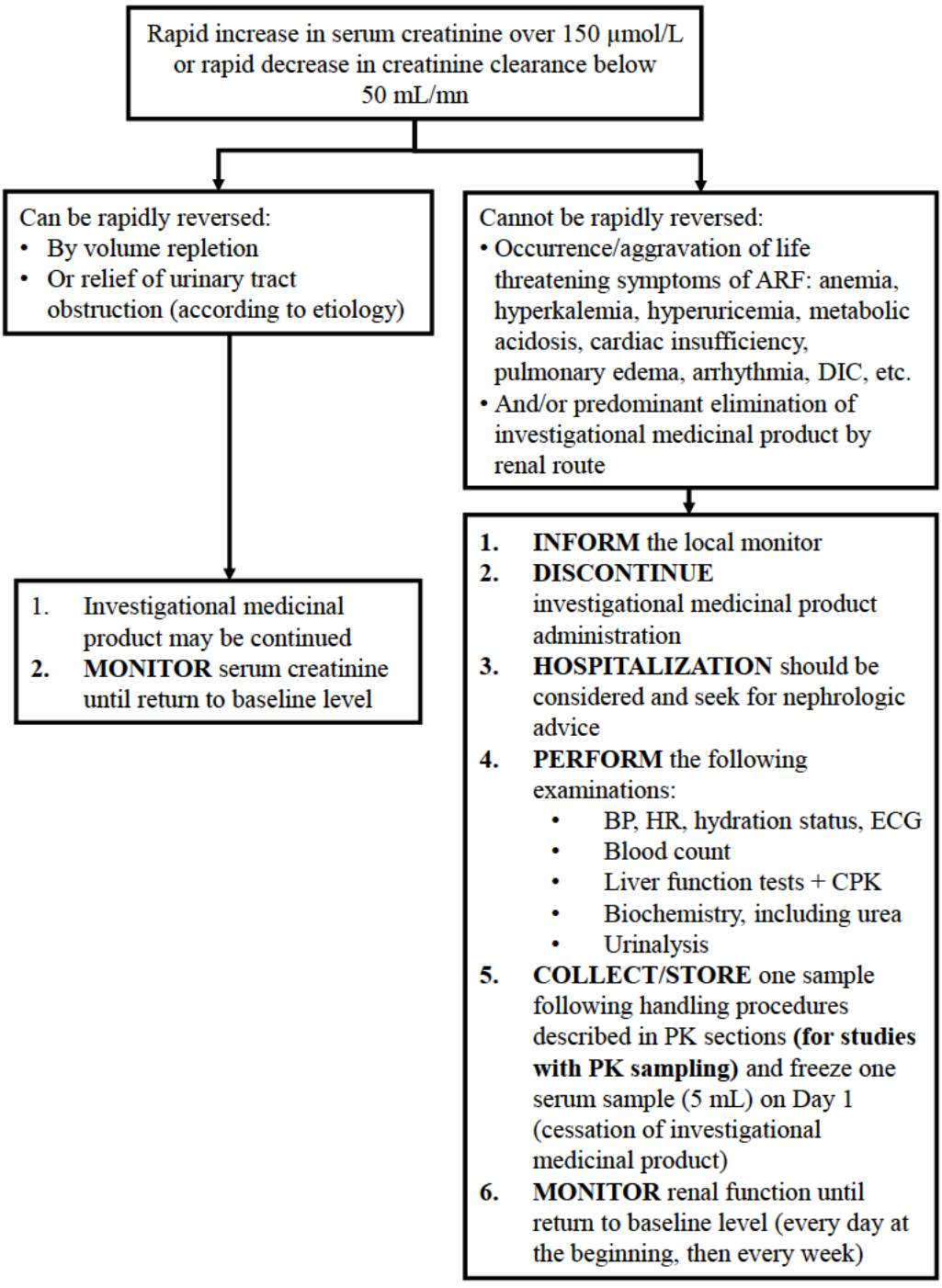
INCREASE IN ALT



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

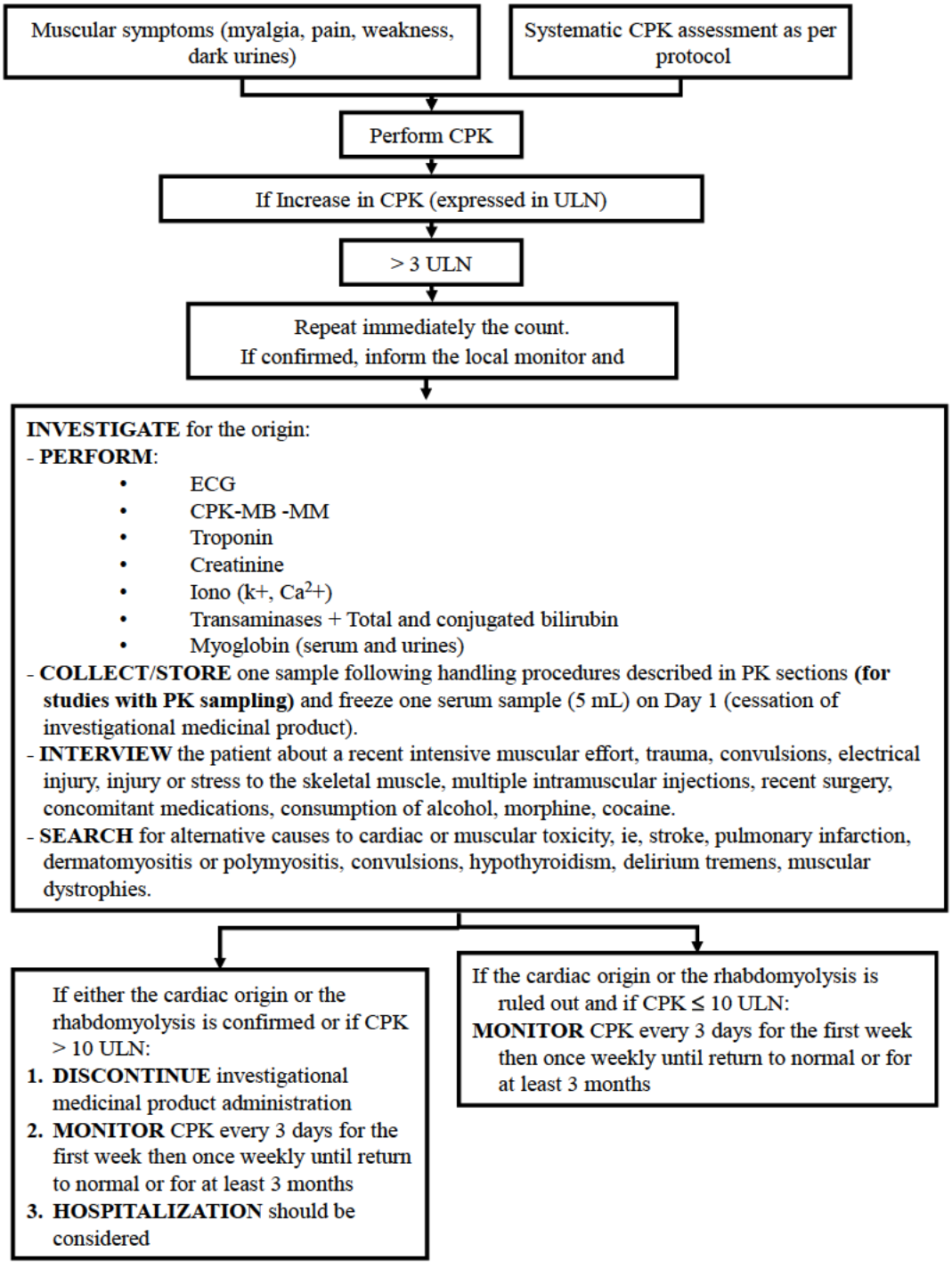
- "Baseline" refers to ALT sampled at baseline visit; or if baseline value unavailable, to the latest ALT sampled before the baseline visit. The algorithm does not apply to the instances of increase in ALT during screening.
- See Section 8.3 for guidance on safety reporting.
- Normalization is defined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

INCREASE IN SERUM CREATININE



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 Section 10.3 is met.

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



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

10.7 APPENDIX 7: LIST OF EXAMPLE DRUGS WITH A POTENTIAL TO CHANGE WITH SAR44168 METABOLISM

The following drugs should not be taken during the study due to their potential to change SAR44168 kinetics due to interaction with P450-mediated metabolism, being potent inducers or inhibitors of CYP3A or CYP2C8 liver enzymes (per the lists of the Drug Interaction Database Program of the University of Washington (www.druginteractioninfo.org).

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

Strong CYP3A Inhibitors:

Viekira Pak
Indinavir/RIT
Tipranavir/RIT
Ritonavir
Cobicistat (GS-9350)
Ketoconazole
Indinavir
Troleandomycin
Telaprevir
Danoprevir/RIT
Elvitegravir/RIT
Saquinavir/RIT
Lopinavir/RIT
Itraconazole
Voriconazole
Mibefradil
LCL161
Clarithromycin
Posaconazole
Telithromycin
Conivaptan
Nefazodone
Nelfinavir
Saquinavir
Ribociclib
Idelalisib
Boceprevir

Note:

VIEKIRA PAK = 150/100 mg paritaprevir/ritonavir + 25 mg ombitasvir + 800 mg dasabuvir for 28 days

Potent CYP3A Inducers:

Rifampin
Mitotane
Avasimibe
Rifapentine
Apalutamide
Phenytoin
Carbamazepine
Enzalutamide
St John's Wort extract

Lumacaftor
Rifabutin
Phenobarbital

Strong CYP2C8 Inhibitors:
Gemfibrozil
Clopidogrel
Letermovir
Teriflunomide
Deferasirox

10.8 APPENDIX 8: LIST OF EXAMPLE DRUGS WITH A POTENTIAL TO AFFECT PLASMA EXPOSURE OF SAR442168 VIA REDUCTION OF GASTRIC ACID

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

Proton Pump Inhibitors:

Esomeprazole
Lansoprazole
Omeprazole
Pantoprazole
Rabeprazole

H2-receptor Antagonists

Cimetidine
Famotidine
Nizatidine
Ranitidine

Other Agents

Antacids, eg, aluminum hydroxide/carbonate
Calcium hydroxide/carbonate
Bismuth subsalicylate
Buffered medications, eg, didanosine

10.9 APPENDIX 9: COUNTRY-SPECIFIC REQUIREMENTS

Not applicable.

10.10 APPENDIX 10: ABBREVIATIONS

AEs: adverse event
AESI: adverse event of special interest
AIC: Akaike information criterion
ALT: alanine aminotransferase
ARR: annualized relapse rate
BTK: Bruton's tyrosine kinase
CNS: central nervous system
CSF: cerebrospinal fluid
C-SSRS: Columbia Suicide Severity Rating Scale
[redacted] [redacted]
DTP: duties and taxes paid
ECG: electrocardiogram
eCRF: electronic case report form
EDSS: Expanded Disability Status Scale
FSH: follicle-stimulating hormone
GCP: Good Clinical Practice
Gd: gadolinium
GEE: generalized estimating equation
HRT: hormone replacement therapy
ICF: informed consent form
ICH: International Council for Harmonisation
IDMC: Independent Data Monitoring Committee
IEC: Independent Ethics Committee
IMP: investigational medicinal product
IRB: Institutional Review Board
IV: intravenous(ly)
IVRS: interactive voice response system
IWRS: interactive web response system
LLN: lower limit of normal
LTS: long-term safety, long-term safety
MCP-Mod: multiple comparison procedure with modelling techniques
mITT: modified intent-to-treat
MRI: magnetic resonance imaging
MS: multiple sclerosis
[redacted] [redacted]
NIMP: noninvestigational medicinal product
NOAEL: no observed adverse effect level
[redacted] [redacted]
PCSA: potentially clinically significant abnormality
[redacted] [redacted]
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
SPMS: secondary progressive multiple sclerosis
TEAE: treatment-emergent adverse event
ULN: upper limit of normal

10.11 APPENDIX 11: PROTOCOL AMENDMENT HISTORY

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

Amended protocol 01: 13-Feb-2019

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

OVERALL RATIONALE FOR THE AMENDMENT

This protocol is being amended in response to comments from US and Canadian health authorities.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis	Update of "participants will be randomly assigned to 1 of 5 doses …" to "participants will be randomly assigned to 1 of 4 doses …"	Typographical error
Section 1.2 Schema	Correction of Graphical Study Design (C1 and C2 switched)	Typographical error
Section 1.3 Schedule of activities	Weeks 2 and 6 hematology tests added	Response to request by Health Canada
Section 5.1 Inclusion criteria	I04: "From inclusion and up to 2 months after the last study dose" added to time during which female participants must use a double contraception method including a highly effective method of birth control.	Response to request by Health Canada
Section 5.1 Inclusion criteria	I04: Definition of menopause edited to match Sanofi template definition	Internal consistency of document
Section 6.7 Intervention after the end of the study	"LTS" changed to "DRI" when referring to current study.	Typographical error

Section # and Name	Description of Change	Brief Rationale
Section 8 Study assessments and procedures	Maximum amount of blood collected per participant over the duration of the study increased from 60 to 70 ml [redacted]	Additional 2 hematology tests added in Weeks 2 and 6 (see Section 1.3)
Section 8.3.2 Time period and frequency for collecting AE and SAE information	Definitions of time periods updated for to match current Sanofi template	Internal consistency with current definitions
Appendix 2 Clinical laboratory tests	Creatine phosphokinase added to protocol-required safety laboratory assessments.	Response to request by US FDA

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