AMENDED CLINICAL TRIAL PROTOCOL 10

Protocol title:	**Long-term extension safety and efficacy study of SAR442168 in participants with relapsing multiple sclerosis**
Protocol number:	**LTS16004**
Amendment number:	**10**
Compound number (INN/Trademark):	**SAR442168 Tolebrutinib/not applicable**
Study phase:	**Phase 2**
Short title:	**Long-term safety and efficacy study of tolebrutinib in relapsing multiple sclerosis**
Sponsor name:	**Genzyme Corporation*** ***Sanofi corporation organized and existing under the laws of France is the ultimate parent of a worldwide group of affiliates including Sanofi US Services Inc., Sanofi Genzyme, and Genzyme Corporation**
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Regulatory agency identifier number(s):

IND:	140884
EudraCT:	2018-004731-76
NCT:	NCT03996291
WHO:	U1111-1223-4256
Other:	Not applicable

Approval Date: 20-Dec-2023 Total number of pages: 106

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, version
Amended Clinical Trial Protocol 10	All	20 December 2023, version 1 (electronic 12.0)
Amended Clinical Trial Protocol 09	All	16 November 2023, version 1 (electronic 11.0)
Amended Clinical Trial Protocol 08	All	19 June 2023, version 1 (electronic 10.0)
Amended Clinical Trial Protocol 07	All	12 December 2022, version 1 (electronic 9.0)
Amended Clinical Trial Protocol 06	All	23 May 2022, version 1 (electronic 8.0)
Amended Clinical Trial Protocol 05	All	29 July 2021, version 1 (electronic 7.0)
Amended Clinical Trial Protocol 04	All	28 October 2020, version 1 (electronic 5.0)
Amended Clinical Trial Protocol 03	All	02 March 2020, version 1 (electronic 4.0)
Amended Clinical Trial Protocol 02	All	30 August 2019, version 2 (electronic 3.0)
Amended Clinical Trial Protocol 01	Czech Republic only	26 June 2019, version 1 (electronic 1.0)
Original Protocol		18 January 2019, version 1 (electronic 1.0)

Amended protocol 10 (20 December 2023)

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

OVERALL RATIONALE FOR THE AMENDMENT

The rationale for this protocol amendment is to update the concomitant medications that are prohibited during the conduct of the study as per Health Authority request.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
10.7 Appendix 7 Example of drugs with a potential to change with SAR442168 metabolism	Updated to provide guidance to the US and any other sites that may be following FDA partial clinical hold.	Update to provide guidance.
10.8.1 Country specific provisions for the US and sites following FDA partial clinical hold conditions	New section added to reflect the prohibited use of CYP3A and CYP2C8 inhibitors and the restriction of grapefruit/grapefruit juice (a CYP3A4 inhibitor).	Update.

Section # and Name	Description of Change	Brief Rationale
10.11 Appendix 11: Protocol amendment history	Updated.	Update.
Throughout the document	Reformatted existing content when necessary. Minor, editorial, stylistic changes as necessary. Updated table of contents, section numbers, abbreviations as necessary.	Update in accordance with Sponsor's standards.

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Protocol title: Long-term extension safety and efficacy study of SAR442168 in participants with relapsing multiple sclerosis

Short title: Long-term safety and efficacy study of tolebrutinib 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]). 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.

Objectives and endpoints

Objectives	Endpoints
Primary	
• To determine the long-term safety and tolerability of SAR442168 in RMS participants	Adverse events (Aes), serious adverse events (SAEs), safety findings on magnetic resonance imaging (MRI), potentially clinically significant abnormalities (PCSAs) in laboratory tests, electrocardiogram (ECG), or vital signs during the study period.
Secondary	
• To evaluate efficacy of SAR442168 on disease activity, assessed by clinical and imaging methods.	• Number of new gadolinium (Gd)-enhancing. T1-hyperintense lesions by brain MRI. • Number of new or enlarging T2 lesions. • Total number of Gd-enhancing T1-hyperintense lesions. • Number of relapses (annualized relapse rate [ARR]) during the study period. • Change in Expanded Disability Status Scale (EDSS) score from baseline over time.

Overall design:

This study is a long-term, follow-up study to determine the safety and efficacy of SAR442168. Participants who completed treatment with SAR442168 in the previous DRI15928 study are eligible for enrollment. Participants will start the treatment after informed consent as soon as possible.

The study will consist of 2 parts:

Part A: Double-blind period of continued treatment with the respective SAR442168 dose administered in the DRI15928 study.

Until the dose of SAR442168 to be used in Phase 3 is determined, participants will continue treatment with their same SAR442168 dose used in the DRI15928 study. The double-blind will be maintained until selection of the Phase 3 dose is made based on the SAR442168 clinical studies including the DRI15928 study.

Part B: Open-label period of a single-group treatment with the selected Phase 3 SAR442168 dose.

Once the SAR442168 dose has been selected, all participants will be switched to open-label treatment with the selected dose.

If the participant is not willing to switch to the selected dose of SAR442168, the participant will be withdrawn from the study and a follow-up visit will be performed 4 to 6 weeks after administration of the last study intervention.

Disclosure Statement: This is a long-term Single Group Treatment study for participants previously treated in the DRI15928 study. It consists of 2 parts: Part A, which is blinded/masked for participants and Investigators during the double-blind period of the study, and Part B which is an open-label period of the study.

Number of participants:

There are no sample size calculations for this long-term extension study.

All participants who completed the DRI15928 study are eligible for enrollment in the LTS16004 study. Therefore, the maximum number of participants enrolled in the LTS16004 study will not exceed that of the DRI15928 study. The Sponsor enrolled 130 participants in the DRI15928 study, of whom 129 completed it. Based on previous trial experience, the Sponsor projects that >75% of those participants will opt into the LTS16004 study.

Intervention groups and duration:

In Part A, participants will continue to receive their previous SAR442168 dose in 1 of 4 dose groups. In Part B all participants will form a single dose group, the selected Phase 3 dose.

Study intervention(s)

Investigational medicinal product: SAR442168

- Formulation: Part A - 2.5 or 15 mg film coated tablet; Part B - 15 or 60 mg film coated tablet.

- Route(s) of administration: oral.
- Dose regimen: once daily.

Noninvestigational medicinal products

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

Due to a potential safety risk related to gadolinium (Gd) deposition in the brain seen with certain contrast agents, these agents should be used in accordance with local recommendations and regulations. Otherwise, use of these agents will be similar to their routine use and will be sourced locally. The study manual will provide more details describing their administration in this trial.

Continued access to intervention after the end of the study

After the end of this study, participants who successfully complete the trial on SAR442168 may be offered the option to participate in a Phase 3 long-term safety (LTS) study for up to an additional 3 years, or until SAR442168 is approved in their respective country, whichever comes first. Details of the Phase 3 LTS study will be described in a separate protocol. If this program is terminated earlier, other available RMS treatments will need to be considered at the discretion of the treating physician.

Statistical considerations:

No statistical comparisons between treatment groups will be made. Summaries using descriptive statistics will be provided by visit for parameters.

Sample size calculations:

There are no sample size calculations for this long-term extension study. Sample size will be based on the elective participation of participants who complete the DRI15928 study, meet the eligibility criteria, and enroll in this LTS16004 study.

Primary analysis:

The safety of long-term SAR442168 treatment will be evaluated using descriptive statistics, summarizing incidence of adverse events (Aes), serious adverse events (SAEs), and clinically significant abnormalities (PCSAs) for clinical laboratory tests, and summarizing safety findings on MRI, electrocardiogram (ECG), and vital signs parameters by visit.

Analysis of secondary endpoints:

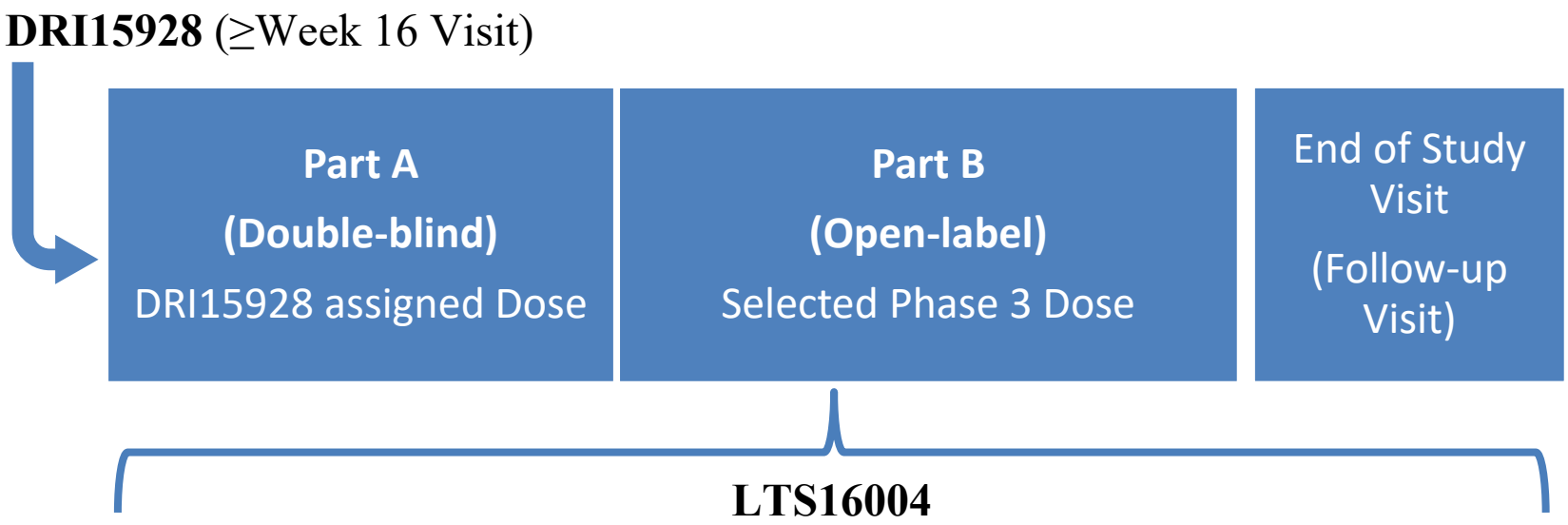
Summaries using descriptive statistics will be provided by visit.

Independent Hepatology Assessment Committee: Yes

Data Monitoring Committee: Yes

1.2 SCHEMA

Figure 1 - Graphical study design



1.3 SCHEDULE OF ACTIVITIES (SOA)

In this clinical study, a month is considered to be a period of 4 weeks (28 days).

Table 1 - A - Schedule of activities (up to Year 1)

Procedure	**Screening**	**Baseline/start of IMP**	**Intervention Phase**						
Month (a window of ±7 days is allowed for all visits after screening)	**W-6 to D1**[a]	**D1**[a]	**M1**	**M3**	**M6**	**M9**	**M12**	**UNSCH**[n]	**Premature End of Treatment**[b]
Informed consent	X							If switch to Part B	
Visit at clinical site[c]	X	X	X	X	X	X	X	X	X
Inclusion/exclusion criteria	X								
Prior/concomitant medications	X	X	X	X	X	X	X	X	X
Study IMP Administration									
SAR442168 (dispensation and accountability)		X	X	X	X	X	X	If switch to Part B	X (Accountability only)
Safety[c]									
Physical examination[d, e]	X	X	X	X	X	X	X	X	X
Height	X								
Body weight	X	X	X	X	X	X	X	If needed	X
Vital signs[e]	X	X	X	X	X	X	X	X	X
12-lead ECG[e]	X	X	X	X	X	X	X	If needed	X
Hematology, biochemistry[e, f]	X[g]	X[g]	X	X	X	X	X	If needed	X
Urinalysis[e, f]	X[g]	X[g]	X	X	X	X	X	If needed	X
β-HCG test (if applicable)[h]	X	X	X	X	X	X	X	If needed	
Serum FSH (if applicable)[i]	X								
Suicidality assessment (C-SSRS)	X	X	X	X	X	X	X	If needed	X

Procedure	**Screening**	**Baseline/start of IMP**	**Intervention Phase**						
Month (a window of ±7 days is allowed for all visits after screening)	**W-6 to D1**[a]	**D1**[a]	**M1**	**M3**	**M6**	**M9**	**M12**	**UNSCH**[n]	**Premature End of Treatment**[b]
Adverse event collection	<----------								---------->
Efficacy									
EDSS		X[j]		X	X	X	X	If MS relapse suspected	X
MRI[o]		X[j]		X	X		X	If needed	X
[redacted]		X	X	X	X	X	X		
Pharmacokinetics									
SAR442168 pharmacokinetic plasma samples								If MS relapse suspected or in case of index AEs	X[p]
Pharmacodynamics / Biomarkers									
Exploratory biomarkers: [redacted]		X[l]						If MS relapse suspected or in case of index AEs	X
Exploratory biomarker plasma samples [redacted]		X		X	X		X		X

Abbreviations: AE: adverse event; β-HCG: beta human chorionic gonadotropin; BTK: Bruton's tyrosine kinase; C-SSRS: Columbia Suicide Severity Rating Scale; [redacted] D: day; ECG: electrocardiogram; EDSS: Expanded Disability Status Scale; FSH: follicle-stimulating hormone; IMP: investigational medicinal product; M: month; MRI: magnetic resonance imaging; MS: multiple sclerosis; [redacted] UNSCH: unscheduled; W; week. Note: All assessments shall be done as designated in this SoA unless not permitted according to local regulations.

a The Week 16 or the follow-up visit of the DRI15928 study may serve as the screening visit for LTS16004 (only tests not done during the Week 16 or follow-up visit of the DRI15928 study will need to be completed during the screening visit of LTS16004). If the participant is not enrolled in to LTS16004 during such visits, screening activities for LTS16004 can be performed at any time from 6 weeks to Day 1 before IMP administration in the LTS16004 study. The baseline visit can be combined with the screening visit (and the last visit of the DRI15928 study). Further guidance will be provided in the Study Reference Manual.

b The participant should return for a follow-up visit 4 to 6 weeks after premature end-of-treatment.

c Monthly (±1 week) telephone calls will be performed between the visits to monitor for any possible safety issues during the first year of the study. If a safety event is suspected, the participant will be asked to come for an unscheduled on-site visit for evaluation.

d A full physical examination must be performed at screening; a brief physical examination is sufficient thereafter. The brief physical examination should be extended as needed at the judgment of the Investigator in the event of new findings.

e Sample or measurement to be performed before IMP administration.

f Tests will be repeated locally after 6 weeks (±1 week) of each planned visit during the first year of the study, starting after Month 3 visit.

g Pre-study tests may be accepted if they are performed between Week -4 and Day 1 (including Week 12 or Week 16 tests in the DRI15928 study).

h Urine β-HCG is sufficient unless a pregnancy is detected or the urine test is inconclusive and a serum test needs to be used for verification or only serum testing is required by local regulation or Institutional Review board (IRB)/International Ethics Committee (IEC).

i For women suspected/reported to have developed menopause since their inclusion in the DRI15928 study, FSH testing will be performed to confirm menopause. However, the participant will continue on the highly effective contraception until FSH result becomes available.

j The last EDSS and MRI obtained in the DRI15928 study are acceptable, if they are performed within 6 weeks prior to Day 1 of the LTS16004 study.

k Substudy at selected sites. Assessments to be performed if feasible.

l Only for participants with delay between end of the DRI15928 study and start of the LTS16004 study.

m For selected sites and participants who consented to the procedure. Refer to Section 8.1.4 for details. This part of the study may be ended prematurely if sufficient data have been gathered.

n Once the dose for Part B is known, an unscheduled visit should be performed as quickly as possible (if the next study visit is not due within 4 weeks) to switch participants to part B on the selected dose.

o For systemic corticosteroids and adrenocorticotropic hormone, a 1-month interval is required prior to the MRI scan.

p PK to be collected only if pEOT visit can be scheduled within a maximum of 24 hours after the last IMP dose.

Table 2 - B - Schedule of activities (Years 2 to 4)

Procedure	**Intervention Phase**													
Month (a window of ±10 days is allowed)	**M15**	**M18**	**M21**	**M24**	**M27**	**M30**	**M33**	**M36**	**M39**	**M42**	**M45**	**M48**	**UNSCH**	**Premature End of Treatment**[a]
Visit at clinical site	X	X	X	X	X	X	X	X		X		X	X	X
Phone call or visit at clinical site									X		X			
Prior/concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study IMP Administration														
SAR442168 (dispensation and accountability)	X	X	X	X	X	X	X	X	X[j]	X	X[j]	X		X (accountability only)
Safety														
Physical examination[b,c]	X	X	X	X	X	X	X	X		X		X	X	X
Body weight				X				X				X	If needed	X
Vital signs[c]	X	X	X	X	X	X	X	X		X		X	X	X
12-lead ECG[c]	X	X	X	X	X	X	X	X		X		X	If needed	X
Hematology, biochemistry[c]	X	X	X	X	X	X	X	X		X		X	If needed	X
Urinalysis[c]	X	X	X	X	X	X	X	X		X		X	If needed	X
β-HCG test (if applicable)[d]				X				X				X	If needed	
Suicidality assessment (C-SSRS)	X	X	X	X	X	X	X	X		X		X	If needed	X
Adverse event collection	<----------													---------->
Efficacy														
EDSS	X	X	X	X	X	X	X	X		X		X	If MS relapse suspected	X
MRI[g, h]		X		X				X				X	If needed	X
[redacted]	X	X	X	X	X	X	X	X		X		X		

Procedure	Intervention Phase													
Month (a window of ±10 days is allowed)	**M15**	**M18**	**M21**	**M24**	**M27**	**M30**	**M33**	**M36**	**M39**	**M42**	**M45**	**M48**	**UNSCH**	**Premature End of Treatment**[a]
Pharmacokinetics														
SAR442168 pharmacokinetic plasma samples													If MS relapse suspected or in case of index AEs	X[i]
Pharmacodynamics / Biomarkers														
Exploratory biomarkers: [redacted]													If MS relapse suspected or in case of index AEs	X
Exploratory biomarker plasma samples [redacted]				X				X				X		X

Abbreviations: AE: adverse event; β-HCG: beta human chorionic gonadotropin; BTK: Bruton's tyrosine kinase; C-SSRS: Columbia Suicide Severity Rating Scale; [redacted] ECG: electrocardiogram; EDSS: Expanded Disability Status Scale; IMP: investigational medicinal product; M: month; MS: multiple sclerosis; MRI: magnetic resonance imaging; [redacted] UNSCH: unscheduled. Note: All assessments shall be done as designated in this SoA unless not permitted according to local regulations.

a The participant should return for a follow-up visit 4 to 6 weeks after premature end-of-treatment.

b A brief physical examination is sufficient. The brief physical examination should be extended as needed at the judgment of the Investigator in the event of new findings.

c Sample or measurement to be taken before IMP administration.

d Urine β-HCG is sufficient unless a pregnancy is detected or the urine test is inconclusive and a serum test needs to be used for verification or only serum testing is required by local regulation or Institutional Review board (IRB)/International Ethics Committee (IEC).

e Substudy at selected sites.

f For selected sites and participants who consented to the procedure. Refer to Section 8.1.4 for details. This part of the study may be ended prematurely if sufficient data have been gathered.

g For systemic corticosteroids and adrenocorticotropic hormone, a 1-month interval is required prior to the MRI scan.

h Starting from M15 (inclusive), a window of ±21 days is acceptable for MRI.

i PK to be collected only if pEOT visit can be scheduled within a maximum 24 hours after the last IMP dose.

j Dispensation at site or via direct-to-patient shipment.

Table 3 - C - Schedule of activities (Year 5)

Procedure	**Intervention phase**						
Month (a window of ±10 days is allowed)	**M51**	**M54**	**M57**	**M60**[k]	**Follow-up visit**[k] (8 weeks after the last IMP administration)	**UNSCH**	**Premature End of Treatment**[a]
Visit at clinical site		X		X	X	X	X
Phone call or visit at clinical site	X		X				
Prior/concomitant medications	X	X	X	X	X	X	X
Study IMP Administration							
SAR442168 (dispensation and accountability)	X[j]	X	X[j]	X (accountability only)			
Safety							
Physical examination[b, c]		X		X	X	X	X
Body weight				X	X	if needed	X
Vital signs[c]		X		X	X	X	X
12-lead ECG[c]		X		X	X	if needed	X
Hematology, biochemistry[c]		X		X	X	If needed	X
Urinalysis[c]		X		X	X	If needed	X
β-HCG test (if applicable)[d]				X		If needed	
Suicidality assessment (C-SSRS)		X		X	X	If needed	X
Adverse event collection	<----------						---------->
Efficacy							
EDSS		X		X	X	If MS relapse suspected	X
MRI[g, h]				X		If needed	X

Procedure	**Intervention phase**						
Month (a window of ±10 days is allowed)	**M51**	**M54**	**M57**	**M60**[k]	**Follow-up visit**[k] (8 weeks after the last IMP administration)	**UNSCH**	**Premature End of Treatment**[a]
[redacted]		X					
Pharmacokinetics							
SAR442168 pharmacokinetic plasma samples						If MS relapse suspected or in case of index AEs	X[i]
Pharmacodynamics/ Biomarkers							
Exploratory biomarkers: [redacted]						If MS relapse suspected or In case of index AEs	X
Exploratory biomarker plasma samples [redacted]				X			X

Abbreviations: AE: adverse event; β-HCG: beta human chorionic gonadotropin; BTK: Bruton's tyrosine kinase; C-SSRS: Columbia Suicide Severity Rating Scale; [redacted]; ECG: electrocardiogram; EDSS: Expanded Disability Status Scale; IMP: investigational medicinal product; M: month; MRI: magnetic resonance imaging; MS: multiple sclerosis; [redacted] UNSCH: unscheduled. Note: All assessments shall be done as designated in this SoA unless not permitted according to local regulations.

a The participant should return for a follow-up visit 4 to 6 weeks after premature end-of-treatment.

b A brief physical examination is sufficient. The brief physical examination should be extended as needed at the judgment of the Investigator in the event of new findings.

c Sample or measurement to be taken before IMP administration.

d Urine β-HCG is sufficient unless a pregnancy is detected or the urine test is inconclusive and a serum test needs to be used for verification or only serum testing is required by local regulation or Institutional Review board (IRB) / International Ethics Committee (IEC).

e Substudy at selected sites.

f For selected sites and participants who consented to the procedure. Refer to Section 8.1.4 for details. This part of the study may be ended prematurely if sufficient data have been gathered.

g For systemic corticosteroids and adrenocorticotropic hormone, a 1 month interval is required prior to the MRI scan.

h Starting from M15 (inclusive), a window of ±21 days is acceptable for MRI.

i PK to be collected only if pEOT visit can be scheduled within a maximum 24 hours after the last IMP dose.

j Dispensation at site or via direct-to-patient shipment.

k At the M60 visit, the participants who have completed the study and remain on SAR442168 may be offered participation in a Phase 3 long-term safety study. Follow-up visit assessment only performed for those participants who are not taking part in the long-term safety study.

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 BTK pathway is an important signaling pathway in B lymphocytes and CNS myeloid cells like microglia. Both of these cell types have been implicated in the pathophysiology of MS. BTK is critical for B-cell activation, differentiation, and maturation, and it also regulates the activation of cells from other hematopoietic lineages such as basophils, mast cells, macrophages, and neutrophils. 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 in the periphery and meninges and by modulating maladaptive microglial cells linked to neuroinflammation in the brain and spinal cord. The goal of this long-term study is to determine the long-term safety and efficacy of SAR442168 in RMS patients and to demonstrate that SAR442168 benefits in MS as measured by MRI are maintained.

Participants completing the DRI15928 study may be enrolled in this long-term extension study. Participants will continue on the same assigned SAR442168 dose in a double-blinded manner until the Phase 3 dose is selected.

2.2 BACKGROUND

Immunomodulatory drugs have been the mainstay of MS therapy. The role of B cells in MS pathogenesis has been validated clinically by ocrelizumab, a monoclonal antibody that selectively depletes CD20-expressing B cells in the periphery (1). 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 (2). Importance of immune cells residing in the CNS is also well known (3) and needs to be considered in MS pathogenesis.

There is still a significant unmet need for therapies that target neuroinflammation with a goal of halting long-term disability and neurodegeneration in people with RMS and with progressive forms of the disease (PPMS and SPMS) (4). Even the most recent high efficacy disease-modifying therapies act mainly on adaptive immunity in the periphery with only modest ability to halt neuroinflammatory and neurodegenerative processes and stop disease progression, as also demonstrated by recent studies in progressive MS (5, 6). 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 (7, 8). 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 adaptive and innate immunity. Accordingly, an inhibitor of BTK signaling targets both aspects of the immune system. BTK inhibits signaling pathways in B lymphocytes and myeloid cells, including CNS microglia. Both cell types have been implicated in MS pathophysiology. 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. While SAR442168 is an irreversible inhibitor of BTK, its pharmacological effects on B-cell function are temporary, as B cells are not depleted and normal signaling can be restored by ongoing protein synthesis of new BTK enzyme over the course of several days in the absence of exposure to the inhibitor. 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 compared to currently available MS therapies.

Repeat-Dose Toxicity Studies:

In a 13-week Good Laboratory Practice (GLP) toxicology study in rats, there were no adverse effects. The no-observed-adverse-effect-level (NOAEL) in rats was [redacted] mg/kg/day, the highest dose administered.

A 6-month oral toxicity study of SAR442168 was conducted in Wistar rats at [redacted] and [redacted] mg/kg/day. BTK inhibition (BTKi), target-related effects on immune function included T-cell dependent antibody response (TDAR) findings of decreased immunoglobulin (Ig) G and IgM responses to antigen at [redacted]2 mg/kg/day, and nematode infestation in the rectum at [redacted]2 mg/kg/day. Hemorrhage in the eye, pancreas, nasal cavity, and mesenteric lymph nodes were observed at [redacted] mg/kg/day. BTK is expressed by human platelets and participates in platelet activation through collagen receptor glycoprotein VI (GPVI), suggesting a target-mediated effect of SAR442168 (9). Pancreatic fibrosis and inflammation were observed in male rats at [redacted] mg/kg/day. Similar pancreatic effects have been documented in rats administered other BTK inhibitors, including LY3337641, GDC-0853, ibrutinib, and acalabrutinib, with no published reports in any other species (10, 11, 12, 13, 14). The findings involved a relatively low number of islets and were not associated with clinical chemistry changes suggestive of abnormal glucose regulation or exocrine pancreas injury including amylase or lipase (10, 11). The pancreatic effects of BTKi are time-, species-, strain-, and sex-specific. The spectrum of these microscopic effects is consistent with spontaneous findings reported in control Crl:CD(SD) rats and may constitute test-article-related acceleration of a common background finding in older rats. Lack of clinical reports of pancreatic dysfunction in patients treated with ibrutinib argue that pancreatic toxicity is unlikely to occur in humans. Cutaneous lesions were observed in rats at [redacted] mg/kg/day, consisting of macroscopic observations and microscopic findings of erosion, ulcer, and focal acanthosis/hyperkeratosis. Cutaneous toxicity is commonly associated with inhibition of epidermal growth factor receptor (EGFR) (15, 16). SAR442168 inhibited EGFR in a kinase screening panel (IC_{50} 4 nM) and was active in a cellular assay for EGFR (364 nM). As such, the cutaneous effects in rats administered

SAR442168 were considered possibly related to off-target inhibition of EGFR. In the lungs, foamy alveolar macrophages were observed at [redacted]2 mg/kg/day. This finding had no apparent impact on the structural integrity or function of the lung parenchyma, was considered an exacerbation of a spontaneous background finding in the rat and was not considered adverse. While a NOAEL was not observed, the adverse effects seen in the 6-month toxicity study of SAR442168 in rats are similar to reported exaggerated pharmacology and/or toxicity of other BTK inhibitors. The low-observed-adverse-effect-level (LOAEL) was [redacted]mg/kg/day. The SAR442168 exposure in Week 26 at the LOAEL (AUC_{0-24}) was [redacted] and [redacted] ng.h/mL, respectively, in males and females.

In a GLP, 4-week toxicity study in dogs, the dose-limiting toxicity included lowered plasma protein and tissue edema, which were reversible upon discontinuation of treatment. The NOAELs in dogs were [redacted]and [redacted] mg/kg, in females and males, respectively. In a 13-week oral toxicity study in dogs, the NOAEL was [redacted] mg/kg/day, the highest dose administered.

A 9-month, oral toxicity study of SAR442168 was conducted in beagle dogs at [redacted] and [redacted]mg/kg/day. Minimal to mild decreases in serum albumin concentration and A:G ratio of unknown mechanism were observed at [redacted] mg/kg/day, consistent with that seen in the 1-month toxicity study in dogs at [redacted] mg/kg/day. A single female dog at [redacted]mg/kg/day exhibited minimal interstitial edema of the pancreas, which correlated with low serum albumin, suggesting that it may have been test article related. Decreased absolute counts and relative proportions of B cells (CD21+) at[redacted] mg/kg/day females and at [redacted] mg/kg/day males were considered related to the pharmacologic mechanism of action. Microscopic findings included minimal to slight decreased cellularity of various lymphoid organs/tissues at [redacted] mg/kg/day; minimal to moderate congestion/hemorrhage in the mesenteric and/or retropharyngeal lymph node, stomach, colon, ileum, testis, and/or kidney at [redacted] mg/kg/day; and associated pigment consistent with hemosiderin in the mesenteric and/or retropharyngeal lymph nodes [redacted]mg/kg/day and Kupffer cells in [redacted] mg/kg/day females and [redacted]mg/kg/day males. As described for the rat, the minimal hemorrhage in various tissues was considered related to the known pharmacology of BTK inhibition (target-related effects on platelet aggregation). Due to the mild severity of findings, and the lack of impact on the health and wellbeing of the animals, these effects were considered non-adverse. The NOAEL was considered [redacted] mg/kg/day. The exposure at the NOAEL (AUC_{0-24h}) was [redacted]and [redacted]ng.h/mL, respectively, in males and females on Day 273 (ie, 9 months). Exposure ratios in the repeat dose toxicity studies are summarized in Table 4.

Table 4 - Exposure ratios in repeat dose toxicity studies in rats and dogs

Species	Type of study (duration/route)	Dose (mg/kg/day)	NOAEL (mg/kg/day)	AUC Exposure at NOAEL (ng.hr/mL) (exposure ratio) SAR442168[a, b, c]
Rat	28-day PO	[redacted]	[redacted]	[redacted]
	13-week PO	[redacted]	[redacted]	[redacted]
	6-month PO[c]	[redacted]	[redacted]	[redacted]
Dog	28-day PO	[redacted]	[redacted]	[redacted]
	13-week PO	[redacted]	[redacted]	[redacted]
	9-month PO	[redacted]	[redacted]	[redacted]

Abbreviations: AUC: area under the curve; F: female; M: male; NOAEL: no-observed-adverse-effect-level; PO: per os (oral).

a AUC_{last} for 28-day and 13- week toxicity studies; AUC_{0-24} for 6- and 9-month toxicity studies.

b SAR442168 exposure ratio based on the [redacted] mg (mixed fasted and fed state) in [redacted] ng.h/mL)

c Low-observed–adverse-effect-level (LOAEL) exposure provided for the 26-week study in rats at Week 26 since a NOAEL was not identified.

Laboratory abnormalities in animals:

Decreased plasma proteins associated with tissue edema were observed in dogs at doses of [redacted] mg/kg/day (1- and 9-month toxicity studies).

Decreased IgG and IgM responses to antigen were observed in rats at doses of [redacted] mg/kg/day.

Decreased absolute counts and relative proportions of B cells (CD21+) were observed in dogs at [redacted] mg/kg/day in females and at [redacted] mg/kg/day in males.

Carcinogenesis, mutagenesis, and impairment of fertility:

Carcinogenicity studies have not yet been conducted with SAR442168.

In genotoxicity studies, SAR442168 tested negative in an in vitro bacterial genotoxicity (Ames) assay. In an in vitro test for chromosome aberration, increased structural aberrations were observed at the highest SAR442168 concentrations tested however, these concentrations were also cytotoxic. SAR442168 tested negative in an in vivo rat bone marrow micronucleus test up to the highest dose evaluated of [redacted] mg/kg/day.

In a fertility study of SAR442168 in male and female rats, there were no compound-related AEs on male reproductive organ weights, male and female reproductive indices, or cesarean section parameters. The NOAEL for parental toxicity, male and female fertility, reproductive performance, and early embryonic development was [redacted] mg/kg/day, the highest dose administered.

In an embryo-fetal toxicity study in rats, decreased mean gravid uterine weight, increased post-implantation loss (early resorptions), decreased number of live fetuses, and minimal decrease in fetal body weight occurred at [redacted] mg/kg/day. There were no external, visceral, or skeletal malformations. The maternal NOEL was [redacted] mg/kg/day and the developmental NOEL was [redacted] mg/kg/day. On Gestation Day 12, the mean plasma AUC_{0-24} at the developmental NOAEL was [redacted] ng.h/mL for SAR442168.

In an embryo-fetal toxicity study in rabbits, dose-related, minimally delayed ossification of the hyoid bone was noted at ≥5 mg/kg/day. This finding was considered non-adverse, reflecting a slight and transient developmental (growth) delay in a few fetuses. There were no effects on intrauterine parameters (eg, post-implantation loss, number of live and dead fetuses, resorptions); and no external, visceral, or skeletal malformations. The maternal and developmental NOAEL were [redacted] mg/kg/day. On Gestation Day 12, the mean plasma AUC_{0-24} at the NOAEL was [redacted] ng.h/mL for SAR442168.

The NOAELs and exposure ratios in the embryo-fetal toxicity studies are summarized in Table 5.

Table 5 - NOAELs and exposure ratios in the embryo-fetal toxicity studies

Species	Type of study (duration/route)	Dose (mg/kg/day)	Embryo-Fetal NOAEL (mg/kg/day)	AUC_{0-24} exposure at NOAEL (ng.hr/mL) (exposure ratio) SAR442168[a]
Pregnant Rat	Embryo-fetal toxicity GD6-17 PO	[redacted]	[redacted]	[redacted]
Pregnant rabbit	Embryo-fetal toxicity GD6-19 PO	[redacted]	[redacted]	[redacted]

Abbreviations: AUC: area under the curve; GD: gestation day; NOAEL: no-observed-adverse-effect level; PO: orally.
a SAR442168 exposure ratio based on the [redacted] mg (mixed fasted and fed state) in [redacted] ng.h/mL).

Renal and hepatic impairment: The pharmacokinetics (PK) of SAR442168 have not been investigated in human subjects with renal or hepatic impairment. Based on the routes of elimination, SAR442168 exposure may increase in participants with hepatic impairment. Therefore, SAR442168 should not be administered to individuals with underlying hepatic impairment until this has been evaluated in clinical studies. Clinically relevant differences are not expected when treating participants with renal impairment, as SAR442168 is not primarily eliminated by the renal route.

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 [SAD]), 40 in the multiple ascending dose [MAD]), and 4 in the cerebrospinal fluid [CSF] exposure phases) received up to 120 mg SAR442168 in the SAD phase, up to 90 mg once daily for 10 days in the MAD phase, and 120 mg (single dose) in the CSF exposure study. No SAEs were reported in Phase 1.

One participant in the MAD 60 mg cohort was unblinded due to decreased platelet count. Platelet counts will therefore be monitored during the study. Reduction in platelets observed during the study did not exceed 100 x 10^9/L. SAR442168 is rapidly absorbed (time to reach maximum observed concentration [t_{max}] is close to 1 hour) and rapidly eliminated (elimination half-life [$t_{1/2}$] was <2.5 hours). When [redacted] mg SAR442168 oral solution was administered with a moderate-fat meal, a mild food effect was observed with an increase of 1.55-fold in AUC and 1.37-fold in maximum serum concentration (C_{max}) (n = 4 participants). 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.

Phase 1 relative bioavailability and food effect for a SAR442168 tablet formulation:
A single-center, 3-period, open-label, randomized, complete crossover study was performed to assess the relative bioavailability and food effect for a novel SAR442168 immediate release, oral solid tablet formulation compared to a reference oral liquid formulation that was used in a Phase 1 SAD/MAD study. This study was performed in a cohort of 14 healthy participants. [redacted] milligrams of SAR442168 oral solution had a similar bioavailability to [redacted] mg SAR442168 as [redacted] tablets in fasted conditions with a ratio (tablet/solution) of 1.0 in area under the concentration-time curve until the last quantifiable concentration (AUC_{last}) and 1.03 in C_{max} for SAR442168. When SAR442168 tablets were administered with a high fat meal, a moderate food effect was observed at [redacted] mg with an increase of 1.80-fold in AUC_{last} and no effect on C_{max} (a 1.18-fold increase) for SAR442168.

New Phase 1 dose escalation single- and multiple-ascending-dose studies (TDU16831/TDR16862) are ongoing to obtain additional safety, tolerability and PK information on SAR442168 and metabolite(s), with a food effect investigation, at higher doses. These doses are higher than the dose range used in the initial first-in-human studies, where no maximum tolerated dose was identified. In addition, exposure margins with preclinical toxicity data enable higher dose exploration. The study aimed at evaluating the safety/tolerability and PK profiles at higher doses, food effect, and PK/PD (exposure-QT) analysis. Cerebrospinal fluid exposure of SAR442168 was measured after administering a single dose of the current Phase 3 formulation [redacted] to compare with exposure after a [redacted] mg dose as determined in the first-in-human study. The additional Phase 1 ECG evaluation at exposures above the highest clinically relevant exposure allows covering of all intrinsic and extrinsic factors affecting the PK of SAR442168.

Drug-drug interactions: The potential for drug-drug interactions has been investigated in vitro with SAR442168 evaluated as a substrate, inhibitor, or inducer of cytochrome P450 (CYP450) metabolizing enzymes. 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.

Based on preclinical drug metabolism studies, SAR442168 is a substrate of the CYP3A4 and CYP2C8 isoenzymes. In healthy participants, a potent CYP3A4 inhibitor (itraconazole 200 mg once daily for 4 days) increased SAR442168 (area under the curve [AUC]) exposure by 1.8-fold (Study INT16385), and a potent CYP2C8 inhibitor (gemfibrozil 600 mg twice daily for 6 days) increased SAR442168 (AUC) exposure by 8.4-fold (Study INT16726). Based on a satisfactory safety and tolerability profile and on the observed exposure in healthy participants who received SAR442168 at a dose of up to [redacted] once daily for 14 days under fed conditions (Study TDR16862), drugs that strongly inhibit CYP3A4, are allowed and drugs that strongly inhibit CYP2C8 are not permitted. In healthy participants, potent CYP3A4 and moderate CYP2C8 induction by rifampicin (600 mg once daily for 8 days) decreased SAR442168 exposure by 6-fold (Study INT16726). Therefore, potent and moderate (based on prediction) CYP3A inducers are not permitted due to their potential to decrease SAR442168 exposure and efficacy (see the list of such drugs in Appendix 7, Section 10.7).

2.3 BENEFIT/RISK ASSESSMENT

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

Benefit assessment:

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

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

[redacted]

[redacted]

Potential risks

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

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

- There was no death or treatment-emergent adverse event (TEAE) leading to permanent treatment discontinuation during the study. One treatment-emergent SAE (MS relapse) was reported in a participant treated with 60 mg SAR442168; the remainder of the reported TEAEs were of mild or moderate intensity.
- There was no direct correlation between the doses of SAR442168 administered and number or intensity of TEAEs. The most common events reported in participants in the SAR442168 treatment arms were headache, upper respiratory tract infection, and nasopharyngitis.
- Two participants had treatment emergent transient alanine aminotransferase (ALT) increase >3 x ULN, 1 during the 30 mg SAR442168 treatment period (at Week 8, 105 U/L [normal range 6 to 34 U/L]) that returned to normal range within 4 days and 1 during the 60 mg SAR442168 treatment period (at Week 4, 107 U/L [normal range 6 to 34 U/L]). The participant in the 60 mg group had slightly elevated ALT at screening (48 U/L) and at baseline (50 U/L); ALT levels returned to the normal range in 8 weeks. Both participants continued study treatment during this period. All other liver enzyme levels for both participants were within normal ranges during the treatment period, and both events were assessed as unrelated to the study drug by the Investigators. Both participants completed the DRI15928 study and successfully rolled over to the long-term safety follow-up study.
- One event of mild petechia in a female participant (at Week 8 in the SAR442168 30 mg group) and 2 events of mild microscopic hematuria in 2 male participants (1 event at Week 16 in the SAR442168 30 mg group and 1 event on Day 1 in the SAR442168 60 mg group, with occult blood noted in urine) were reported during the treatment period in the SAR442168 Phase 2b trial. The hematology results were clinically insignificant for all 3 participants from the onset of the events. The participant with mild petechia had benign pigmentary lesions noted during screening, and the event was assessed as related to the study by the Investigator. Details of the anatomic location and clinical presentation of the 2 skin conditions were unavailable. The 2 events of mild microscopic hematuria were assessed as unrelated to the study drug.

- No severe infections occurred. The most frequently reported (≥3 events total) in the SAR442168 treatment period were upper respiratory tract infection, nasopharyngitis, gastroenteritis, and respiratory tract infection.
- No clinically significant cytopenia, including thrombocytopenia and neutropenia, was reported or detected based on hematologic lab results, and no cardiac arrhythmia was observed via ECG monitoring during the study.

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

- Bleeding (hemorrhage)
- Infections
- Cytopenia including thrombocytopenia
- Atrial arrhythmias (atrial fibrillation and atrial flutter)
- Liver enzymes (alanine aminotransferase and aspartate transaminase) elevation

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

Treatment-emergent SAEs of drug-induced liver injury (DILI) were reported in the ongoing Phase 3 trials; cases occurred between Months 1 to 3, with potential confounders identified for some of the cases.

Assessment of COVID-19 in trial participants:

Antiviral responses are likely to be driven mainly by T cells, in particular CD8+ cytotoxic T lymphocytes, and natural killer cells, and less so, at least initially, by B cells (17, 18). In vitro and cell-based assays indicate that SAR442168 does not deplete B lymphocytes and does not exhibit significant cellular off-target activity in human T lymphocytes. In the preceding Phase 2b study in participants with RMS (DRI15928), the mean counts of CD19+ B cells, CD4 and CD8 T cells, CD16+56 natural killer cells, and the levels of IgG and IgM remained stable at the end of 12 weeks of treatment with SAR442168.

Infections are an important potential risk for SAR442168, and severe infections are being monitored as an adverse event of special interest (AESI) in all ongoing and future clinical trials. In the preceding Phase 2b trial in 130 patients with RMS, 23.8% of participants reported only mild or moderate infections at the end of 12 weeks of treatment with SAR442168. No participant discontinued treatment due to infection or any other TEAE. At present, it is unknown if people with MS are at increased risk for SARS CoV-2 infection, acquiring COVID-19 or developing severe COVID-19 (17).

In the current trial, eligibility criteria exclude people with known risk factors for COVID-19 including advanced age and comorbidities that may put patients at higher risk for serious illness such as chronic cardiovascular disease, liver disease, kidney disease, respiratory system compromise, and malignancies. Concomitant use of immunosuppressive or chemotherapeutic medications is excluded.

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

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

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

Overall benefit: risk conclusion

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

Drug-induced liver injury has been identified in the ongoing Phase 3 trials. The reported events occurred in Months 1 to 3 after the start of the IMP. Exclusion criteria and monitoring frequency have been updated in all actively recruiting protocols.

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

3 OBJECTIVES AND ENDPOINTS

Table 6 - Objectives and endpoints

Objectives	Endpoints
Primary	
• To determine the long-term safety and tolerability of SAR442168 in RMS participants	Adverse events (AEs), serious adverse events (SAEs), safety findings on magnetic resonance imaging (MRI), potentially clinically significant abnormalities (PCSAs) in laboratory tests, electrocardiogram (ECG), or vital signs during the study period.
Secondary	
• To evaluate efficacy of SAR442168 on disease activity, assessed by clinical and imaging methods.	• Number of new gadolinium (Gd)-enhancing. T1-hyperintense lesions by brain MRI. • Number of new or enlarging T2 lesions. • Total number of Gd-enhancing T1-hyperintense lesions. • Number of relapses (annualized relapse rate [ARR]) during the study period. • Change in Expanded Disability Status Scale (EDSS) score from baseline over time.
Tertiary/exploratory	
To evaluate efficacy of SAR442168 on disease activity and the pharmacodynamics (PD) of SAR442168.	• [redacted] in case of index AEs (cytopenia and arrhythmias). • [redacted] • Change in volume of T2-lesions from baseline over time. • Change in brain volume, including regional changes, over time. • Change in the number of T1‑hypointense lesions from Baseline over time. • Change in myelin integrity and other features of MRI lesions as measured by magnetization transfer ratio and susceptibility-weighted imaging MRI over time. • Proportion of participants with no new MRI disease activity through the end of the study. • Proportion of relapse-free participants through the end of the study. • [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 to assess the efficacy of SAR442168. 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 count of new 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.

Relapse-related endpoints (annualized relapse rate [ARR], proportion of relapse-free participants) are widely used as endpoints in clinical trials.

The EDSS is widely used to measure neurological disability in clinical trials and routine settings (19).

4 STUDY DESIGN

4.1 OVERALL DESIGN

This study is a long-term follow-up study to determine the safety and efficacy of SAR442168. Participants who completed treatment with SAR442168 in the previous DRI15928 study are eligible for enrollment. Participants will start the treatment after informed consent as soon as possible.

The study will consist of 2 parts:

Part A: Double-blind period of continued treatment with the respective SAR442168 dose administered in the DRI15928 study

Until the dose of SAR442168 to be used in Phase 3 is determined, participants will continue treatment with their same SAR442168 dose used in the DRI15928 study. Cohort 1 of the DRI15928 study that exits the trial receiving placebo from Weeks 13 to 16 will receive the active treatment dose assigned to them at randomization and administered during Weeks 1 to 12. The double-blind will be maintained until the selection of the Phase 3 dose is made based on the SAR442168 clinical studies including the DRI15928 study.

Part B: Open-label period of a single-group treatment with the Phase 3 dose, 60 mg SAR442168.

All participants providing consent to Part B of the study will be switched to open-label treatment with the selected dose.

If the participant is not willing to switch to the selected dose of SAR442168, the participant will be withdrawn from the study and a follow-up visit will be performed 4 to 6 weeks after the last study intervention.

The Independent Data Monitoring Committee (IDMC) will follow safety data periodically as detailed in the DMC charter. Additional ad hoc IDMC reviews may occur at any time should a safety risk be suspected.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Until the start of Part B of this study, participants will continue treatment with their same SAR442168 dose used in the DRI15928 study. The double-blind period (ie, Part A) will reduce the potential for bias in the evaluations and data collection to support safety and efficacy of several doses of SAR442168 beyond 12 weeks of treatment, and pooled analysis to evaluate efficacy and safety.

Open-label treatment with the selected Phase 3 SAR442168 dose during Part B will provide long-term safety data on SAR442168. Efficacy data will be collected as supportive data. Open-label treatment should introduce minimal bias for interpreting MRI and other endpoints such as biomarkers and protocol defined MS relapse. Moreover, regular training of EDSS assessors will help minimize potential bias for interpreting disability outcomes.

4.3 JUSTIFICATION FOR DOSE

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

In this study, doses of 5, 15, 30, and 60 mg SAR442168 were tested in a 12-week double-blind treatment period with the number of new Gd-enhancing T1-hyperintense lesions at the end of the 12 weeks of SAR442168 treatment as the primary endpoint. The results demonstrated a dose-response relationship for SAR442168 as evidenced by a reduction in the number of new Gd-enhancing T1-hyperintense brain lesions detected by brain MRI after 12 weeks of treatment. There was an 85% relative reduction in lesions at 12 weeks in the 60 mg dose group as compared with placebo. This was obtained from the negative binomial regression model adjusted for baseline Gd-enhancing T1-hyperintense lesion activity. The dose-response relationship for the secondary endpoint of new or enlarging T2 lesions also supported the choice of the 60 mg dose.

Analysis of the PK data and effect of fed status on SAR442168 exposure showed a positive food effect with an increase in $AUC_{0\text{-}24}$ of approximately 2-fold. Moreover, the correlation between the treatment response and the exposure to SAR442168 showed that higher exposure was associated with low numbers of new Gd-enhancing T1-hyperintense lesions after 12 weeks of treatment. Approximately half the participants took SAR442168 with food during the Phase 2b trial with no apparent safety or tolerability issues. Taken together, these data support the recommendation to take SAR442168 with a meal.

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

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he/she has completed Parts A and B of the trial, 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 protocol waivers or exemptions, is not permitted.

5.1 INCLUSION CRITERIA

Participants will be enrolled in this study upon written and signed informed consent.

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

Age

Not applicable.

Type of participant and disease characteristics

I 01. Participants must have completed treatment in the DRI15928 study before screening.

I 02. Female participants must continue to use an acceptable effective contraception method of birth control from inclusion and until 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 plasma follicle-stimulating hormone (FSH) level >30 UI/L.

I 03. Deleted in Amended Protocol 03.

I 04. Deleted in Amended Protocol 03.

I 05. Deleted in Amended Protocol 03.

Weight

Not applicable.

Informed Consent

I 06. 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 a confirmed concomitant laboratory or ECG abnormality or medical condition deemed by the Investigator incompatible with continuation of SAR442168 treatment.

E 02. The participant has received any live (attenuated) vaccine (including but not limited to varicella zoster, oral polio, and nasal influenza) between the last DRI15928 visit and the first treatment visit in the LTS16004 study.

Prior/concomitant therapy

E 03. The participant has received a non-study MS disease-modifying treatment between the last visit in Study DRI15928 and inclusion in Study LTS16004, which by judgment of the Investigator may add unjustified risk to switching back and continuing treatment with SAR442168. The participant has received any of the medications/treatments listed in table below within the specified time frame. Note: the participant may be considered eligible if the washout period is completed after the last dose of such non-study disease-modifying treatment, except for interferon or glatiramer acetate treatment.

Medication	Exclusionary if used/used within required wash-out period
Systemic corticosteroids, adrenocorticotropic hormone	1 month prior to MRI scan
Dimethyl fumarate	1 month prior to dosing with SAR442168
Intravenous (IV) immunoglobulin, fingolimod, natalizumab (participants who have discontinued natalizumab in the 6 months prior to randomization should be evaluated to rule out progressive multifocal leukoencephalopathy)	2 months prior to dosing with SAR442168
Teriflunomide	2 years prior to dosing with SAR442168 or 1 month prior to dosing with SAR442168 if participant undergoes an accelerated elimination procedure before randomization
B-cell-depleting therapies such as ocrelizumab and rituximab	6 months prior to dosing with SAR442168 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 dosing with SAR442168
Highly immunosuppressive/chemotherapeutic medications: mitoxantrone up to 120 mg/m^2 body surface area, cyclophosphamide, cladribine	2 years prior to dosing with SAR442168
Alemtuzumab	4 years prior to dosing with SAR442168.
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 04. The participant is receiving strong inducers or inhibitors of CYP3A or CYP2C8 hepatic enzymes. Note: Such drugs need to be stopped at least 5 half-lives before study drug administration.

E 05. 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 beforehand.

Prior/concurrent clinical study experience

E 06. The participant is taking part in another interventional clinical trial of another drug substance.

E 07. Uncooperative behavior or any condition that could make the participant potentially non-adherent with the study procedures.

Other exclusions

E 08. The participant is accommodated in an institution because of regulatory or legal order; prisoners or subjects who are legally institutionalized.

E 09. Participants not suitable for participation, whatever the reason, as judged by the Investigator, including medical or clinical conditions, or participants potentially at risk of noncompliance to study procedures.

E 10. The participant is dependent on the Sponsor or Investigator (in conjunction with Section 1.61 of the International Council for Harmonization [ICH] Good Clinical Practice [GCP] Ordinance E6).

E 11. Participants are employees of the clinical study site or other individuals directly involved in the conduct of the study, or immediate family members of such individuals.

E 12. Sensitivity to any of the study interventions, or components thereof, or drug or other allergy that, in the opinion of the Investigator, contraindicates participation in the study.

E 13. The participant is pregnant or is a breastfeeding woman.

5.3 LIFESTYLE CONSIDERATIONS

5.3.1 Meals and dietary restrictions

The IMP shall be taken with meals. Whenever possible, the mealtime (eg, breakfast, lunch, etc) should be consistent throughout the study. The typical time of day at which the IMP is administered will be collected at each visit. In case the mealtime for IMP administration needs to be changed, a gap of a minimum of 12 hours between 2 doses should be maintained.

5.3.2 Caffeine, alcohol, and tobacco

For each visit, participants will abstain from ingesting caffeine- or xanthine-containing products (eg, coffee, tea, cola drinks, and chocolate) for 2 hours before the on-site study drug administration.

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

For each visit, participants will abstain from alcohol for 24 hours before the on-site study drug administration.

5.3.3 Activity

Not applicable.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the LTS16004 study but cannot continue due to eligibility criteria. The likelihood of screen failure in this extension study is very low. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure reasons, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) will not be rescreened, unless they fail due to a medical condition which precludes continuation of the intervention, which is expected to resolve. In such case screening examinations can be repeated within 6 weeks to re-evaluate eligibility.

5.5 CRITERIA FOR TEMPORARILY DELAYING ENROLLMENT AND ADMINISTRATION OF STUDY INTERVENTION

During a regional or national emergency declared by a governmental agency, if the site is unable to adequately follow protocol-mandated procedures, contingency measures proposed in Section 10.9, Appendix 9: Contingency measures for a regional or national emergency that is declared by a governmental agency should be considered for screening, enrollment, randomization, and administration of the study intervention.

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 investigational medicinal product (IMP) and a noninvestigational medicinal product (NIMP).

6.1.1 Investigational medicinal product

In study Part A participants will continue their previous SAR442168 dose in one of 4 dose groups as in the DRI15928 study. Participants in Cohort 1 of the DRI15928 study that exited the trial after receiving placebo from Weeks 13 to 16 will receive the active treatment dose assigned to them at randomization and administered during Weeks 1 to 12. During Part A, to maintain blinding, participants will receive 4 tablets once per day in a blinded fashion. The 4 tablets taken daily consist of some combination of 2.5 mg, 15 mg, or placebo to achieve the assigned dose. In Part B all participants will form a single dose group assigned to receive the selected Phase 3 dose. The IMP should be administered with a meal. The meal (breakfast, lunch, or dinner) should be consistent in terms of time throughout the study. Details for the interventions are provided in Table 7.

Table 7 - Overview of study interventions administered

ARM name	IMP	NIMP
Intervention name	SAR442168	Contrast medium
Type	Drug	Diagnostic Test
Dose formulation	Film coated tablet	Not applicable
Unit dose strength(s)	2.5 or 15 mg tablets (Part A) 15 or 60 mg tablets (Part B)	Not applicable
Dosage level(s)	In study Part A participants will continue previous SAR442168 dose in one of 4 dose groups. In Part B all participants will receive 60 mg dose.	A radiological, signal-enhancing, intravenous contrast medium will be used for T1 contrast enhanced MRI sequences. A locally approved medium will be used.
Route of administration	Oral	IV injection
IMP and NIMP	IMP	NIMP
Packaging and labeling	The IMP will be packaged in wallets, which will further be packaged in Part A into visit boxes. Each wallet and box will be labeled as required per country requirements.	Not applicable
[Current/Former name(s) or alias(es)]	Not applicable	Not applicable

Abbreviations: IMP: investigational medicinal product; IV: intravenous; NIMP: noninvestigational medicinal product.

Investigational medicinal product will be dispensed at regular site visits or at an unscheduled visit at the time of the switch to Part B.

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

For a regional or national emergency declared by a governmental agency that results in travel restrictions, confinement, or restricted site access, contingency measures are included in Section 10.9, Appendix 9: Contingency measures for a regional or national emergency that is declared by a governmental agency.

6.1.2 Noninvestigational medicinal product

A radiological, signal-enhancing, IV contrast medium will be used for T1 contrast-enhanced MRI sequences. A locally approved contrast agent 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 and regulations (20).

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

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

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

Any quality issue noticed with the receipt or use of an IMP (deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc.) must be promptly notified to the Sponsor. Some deficiencies may be recorded through a complaint procedure (see Section 8.3.12).

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

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

In the DRI15928 study, 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.

During the double-blind period of LTS16004 study, participants will continue treatment with the dose of SAR442168 assigned during the DRI15928 study. Investigators will remain blinded to each participant's assigned cohort (sequence) and dose during the double-blind period of 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

During the double-blind period of this study, this study is blinded for SAR442168 dose. Participants will continue treatment with their same SAR442168 dose used in the DRI15928 study.

During the double-blind period of this study, 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 IDMC will be used to periodically monitor safety data from this study. During the double-blind period 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.

Once the dose for the Part B is selected, all participants will be switched to the open-label treatment with this selected dose. From this point, the Investigators will be provided the results of the MRI reports. With yearly MRI being the standard in normal clinical practice for proper management of MS patients, Investigators will be provided MRI reports in the unlikely event that the DRI15928 and Part A of the LTS16004 study stretch longer than a year.

6.4 STUDY INTERVENTION COMPLIANCE

At the end of each on-site visit, the participants will receive IMP quantities up to the next visit (onsite or phone visit) as well as a diary where they will record all doses not taken at the investigational site. The diary will be kept as source data in the participant's study file.

It is the responsibility of the Investigator to check the participant's compliance to the IMP. Participant's compliance is tracked by counting dispensed and unused tablets at each on-site visit and checking with the completed participant diary 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, participant diary, 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.

Participants must abstain from taking prescription or nonprescription herbal medications containing St. John's wort extract within 14 days before the start of study intervention until completion of the follow-up visit unless, in the opinion of the Investigator and Sponsor, the medication will not interfere with the study.

Therapies for MS noted in the exclusion criterion E03 are not permitted after randomization while the participant is receiving study treatment. Short-term use (3 to 5 days) of glucocorticoids (eg, for MS relapse treatment or an acute illness) and local corticosteroids (eg, cutaneous, nasal, ocular, otic, intra-articular) are allowed.

It is recommended that symptomatic treatments for MS (eg, walking, fatigue, spasticity, incontinence, pain) and/or significant non-drug treatment such as physical therapy, should be maintained at a stable dose or schedule for the duration of the treatment period, if clinically feasible.

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

Paracetamol/acetaminophen, at doses of ≤3 grams/day and acetylsalicylic acid (aspirin) ≤81 mg/day are permitted for use at any time during the study. A short courses (up to 5 days) of NSAIDs (other than acetylsalicylic acid >81 mg/day), preferably selective cyclooxygenase-2 inhibitors at the lowest effective 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 eCRF. Other concomitant medication may be considered on a case-by-case basis by the Investigator in consultation with the medical monitor if required.

In addition, Section 5.2 contains a list of prohibited anticoagulant/antiplatelet therapies in this study.

CYP inhibitor/inducer

Potent and moderate inducers of CYP3A or potent inhibitors of CYP2C8 hepatic enzymes are not allowed throughout the study (Appendix 7, Section 10.7).

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

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 during the double-blind period of the study. Treatment might need to be interrupted or permanently discontinued if deemed necessary due to an AE (Section 10.3 and Section 8.3).

6.7 INTERVENTION AFTER THE END OF THE STUDY

After the end of this study, participants who successfully complete the trial on SAR442168 may be offered the option to participate in a Phase 3 LTS study for up to an additional 3 years, or until SAR442168 is approved in their respective country, whichever comes first. Details of the Phase 3 LTS study will be described in a separate protocol.

If this program is terminated earlier, other available RMS treatments will need to be considered at discretion of treating physician.

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 study intervention for abnormal liver function should be considered by the Investigator when a participant meets one of the conditions outlined in 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 schedule of activities (SoA) (Section 1.3) for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

Any abnormal laboratory value or ECG parameter will be confirmed within 24 hours to inform the decision whether to discontinue the IMP for the concerned participant.

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

If possible, and after the definitive discontinuation of intervention, the participants will be assessed using the procedure normally planned for the last dosing day with the IMP including a PK sample if the pEOT visit can be scheduled within a maximum of 24 hours after the last IMP dose. Details are provided in the SoA (Section 1.3). 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 discontinuation of the IMP may be considered by the Investigator because of suspected AEs and/or laboratory abnormalities and/or ECG abnormalities AEs or disruption of the clinical trial due to a regional or national emergency declared by a governmental agency (Appendix 9 [Section 10.9: Contingency measures for a regional or national emergency that is declared by a governmental agency]) or another illness or if there is a need for a prohibited concomitant medication. Treatment can be resumed later when it is considered safe and appropriate. For all temporary discontinuations, the duration should be recorded by the Investigator in the appropriate pages of the eCRF.

Temporary discontinuation of the IMP decided by the Investigator corresponds to more than one missed dose.

The following shall lead to temporary treatment discontinuation:

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

Analysis of missed doses will be described in the Statistical Analysis Plan.

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 has considered, based on his/her 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). For any SAE deemed to be

related to the IMP or with an unknown cause, the IMP should be permanently withdrawn, and participants will not be rechallenged. However, participants should continue regular study visits until study completion.

For a regional or national emergency declared by a governmental agency, contingency measures are included in Section 10.9, Appendix 9: Contingency measures for a regional or national emergency that is declared by a governmental agency.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons.

- See SoA (Section 1.3) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.
- If participants no longer wish to take the IMP, they will be encouraged to remain in the study.

The Investigators should discuss with the participants about the key visits to attend. The value of all their study data collected during their continued involvement will be emphasized as important to the public health value of the study.

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

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

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

Participants who have withdrawn from the study cannot be re-enrolled in the study. Their inclusion and intervention numbers must not be reused.

7.3 LOST TO FOLLOW UP

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if 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.

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

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.

- 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 and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) or during the DRI15928 study and obtained before signing the informed consent form (ICF) may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA (Section 1.3).
- In case of premature discontinuation of study intervention, the end-of-treatment visit will be conducted.
- 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 200 mL. Additional repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

For a regional or national emergency declared by a governmental agency, contingency measures are included in Section 10.9, Appendix 9: Contingency measures for a regional or national emergency that is declared by a governmental agency.

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 (20).

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.

Number of new and total number of T1 Gd-enhancing hyperintense as well as new/enlarging T2 lesions will be evaluated at the visits specified in 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 last MRI obtained in the DRI15928 study, if performed within 6 weeks prior to Day 1 of the LTS16004 study, will be acceptable as the baseline MRI for this study. Standardized endpoint evaluation will be assured by central review of brain MRI scans. Blinded central review will be performed for all MRI-derived endpoints. In Part A, MRI reviewers will be blinded to treatment assignments and to other participant data. In Part B, MRI reviewers will not be blinded. 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 8.3.6. In case of detection of non-MS findings in Part A, the MRI report needs to be communicated to the Treating Investigator, without disclosing normal MS findings to Investigators or to the site team if not relevant to any safety concern. In Part B, Investigators will receive MRI reports from the central MRI reader at regular intervals.

Details of MRI sequences, including exploratory sequences, will be provided in study reference manuals.

8.1.2 MS Relapse

8.1.2.1 Unscheduled assessment visits for a suspected MS 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 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 and PK and [redacted] samples will be collected.

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 8.3.6 for reporting rules).

Unscheduled visits as detailed in the SoA (Section 1.3) must be categorized as being related to MS (or not), 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, with or without recovery.
- Be present at normal body temperature (ie, no infection, excessive exercise, or excessively high ambient temperature), and
- Be preceded by ≥30 days of clinical stability (including no previous MS relapse).

Note: An exacerbation or recurrence of symptoms and signs 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 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 Statistical Analysis Plan.

8.1.3 Expanded Disability Status Scale (EDSS) evaluation

The Investigator will perform the EDSS evaluation (19) 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 and if measured, it will contribute to the EDSS score. Details of EDSS assessment and scoring are described in the study manual.

[redacted]

8.2 SAFETY ASSESSMENTS

Planned 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.

The last EDSS and MRI obtained in the DRI15928 study are acceptable if they are performed within 6 weeks prior to Day 1 of the LTS16004 study.

8.2.1 Physical examinations

- A 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.
- A 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 previous finding should be reported as a new AE.
- The SoA (Section 1.3) 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.
- 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

Single 12-lead ECG will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals. At least one longer rhythm monitoring recording of ≥30 sec 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 QTcF withdrawal criteria and any additional QTcF readings that may be necessary. In case the ECG machine does not automatically calculate QTcF, manual calculation using a nomogram or an automatic website calculator (eg, https://reference.medscape.com/calculator/48/ecg-corrected-qt) is acceptable.

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 CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 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.

- 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 CRF.

8.2.5 Suicidal ideation and behavior risk monitoring

SAR442168 is considered to be CNS-active, and therefore routine suicide risk monitoring will be performed. The Columbia Suicide Severity Rating Scale (C-SSRS) and thorough clinical evaluation of complaints will be used for suicide risk assessment. Any observation or event of clinical importance will be reported as AEs.

8.2.5.1 Columbia Suicide Severity Rating Scale

The C-SSRS will be 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 event of special interest

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

- Pregnancy of a female participant entered in a study as well as pregnancy occurring in a female partner of a male participant entered in a study with IMP/NIMP
  - Pregnancy occurring in a female participant entered in the clinical trial or in a female partner of a male participant entered in the clinical trial. It will be qualified as an SAE only if it fulfills one of the seriousness criteria (see Appendix 3 [Section 10.3]),
  - In the event of pregnancy in a female participant, 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 (eg, ≥2 tablets of the IMP within a 12-hour interval).
- Increase in alanine transaminase (ALT)
  - Any increase of ALT >3 x upper limit of normal (ULN).
- **Other project specific AESI(s)**
  - ECG observation of atrial fibrillation or atrial flutter
  - Severe infection that may or may not meet seriousness criteria (eg, a severe opportunistic infection)
  - Moderate or severe hemorrhagic events, including but not limited to symptomatic bleeding, bleeding in a critical area or organ such as the CNS, or intraocular bleeding.
  - Thrombocytopenia, platelet count <75 x 10^9/L (see Appendix 6, Section 10.6 for management flow chart).

The definitions of AEs and SAEs 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 Index adverse events

The following are considered as index AEs for which PK and PD [redacted] sample(s) will be collected: cytopenias (eg, thrombocytopenia, neutropenia) and cardiac arrhythmias (atrial fibrillation and atrial flutter).

8.3.3 Time period and frequency for collecting AE and SAE information

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

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

During Visit 1, the ongoing AEs/SAEs from the DRI15928 study and any AE/SAE that occurred between the final visit of the DRI15928 study and Visit 1 of the LTS16004 study are also to be recorded.

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

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

8.3.4 Method of detecting AEs and SAEs

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

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

8.3.5 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).

8.3.6 Regulatory reporting requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRBs)/Independent Ethics Committees (IEC), and Investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor 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 a SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.7 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.

8.3.8 Cardiovascular and death events

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

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.

8.3.9 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.

8.3.10 Reporting of safety findings from magnetic resonance imaging

Magnetic resonance imaging scans should be reviewed locally for any non-MS pathology. In case of such findings, the relevant information needs to be provided to the Investigator for appropriate safety reporting and to ensure the appropriate management of the participant's identified safety finding. 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 should not be reported as AEs unless they are deemed unusual and thus a distinct safety finding.

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

See Section 8.3.9 and Section 8.3.10.

8.3.12 Guidelines for reporting product complaints

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

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

8.3.12.1 Medical devices

Not applicable.

8.4 TREATMENT OF OVERDOSE

To date, no specific antidote or detoxification measure can be recommended for an overdose of SAR442168. In case of a suspected overdose, the participant should be treated symptomatically.

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. If feasible, obtain a plasma sample for PK analysis within 24 hours of the last documented IMP dose.
4. Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

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

8.5 PHARMACOKINETICS

Whole blood samples of approximately 2 mL will be collected for measurement of plasma concentrations of SAR442168 in the event of either a suspected MS relapse or an index AE or at the pEOT visit, if feasible (only if the pEOT visit can be scheduled within a maximum of 24 hours after the last IMP dose). Instructions for the collection and handling of biological samples will be provided by the Sponsor. The actual date and time (24-hour clock time) of each sample will be recorded. Time of the last meal before PK sampling will be collected to document any meal influence on PK parameters. If warranted and agreed upon between the Investigator and the Sponsor, additional PK samples may be collected (eg, for retesting, pEOT, or if clinically indicated).

During the double-blind period of the study, drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel.

8.6 PHARMACODYNAMICS

Venous blood samples of approximately 6 mL will be collected for measurement of [redacted] in the event of either a suspected MS relapse or an index AE. [redacted] will be prepared from whole blood [redacted]. Samples of blood for [redacted] will be collected in all participants from sites selected by their capability to send them rapidly to the central laboratory for processing. The details [redacted] and bioanalytical methods will be specified in the study manual. [redacted] will be reported using descriptive statistics.

8.7 GENETICS

Genetics is not evaluated in this study.

8.8 BIOMARKERS

Plasma and serum samples for biomarker research are required and will be collected from all participants in this study as specified in the SoA (Section 1.3).

Samples from all participants will be tested for [redacted] to evaluate their associations with observed clinical responses.

Detailed procedures of sample preparation, storage, shipment, and destruction of these samples will be described in the specific laboratory manual.

8.9 HEALTH ECONOMICS OR MEDICAL RESOURCE UTILIZATION AND HEALTH ECONOMICS

Not applicable.

8.10 USE OF BIOLOGICAL SAMPLES AND DATA FOR FUTURE RESEARCH

Future research may help further the understanding of disease subtypes, disease biology, related conditions, drug response and toxicity, and can help identify new drug targets or biomarkers that predict participant response to treatment. Therefore, data and biological samples will be stored and used for future research when consented to by participants (see Section 10.1.3) unless prohibited by local laws or IRBs/IECs (in such case, consent for future use of sample will not be included in the local ICF).

For participants who consent to the storage and use of their data and remaining and/or extra clinical samples, data and samples may be used after the study ends for future research related either to the study intervention, the mechanism of action, and the disease or its associated conditions. Such research may include, but is not limited to, performing assessments on [redacted]. If future research on genetic material is performed, this will also be limited to the purpose of addressing research questions related to [redacted]

In the event future research is conducted for other purposes, the study participants will be informed of those purposes and will be given means to object to those research projects.

Data and samples will be used in compliance with the information provided to participants in the ICF Part 2 (future research).

All study participant data and samples will be coded such that no participant direct identifiers will be linked to them. Coded data and samples may be transferred to a Sponsor site (or a subcontractor site), which may be located outside of the country where the study is conducted. The Sponsor adopts safeguards for protecting participant confidentiality and personal data (see Section 10.1.4).

The samples will be stored for a maximum of 15 years after the end of the study. Any samples remaining at the end of retention period will be destroyed. If a participant requests destruction of his/her samples before the end of the retention period, the Investigator must notify the Sponsor (or its contract organization) in writing. In such case, samples will be destroyed and related coded data will be anonymized unless otherwise required by applicable laws.

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

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

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

This is a long-term safety and efficacy follow-up study for participants who have been treated with SAR442168, therefore, there is no statistical hypothesis assumed.

9.2 SAMPLE SIZE DETERMINATION

There are no sample size calculations for this long-term extension study.

All participants who complete the DRI15928 study will be eligible for enrollment in the LTS16004 study. The Sponsor enrolled 130 participants in the DRI15928 study, 129 of whom completed that study.

9.3 POPULATIONS FOR ANALYSES

For purposes of analysis, the following populations are defined (Table 8):

Table 8 - Populations for analyses

Population	Description
Enrolled/safety	All participants who sign the informed consent form.
Efficacy	All participants who sign the informed consent form and receive at least 1 dose of SAR442168 in this study.

9.4 STATISTICAL ANALYSES

The statistical analysis plan will be developed and finalized before database lock, or an ad hoc interim analysis, 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 of the primary and secondary endpoints.

9.4.1 Efficacy analyses

All efficacy analyses will be performed on the Efficacy Population.

Table 9 - Efficacy analyses

Endpoint	Statistical Analysis Methods
Secondary endpoints: • Number of new Gd-enhancing T1-hyperintense lesions by brain MRI. • Number of new or enlarging T2 lesions. • Total number of Gd-enhancing. T1-hyperintense lesions. • Number of relapses (ARR) during the study period. • Change in EDSS score from baseline over time.	Overall summary using descriptive statistics, by visit.
Exploratory	The exploratory efficacy endpoints listed in Section 3 will be descriptively summarized.

Abbreviations: ARR: annualized relapse rate; EDSS: Expanded Disability Status Scale; Gd: gadolinium.

9.4.2 Safety analyses

All safety analyses will be performed on the Safety Population.

Table 10 - Safety analyses

Endpoint	Statistical analysis methods
Adverse events - AEs, SAEs	Overall summaries of incidence using descriptive statistics.
Clinical laboratory tests - PCSAs	Overall summaries of incidence using descriptive statistics, by visit.
Safety findings on MRI	Overall summaries using descriptive statistics, by visit.
ECG	Overall summaries using descriptive statistics by visit for parameters.
Vital signs	Overall summaries using descriptive statistics by visit for parameters.

Abbreviations: AE: adverse event; ECG: electrocardiogram; MRI: magnetic resonance imaging; PCSA: potentially clinically significant abnormalities; SAE: serious adverse event.

9.4.3 Other analyses

Pharmacokinetics and PD analyses will be described in the statistical analysis plan finalized before database lock. Pharmacokinetic data from the DRI15928 study will be considered for the analysis in this LTS16004 study.

For a regional or national emergency declared by a governmental agency, contingency measures are included in Section 10.9, Appendix 9: Contingency measures for a regional or national emergency that is declared by a governmental agency.

9.5 INTERIM ANALYSES

The Statistical Analysis Plan will describe any ad hoc and interim analyses in greater detail.

9.5.1 Independent Data Monitoring Committee

An IDMC will follow safety data periodically as detailed in the IDMC Charter until the dose selection is completed. Monitoring frequency will be reduced if no major safety issues are identified. Additional ad hoc IDMC reviews may occur at any time should a safety risk be suspected. Unblinded IDMC reports will be provided by an independent unblinded statistician for IDMC data reviews during the Part A period.

The IDMC will be convened when the DRI15928 study results are available, and the IDMC may recommend stopping one or more SAR442168 dose levels in the LTS16004 study before the dose of SAR442168 to be used in Phase 3 is determined due to safety reasons (including lack of efficacy) and switch participants to another dose level.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and the applicable amendments and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines,
  - Applicable ICH GCP Guidelines,
  - Applicable laws and regulations.
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to the health authorities (competent regulatory authority) as required by local regulation and to an IRB/IEC by the Investigator and reviewed and approved- when applicable - by those health authorities and the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC;
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures,
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.2 Financial disclosure

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

10.1.3 Informed consent process

- The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

The ICF contains a separate section that addresses the use for research of participants' data and/or samples (remaining mandatory ones). Future research is to be defined in Core Study Informed Consent Form (CSICF) Part 2: consent for use of leftover samples and associated coded data for future research, and consent for performance of genetic analyses on biological samples. Each option is subject to an independent consent and must be confirmed by ticking a checkbox in CSICF Part 3. The Investigator or authorized designee will explain to each participant the objectives of the exploratory research and why data and samples are important for future research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

10.1.4 Data protection

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

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

Protection of participant data

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

Participant race and ethnicity will be collected in this study because these data are required by regulatory agencies (eg, on Afro-American population for the United States Food and Drug Administration or on 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 which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- When archiving or processing personal data pertaining to the Investigator and/or to the participants, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.
- Participants must be informed that their study-related data will be used for the whole "drug development program", ie, for this trial as well as for the following steps necessary for the development of the investigational product, including to support negotiations with payers and publication of results.

Protection of data related to professionals involved in the study

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

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

Professionals have the right to request the access to and the rectification of their personal data, as well as their erasure (where applicable) by contacting the Sanofi Data Protection Officer: Sanofi DPO - 46 Avenue de la Grande Armée - 75017 Paris - France (to contact Sanofi by email, visit https://www.sanofi.com/en/our-responsibility/sanofi-global-privacy-policy/contact).

10.1.5 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.

Independent Hepatology Assessment Committee

An expert committee of 3 independent hepatologists will review all cases of potential DILI and will provide guidance on case evaluation and risk mitigation. The Hepatology Assessment Committee recommendations will be made available to the DMC. Details of the responsibilities of the Independent Hepatology Assessment Committee and its workflow will be described in a separate charter.

10.1.6 Dissemination of clinical study data

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

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

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

Professionals involved in the study or in the drug development program

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

10.1.7 Data quality assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in separate study documents.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 25 years after the signature of the final study report unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.8 Source documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in 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

10.1.10 Publication policy

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

10.2 APPENDIX 2: CLINICAL LABORATORY TESTS

The tests detailed in Table 11 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 11 - Protocol-required 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	
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
	Glucose	Calcium	Alkaline phosphatase	Serum FSH Serum human chorionic gonadotropin (HCG) pregnancy test
	Creatine phosphokinase (CPK)[b]			
Routine urinalysis (central)	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if blood or protein)			
Other screening tests (local)	• Urine human chorionic gonadotropin (HCG) pregnancy test (as needed for women of childbearing potential)[c] 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 observations of ALT >3 × ULN are given in Appendix 6, Section 10.6. Clinical laboratory findings 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 suggest severe liver injury must be reported as an SAE.

b Required in Year 1 only

c Local urine testing is sufficient unless a pregnancy is detected or the urine test is inconclusive and a serum test needs to be used for verification, or only serum testing is required by local regulation or IRB/IEC.

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 fulfil the definition of an AE or SAE.
- The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE.

Events NOT meeting the AE definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant’s condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant’s condition.

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

DEFINITION OF SAE

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

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

a) **Results in death**

b) **Is life-threatening**

The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c) **Requires inpatient hospitalization or prolongation of existing hospitalization**

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

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

d) **Results in persistent disability/incapacity**

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

e) **Is a congenital anomaly/birth defect**

f) Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

RECORDING AND FOLLOW-UP OF AE AND/OR SAE

AE and SAE recording

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

Assessment of 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 a 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 IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report to the Sponsor’s representative. However, **it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor’s representative.**
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

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

REPORTING OF SAES

SAE reporting to the Sponsor's representative via an electronic data collection tool

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

SAE reporting to the Sponsor's representative via paper CRF

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

10.4 APPENDIX 4: CONTRACEPTIVE GUIDANCE AND COLLECTION OF PREGNANCY INFORMATION

DEFINITIONS:

Woman of childbearing potential

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

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

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), Investigator discretion should be applied to determining study entry.

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

3. Postmenopausal female
   - A postmenopausal state is defined as no menses for ≥12 months with plasma FSH level >30 UI/L or as per laboratory reference range.
   - 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 acceptable non-estrogen hormonal 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

None.

Female participants

Female participants of childbearing potential are eligible to participate if they agree to use an acceptable effective contraception method consistently and correctly as described in Table 12.

Table 12 - Contraceptive methods allowed during the study

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

b Considered effective, but not highly effective - failure rate of ≥1% per year. Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception.

c Male condoms and female condoms should not be used together (due to risk of failure with friction).

d If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those that inhibit ovulation as the primary mode of action.

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 time points specified in the SoA (Section 1.3) 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 8.3.6. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.

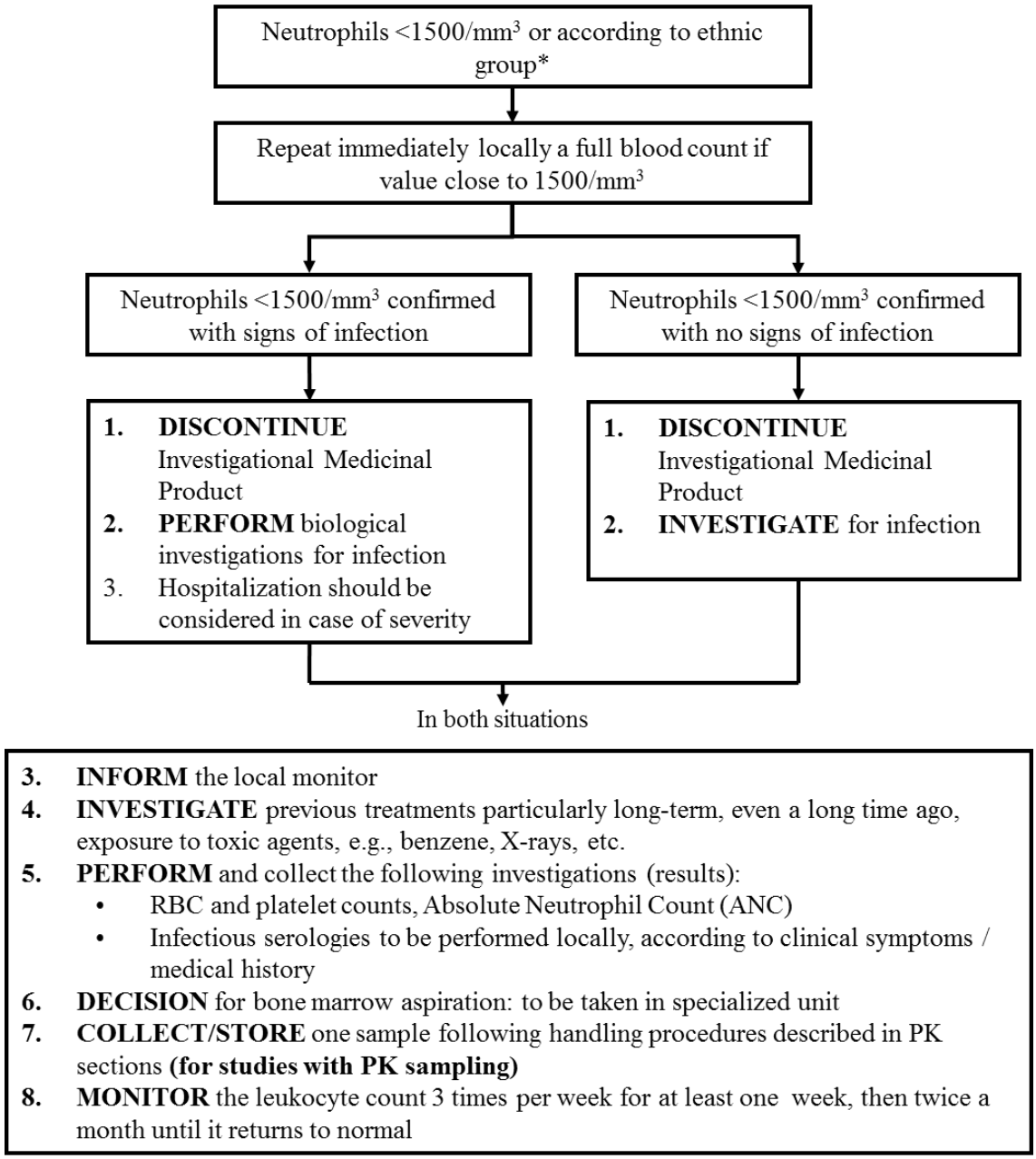
10.5 APPENDIX 5: GENETICS

No additional genetic test will be collected in this study. Results of genetic tests from the DRI15928 study will be used for data analyses for any correlation with efficacy or safety.

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

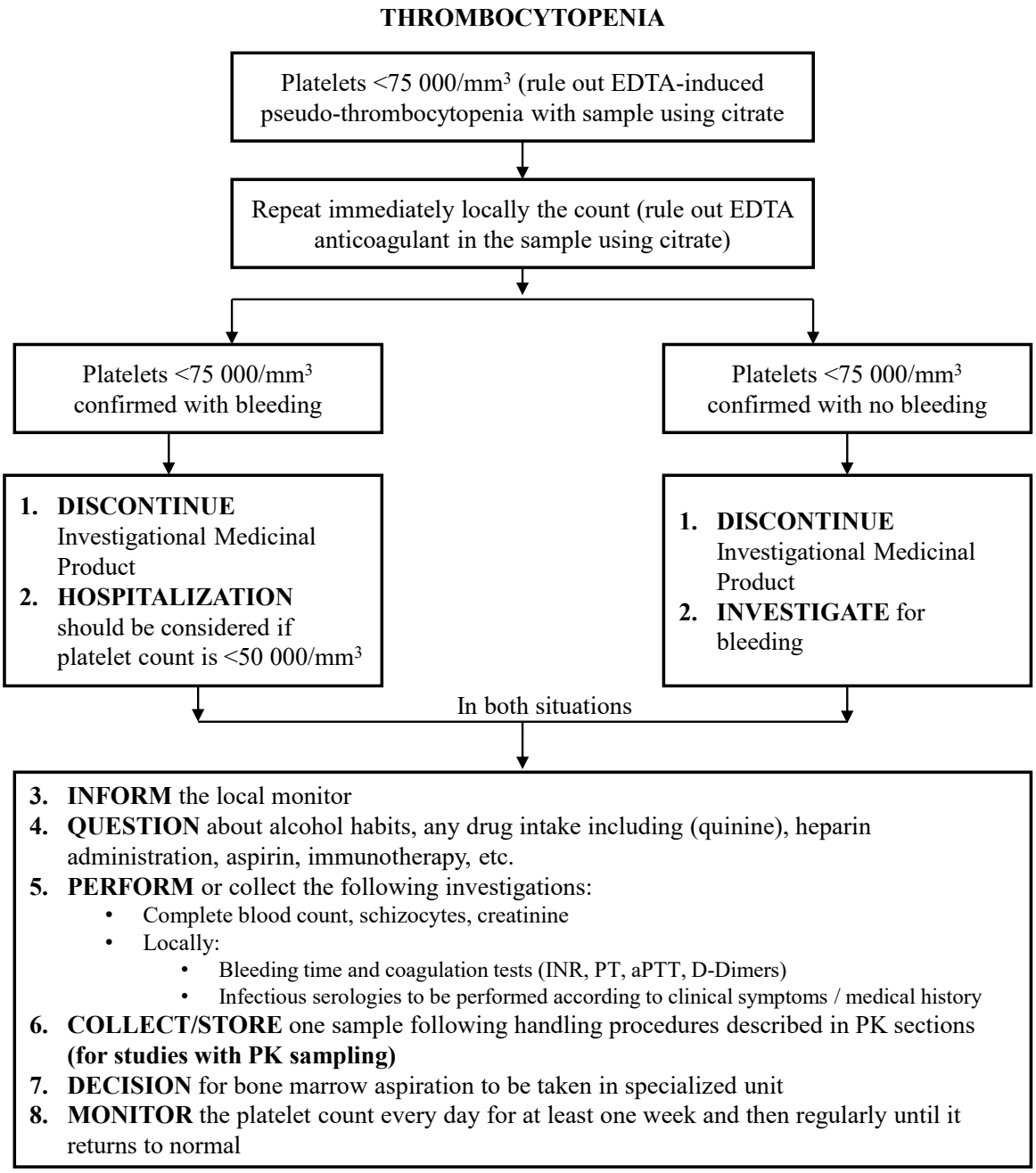
These actions are required for ALT increase and thrombocytopenia events ONLY. For all other safety events described, these are suggested per the Investigator's medical judgement.

NEUTROPENIA



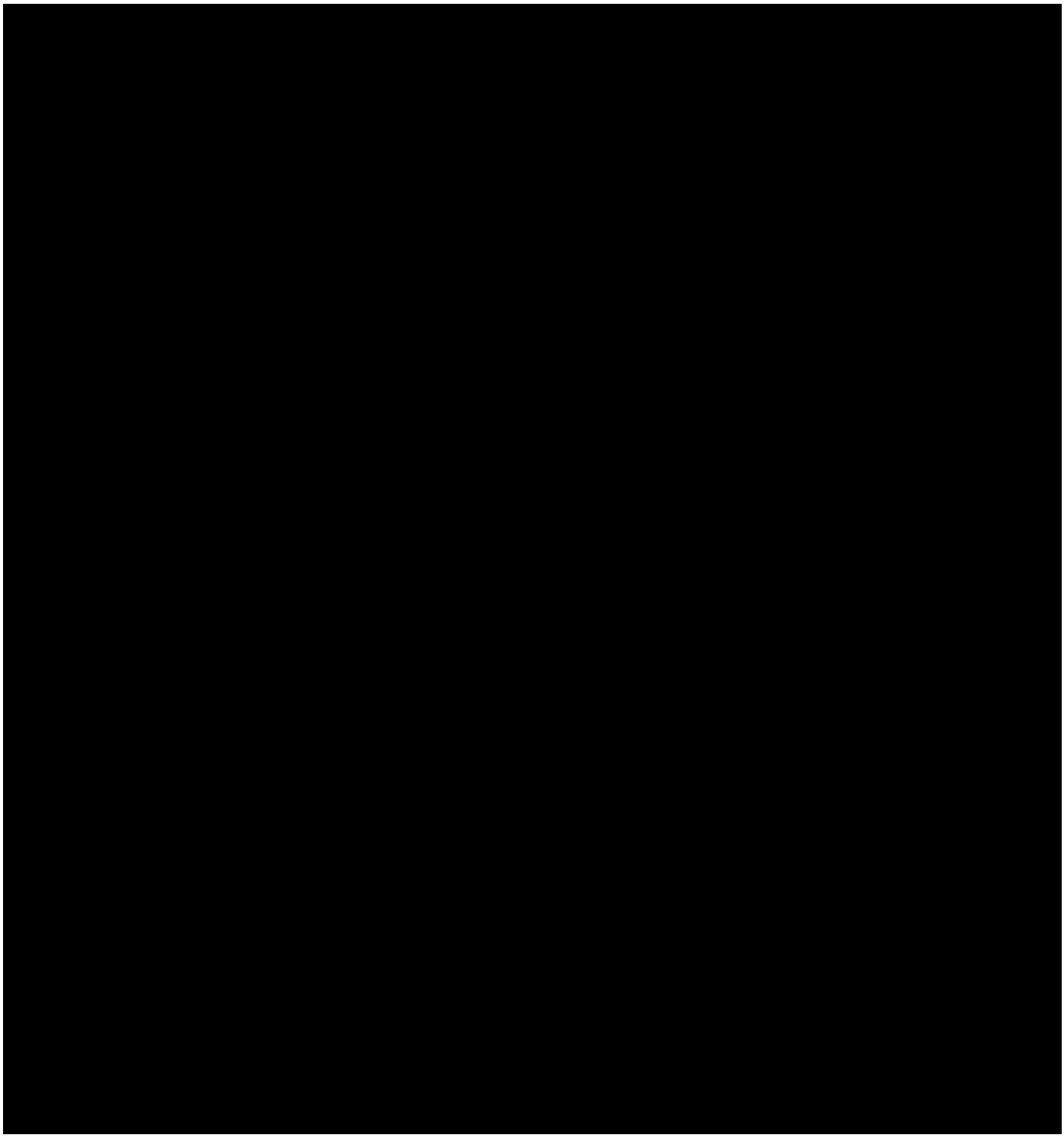
* For individuals of African descent, the relevant value of concern is <1000/mm3

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

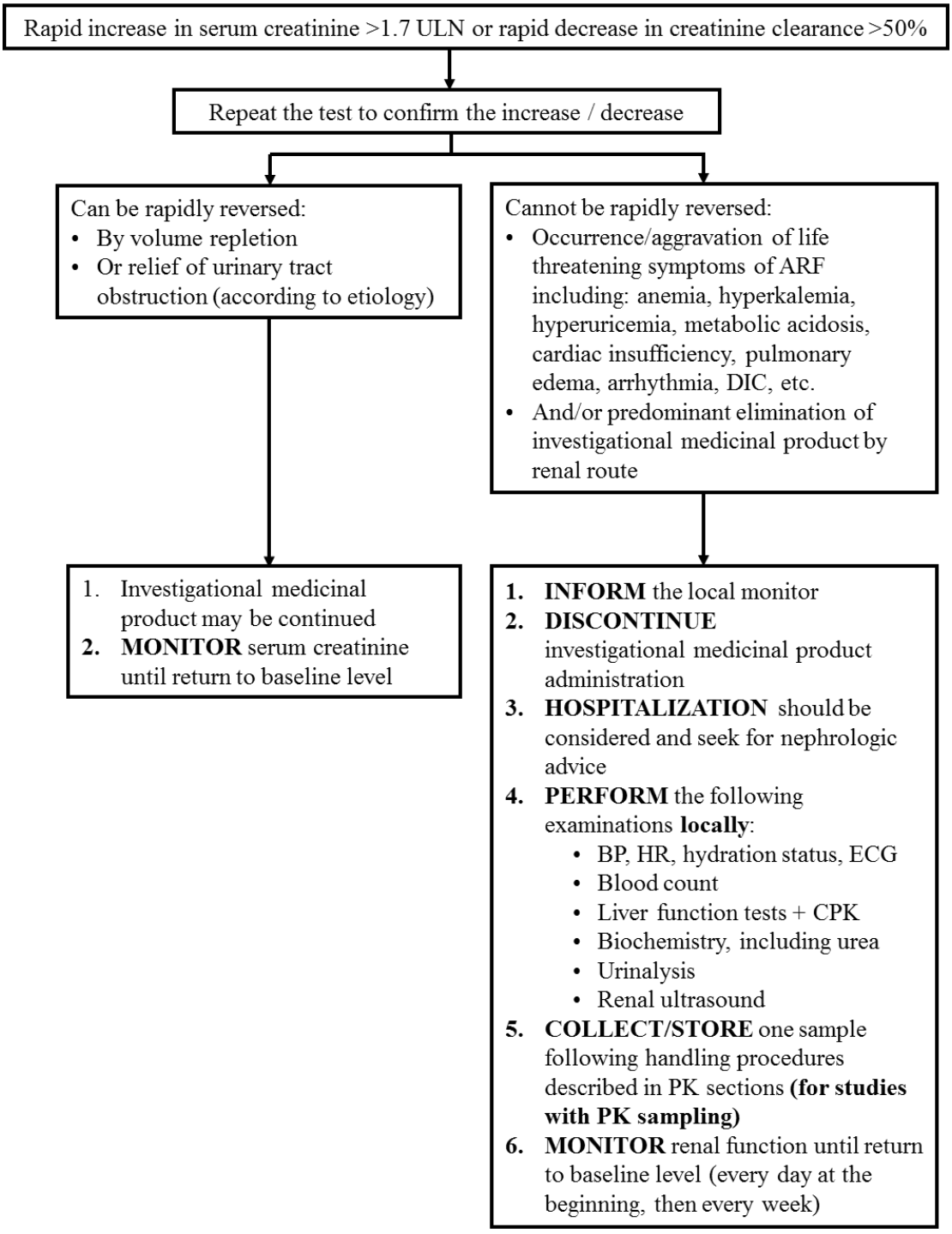


Thrombocytopenia is to be recorded as an AE only if at least 1 of the criteria listed in the general guidelines for reporting AEs in Section 10.3 is met.

[redacted]

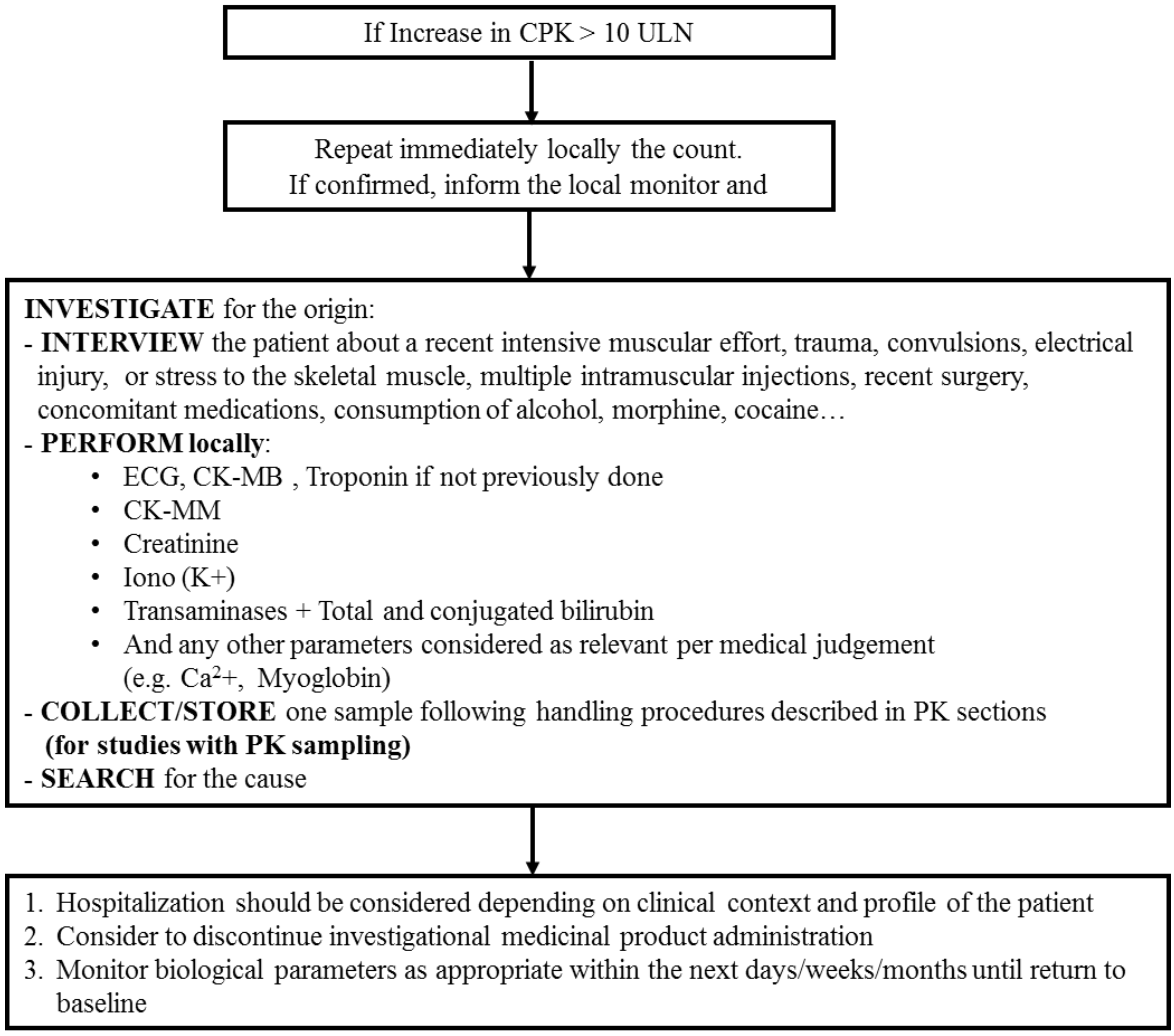


INCREASE IN SERUM CREATININE in patients with normal baseline (creatininemia between 45 µmol/L and 84 µmol/L)



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

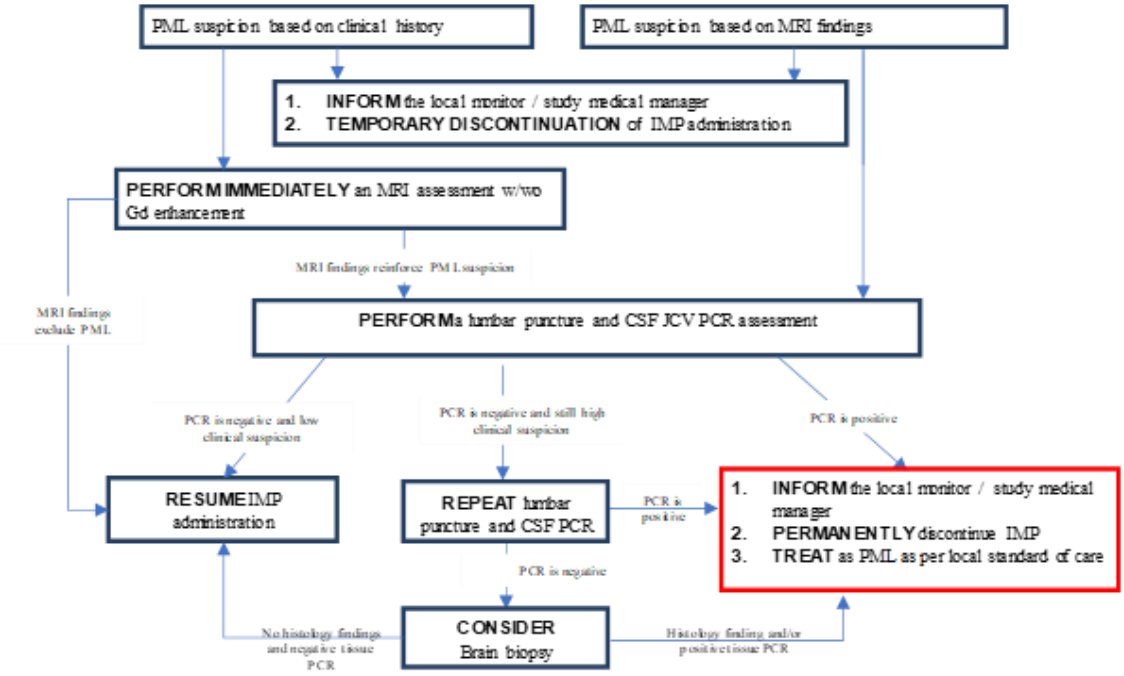
INCREASE IN CPK OF NON-CARDIAC ORIGIN AND NOT RELATED TO INTENSIVE PHYSICAL ACTIVITY



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

SUSPECTED PML

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



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

Clinical manifestations or MRI lesions features suspicious for PML are proposed in Table 13 (based on [21] and [22]).

Table 13 - Clinical and MRI features suggestive of PML

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

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

- The detection of John Cunningham virus (JCV) DNA in the CSF of a patient with clinical and MRI features suggestive of PML establishes the diagnosis of PML.

- If JCV DNA is not detected in CSF and if clinical suspicion of PML remains high, another lumbar puncture should be performed.
- If diagnosis remains uncertain and suspicion of PML remains high, a brain biopsy may be considered to establish a definitive diagnosis.

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

10.7 APPENDIX 7: LIST OF EXAMPLE DRUGS WITH A POTENTIAL TO CHANGE WITH SAR442168 METABOLISM

The following drugs should not be taken during the study concomitantly with IMP due to their potential to change SAR442168 kinetics due to interaction with P450-mediated metabolism, being potent and moderate inducers of CYP3A or potent inhibitors of CYP2C8 liver enzymes (Table 14).

Additionally, participants in the US and any other sites following FDA partial clinical hold conditions must not take medications that are mild, moderate, or potent inhibitors of CYP3A or CYP2C8 (Table 15).

Please note that the lists provided in Table 14 and Table 15 are not exhaustive and that the product information of drugs intended for concomitant use should be consulted.

Table 14 - Potent and moderate CYP3A inducers and potent CYP2C8 inhibitors

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

Table 15 - Mild, moderate, and potent inhibitors of CYP3A and CYP2C8, and moderate and potent inducers of CYP3A

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

10.8 APPENDIX 8: COUNTRY-SPECIFIC REQUIREMENTS

Only Part A of this protocol, the double-blind period of continued treatment with the respective SAR442168 dose administered in the DRI15928 study, applies to the Czech Republic. For Part B, the open-label period of a single-group treatment with the selected Phase 3 SAR442168 dose, a substantial amendment will be submitted with the defined optimal dose and rationale for the dose supported by clinical data from Study DRI15928 and by preclinical data. See Section 4 for details.

10.8.1 Country-specific provisions for the US and sites following FDA partial clinical hold conditions

In addition to refraining from medications that are moderate and potent inducers of CYP3A, participants must not take medications that are mild, moderate, and potent inhibitors of CYP3A or CYP2C8 hepatic enzymes throughout the conduct of the trial (see Appendix 7, Section 10.7).

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

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

10.9 APPENDIX 9: CONTINGENCY MEASURES FOR A REGIONAL OR NATIONAL EMERGENCY THAT IS DECLARED BY A GOVERNMENTAL AGENCY

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

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

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote or on-site monitoring) are provided in separate study documents.

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

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

10.9.1 Informed consent

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

10.9.2 Study procedures

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

1. New screenings during a regional or national emergency declared by a governmental agency can be performed only if allowed by local competent authorities and after Sponsor's agreement is obtained. Rescreening will be permitted when the situation normalizes and only if allowed by local competent authorities and after Sponsor's agreement is obtained.
2. If on-site visits or alternative location (out of participant's home) are not possible, all visits from Week 1 (including those planned to be done on site) will be performed at home by a trained healthcare professional and, if allowed, by local competent authorities for:
   - Treatment administration
   - Blood sampling for safety (at least hematology, hepatic function panel, coagulation panel) other safety assessment (at least serum creatinine for eGFR calculation), and pregnancy test (if applicable)
   - Measuring vital signs
   - Monitoring of injection site reactions, AEs and SAEs

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

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

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

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

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

10.9.3 Temporary discontinuation

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

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

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

10.9.4 Statistical analysis

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

10.10 APPENDIX 10: ABBREVIATIONS

AE:	adverse event(s)
ALT:	alanine transaminase
ARR:	annualized relapse rate
AUC_{last}:	area under the concentration-time curve until the last quantifiable concentration
BTK:	Bruton's tyrosine kinase
CFR:	Code of Federal Regulations
[redacted]	[redacted]
C_{max}:	maximum serum concentration
CNS:	central nervous system
CSF:	cerebrospinal fluid
C-SSRS:	Columbia Suicide Severity Rating Scale
CYP450:	cytochrome P450
DILI:	drug-induced liver injury
eCRF:	electronic case report form
FSH:	follicle-stimulating hormone
GCP:	Good Clinical Practice
Gd:	gadolinium
GLP:	Good Laboratory Practice
HCG:	human chorionic gonadotropin
HRT:	hormonal replacement therapy
IC_{50}:	half maximal inhibitory concentration
ICF:	informed consent form
ICH:	International Council for Harmonisation
IEC:	Independent Ethics Committees
Ig:	immunoglobulin
IMP:	investigational medicinal product
IRB:	Institutional Review Board
IV:	intravenous
IVRS:	interactive voice response system
IWRS:	interactive web response system
JCV:	John Cunningham virus
LOAEL:	low observed adverse effect level
LTS:	long-term safety
MAD:	multiple ascending dose
MRI:	magnetic resonance imaging

MS:	multiple sclerosis
NIMP:	noninvestigational medicinal product
NOAEL:	no observed adverse effect level
PCSAs:	potentially clinically significant abnormalities
PD:	pharmacodynamics(s)
PK:	pharmacokinetic(s)
PML:	progressive multifocal leukoencephalopathy
PPMS:	primary progressive multiple sclerosis
QTcF:	QT interval corrected using Fridericia's formula
RMS:	relapsing multiple sclerosis
SAD:	single ascending dose
SAE:	serious adverse event(s)
[redacted]	[redacted]
SoA:	schedule of activities
SPMS:	secondary progressive multiple sclerosis
$t_{1/2}$:	elimination half life
TDAR:	T-cell dependent antibody response
TEAE:	treatment-emergent adverse event
t_{max}:	time to reach maximum observed concentration
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 (TOC).

10.11.1 Amended protocol 01 (26 June 2019)

This amended protocol (amendment 01) was considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it did not significantly impact the safety or physical/mental integrity of participants or the scientific value of the study.

OVERALL RATIONALE FOR THE AMENDMENT

This protocol (amendment 01) was amended in response to a request from the Czech Republic Health Authority for a clear statement that only Part A of the protocol will be implemented in the Czech Republic until a substantial amendment, including the dose choice and rationale for dose choice for Part B, is approved.

Protocol amendment summary of changes table for amended protocol 01

Section # and Name	Description of Change	Brief Rationale
Section 10.8 Appendix 8: Country-specific requirements	Specification that only Part A of the protocol will be implemented in the Czech Republic until a substantial amendment including the dose choice and rationale for dose choice for Part B is approved.	Response to Czech Republic Health Authority request.

10.11.2 Amended protocol 02 (30 August 2019)

In Europe, this amended protocol (amendment 02) was considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it significantly impacted the safety or physical/mental integrity of participants.

OVERALL RATIONALE FOR THE AMENDMENT

This protocol (amendment 02) was primarily amended in response to comments from health authorities and ethics committees during the initial clinical trial application process. Furthermore, Sanofi Genzyme used that opportunity to update with new available information.

Protocol amendment summary of changes table for amended protocol 02

Section # and Name	Description of Change	Brief Rationale
All	Reformatting of existing content throughout the document, when necessary. Minor editorial changes are not described in the table below.	Update in accordance with sanofi-aventis standards
Cover page	Addition of IND and NCT numbers	Clarification
Section 1.1 Synopsis	Addition of “film coated” tablet (# in the ‘Intervention groups and duration’ section)	Consistency with the IB
	Addition of “safety findings on MRI” (#in the ‘Primary analysis’ section)	Consistency with the IB
Section 1.3 Schedule of activities	Addition of “If needed” in the UNSCH column for MRI (Tables 1 and 2)	Clarification
	Update of footnotes for Tables 1 (e, f, h), 2 (d), and 3 (d)	Clarification
Section 2.2 Background	Revision and update of the entire section with new information from the 6- and 9-month toxicology report, as well as embryofetal studies, with the addition of the inclusion of tables NOAELs and exposure ratios	Inclusion of new information from the animal toxicology studies
	Change of "thrombocytopenia" for "decreased platelet count" (#section Phase 1 first-in-human single-ascending-dose/multiple-ascending-dose study')	Clarification

Section # and Name	Description of Change	Brief Rationale
Section 2.3 Benefits and risks	Revision of the entire section	Update with new information
	Change of "thrombocytopenia" for "decreased platelet count"	Clarification
Section 5.1 Inclusion criteria I 02	Clarification that the effective method of birth control should be taken from inclusion and up to 2 months after the last study dose	Alignment with changes made to the DRI15928 study
	Menopause is defined as being amenorrheic for ≥12 months as supposed to 2 ≥years	Correction of error
Section 5.2 Exclusion criterion E03	Deletion of teriflunomide plasma level values before randomization	Alignment with the Aubagio washout leaflet instructions that blood level of 0.02 mg/L is applicable only to participants seeking to achieve pregnancy
Section 5.2 Exclusion criterion E05	Deletion of the dose of aspirin (>80mg/day)	All doses for aspirin prohibited
Section 5.2 Exclusion criterion E12	Deletion of this exclusion criteria: “Any specific situation during study implementation/course that may rise ethics considerations”.	Alignment with changes made to the DRI15928 study
Section 5.2 Exclusion criterion E13	Addition of the below criteria as E13: “The participant is pregnant or is a breastfeeding woman”.	Alignment with changes made to the DRI15928 study
Section 5.3.1 Meals and dietary constrictions	Clarification that the IMP can be taken with or without food; and the time of day and whether IMP is taken with or without food should be as consistent as possible throughout the study. Usual time of day and way of administration (with or without food) will be recorded at every study visit.	Alignment with changes made to the DRI15928 study
Section 6.1.1 Investigational medicinal product	Clarification that the time of day and whether IMP is taken with or without food should be as consistent as possible throughout the study	Alignment with changes made to the DRI15928 study
Section 6.3 Methods of blinding	Addition that once the dose for the Part B is selected, all participants will be switched to the open-label treatment with this selected dose. From this point, the investigators will be provided the results of the MRI reports. With yearly MRI being the standard in normal clinical practice for proper management of MS patients, investigators will be provided MRI reports in the unlikely event that the DRI15928 and Part A of the LTS16004 study stretch longer than a year.	Clarification following the HA’s request.
Section 6.5 Concomitant therapy	Clarification that NSAIDs can be given during the course of the study, proton pump inhibitors should be avoided, and antacids and H2-receptor antagonists should be staggered	Alignment with changes made to the DRI15928 study
Section 7.1.2.1 Rechallenge	Addition of clarification to not rechallenge participants after SAEs attributable to the IMP or with unknown cause in the DRI study	Clarification following the HA’s request

Section # and Name	Description of Change	Brief Rationale
Section 8.1.1 MRI assessments	Addition that in Part A, MRI reviewers will be blinded to treatment assignments and to other participant data. In part B, MRI reviewers will not be blinded	Clarification
Section 8.2.5 Suicidal ideation and behavior risk monitoring	Addition that SAR442168 is considered to be CNS-active, and therefore routine suicide risk monitoring will be performed	Alignment of text with the DRI15928 study and clarification for C-SSRS
Section 9.4.1 Efficacy analyses	Addition of footnote in Table 9.	Clarification
Section 9.4.2 Safety analyses	Addition of footnote in Table 10	Clarification
Section 10.1.1 Regulatory and Ethical considerations (#bulletpoint 2)	Original text modified as “the protocol, protocol amendments, ICF, IB, 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 – when applicable- by those health authorities and the IRB/IEC before the study is initiated”.	Alignment with changes made to the DRI15928 study and as a request by the HA.
Section 10.4 Contraception guidance (#Table 10)	Deletion of footnote	Alignment with the revised inclusion criterion I 02
Section 10.8 Appendix 8	Creation of appendix “List of example drugs with a potential to affect plasma exposure of SAR442168 via reduction of gastric acid”	Alignment with changes made to the DRI15928 study
Section 10.11 Appendix 11 (Protocol amendment history)	Addition of reasons for amended protocol 01	Update of the protocol amendment history

10.11.3 Amended protocol 03 (02 March 2020)

In Europe, this amended protocol (amendment 03) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it significantly impacts the safety or physical/mental integrity of participants.

OVERALL RATIONALE FOR THE AMENDMENT

This protocol is amended based on the efficacy and safety findings from the DRI5928 trial, which demonstrated that the dose of 60 mg taken with a meal is the most appropriate dose for further investigation. This is the recommended dose for Part B of this study (LTS16004). Furthermore, the Sponsor uses this opportunity to update with new available information.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Throughout the document	Reformatting of existing content throughout the document, when necessary. Minor, editorial changes are done throughout the document as necessary.	Update in accordance with sanofi-aventis standards.
Cover page	Addition of 'not applicable' for 'other' identifier number.	Clarification.
1.1 Synopsis # Intervention groups and duration	Addition of 60 mg dose following dose selection for further investigations based on Phase 2b data (DRI15928).	Availability of Phase 2b data.
1.1 Synopsis # Post-trial access to study medication	Clarification that 'the study will continue up to 5 years or until SAR442168 is approved…'	Clarification.
1.3 Schedule of activities	<u>Table 1 - A:</u> - Modification of footnotes 'a', e', and 'g'. - Addition of footnotes 'm' and 'n'. - Addition of "If switch to part B" in the UNSCH column for informed consent and IMP administration rows. - Annotations for screening and baseline check boxes in hematology, biochemistry and urinalysis assessments were corrected to 'g'. - Annotation "e" for exploratory biomarker plasma samples assessments was shifted to 'Exploratory biomarker plasma samples [redacted] from 'baseline visit'. <u>Table 2 - B</u>: - Addition of footnote 'f. - Addition of year 4 checkbox for MRI in the event of premature EOT. <u>Table 3 – C:</u> - Footnote 'f' was newly inserted. - Annotation 'a' removed from 'follow-up visit' column. <u>Tables 1-A, 2-B, 3-C:</u> - Additional efficacy endpoint [redacted] added. - Addition of note to clarify that all assessments shall be done as designated in this SoA unless not permitted according to local regulations added in tables 1- A, 2-B, and 3-C. - Table heading 'phase' changes to 'procedure".	Clarifications and correction of errors from the LTS16004 amended protocol 02.
2.2 Background	Nonclinical data updated.	New information updated.
2.3 Benefit/Risk Assessment	Update of the safety profile with information from the DRI15928 trial.	New information updated.
3 Objectives and Endpoints	Addition of [redacted] as a tertiary/exploratory endpoint.	Addition of new assessment as a pilot study in a subset of participants before inclusion in the Phase 3 studies.

Section # and Name	Description of Change	Brief Rationale
4.1 Overall design	Addition of 60 mg dose following the dose selection for Phase 3 studies.	Update with new information.
4.3 Justification for Dose	Update with information from the DRI15928 trial.	Update with new information and per commitment to the Health Authorities (HAs).
5.1 Inclusion criteria # I 02	Modification of inclusion criterion 02.	No safety concerns identified in the embryo-fetal studies.
# I 03, I 04, and I 05	Deletion of inclusion criteria 03, 04, and 05.	No safety concerns identified in the embryo-fetal studies.
5.3.1 Meals and dietary restrictions	New recommendations that the IMP should be taken with meals whenever possible. The meal (eg, breakfast, lunch, etc.) should be consistent throughout the study. The typical time of day at which the IMP is administered will be collected at each visit.	Update following new PK information.
6.1.1 investigational medicinal product	New recommendations that the IMP should be taken with meals and that it will be dispensed at regular site visits or at an unscheduled visit at the time of the switch to Part B. Update of table 7 with dosing information following the dose selection from the DRI15928 trial.	Availability of Phase 2 data.
6.7 Intervention after the End of the Study	Clarification that 'the study will continue up to 5 years or until SAR442168 is approved…'.	Clarification.
[redacted]	Subsection added.	New assessment for tertiary endpoint.
10.2 Appendix 2: Clinical Laboratory Tests #Table11	Deletion of "urine drug screen" from the routine urinalysis subsection.	Urine drug screen is not part of the routine urinalysis.
10.4 Appendix 4: Contraceptive Guidance And Collection Of Pregnancy Information	Guidance updated. Deleted contraception guidance for male participants.	No safety concerns identified in the embryo-fetal studies.
10.8 Appendix 8: List Of Example Drugs With A Potential To Affect Plasma Exposure Of SAR442168 Via Reduction Of Gastric Acid	Addition of list of example drugs with a potential to affect plasma exposure of SAR442168 via reduction of gastric acid.	Correction of error from the LTS16004 amended protocol 02.
10.10 Appendix 10: Abbreviations	New abbreviations added.	To harmonize the list of abbreviations with the body of the protocol.
11 References	List updated.	To harmonize the list of references with the body of the protocol.

10.11.4 Amended protocol 04 (28 October 2020)

In Europe, this amended protocol (amendment 04) is considered to be nonsubstantial 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 because it does not significantly impact the safety or physical/mental integrity of participants.

OVERALL RATIONALE FOR THE AMENDMENT

This protocol is amended primarily to add an additional timepoint for MRI assessment.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of activities	MRI at Month 18 added in Table 2-B.	Additional efficacy assessment.
	[redacted] removed from screening, unscheduled, Month 60, premature end-of-treatment, and follow-up visits.	Correction of errors.
	Table 1, footnote c: A window of ±1 week is applied to monthly phone calls in Year 1.	Clarifications.
	Exploratory biomarkers added to premature end-of-treatment visit in Table 2.	
	"If needed" removed from exploratory biomarkers for unscheduled visits in Table 3.	
	Reference to footnote c, "Sample or measurement to be taken before IMP administration", added to exploratory biomarkers.	
	Tables 1 to 3, footnotes, m, f, and f (respectively) edited to reflect that the [redacted] portion of the study may be terminated early if sufficient data are gathered.	
	A month is defined as 4 weeks.	
Section 1.3 Schedule of activities [redacted]	Language regarding [redacted] periods clarified in Tables 1, 2, and 3 and [redacted]	Clarification.
Section 5.5 Criteria for temporarily delaying enrollment and administration of study intervention	Section added to allow flexibility in case of a regional or national emergency declared by a governmental agency.	COVID-19.
Section 6.1.1 Investigational medicinal product Section 7.1.2.1 Rechallenge Section 8 Study assessments and procedures Section 9.4.3 Other analyses	Reference added to Appendix 10: Contingency measures for a regional or national emergency that is declared by a governmental agency.	COVID-19.
8.1.3 Expanded Disability Status Scale (EDSS) evaluation	Fatigue, if measured, will contribute to the EDSS score.	Correction.

Section # and Name	Description of Change	Brief Rationale
Section 10.10 Appendix 10: Contingency measures for a regional or national emergency that is declared by a governmental agency	Appendix added containing contingency measures for a regional or national emergency that is declared by a governmental agency.	COVID-19.
Throughout the document	Reformatting of existing content when necessary. Minor, editorial, stylistic changes as necessary. Update table of contents, section numbers as necessary.	Update in accordance with Sponsor's standards.

10.11.5 Amended protocol 05 (29 July 2021)

In Europe, this amended protocol (amendment 05) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

The primary reason for this amendment is the availability of new information from drug-drug interaction studies.

Section # and Name	Description of Change	Brief Rationale
Title page and 1.1 Synopsis	Added INN, substituted tolebrutinib for SAR442168 in short title.	Reflection of new INN.
1.3 Schedule of Activities, footnote	Footnote o (Table 1-A) and g (Tables 2-B and 3-C): Clarified the interval required between the use of a systemic corticosteroid and MRI scan.	Alignment with exclusion criterion E03.
	Footnote h (Tables 2-B and 3-C): Increased the window to ±21 days for MRI starting from M15.	To increase flexibility.
	Footnote p (Table 1-A) and i (Tables 2-B and 3-C): timing of PK clarified.	Clarification.
2.2 Background	Update with information about new studies. Update of the drug-drug interaction profile.	Update so that information is current. Update based on outcomes from PK results of drug-drug interaction studies.
2.3 Benefit/risk assessment	Added assessment of risks for trial participants due to COVID-19.	COVID-19 pandemic.
5.3.1 Meals and dietary restrictions	Clarification of IMP administration details to specify that a gap of a minimum of 12 hours between 2 doses should be maintained in case the mealtime of IMP administration needs to be changed.	Clarification of the minimum time between 2 IMP doses.
	Removed the restrictions related to consumption of grapefruit or grapefruit juice.	Update based on outcomes from PK results of drug-drug interaction studies investigating concomitant use of SAR442168 with drugs such as itraconazole.

Section # and Name	Description of Change	Brief Rationale
6.5 Concomitant therapy	Added abstention from prescription or nonprescription herbal medications containing St. John's wort extract.	St. John's wort is a CYP3A inducer. Abstention is to prevent potential loss of efficacy.
	Added concomitant use of short-term use (3 to 5 days) of glucocorticoids (eg, for MS relapse treatment or an acute illness) and local corticosteroids (eg, cutaneous, nasal, ocular, otic, intra-articular).	Clarification for use of cutaneous corticosteroids and short-term corticosteroids.
	Added that live (attenuated) vaccines should not be administered during the intervention period.	Alignment with exclusion criterion E02.
	Updated language regarding symptomatic treatment and NSAIDs.	Clarity.
	Added information about CYP inhibitors/inducers.	Update based on outcomes from PK results of drug-drug interaction studies.
6.5 Concomitant therapy	Clarified that treatments excluded in E03 cannot be used during the study.	Clarification.
6.5 Concomitant therapy 10.7 Appendix 7: List of example drugs with a potential to change SAR442168 metabolism 10.8 Appendix 8: List of example drugs with a potential to affect plasma exposure of SAR442168 via reduction of gastric acid	Updated for antacid drugs: Removed restrictions related to antacid drugs as concomitant use of proton-pump inhibitors (PPIs), H2 receptor antagonists, and antacids is allowed. Updated guidance for CYP inhibitors/inducers: potent or moderate inducers of CYP3A or potent inhibitors of CYP2C8 hepatic enzymes are not permitted throughout the study. Clarified whether concomitant use of potent CYP3A inhibitors is allowed. Deleted Appendix 8.	Update based on outcomes from PK results of drug-drug interaction studies, investigating concomitant use of SAR442168 with drugs such as itraconazole, gemfibrozil, rifampicin and pantoprazole.
7.1.1 Definitive discontinuation 8.5 Pharmacokinetic	To add that collection of the pharmacokinetic (PK) sample at premature end of treatment (pEOT) visit, if the visit can be scheduled within a maximum 24 hours from the last IMP dose.	Clarity.
7.1.2 Temporary discontinuation	Added the possibility of temporary discontinuation due to a regional or national emergency or a need for a prohibited concomitant medication. Specified events of serum creatinine, creatine phosphokinase, and liver enzymes increase, cytopenias, cardiac arrythmias, and suicidality as reasons for temporary discontinuation.	Flexibility. Clarity.
8.1.1 Magnetic resonance imaging assessments	Allowed Investigators to see regular MRI reports during the open label part of the study.	Flexibility.
8.1.2.2 Definition of multiple sclerosis relapse	Specified that a relapse must be preceded by at least 30 days of clinical stability and last for >24 hours, with or without recovery.	Clarity

Section # and Name	Description of Change	Brief Rationale
8.2.3 Electrocardiograms	Added allowance of manual calculation of QT interval corrected using Fridericia's formula (QTcF). Specified that "longer" ECG recording means ≥30 sec.	To allow flexibility, as some automated electrocardiograms do not provide this parameter. All other electrocardiogram parameters will be automatically provided. Clarity.
8.3.1 Adverse events of special interest	Updated definitions of project-specific adverse events of special interest related to cardiac and moderate or severe hemorrhagic events, severe infection, and thrombocytopenia. Definition of overdose is revised. Removed requirement for asymptomatic overdoses to be reported as AESIs.	Clarity. Update of template.
8.3.10 Reporting of safety findings from magnetic resonance imaging	Clarified safety reporting.	Clarity.
8.4 Treatment of overdose	Corrected the language to clarify that plasma sample for PK analysis is to be obtained within 24 hours of the last documented IMP dose (rather than the last dose of SAR442168).	Correction of error.
8.5 Pharmacokinetics	Added optional additional PK samples, eg, for retesting or if clinically indicated.	Flexibility.
10.2 Appendix 2: Clinical laboratory tests	Table 11: Footnote a was updated to clarify clinical laboratory abnormalities for liver injury.	Clarity.
Section 10.4 Appendix 4: Contraceptive guidance and collection of pregnancy information	Added "or as per laboratory reference range" to definition of high FSH level for post-menopausal status.	Clarity.
10.6: Appendix 6: Liver and other safety: actions and follow-up assessments	Changed section title from "suggested actions" to "actions." Added clarifying guidance before algorithms. Updated thrombocytopenia algorithm. Updated ALT algorithm. Added suspected PML algorithm.	Title, guidance, ALT algorithm clarified. Thrombocytopenia algorithm updated to align with CTCAE standards. PML algorithm added to align with trials in the Phase 3 program.
Throughout the document	Reformatting of existing content when necessary. Minor, editorial, stylistic changes as necessary. Update table of contents, section numbers, references as necessary.	Update in accordance with Sponsor's standards.

10.11.6 Amended protocol 06 (23 May 2022)

Amended protocol 06 (23 May 2022)

In Europe, this amended protocol (amendment 06) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

The primary driver for this amendment is to update the liver monitoring to mitigate risk of drug-induced liver injury and to change the time between onsite visits to every 6 months after the Month 36 visit.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Cover page	Sponsor's legal address updated.	Update.
1.1 Synopsis 10.1.5 Committees structure	Independent Hepatology Assessment Committee added.	To evaluate on an ongoing basis cases of potential liver injury.
1.3 Schedule of Activities	On site visits changed to every 6 months after M36 visit with phone calls between 2 onsite visits	To increase flexibility.
2.3 Benefit/risk assessment.	Text related to drug-induced liver injury identified in an ongoing Phase 3 trial added.	Update.
5.3.2 Alcohol, caffeine, and tobacco	Recommendation for alcohol consumption during study updated.	To mitigate the risk of DILI.
6.1.1 Investigational medicinal product	IMP supply to the participant via a Sponsor-approved courier company defined as direct to patient shipment	Clarification.
6.2 Preparation/handling/ storage/accountability	Duties and taxes paid shipment replaced by direct-to-patient shipment	Correction.
6.4 Study intervention compliance	Participant will receive IMP up to next visit (on site or phone call visit)	Clarification.
7.2 Participant discontinuation/withdrawal from the study	Sentence "The participant will be permanently discontinued both from the study intervention and from the study at that time" removed.	Correction. Participant will be followed up to the scheduled date of study completion.
8 Study assessments and procedures	Maximum amounts of blood to be collected updated.	Update for accuracy.
10.6 Appendix 6: Liver and other safety: actions and follow-up assessments	ALT algorithm and related instructions updated.	Updated monitoring request as per new exclusion threshold for ALT level in actively recruiting studies
10.10 Appendix 11: Abbreviations	Updated.	Update.

Section # and Name	Description of Change	Brief Rationale
10.11: Appendix 12: Protocol amendment history	Updated.	Update.
Throughout the document	Reformatting of existing content when necessary. Minor, editorial, stylistic changes as necessary. Updated table of contents, section numbers, references, abbreviations as necessary.	Update in accordance with Sponsor's standards.

10.11.7 Amended protocol 07 (12 December 2022)

In Europe, this amended protocol (amendment 07) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

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

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Cover page	Sponsor disclaimer added at 'Sponsor name'. 'Not applicable' added at 'Trademark'.	Update.
1.3 Schedule of activities (SoA) (Table 2 and Table 3)	Phone call procedure updated to clarify that this can also be a visit at the clinical site.	Update.
2.3 Benefit/Risk assessment	Updated information about drug-induced liver injury.	Update.
10.1.6 Dissemination of clinical study data	Addition of 'euclinicaltrials.eu' in the list of websites where Sanofi shares information about clinical trials. 'Clinicalstudydatarequest.com' replaced with 'vivli.org'.	Update.
10.6 Appendix 6: Liver and other safety: actions and follow-up assessments	Increase in ALT algorithm flowchart and related instructions updated.	Update.
10.11: Appendix 12: Protocol amendment history	Updated.	Update.
10.11.5 Amended protocol 05 (29 July 2021)	Added statement related to consideration of changes to be substantial and overall rationale for the amendment.	Correction.
Throughout the document	Reformatting of existing content when necessary. Minor, editorial, stylistic changes as necessary. Updated table of contents, section numbers, abbreviations, as necessary.	Update in accordance with Sponsor's standards.

10.11.8 Amended protocol 08 (19 June 2023)

In Europe, this amended protocol (amendment 08) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

The rationale for this protocol amendment is to add the option for participants to continue to receive SAR442168 (tolebrutinib) in a separate clinical trial.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis, and 6.7 Intervention after the End of the Study	Added the option for the participants to roll over in a Phase 3 LTS clinical trial.	To provide a continued treatment option in a Phase 3 long term study that will also include participants from Phase 3 trials.
1.1 Synopsis	Revised “Post-trial access to study medication” to “Continued access to intervention after the end of the study”	Clarification.
1.3 Schedule of activities (SoA) (Table 3)	Footnote k added.	To clarify the last visit for participants rolling over in a Phase 3 LTS.
2.3 Benefit/risk assessment	Removed “all” for the identified risk for tolebrutinib and removed “to mitigate risk for hepatic injury”.	Update to keep consistency with Investigator’s Brochure.
8.3.1 Adverse event of special interest	Acute hypersensitivity/anaphylaxis removed from list of adverse events of special interest.	Found to be unnecessary due to lack of safety signal in previous studies.
8.10 Use of biological samples and data for future research	Added details about the future use of participant’s biological samples and data.	To keep consistency with ICF and Sponsor standards related to data privacy guidelines.
10.1.3 Informed consent process	Clarification of informed consent process.	To keep consistency with ICF and Sponsor standards related to data privacy guidelines.
10.1.4 Data protection	Sponsor’s data privacy and protection responsibilities clarified. Data protection for professionals involved in the study clarified.	To be compliant with data privacy guidelines.
10.1.6 Dissemination of clinical study data	Sharing of information about funding made to healthcare organizations and healthcare professionals clarified.	To be compliant with Sanofi standards.

Section # and Name	Description of Change	Brief Rationale
10.4 Appendix 4: Contraceptive guidance and collection of pregnancy information	Clarification of highly effective and acceptable methods of contraception.	Clarification.
10.7 Appendix 7: List of example drugs with a potential to change with SAR442168 metabolism	Removed the reference to www.druginteractioninfo.org	Only keeping the recommendation for the sites to refer to the drug label for metabolic interactions.
	Removed Modifinil from the list of moderate CYP3A Inducers.	Correction of error as, according to the label, modafinil is a weak CYP3A inducer, and therefore not prohibited.
Throughout the document	Reformatting of existing content when necessary. Minor, editorial, stylistic changes as necessary. Updated table of contents, section numbers, abbreviations, as necessary.	Update in accordance with Sponsor's standards.

10.11.9 Amended protocol 09 (16 November 2023)

In Europe, this amended protocol (amendment 09) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

The rationale for this protocol amendment is to update the testing requirements in the "Increase in ALT algorithm", as per health authority request.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
10.6 Appendix 6: Liver and other safety: actions and follow up assessments	Increase in ALT algorithm related assessments updated; Rechallenge restrictions updated.	Update
Throughout the document	Reformatting of existing content when necessary. Updated table of contents, abbreviations as necessary.	Update in accordance with Sponsor's standards.

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