AMENDED CLINICAL TRIAL PROTOCOL 05

Protocol title:	**A Phase 2, multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of SAR443820 in adult participants with amyotrophic lateral sclerosis, followed by an open-label extension.**
Protocol number:	**ACT16970**
Amendment number:	**05**
Compound number (INN/Trademark):	**SAR443820** **Not applicable**
Brief title:	Phase 2 study for SAR443820 in participants with amyotrophic lateral sclerosis (ALS)
Study phase:	**2**
Sponsor name:	**Sanofi-Aventis Recherche & Développement**
Legal registered address:	**1 avenue Pierre Brossolette** **91380 Chilly-Mazarin, France** **Manufacturer: Same as Sponsor**
Monitoring team's representative name and contact information	

Regulatory agency identifier number(s):

IND:	151444
EudraCT:	2021-004156-42
NCT:	NCT05237284
WHO:	U1111-1263-5766
EUDAMED:	Not applicable
Other:	Not applicable

Date: 13-Dec-2023 Total number of pages: 117

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, version
Amended Clinical Trial Protocol 05	All	13 December 2023, version 1 (electronic 11.0)
Amended Clinical Trial Protocol 04	All	12 May 2023, version 1 (electronic 6.0)
Amended Clinical Trial Protocol 03	All	06 Mar 2023, version 1 (electronic 5.0)
Amended Clinical Trial Protocol 02	All	02 December 2022, version 1 (electronic 4.0)
Amended Clinical Trial Protocol 01	All	07 April 2022, version 1 (electronic 1.0)
Original Protocol		10 November 2021, version 1 (electronic 3.0)

Amended protocol 05 (13 December 2023)

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

An idenfied risk of ALT increase/drug induced liver injury (DILI) for SAR443820 is added based on interal data review.

The main purpose of the protocol amendment 05 is to increase liver chemistry monitoring frequency in Part A to detect ALT increase early if occurs and pause IMP administration immediately in Part B (open-label extension) to minimize the risk of further exposure to SAR443820. Also, clarification on alcohol restriction during the study and a few additional diagnostic tests as mandatory tests in case of events of ALT increase are added.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis, 1.2 Schema, 1.3.1 Part A 4.1 Overall Design	Replaced the phone visit with a site visit and include a liver chemistry test at Week 20 (Part A). Added 3 visits which include a liver chemistry test at Week 21, Week 22 and Week 23.	To allow early detection of ALT increases through weekly liver chemistry testing for participants who are still in Part A and collect data to optimize the characterization of the safety profile of SAR443820. As of 05 December 2023, all participants have passed the Week 19 time point, therefore no additional weekly visits to be added prior to the Week 20 visit.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 1.2 Schema, 1.3.2 Part B 4.1 Overall Design	Paused all SAR443820 administration in Part B	To minimize the risk for participants who are on SAR443820 until DMC recommendation to resume dosing based on benefit-risk considerations when Part A data is available.
1.3.1 Part A	"Only liver chemistry monitoring will be conducted, which includes testing of alanine transaminase (ALT), aspartate aminotransferase (AST), bilirubin direct, bilirubin total and alkaline phosphatase" were added in the footnote p in Part A and j in Part B.	To clarify the extend of liver chemistry monitoring tests to be performed.
1.3.1 Part A 1.3.2 Part B	Edited footnote b in Part A and footnote e in Part B to provide instructions on what assessment should be performed in the scheduled visits if participants continue in the study after early IMP discontinuation visit.	To simplify the follow-up visits for participants continuing in the study without IMP administration
2.3.1 Risk assessment 2.3.3 Overall benefit/risk conclusion	Added an identified risk of ALT increase/DILI for SAR443820. Added clinical data and mitigation strategy supporting the potential risk of ALT increase.	To update the risk of SAR443820 based on current data from the ongoing clinical trial and minimize the risk for participants.
5.3.2 Caffeine, alcohol, and tobacco	Added the instruction for participants to limit the consumption of alcohol during the study	To minimize exposure to alcohol during the study, to not exacerbate potential liver injury risks of SAR443820
7.1.2 Temporary discontinuation 7.1.2.1 Study intervention restart or rechallenge after temporary discontinuation of study intervention	Added guidance on temporary discontinuation with regard to pause of IMP administration during Part B Added information on temporary discontinuation criteria in case a participant can not follow the scheduled liver chemistry monitoring. Modified the statement on the conditions to restart/rechallenge IMP	Clarification To clarify the criteria for IMP rechallenge and refer to 10.6 Appendix 6 to avoid repetitive information
10.6 Appendix 6: liver and other safety: actions and follow-up assessments	Added a Hepatitis B surface antigen test and modified a liver ultrasound from optional to a mandatory test. Replaced "When ALT< 2 ULN (if baseline ALT ≤2 ULN) or baseline (if baseline ALT> 2 ULN)" to "When the rechallenge criteria are met as described in the box below" in ALT increase algorithm. Modified the IMP rechallenging criteria from "ALT/AST decreases below 2 x ULN" to "ALT and AST both decrease < 2 x ULN)	To enhance the possibility of finding potential causes of ALT increase. To clarity the criteria of IMP rechallenge after ALT increase and avoid repetitive information
10.11 Appendix 11 Blood volume details	Blood volume updated due to additional liver chemistry monitoring at Week 20, Week 21, Week 22 and Week 23.	Update
10.13 Appendix 13: Protocol amendment history	Summary of changes pertaining amendment 04 were moved to appendices	Administrative change

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Protocol title:

A Phase 2, multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of SAR443820 in adult participants with amyotrophic lateral sclerosis, followed by an open-label extension.

Brief title:

Phase 2 study for SAR443820 in participants with amyotrophic lateral sclerosis (ALS)

IND:	151444
EudraCT:	2021-004156-42
NCT:	NCT05237284
WHO:	U1111-1263-5766
EUDAMED	Not applicable
Other	Not applicable

Rationale:

SAR443820 is a selective, orally bioavailable, central nervous system (CNS)-penetrant, receptor-interacting serine/threonine-protein kinase 1 (RIPK1) inhibitor. The aim of this Phase 2 study is to determine the efficacy, safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of SAR443820 in treating adult participants with amyotrophic lateral sclerosis (ALS).

Multiple pathways have been suggested to be involved in ALS pathogenesis, including pathways involved in oxidative stress, mitochondrial dysfunction, axonal damage, excitotoxicity, neuroinflammation, and protein aggregation (1). Treatment targeting the common mediator of these mechanisms can provide more robust disease intervention than targeting any individual pathway. More specifically, inhibition of microglial activation and inflammatory-driven neuronal death, the common consequence of multiple pathways in the pathophysiology of ALS, has the potential to provide an effective treatment for this relentless disease.

RIPK1 is an intracellular protein involved in the regulation of inflammation, cytokine release, and cell death. RIPK1 is activated in response to several inflammatory stimuli, most notably tumor necrosis factor alpha (TNF-α) signaling through its receptor 1 (TNF1), with subsequent RIPK1 initiation of a complex signaling cascade that triggers intracellular responses, including cytokine release, microglial activation, and necroptosis, a regulated form of cell death (2, 3). Inhibition of RIPK1 activity has been shown to protect against necroptotic cell death in vitro across a range of cell death models (4, 5, 6). Similarly, in various animal models of diseases ranging from Alzheimer's disease (AD) to multiple sclerosis (MS), inhibition of RIPK1 protects against their respective pathologies and attributed cell death (7, 8, 9, 10). These nonclinical findings, coupled

with observations of increased RIPK1 activity in human diseases (6, 7, 11), suggest that inhibition of RIPK1 could ameliorate ALS.

The RIPK1 pathway is activated in spinal cords from patients with ALS. These postmortem samples show elevated levels of RIPK1 and its downstream signaling partners, receptor-interacting serine/threonine-protein kinase 3 (RIPK3) and mixed lineage kinase domain–like pseudokinase (MLKL) (8). Similar increases have been observed in the spinal cord of the SOD1 (G93A) transgenic mouse with ALS. Furthermore, both genetic inhibition of the RIPK1 pathway (RIPK3 -/-) and treatment with a RIPK1 inhibitor reduced axonal pathology and delayed the onset of motor dysfunction in this model (8). Several ALS-inducing mutations, including TANK-binding kinase 1 (TBK1) and optineurin (OPTN), have been shown to sensitize cells to RIPK1-dependent cell death and inflammation (8, 12, 13). Notably, another RIPK1 activity inhibitor, transforming growth factor β-activated kinase 1 (TAK1), declines with age, which may predispose the CNS to neuroinflammation and neurodegeneration in the setting of genetic or environmental stresses (13).

In summary, both preclinical and patient-derived data have suggested RIPK1 may be a key mediator of necroptosis and inflammatory pathways in ALS. SAR443820, a CNS-penetrant inhibitor of RIPK1, has the potential to modify the course of neurodegenerative processes and slow disease progression in patients with ALS. Therefore, the aim of this Phase 2 study is to determine the efficacy, safety, and tolerability of SAR443820 in participants with ALS.

Objectives and endpoints

Part A

Objectives	Endpoints
Primary	
• To assess the effect of SAR443820 compared to placebo in reducing ALS progression as measured by the Amyotrophic Lateral Sclerosis Functional Rating Scale Revised (ALSFRS-R)	• Change from baseline in the ALSFRS-R total score to Week 24
Secondary	
• To assess the effect of SAR443820 compared to placebo on a combined assessment of function and survival, respiratory function, muscle strength, and quality of life (QoL)	• Combined assessment of the function and survival (CAFS) score at Week 24 • Change from baseline in slow vital capacity (SVC) to Week 24 • Change from baseline in muscle strength to Week 24 • Change from baseline in Amyotrophic Lateral Sclerosis Assessment Questionnaire (ALSAQ-5) to Week 24
• To assess the pharmacodynamic (PD) effect of SAR443820 compared to placebo on a key disease biomarker	• Change from baseline in serum neurofilament light chain (NfL) to Week 24
• To assess the safety and tolerability of SAR443820 compared to placebo	• Incidence of adverse events (AE), serious adverse events (SAE), treatment-emergent adverse events (TEAE), potentially clinically significant abnormalities (PCSA) in laboratory tests, electrocardiogram (ECG), and vital signs over 24 weeks

Objectives	Endpoints
• To assess the pharmacokinetics (PK) of SAR443820	• Plasma concentration of SAR443820
Tertiary	
[redacted] SAR443820 [redacted]	[redacted]
• To assess the effects of SAR443820 compared to placebo on neurodegeneration and inflammation disease biomarkers	• Change from baseline in soluble triggering receptor expressed on myeloid cells-2 (sTREM2) in plasma, chitinase-3-like protein-1 (CHI3L1), a selected panel of cytokines and chemokines in serum, and extracellular domain of p75 (p75ECD) in urine to Week 24

Part B

Objectives	Endpoints
Primary	
• To assess the long-term effects of SAR443820 on function and survival	• Combined assessment of the function and survival (CAFS) score at Week 52
Secondary	
• To assess the long-term effects of SAR443820 on disease progression, survival, respiratory function, and quality of life (QoL)	• Combined assessment of the function and survival (CAFS) score at Week 76 and Week 104 • Change from baseline in the ALSFRS-R total score to Week 52, Week 76, and Week 104 • Time from baseline to the occurrence of either death or permanent assisted ventilation (>22 hours daily for >7 consecutive days), whichever comes first • Time from baseline to the occurrence of death • Change from baseline in slow vital capacity (SVC) to Week 52, Week 76, and Week 104 • Change from baseline in Amyotrophic Lateral Sclerosis Assessment Questionnaire (ALSAQ-5) to Week 52, Week 76, and Week 104
• To assess the long-term effect of SAR443820 on a key disease biomarker	• Change from baseline in serum neurofilament light chain (NfL) to Week 52

Objectives	Endpoints
• To assess the long-term safety and tolerability of SAR443820	• Incidence of adverse events (AE), serious adverse events (SAE), treatment-emergent adverse events (TEAE), potentially clinically significant abnormalities (PCSA) in laboratory tests, electrocardiogram (ECG), and vital signs during Part B
• To assess the pharmacokinetics (PK) of SAR443820	• Plasma concentration of SAR443820
Tertiary	
[redacted] SAR443820 [redacted]	[redacted]
[redacted] SAR443820 [redacted]	[redacted]

For China, please see Appendix 8 (Section 10.8) for details.

Overall design:

Study ACT16970 is a Phase 2, randomized, double-blind, placebo-controlled study followed by an open-label extension period.

Brief summary:

This is a parallel-treatment, phase 2, randomized, double-blind study to assess the efficacy, safety, tolerability, PK, and PD of 20 mg twice daily (BID) oral SAR443820 compared with placebo in male and female participants aged 18 to 80 years with ALS followed by an open-label, long-term extension period.

Study ACT16970 consists of 2 parts (A and B) as follows:

Part A is a 24-week, double-blind, placebo-controlled part, preceded by a screening period of up to 4 weeks before Day 1.

On Day 1 of Part A, participants will be randomized in a 2:1 ratio to the SAR443820 treatment arm or matching placebo arm as listed below:

- Treatment arm: SAR443820, 20 mg, BID
- Placebo arm: Placebo, BID

Randomization will be stratified by the geographic region of the study site, region of ALS onset (bulbar vs other areas), use of riluzole (yes vs no), use of edaravone (yes vs no) and use of the combination of sodium phenylbutyrate and taurursodiol (named Relyvrio® in the USA and Albrioza® in Canada) (yes vs no). Participants will attend in-clinic study assessments at baseline (Day 1), Week 2, Week 4, Week 6, Week 8, Week 10, Week 12, Week 16, Week 20, Week 21, Week 22, Week 23 and Week 24. All ongoing participants at Week 24 will rollover to open-label extension (Part B). The Week 24 Visit is the end of Part A and the beginning of Part B.

Part B is an open-label, long-term extension period that starts from Week 24 and continues up to Week 106. The objectives of Part B are to provide extended access to SAR443820 participants in Part A and to further evaluate the safety and efficacy of long-term SAR443820 treatment. The treatment assignment of participants at randomization in Part A will remain blinded to Investigators, participants, and site personnel until the end of Part B. Every participant, except those who discontinue IMP treatment permanently in Part A, will receive BID oral tablets of 20 mg SAR443820 in Part B.

The study duration includes an up to 4-week screening period, 24-week double-blind treatment period in Part A, 80-week open-label treatment period in Part B, and 2-week post-treatment follow-up period, with a maximum total study duration of 110 weeks.

Number of participants:

Approximately 326 participants will be screened to achieve 261 participants randomly assigned to the study intervention (based on a 20% screening failure rate).

Intervention groups and duration:

Part A of the study will last for 24 weeks, and participants will receive 20 mg BID oral SAR443820 or placebo in a double-blind fashion for 24 weeks. All ongoing participants at Week 24 will rollover to open-label extension (Part B).

Part B begins at the end of Week 24 and continues up to Week 106. All participants, except those who discontinue IMP treatment permanently in Part A, will receive BID oral tablets of 20 mg SAR443820 in Part B.

Study intervention(s)

SAR443820 or placebo matched to SAR443820.

Investigational medicinal product(s) (IMP)

- Formulation: Both SAR443820 and matched placebo will be formulated in tablets.
- Route(s) of administration: Tablets will be taken orally. The suggested method for investigational medicinal product (IMP) administration in detail is listed in Section 6.

- Dose regimen:
  - Part A:
    - Treatment arm: SAR443820, 20 mg, BID
    - Placebo arm: Placebo, BID
  - Part B:
    - All participants: SAR443820, 20 mg, BID.

Based on a data review, in accordance with Data Monitoring Committee (DMC) recommendations leading to an urgent safety measure submitted on 05 December 2023, the sites have been instructed to pause the administration of SAR443820 in Part B (open-label extension) immediately. All participants in Part B will be encouraged to continue follow-up visits, but no doses of SAR443820 should be administered. Rollover to Part B for follow-up visits after completing Part A is also encouraged, but without taking SAR443820 in Part B. The decision of whether resuming SAR443820 administration in Part B will be made based on DMC recommendation when Part A data is available and benefit risk ratio will be evaluated.

Noninvestigational medicinal products(s)

No noninvestigational medicinal products (NIMP) will be provided by the Sponsor.

As of November 2022, riluzole and edaravone constitute the standard of care and are the currently approved treatment options for patients with ALS in the United States, Canada, China, and Japan. Riluzole has also been approved in the European Union (EU) for ALS treatment. The combination of sodium phenylbutyrate and taurursodiol has been approved in the USA and Canada for ALS treatment. Since riluzole, edaravone and the combination of sodium phenylbutyrate and taurursodiol are the standard of care for ALS, they are considered to be NIMP in our study. The dosing of riluzole, edaravone and the combination of sodium phenylbutyrate and taurursodiol should be consistent with local labeling requirements.

Riluzole:

- Route of administration: oral
- Dose regimen: as per the label

Edaravone:

- Route of administration: intravenous (IV) or oral
- Dose regimen: as per the label

Combination of sodium phenylbutyrate and taurursodiol:

- Route of administration: oral
- Dose regimen: as per the label

Devices

Not applicable.

Poststudy access to the study medication

In addition to the 104 weeks of treatment with the IMP in Part A and Part B of this trial, a separate, open-label, long-term safety follow-up study may be proposed for the participants in this study if a positive benefit/risk ratio is confirmed in this trial. The details of the long-term study will be provided in a separate protocol.

Statistical considerations:

Sample size determination:

A sample size of 261 participants in total is needed to achieve an 80% power to detect a 30% reduction in SAR443820 compared with placebo in change of the Amyotrophic Lateral Sclerosis Functional Rating Scale Revised (ALSFRS-R) from baseline to Week 24, assuming a change of [redacted] points from baseline in ALSFRS-R in the placebo arm with a standard deviation of [redacted] points at Week 24, and a 20% drop-out rate. Sample size is estimated via simulation with a 2-sided 5% significance level.

Primary endpoint in Part A: The primary efficacy endpoint in Part A is the change from baseline in the ALSFRS-R total score to Week 24.

The **primary estimand** will be the difference (SAR443820 vs placebo) in the mean change from baseline in the ALSFRS-R score estimated in the intent-to-treat (ITT) population regardless of whether participants completed the treatment period. This estimand corresponds to a "treatment policy strategy" and will be using all available data and missing data will not be imputed.

The primary analysis will be based on the primary estimand, which includes data collected for the primary endpoint for all participants included in the ITT population.

A mixed-effect model with repeated measure (MMRM) model will be fitted to change from baseline in the ALSFRS-R score, which will include the fix effects of treatment (SAR443820 or placebo), visit (as a categorical variable), baseline ALSFRS-R score, baseline serum neurofilament light chain (NfL), randomization strata of the geographic region of the study site, ALS onset region (bulbar or other areas), use of riluzole (yes or no), use of edaravone (yes or no), use of the combination of sodium phenylbutyrate and taurursodiol (yes vs no), treatment-by-visit interaction, baseline NfL-by-visit interaction and baseline ALSFRS-R score-by-visit interaction. The least squares mean difference in the ALSFRS-R change from baseline at Week 24 between SAR443820 and placebo, together with the p-value and the 95% confidence interval (CI) for the difference, will be estimated from the MMRM model.

Subgroup analysis will be specified in the SAP.

Main secondary endpoints in Part A: The key secondary efficacy endpoints include the combined assessment of function and survival (CAFS) score at Week 24, and change from baseline in slow vital capacity (SVC), muscle strength, Amyotrophic Lateral Sclerosis Assessment Scales - 5 items (ALSAQ-5), and serum NfL to Week 24. All the secondary efficacy endpoints will be analyzed based on the ITT population.

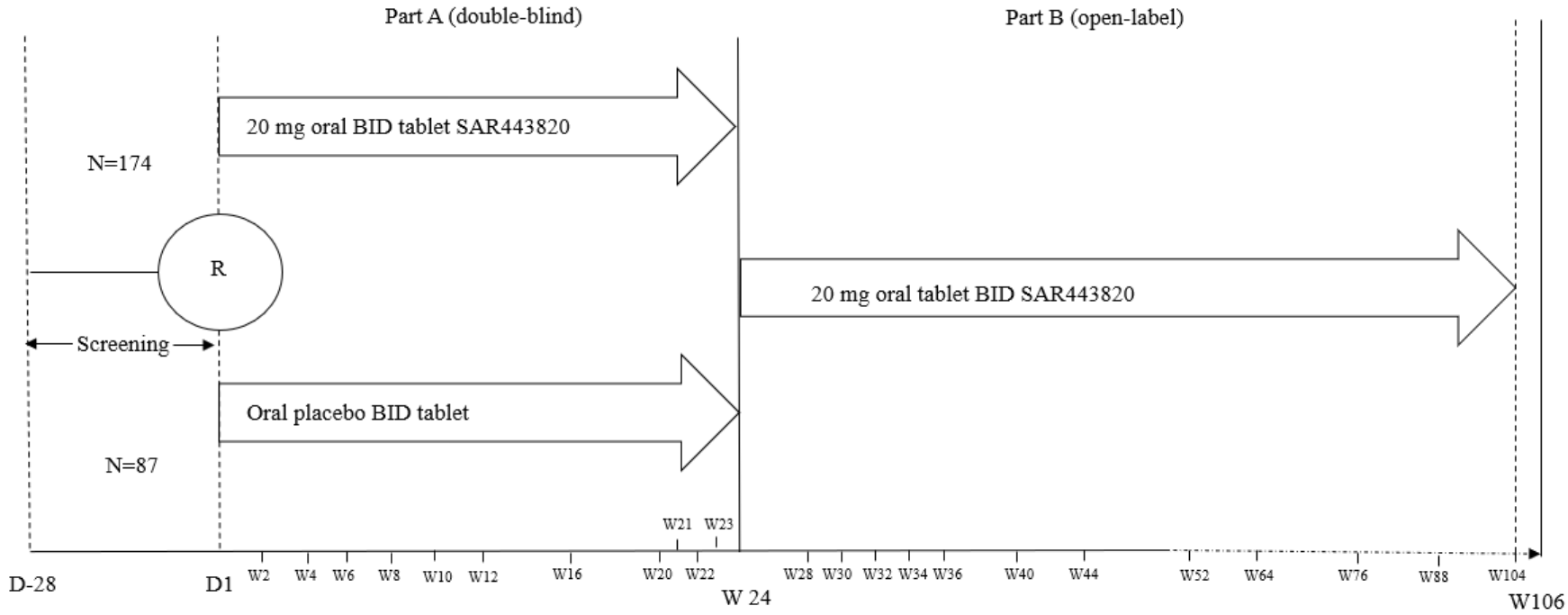
For continuous variables, an MMRM approach under the missing at random (MAR) assumption will be used. This model will include the fixed effect of treatment (SAR443820 or placebo), visit as a categorical variable, baseline value of the endpoint, baseline NfL (if different from the baseline value of the endpoint), randomization strata of the geographic region of the study site, ALS onset region (bulbar or other areas), use of riluzole (yes or no), use of edaravone (yes or no), use of the combination of sodium phenylbutyrate and taurursodiol (yes vs no), treatment-by-visit interaction, baseline value of endpoint-by-visit interaction and baseline NfL-by-visit interaction (if different from the baseline value of the endpoint-by-visit interaction). The primary comparison of interest will be the difference between SAR443820 and placebo at Week 24, carried out using contrast within the treatment-by-time interaction term.

Primary endpoint in Part B: The primary endpoint in Part B is the CAFS at Week 52. Comparison will be conducted between participants who receive SAR443820 and those who receive placebo in Part A.

Data Monitoring Committee: Yes

1.2 SCHEMA

Figure 1 - Graphical study design



AE = adverse event; BID = twice daily; D = day; N = number of participants; PK = pharmacokinetic(s); R = randomization; SAE = serious adverse event; W = week; FU = follow up.
As of 5 December 2023, the administration of SAR443820 will be paused immediately until DMC recommendation to resume dosing based on benefit-risk considerations when Part A data is available.

1.3 SCHEDULE OF ACTIVITIES

1.3.1 Part A

Procedure	Screening (up to 4 weeks before Day 1)	Intervention period (Part A)														Early IMP discontinuation visit[b]
		Day 1		Week 2 (Day 15±3)	Week 4 (Day 29±3)	Week 6 (Day 43±3)	Week 8 (Day 57±3)	Week 10 (Day 71±3)	Week 12 (Day 85±3)	Week 16 (Day 113±3)	Week 20 (Day 141±3)	Week 21 (Day 148±3)	Week 22 (Day 155±3)	Week 23 (Day 162±3)	Week 24 (Day 169±3)[a]	
		Predose (baseline)	Postdose													
Visit	1[c]	2		3	4	4.5	5	5.5	6	7	8	8.25	8.5	8.75	9	
Visit location or medium	Site	Site		Site	Site	Site[d]	Site	Site[d]	Site[d]	Site	Site[d]	Site[d]	Site[d]	Site[d]	Site	Site
Informed consent	X															
Eligibility check (inclusion and exclusion criteria)	X	X														
Demography	X															
Randomization		X[e]														
Study intervention dispensing and reconciliation[f]		X		X[g]	X		X			X					X[h]	X[g]
Physical examination[i]	X	X		X	X		X			X					X	X
Height	X															
Weight	X	X		X	X		X			X					X	X
12-lead ECG	X	X		X			X								X	X
Vital signs[j]	X	X	X[k]	X	X		X			X					X	X

Procedure	Screening (up to 4 weeks before Day 1)	Intervention period (Part A)														Early IMP discon-tinuation visit[b]
		Day 1		Week 2 (Day 15±3)	Week 4 (Day 29±3)	Week 6 (Day 43±3)	Week 8 (Day 57±3)	Week 10 (Day 71±3)	Week 12 (Day 85±3)	Week 16 (Day 113±3)	Week 20 (Day 141±3)	Week 21 (Day 148±3)	Week 22 (Day 155±3)	Week 23 (Day 162±3)	Week 24 (Day 169±3)[a]	
		Predose (baseline)	Postdose													
Visit	1[c]	2		3	4	4.5	5	5.5	6	7	8	8.25	8.5	8.75	9	
Visit location or medium	Site	Site		Site	Site	Site[d]	Site	Site[d]	Site[d]	Site	Site[d]	Site[d]	Site[d]	Site[d]	Site	Site
C-SSRS questionnaire	X	X[l]		X[l]	X[l]		X[l]			X[l]					X[l]	X[l]
Neurological examination[m]	X	X		X	X		X			X					X	X
Past and current medical conditions (includes substance usage)[n]	X	X														
Serum β-HCG test (WOCBP only)	X															X
Serum FSH and estradiol[o]	X															
Urine pregnancy test (WOCBP only)		X		X	X		X		X	X	X				X	
HIV and hepatitis B and C screening	X															
Laboratory tests for hematology and chemistry	X	X		X	X	X[p]	X	X[p]	X[p]	X	X[p]	X[p]	X[p]	X[p]	X	X

Procedure	Screening (up to 4 weeks before Day 1)	Intervention period (Part A)														Early IMP discon-tinuation visit[b]
		Day 1		Week 2 (Day 15±3)	Week 4 (Day 29±3)	Week 6 (Day 43±3)	Week 8 (Day 57±3)	Week 10 (Day 71±3)	Week 12 (Day 85±3)	Week 16 (Day 113±3)	Week 20 (Day 141±3)	Week 21 (Day 148±3)	Week 22 (Day 155±3)	Week 23 (Day 162±3)	Week 24 (Day 169±3)[a]	
		Predose (baseline)	Postdose													
Visit	1[c]	2		3	4	4.5	5	5.5	6	7	8	8.25	8.5	8.75	9	
Visit location or medium	Site	Site		Site	Site	Site[d]	Site	Site[d]	Site[d]	Site	Site[d]	Site[d]	Site[d]	Site[d]	Site	Site
Blood draw for optional DNA collection				X[q]	X[q]											
SVC	X	X					X			X					X	X
ALSFRS-R	X	X			X		X		X	X	X				X	X
ALSAQ-5		X					X			X					X	X
[redacted]	[redacted]															
Muscle strength[r]		X					X			X					X	X
[redacted]	[redacted]															
Blood sample for plasma PK[t]			X[u]	X[v]			X[v, w]									
Blood samples for plasma sTREM2	X	X					X			X					X	X

Procedure	Screening (up to 4 weeks before Day 1)	Intervention period (Part A)													Early IMP discon-tinuation visit[b]
		Day 1		Week 2 (Day 15±3)	Week 4 (Day 29±3)	Week 6 (Day 43±3)	Week 8 (Day 57±3)	Week 10 (Day 71±3)	Week 12 (Day 85±3)	Week 16 (Day 113±3)	Week 20 (Day 141±3)	Week 21 (Day 148±3)	Week 22 (Day 155±3)	Week 23 (Day 162±3)	Week 24 (Day 169±3)[a]	
		Predose (baseline)	Postdose													
Visit	1[c]	2		3	4	4.5	5	5.5	6	7	8	8.25	8.5	8.75	9	
Visit location or medium	Site	Site		Site	Site	Site[d]	Site	Site[d]	Site[d]	Site	Site[d]	Site[d]	Site[d]	Site[d]	Site	Site
Blood samples for serum biomarkers, including NfL, CHI3L1, cytokine and chemokine panel[x]	X	X					X			X					X	X
Urine sample for biomarker analysis (p75ECD)[y]	X	X					X			X					X	X
Urine sample for urinalysis	X	X		X	X		X			X					X	X
Blood sample for archiving		X														
AE review		←----------												----------→		X
SAE review		←----------												----------→		X

Procedure	Screening (up to 4 weeks before Day 1)	Intervention period (Part A)													Early IMP discon-tinuation visit[b]
		Day 1		Week 2 (Day 15±3)	Week 4 (Day 29±3)	Week 6 (Day 43±3)	Week 8 (Day 57±3)	Week 10 (Day 71±3)	Week 12 (Day 85±3)	Week 16 (Day 113±3)	Week 20 (Day 141±3)	Week 21 (Day 148±3)	Week 22 (Day 155±3)	Week 23 (Day 162±3)	Week 24 (Day 169±3)[a]	
		Predose (baseline)	Postdose													
Visit	1[c]	2		3	4	4.5	5	5.5	6	7	8	8.25	8.5	8.75	9	
Visit location or medium	**Site**	**Site**		**Site**	**Site**	**Site**[d]	**Site**	**Site**[d]	**Site**[d]	**Site**	**Site**[d]	**Site**[d]	**Site**[d]	**Site**[d]	**Site**	**Site**
Concomitant therapy and procedures recording		←----------												----------→		X

Abbreviations: AE = adverse event; ALS = amyotrophic lateral sclerosis; ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire – 5; ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale – Revised; β-HCG = beta human chorionic gonadotropin; CHI3L1 = chitinase-3-like protein 1; C-SSRS = Columbia Suicide Severity Rating Scale; DTP = direct-to-patient; ECG = electrocardiogram; [redacted]; FSH = follicle stimulating hormone; [redacted] HIV = human immunodeficiency virus; IFNγ = interferon γ; IL = interleukin; IMP = investigational medicinal product; IP-10 = interferon gamma-induced protein 10; MCP = monocyte chemoattractant protein; MIP1 = macrophage inflammatory protein-1; NfL = neurofilament light chain; p75ECD = extracellular domain of p75; PK = pharmacokinetic(s); SAE = serious adverse event; sTREM2 = soluble triggering receptor expressed on myeloid cells 2; SVC = slow vital capacity; TARC = thymus- and activation-regulated chemokine; TNF = tumor necrosis factor; WOCBP = woman of childbearing potential

a The Week 24 visit is considered as both the last visit for Part A and the first visit for Part B. For all participants, last dose of double-blind IMP should be taken on the day prior to the Week 24 visit. Week 24 visit will consist of first open-label (Part B) IMP. All assessments for end of Part A should be completed prior to first dose of open-label IMP.

b For participants who prematurely discontinue IMP, the early discontinuation visit will happen 2 weeks (±3 days) after the last dose of the IMP. If, after the early IMP discontinuation visit, participants decide to continue the study, they will follow the same schedule for visits, but only ALSFRS-R, SVC, blood samples for plasma sTREM2, blood samples for serum biomarkers, including NfL, CHI3L1, cytokine and chemokine panel and urine sample for biomarker analysis (p75ECD), vital signs, physical examination, neurological examination, AE review, SAE review and concomitant therapy and procedures recordings will be performed in the visits, as applicable according to the schedule of activities.

c The screening visit can be performed over up to 2 days if needed (they do not need to be consecutive days) to minimize the burden on participants.

d Alternatively, the Week 6, Week 10, Week 12, Week 20, Week 21, Week 22, and Week 23 visit can be conducted by phone. If the study visit is conducted by phone, the blood sample must be collected at a local clinic or at home by a nurse, and the sample must be tested at a local lab or the central lab. In case of testing at a local lab, the study site staff must contact participants, within 2 working days after the results are expected to be available, to collect results of blood test.; For Week 12, and Week 20 visit, if conducted by phone, 1) the urine pregnancy test will be provided directly to participants and self-conducted at home. The study site staff will call the participants to remind them to conduct the pregnancy test and collect the result. If pregnancy test result is positive, participant should discontinue IMP immediately; 2) ALSFRS-R will be measured through the phone call.

e Participants will be randomized in a 2:1 ratio to the SAR443820 treatment arm or placebo arm. The randomization will be stratified by the geographic region of the study site, region of ALS onset (bulbar vs other areas), use of riluzole (yes vs no), and use of edaravone (yes vs no) and use of the combination of sodium phenylbutyrate and taurursodiol (yes vs no).

f In addition to the IMP being dispensed in the clinic, the IMP may be dispensed for home administration via DTP services, except if prohibited by local regulatory authorities.

g Only IMP reconciliation will be done at this visit.

h Reconciliation of the IMP dispensed in Part A and dispensation of the open-label IMP in Part B at this visit (Week 24).
i A full physical examination will be performed at the screening visit, and a brief physical examination will be performed at all other visits. The skin and lymph nodes need to be checked at each site visit.
j Vital signs include blood pressure, heart rate, respiratory rate, and temperature.
k Postdose vital signs should be measured at least 10 minutes after the second PK sample collection (recommended to be measured within 10 to 30 minutes after the second PK sample collection).
l The "Since Last Visit" version of the C-SSRS will be used.
m A full neurological examination will be performed at the screening visit, and a brief neurological examination pertaining to cranial nerves, coordination/cerebellar function, reflexes, and motor function will be performed at other visits.
n Substances include drugs of abuse, alcohol, tobacco, and caffeine.
o Only in female participants, if needed to establish menopausal status.
p Only liver chemistry monitoring will be conducted, which includes testing of alanine transaminase (ALT), aspartate aminotransferase (AST), bilirubin direct, bilirubin total and alkaline phosphatase.
q Optional one-time blood draw for DNA analysis can be completed at either Week 2 or Week 4 visit.
r The muscles measured include both upper-limb and lower-limb muscle groups. Bilateral hand grip will be measured using a Jamar grip dynamometer and all other muscles included in this study will be measured using a handheld dynamometer.
[redacted].
t The IMP can be taken under either fasting or non-fasting condition.
u Two samples for PK will be collected at this visit, 1 within 15 minutes to 1 hour and another within 1 to 3 hours after the morning dose of IMP. There will be at least 45 minutes between the 2 samplings.
v One sample for PK will be collected within 1 hour before the morning dose of IMP.
w One sample for PK will be collected within 15 minutes to 3 hours after the morning dose of IMP.
x The cytokines measured in this study include IFN-γ, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL12p70, IL-13, and TNF-α. The chemokines measured in this study include eotaxin-1, eotaxin-3, TARC, IP-10, MIP1α, MIP1β, MCP1, and MCP4.
y This assessment will not be conducted in China (see Appendix 8 [Section 10.8]).

1.3.2 Part B

Procedure[b]	Intervention period (Part B)[a]												Last follow-up visit[c]	Early IMP discontinuation visit[e]
	Week 28 (Day 197±3)	Week 30 (Day 211±3)	Week 32 (Day 225±3)	Week 34 (Day 239±3)	Week 36 (Day 253±3)	Week 40 (Day 281±3)	Week 44 (Day 309±3)	Week 52 (Day 365±3)	Week 64 (Day 449±3)	Week 76 (Day 533 ±3)	Week 88 (Day 617 ±7)	Week 104 (Day 729 ±7)		
Visit	**10**	**10.25**	**10.5**	**10.75**	**11**	**11.5**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	
Visit location or medium	**Site**	**Site[d]**	**Site[d]**	**Site[d]**	**Site**	**Site[d]**	**Site**	**Site**	**Site**	**Site**	**Site**	**Site**	**Site**	**Site**
Study intervention dispensing and reconciliation[f]	X				X		X	X	X	X	X	X[g]		X[g]
Physical examination[h]	X				X		X	X	X	X	X	X	X	X
Neurological examination[i]	X				X		X	X	X	X	X	X	X	X
Laboratory tests for hematology and chemistry	X	X[j]	X[j]	X[j]	X	X[j]	X	X	X	X	X	X	X	X
12-lead ECG	X				X			X		X		X	X	X
C-SSRS questionnaire[k]	X				X		X	X	X	X	X	X	X	X
Vital signs[l]	X				X		X	X	X	X	X	X	X	X
Weight	X				X		X	X	X	X	X	X	X	X
SVC	X				X		X	X	X	X	X	X		X
ALSFRS-R	X				X		X	X	X	X	X	X		X
ALSAQ-5	X				X		X	X	X	X	X	X		X
[redacted]	[redacted]													
Blood sample for plasma PK	X[m]													

Procedure[b]	Intervention period (Part B)[a]												Last follow-up visit[c]	Early IMP discontinuation visit[e]
	Week 28 (Day 197±3)	Week 30 (Day 211±3)	Week 32 (Day 225±3)	Week 34 (Day 239±3)	Week 36 (Day 253±3)	Week 40 (Day 281±3)	Week 44 (Day 309±3)	Week 52 (Day 365±3)	Week 64 (Day 449±3)	Week 76 (Day 533 ±3)	Week 88 (Day 617 ±7)	Week 104 (Day 729 ±7)		
Visit	**10**	**10.25**	**10.5**	**10.75**	**11**	**11.5**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	
Visit location or medium	**Site**	**Site[d]**	**Site[d]**	**Site[d]**	**Site**	**Site[d]**	**Site**	**Site**	**Site**	**Site**	**Site**	**Site**	**Site**	**Site**
Blood samples for serum NfL	X				X		X	X						X[n]
Urine sample for urinalysis	X				X		X	X	X	X	X	X	X	X
Urine pregnancy test (WOCBP only)[o]	X		X		X	X	X	X	X	X	X	X		
Serum β-HCG test (WOCBP only)													X	X
[redacted]														
AE review	←----------											----→		X
SAE review	←----------											----→		X
Concomitant therapy and procedures recording	←----------											----→		X

Abbreviations: AE = adverse event; ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire–5; ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale – Revised; β-HCG = beta human chorionic gonadotropin; C-SSRS = Columbia Suicide Severity Rating Scale; DTP = direct-to-patient; ECG = electrocardiogram; [redacted]; IMP = investigational medicinal product; NfL=neurofilament light; PK = pharmacokinetic(s); SAE = serious adverse event; SVC = slow vital capacity; WOCBP = woman of childbearing potential

a An urgent safety measure was submitted on 05 December 2023 to request pause of SAR443820 administration in Part B (open-label extension) immediately. All participants in Part B will be encouraged to continue follow-up visits, but no doses of SAR443820 should be administered until DMC recommendation to resume dosing based on benefit-risk considerations when Part A data is available.

b The first visit for Part B is the Week 24 Visit in Part A.

c The last follow-up visit will happen 2 weeks (±3 days) after Week 104 visit (Visit 17).

d Alternatively, the Week 30, Week 32, Week 34 and Week 40 visit can be conducted by phone. The blood sample at these visits must be collected either at study site, at a local clinic or at home by a nurse. In case of testing at a local lab, the study site staff must contact the participant, within 2 working days after the results are expected to be available, to collect results of blood test and update them in the eCRF. When Week 32 and Week 40 visits are conducted by phone, the urine pregnancy test will be provided directly to participants and self-conducted at home. The study site staff will call the participants to remind them to conduct the pregnancy test and collect the result. If pregnancy test result is positive, participant should discontinue IMP immediately.

e For participants who prematurely discontinue IMP, the early IMP discontinuation visit will happen 2 weeks (±3 days) after the last dose of the IMP. If, after the IMP discontinuation visit, participants decide to continue the study, they will follow the same schedule for visits, but only ALSFRS-R, blood sample for NfL, vital signs, physical examination, neurological examination, AE review, SAE review and concomitant therapy and procedures recordings will be performed in the visits, as applicable according to the schedule of activities.

f In addition to the IMP being dispensed in the clinic, the IMP may be dispensed for home administration via DTP services, except if prohibited by local regulatory authorities.

g Only IMP reconciliation will be done at this visit.

h A brief physical examination will be performed at each visit. The skin and lymph nodes need to be checked at each visit.

i A brief neurological examination pertaining to cranial nerves, coordination/cerebellar function, reflexes, and motor function will be performed at each visit.

j Only liver chemistry monitoring will be conducted, which includes testing of alanine transaminase (ALT), aspartate aminotransferase (AST), bilirubin direct, bilirubin total and alkaline phosphatase.

k The “Since Last Visit” version of the C-SSRS will be used.

l Vital signs include blood pressure, heart rate, respiratory rate, weight, and temperature.

m One sample for PK will be collected within 1 hour before the morning dose of IMP. This PK sample can be taken under either fasting or non-fasting condition.

n The blood sample for serum NfL will be collected only when the participant terminates IMP before Week 52.

o Monthly urine pregnancy tests will be provided directly to participants and self-conducted by them at home when not coinciding with a clinic visit. The study site staff will call the participants to remind them to conduct the monthly pregnancy tests and collect the results. If pregnancy test result is positive, participant should discontinue IMP immediately.

2 INTRODUCTION

SAR443820 is a novel, potent, selective, CNS-penetrant RIPK1 inhibitor that is being developed for neurodegenerative diseases, including ALS.

2.1 STUDY RATIONALE

SAR443820 is a selective, orally bioavailable, CNS-penetrant, RIPK1 inhibitor. The aim of this placebo-controlled Phase 2 study is to determine the efficacy, safety, tolerability, PK, and PD of SAR443820 in treating adult participants with ALS.

Multiple pathways have been suggested to be involved in ALS pathogenesis, including pathways involved in oxidative stress, mitochondrial dysfunction, axonal damage, excitotoxicity, neuroinflammation, and protein aggregation (1). Treatment targeting the common mediator of these mechanisms can provide a more robust disease intervention than targeting any individual pathway. More specifically, inhibition of microglial activation and inflammatory-driven neuronal death, the common consequence of multiple pathways in the pathophysiology of ALS, has the potential to provide an effective treatment for this relentless disease.

RIPK1 is an intracellular protein involved in the regulation of inflammation, cytokine release, and cell death. RIPK1 is activated in response to several inflammatory stimuli, most notably TNF-α signaling through its receptor 1 (TNF1), with subsequent RIPK1 initiation of a complex signaling cascade that triggers intracellular responses, including cytokine release, microglial activation, and necroptosis, a regulated form of cell death (2, 3). Inhibition of RIPK1 activity has been shown to protect against necroptotic cell death in vitro across a range of cell death models (4, 5, 6). Similarly, in various animal models of diseases ranging from AD to MS, inhibition of RIPK1 protects against their respective pathologies and attributed cell death (7, 8, 9, 10). These nonclinical findings, coupled with observations of increased RIPK1 activity in human diseases (6, 7, 11), suggest that inhibition of RIPK1 could ameliorate ALS.

The RIPK1 pathway is activated in spinal cords from patients with ALS. These postmortem samples show elevated levels of RIPK1 and its downstream signaling partners, RIPK3 and MLKL (8). Similar increases have been observed in the spinal cord of the SOD1 (G93A) transgenic mouse with ALS. Furthermore, both genetic inhibition of the RIPK1 pathway (RIPK3 -/-) and treatment with a RIPK1 inhibitor reduced axonal pathology and delayed the onset of motor dysfunction in this model (8). Several ALS-inducing mutations, including TBK1 and OPTN, have been shown to sensitize cells to RIPK1-dependent cell death and inflammation (8, 12, 13). Notably, another RIPK1 activity inhibitor, transforming growth factor β-activated kinase-1 (TAK1), declines with age, which might predispose the CNS to neuroinflammation and neurodegeneration in the setting of genetic or environmental stresses (13).

In summary, both preclinical and patient-derived data have suggested RIPK1 may be a key mediator of necroptosis and inflammatory pathways in ALS. SAR443820, a CNS-penetrant inhibitor of RIPK1, has the potential to modify the course of neurodegenerative processes and slow disease progression in patients with ALS. Therefore, the aim of this Phase 2 study is to assess the efficacy, safety, and tolerability of SAR443820 in treating participants with ALS.

2.2 BACKGROUND

ALS is a fatal neurodegenerative disorder characterized by progressive loss of motor neurons in the cortex, brain stem, and spinal cord. Relentless and progressive muscle atrophy and weakness are hallmarks of ALS. Most patients with ALS die from respiratory failure within 3 to 5 years after disease onset. Among the 3 Food and Drug Administration (FDA)-approved ALS treatments, riluzole and edaravone demonstrate only a moderate effect either on survival or functional decline, respectively, and more data is needed to further support the treatment effect of the recently approved treatment, the combination of sodium phenylbutyrate and taurursodiol. Therefore, there is still a significant unmet medical need for treating individuals with ALS.

SAR443820 has demonstrated strong RIPK1 inhibition with high potency in vitro in various cell types. Refer to the SAR443820 Investigator's Brochure (IB) for a detailed description of the chemistry, pharmacology, efficacy, and safety of SAR443820.

2.3 BENEFIT/RISK ASSESSMENT

2.3.1 Risk assessment

Table 1 - Risk assessment (identified risk of clinical significance)

Identified risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Study intervention(s)		
ALT increase/Drug induced liver injury (DILI)	During clinical trials with SAR443820, mild-severe ALT increases have been reported, including 2 SUSARs with total bilirubin increase > 2 ULN reported in the ALS patients. These events often involved patients who were also taking concomitant medications that are known to induce liver function abnormalities, or who had concomitant diseases that could also affect ALT level.	Implemented through an USM dated on 5th December 2023, all participants in Part A are requested to conduct weekly liver chemistry monitoring and all participants in Part B are requested to pause SAR443820 immediately until DMC recommendation to resume dosing based on benefit-risk considerations when Part A data is available. Additionally, all participants are requested to limit their alcohol consumption during the whole study period. Detailed instructions to be followed in case of the occurrence of an AESI of ALT increase >3ULN are described in Appendix 6 in this protocol, and cover ALT monitoring, IMP administration, etiology assessment and IMP rechallenge.

Abbreviations: ALT=alanine transaminase; DILI=drug induced liver injury; IMP=investigational medicinal product, SUSAR=suspected unexpectedserious adverse event, ULN=upper limit normal, USM=urgent safety measure, AESI=adverse event of special interest

Table 2 - Risk assessment (potential risk of clinical significance)

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Study intervention(s)		
Convulsion	Convulsions are considered to be a potential risk based on nonclinical findings in single-dose, 9-day and 28-day nonhuman primate toxicity studies and in a 6-month rat study. In nonhuman primate studies, the following were observed: Convulsions/tremors at a dose of 75 mg/kg in the single-dose study, at a dose of 100 mg/kg/day in the 9-day study, and at a dose of 60 mg/kg/day in the 28-day study. No convulsions have been observed up to the dose level of [redacted] mg/kg/day in both the 3-month and 9-month studies. In the 6-month study in rats, convulsions were noted at a dose of 400 mg/kg/day (males) and 200 mg/kg/day (females). Convulsions and other findings that necessitated euthanasia were also observed in a single female rat receiving 50 mg/kg/day.	Based on the uncertainty in the interspecies translatability of convulsive risk, a conservative safety approach to limit human exposure (ie, C_{max} and AUC) was taken regarding the selected dose of 20 mg BID, which maintained a [redacted] to the NOAEL exposure (C_{max} and AUC) in the 3-month toxicology study in nonhuman primates. Moreover, to mitigate the risk, participants with a history of seizure will not be eligible to participate in this study. Additionally, concomitant medications that may increase significantly exposure [redacted] (including strong and moderate CYP3A4 inhibitors) are not allowed in this study. Patients in whom exposure may be [redacted] (participants weighing <45 kg or patients with a moderate or severe hepatic impairment) will also be excluded from this study.
Immunomodulatory Effects	Findings consistent with immune system modulation were observed with SAR443820 in the 3-month and 9-month nonhuman primate studies. These findings included mononuclear cell infiltrates in various tissues and changes in lymphoid tissues (increased/decreased cellularity and/or increased germinal centers). None of these microscopic findings for SAR443820 were considered adverse based on their incidence, severity, and/or recoverability or the lack of clinical pathology correlates or relevant clinical observations.	Frequent monitoring of the results of a hematology test, physical examinations (eg, skin, lymph nodes), and occurrence of infections TEAEs are planned.
Pregnancy maintenance and embryo-fetal toxicity	Adverse, test article-related effects on litter viability/pregnancy maintenance were noted at 200 mg/kg/day in a rat embryo-fetal development study. Two rats given 200 mg/kg/day were pregnant but had total litter loss. In addition, test article-related increases in early resorptions, late resorptions, total resorptions, post implantation loss, post-implantation loss percentage, and reduced fetal weight were observed for groups administered 20, 60, or 200 mg/kg/day.	Pregnant females are not allowed to participate in this study and monthly pregnancy testing is requested for all female participants of childbearing potential. Pregnancy of a female participant will lead to permanent IMP discontinuation in the participant. Additionally, contraceptive use by female participants of childbearing potential is requested during study period.
Study procedures		
Blood drawing	Pain or other discomfort from collection of blood samples.	Minimize the frequency and amount of blood drawing.

Abbreviations: AESI = adverse event of special interest; ALT = alanine transaminase; AUC = area under the curve; BID = twice daily; C_{max} = maximum plasma concentration; CYP = cytochrome P450; IMP = investigational medicinal product; NOAEL = no-observed-adverse-effect level; TEAEs = treatment-emergent adverse events. ULN = upper limit of normal.

2.3.2 Benefit assessment

SAR443820 is expected to slow disease progression, improve quality of life (QoL), and prolong survival for participants with ALS based on scientific rationale and preclinical data.

2.3.3 Overall benefit/risk conclusion

In the completed first-in-human studies, SAR443820 was found to be safe and well-tolerated up to the highest doses administered, ie, a single dose of [redacted] mg and multiple 14-day dose of 20 mg BID, in 100 healthy subjects who received SAR443820 as of April 2022. In addition, a preliminary physiological based pharmacokinetic modeling and simulation (PBPK) model indicates that at a dose of 20 mg SAR443820 BID, [redacted] value determined in vivo using the pS166-RIPK1 inhibitor assay in peripheral blood mononuclear cells (PBMC), which supports the potential for clinical efficacy. Convulsions believed to be SAR443820-related have been observed in [redacted] The risk of convulsions will be mitigated through 1) limiting the dose chosen in this study with maximum plasma concentration (C_{max}) and area under the curve (AUC) [redacted] at the no-observed–adverse-effect-level (NOAEL) in the 3-month monkey study; 2) excluding participants with a history of seizures; 3) excluding concomitant medications that may increase exposure [redacted] (potent and moderate cytochrome P450 (CYP)3A4 inhibitors); and 4) excluding participants with moderate or severe hepatic impairment. Since immunomodulatory effects of SAR443820 were observed in the 3-month nonhuman primate study but not in the first-in-human study in healthy volunteers, frequent monitoring of safety through hematology tests, physical examinations (eg, skin, lymph nodes), and the occurrence of infection, will be implemented in both Parts A and B. Considering the measures taken to minimize risk to participants in this study, the potential risks identified in association with SAR443820 are justified by the anticipated benefits that may be afforded to participants with ALS.

In the ongoing study ACT16970, a limited number of cases meeting criteria for severe DILI have been reported. ALT and bilirubin levels fully recovered in these cases after stopping the IMP and riluzole. These blinded data suggest that DILI is an identified risk of SAR443820, in particular when used in combination with hepatotoxic concomitant medications. The exact mechanism is not known. In nonclinical studies in rats and monkeys, non-adverse microscopic changes were noted in the liver without ALT increases. In Phase 1 studies, there were three mild (<3 ULN) asymptomatic cases of ALT increase (all recovered). Risk minimization measures during the study include limitation of alcohol consumption, although a relationship with alcohol use has not been established. In addition, frequent monitoring of liver chemistry is implemented to allow for early detection and mitigation. The Benefit Risk ratio remains acceptable for the use of SAR443820 in participants with ALS.

3 OBJECTIVES AND ENDPOINTS

Table 3 - Objectives and endpoints

Part A

Objectives	Endpoints
Primary	
• To assess the effect of SAR443820 compared to placebo in reducing ALS progression as measured by the Amyotrophic Lateral Sclerosis Functional Rating Scale Revised (ALSFRS-R)	• Change from baseline in the ALSFRS-R total score to Week 24
Secondary	
• To assess the effect of SAR443820 compared to placebo on a combined assessment of function and survival, respiratory function, muscle strength, and quality of life (QoL)	• Combined assessment of the function and survival (CAFS) score at Week 24 • Change from baseline in slow vital capacity (SVC) to Week 24 • Change from baseline in muscle strength to Week 24 • Change from baseline in Amyotrophic Lateral Sclerosis Assessment Questionnaire (ALSAQ-5) to Week 24
• To assess the pharmacodynamic (PD) effect of SAR443820 compared to placebo on a key disease biomarker	• Change from baseline in serum neurofilament light chain (NfL) to Week 24
• To assess the safety and tolerability of SAR443820 compared to placebo	• Incidence of adverse events (AE), serious adverse events (SAE), treatment-emergent adverse events (TEAE), potentially clinically significant abnormalities (PCSA) in laboratory tests, electrocardiogram (ECG), and vital signs over 24 weeks
• To assess the pharmacokinetics (PK) of SAR443820	• Plasma concentration of SAR443820
Tertiary	
[redacted] SAR443820 [redacted]	[redacted]
• To assess the effects of SAR443820 compared to placebo on neurodegeneration and inflammation disease biomarkers	• Change from baseline in soluble triggering receptor expressed on myeloid cells-2 (sTREM2) in plasma chitinase-3-like protein-1 (CHI3L1), a selected panel of cytokines and chemokines in serum, and extracellular domain of p75 (p75ECD) in urine to Week 24

Part B

Objectives	Endpoints
Primary	
• To assess the long-term effects of SAR443820 on function and survival	• Combined assessment of the function and survival (CAFS) score at Week 52
Secondary	
• To assess the long-term effects of SAR443820 on disease progression, survival, respiratory function, and quality of life (QoL)	• Combined assessment of the function and survival (CAFS) score at Week 76 and Week 104 • Change from baseline in the ALSFRS-R total score to Week 52, Week 76, and Week 104 • Time from baseline to the occurrence of either death or permanent assisted ventilation (>22 hours daily for >7 consecutive days), whichever comes first • Time from baseline to the occurrence of death • Change from baseline in slow vital capacity (SVC) to Week 52, Week 76, and Week 104 • Change from baseline in Amyotrophic Lateral Sclerosis Assessment Questionnaire (ALSAQ-5) to Week 52, Week 76, and Week 104
• To assess the long-term effect of SAR443820 on a key disease biomarker	• Change from baseline in serum neurofilament light chain (NfL) to Week 52
• To assess the long-term safety and tolerability of SAR443820	• Incidence of adverse events (AE), serious adverse events (SAE), treatment-emergent adverse events (TEAE), potentially clinically significant abnormalities (PCSA) in laboratory tests, electrocardiogram (ECG), and vital signs during Part B
• To assess the pharmacokinetics (PK) of SAR443820	• Plasma concentration of SAR443820
Tertiary	
[redacted] SAR443820 [redacted]	[redacted]
[redacted] SAR443820 [redacted]	[redacted]

For China, please see Appendix 8 (Section 10.8) for details.

3.1 APPROPRIATENESS OF MEASUREMENTS

3.1.1 Measurements for efficacy assessment

The primary endpoint of this study is the change of ALS disease progression as measured by the ALSFRS-R, which is a validated and established outcome measurement of therapeutic efficacy for ALS. The ALSFRS-R is a widely accepted measure of ALS progression used by clinical trialists and regulatory bodies (14).

The CAFS is a measurement ranking the clinical outcomes of patients with ALS based on survival time and change in the ALSFRS-R score (15). The combined endpoint can decrease the confounding effect of mortality on the results of an analysis of functional outcomes as it appropriately accounts for and weights mortality in the analysis of function.

For the survival assessment, in addition to mortality, a composite time-to-event endpoint recording the time to death or permanent continuous ventilator dependence, whichever occurs first, will be assessed as 1 of the efficacy endpoints since survival data may be confounded by the use of ventilation strategies. This approach is consistent with guidance from the FDA and European Medicines Agency (EMA) (14, 16).

The SVC percentage of predicted normal provides a quantitative means to assess reductions in the strength of the diaphragm and other respiratory muscles. The SVC change over time has been demonstrated to be associated with meaningful clinical events, including the time to respiratory insufficiency or death (17).

Muscle weakness is a typical feature of ALS and an important determinant of participants' daily function and QoL. Handheld dynamometry provides a quantitative means to assess limb muscle strength.

The ALSAQ-5 has been demonstrated to be a sensitive and reliable instrument for estimating QoL in patients with ALS (18) and provides similar results to the ALSAQ-40 but with a considerable reduction in patient burden (19).

[redacted]

[redacted]

3.1.2 Pharmacokinetic assessments

Whole blood samples will be collected for measurement of the plasma concentration of SAR443820 as specified in the schedule of assessments (SoA).

3.1.3 Pharmacodynamic assessments

Serum blood samples will be used to measure changes in NfL, a marker of neuronal injury. Levels of NfL in both CSF and plasma have been reported to be increased and stable over time in participant with ALS compared to healthy controls. Patients with ALS with a fast progression rate have demonstrated higher levels of NfL in CSF and plasma than those with a slow progression rate (21). Only serum NfL will be measured in this study to reduce the collection burden on participants.

Blood samples will also be collected to measure changes in markers of neuroinflammation, including soluble triggering receptor expressed on myeloid cells 2 (sTREM2) in plasma, Chitinase-3-like protein 1 (CHI3L1), and several cytokines in serum (interferon gamma [IFNγ], interleukin [IL]-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL12p70, IL-13, and TNF-α) and chemokines (eotaxin 1, eotaxin 3, thymus- and activation-regulated chemokine [TARC], interferon gamma-induced protein-10 [IP-10], macrophage inflammatory protein (MIP) (MIP1α and MIP1β), monocyte chemoattractant proteins (MCP) 1 and 4 (MCP1 and MCP4).

Urine samples will be collected to measure changes in the level of neurotrophin receptor extracellular domain p75 ($p75^{ECD}$).

3.1.4 Safety and tolerability assessment

Adverse events (AE), serious adverse events (SAE), treatment-emergent adverse events (TEAE), adverse events of special interest (AESI), electrocardiogram (ECG), vital signs, and laboratory test analyses will be reported.

4 STUDY DESIGN

4.1 OVERALL DESIGN

Study ACT16970 is a Phase 2, randomized, double-blind, placebo-controlled, 2 parallel-group study followed by an open-label, long-term extension period.

The study consists of 2 parts (A and B) as follows:

Part A is a 24-week, double-blind, placebo-controlled part, preceded by a screening period of up to 4 weeks before Day 1.

- A screening period of up to 4 weeks, designed to evaluate the suitability of participants to participate in the study in terms of ALS diagnosis, ALS duration, and ALS progression rate; respiratory function (SVC); and safety screening evaluations. No IMP will be administered in this period.
- A double-blind treatment period with a total duration of 24 weeks for each participant:
  - Participants will be randomized in a ratio of 2:1 to receive 20 mg BID SAR443820 (n=174) or placebo BID (n=87).
  - Randomization will be stratified by the geographic region of the study site, region of ALS onset (bulbar vs other areas), use of riluzole (yes vs no), and use of edaravone (yes vs no) and use of the combination of sodium phenylbutyrate and taurursodiol (yes vs no). Participants will attend in-clinic study assessments at baseline (Day 1), Week 2, Week 4, Week 6, Week 8, Week 10, Week 12, Week 16, Week 20, Week 21, Week 22, Week 23, and Week 24. All ongoing participants at Week 24 will rollover to open-label extension (Part B).
- Participants who discontinue the treatment or choose not to enter Part B will have their follow-up visit 2 weeks after the last dose of the study intervention.

Part B is an open-label, long-term extension of Part A. Part B starts from Week 24 and continues up to Week 106.

- The study intervention assignment of participants in Part A will remain double-blinded during Part B unless there is medical need to unblind the study intervention assignment.
- All participants will receive 20 mg BID SAR443820 in Part B starting from Week 24, except those who discontinue IMP treatment permanently in Part A.

  Based on a data review, and in accordance with Data Monitoring Committee (DMC) recommendations, sites have been instructed on 5th December 2023 to pause the administration of SAR443820 in Part B (open-label extension) immediately. All participants in Part B will be encouraged to continue follow-up visits, but no doses of SAR443820 should be administered. Rollover to Part B for follow-up visits after completing Part A is also encouraged, but without taking SAR443820 in Part B. The decision of whether resuming SAR443820 administration in Part B will be made based on DMC recommendation when Part A data is available and benefit risk ratio will be evaluated.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The participants enrolled in this study will be at an early stage of ALS to capture the effect of treatment on the disease course, especially because the mechanism of action of SR443820 modifies the disease pathology, rather than providing symptomatic alleviation. Participants who have a very slow ALS progression rate (<0.5 points/month in ALSFRS-R) prior to the screening visit will be excluded from the study to ensure that the study efficacy results will be interpretable. Part A of this study uses a randomized, double-blind, placebo-controlled design as it is the gold standard to demonstrate the efficacy and safety of SAR443820. Meanwhile, Part B of this study is an open-label extension during which both safety and efficacy data are collected to characterize the long-term treatment effects of SAR443820.

4.3 JUSTIFICATION FOR DOSE

The choice of the dose of 20 mg BID SAR443820 is based on all available nonclinical and clinical data at the time of protocol development.

The NOAEL was [redacted] mg/kg/day in nonhuman primates (cynomolgus monkeys). A [redacted] this NOAEL was implemented as the human exposure cap in Phase 1 single ascending dose (SAD) and multiple ascending dose (MAD) studies.

Overall, in the first-in-human study, SAR443820 up to a highest single dose of [redacted] mg and multiple 14-day dose of 20 mg BID, was found to be safe and well tolerated. In the Phase 1a SAD study, there were no SAEs. All the TEAEs were of mild to moderate intensity except 1 severe TEAE (blood creatine phosphokinase [CPK] increase of Grade 3) reported in the placebo group. Since convulsions [redacted] mg and [redacted]. In the MAD study, no SAEs, other than dose limiting AEs or laboratory findings, were reported. All the AEs reported in the MAD study were of mild to moderate intensity. At 20 mg BID, the highest dose administered, the mean observed C_{max} was 1.22 µM and the $AUC_{0\text{-}24h}$ (corresponding to $AUC_{0\text{-}12h}$ *2) was 15.0 µM*hour. These values are estimated to be [redacted], respectively.

The dose of 20 mg BID SAR443820 is estimated to provide a high level of target engagement required for obtaining a clinical effect. Internal preclinical data in animal models suggest CNS [redacted] is a predictor of a clinical therapeutic effect. Preliminary data indicate a good penetration of SAR443820 in CSF with mean values of the CSF/unbound plasma ratio of at least 0.81 and 1.27 before and after plasma t_{max}, respectively. A preliminary PBPK model indicates that at a dose of 20 mg BID, [redacted], which has been determined in vivo using the pS166-RIPK1 inhibitor assay in PBMC.

Therefore, 20 mg BID, which has been demonstrated to be well tolerated in healthy subjects, is selected for this Phase 2 study to achieve the best potential treatment effectiveness in participants with ALS while maintaining [redacted] to the NOAEL exposure in the nonhuman primate study.

4.4 END OF STUDY DEFINITION

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled assessment and/or procedure shown in the SoA for the last participant in the study globally.

A participant is considered to have completed the study if he/she has completed all phases of the study, including the last visit or the last scheduled procedure as shown in the SoA (Section 1.3).

5 STUDY POPULATION

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

5.1 INCLUSION CRITERIA

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

Age

I 01. Participants must be 18 to 80 years of age inclusive, at the time of signing the informed consent form.

Type of participant and disease characteristics

I 02. Participants must have been diagnosed with possible, clinically probable ALS, clinically probable laboratory-supported ALS, or clinically definite ALS according to the revised version of the El Escorial World Federation of Neurology criteria (22).

I 03. Participants must have an ALS disease duration (from first symptom onset to the screening visit) ≤2 years.

I 04. Participants must have an ALSFRS-R prestudy slope ≥0.5 points/month prior to the screening visit (ΔALSFRS-R = (48 - ALSFRS-R score at the screening visit)/duration in months between the screening visit and disease onset).

I 05. Participants must have an upright (sitting position) SVC ≥60% of the predicted value as adjusted for sex, age, and height at the screening visit.

I 06. Participants must be able to swallow the study tablets at the screening visit.

I 07. Participants must either not currently receiving riluzole or on a stable dose of riluzole for at least 4 weeks before the screening visit. Participants receiving riluzole are expected to remain on the same dose throughout the duration of the study.

I 08. Participants must either not currently receiving edaravone or are on the approved standard schedule of edaravone treatment. Participants receiving edaravone must have completed at least 1 cycle of treatment before the screening visit and are expected to continue edaravone treatment throughout the duration of the study.

Weight

I 09. Participants with a body weight no less than 45 kg and body mass index (BMI) no less than 18.0 kg/m^2 at the screening visit.

Sex, contraceptive/barrier method and pregnancy testing requirements

I 10. All

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

a) Male participants

Male participants are eligible to participate if they agree to the following during the study period and for at least 92 days following their last dose of the IMP:

- Refrain from donating or cryopreserving sperm

PLUS, either:

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

OR

- Must agree to use contraception/barrier method as detailed below:

- A male condom and an additional highly effective contraceptive method as described in Appendix 4 (Section 10.4) when having sexual intercourse with a woman of childbearing potential (WOCBP) who is not currently pregnant.

b) Female participants

Female participants are eligible to participate if they are not pregnant or breastfeeding and 1 of the following conditions applies:

- Are woman of nonchildbearing potential (WONCBP) as defined in Appendix 4 (Section 10.4)

OR

- Are WOCBP and agree to use a contraceptive method that is highly effective (with a failure rate of <1% per year), preferably with low user dependency, as described in Appendix 4 (Section 10.4) during the study intervention period (to be effective before starting the study intervention) and for at least 32 days after the last administration of the IMP and agree not to donate or cryopreserve eggs (ova, oocytes) for the purpose of reproduction during this period.
- WOCBP must have a negative highly sensitive pregnancy test within 24 hours before the first administration of the study intervention, see Section 8.2.6.
- If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

Informed consent

I 11. Participants must be capable of giving signed informed consent as described in Appendix 1 (Section 10.1), which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

Criteria added in amended protocol

I 12. Participants must either not currently be receiving the combination of sodium phenylbutyrate and taurursodiol or are on the approved standard schedule of the combination of sodium phenylbutyrate and taurursodiol treatment for at least 4 weeks before the screening visit. Participants receiving the combination of sodium phenylbutyrate and taurursodiol are expected to remain on the approved standard schedule throughout the duration of the study

5.2 EXCLUSION CRITERIA

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

Medical conditions

E 01. Participants with a history of seizure or epilepsy (History of febrile seizure during childhood is allowed).

E 02. Participants with central IV lines, such as a peripherally inserted central catheter (PICC) or midline or port-a-cath lines.

E 03. Participants with a significant cognitive impairment, psychiatric disease, other neurodegenerative disorder (eg, Parkinson disease or AD), substance abuse, other causes of neuromuscular weakness, or any other condition that would make the participants unsuitable for participating in the study or could interfere with assessment or completing the study in the opinion of the Investigator.

E 04. Participants with a history of recent serious infection (eg, pneumonia, septicemia) within 4 weeks of the screening visit; infection requiring hospitalization or treatment with IV antibiotics, antivirals, or antifungals within 4 weeks of screening; or chronic bacterial infection (such as tuberculosis) deemed unacceptable as per the Investigator’s judgment.

E 05. Participants with an active herpes zoster infection within 2 months prior to the screening visit.

E 06. Participants with a documented history of attempted suicide within 6 months prior to the screening visit, present with suicidal ideation of category 4 or 5 on the Columbia Suicide Severity Rating Scale (C-SSRS), or in the Investigator’s judgment are at risk for a suicide attempt.

E 07. Participants with a history of unstable or severe cardiac, pulmonary, oncological, hepatic, or renal disease or another medically significant illness other than ALS precluding their safe participation in this study.

E 08. Participants who are pregnant or are currently breastfeeding.

E 09. Participants with a known history of allergy to any ingredients of SAR443820 (mannitol, lactose monohydrate, sodium starch glycolate, colloidal silicon dioxide, magnesium stearate, hypromellose, titanium dioxide, polyethylene glycol, and microcrystalline cellulose).

Prior/concomitant therapy

E 10. Participants who have received any strong or moderate CYP3A4 inhibitors or strong CYP3A4 inducers listed in Appendix 10, Section 10.10, Table 8 within the specified washout period before the screening visit.

E 11. Participants who have received a live vaccine within 14 days before the screening visit.

Prior/concurrent clinical study experience

E 12. Participants with concurrent participation in any other interventional clinical study or who have received treatment with another investigational drug (eg, sodium phenylbutyrate or taurursodiol) within 4 weeks or 5 half-lives of the investigational agent before the screening visit, whichever is longer.

E 13. Participants who have received stem cell or gene therapy for ALS at any time in the past.

Diagnostic assessments

E 14. Participants with a positive human immunodeficiency virus (HIV) antibody test.

E 15. Participants with abnormal laboratory test(s) at the screening visit including the following:
- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3.0 × upper limit of normal (ULN)
- Bilirubin >1.5 × ULN unless the participant has documented Gilbert syndrome (isolated bilirubin >1.5 × ULN is acceptable if bilirubin is fractionated and direct bilirubin is <35%)
- Serum albumin <3.5 g/dL
- Estimated glomerular filtration rate <60 mL/min/1.73 m^2 (Modification of Diet in Renal Disease [MDRD])
- Other abnormal laboratory values or ECG changes that are deemed clinically significant as per the Investigator's judgment

E 16. Participants with hepatitis B surface antigen (HBsAg) or antihepatitis B core antibodies (anti-HBcAb) at the screening visit or within 3 months prior to the first dose of the study intervention. Serologies consistent with a resolved infection or vaccination, such as the presence of HBsAb, may not exclude potential participants from the trial.

E 17. Participants with a positive hepatitis C antibody test result at the screening visit or within 3 months prior to starting the study intervention. NOTE: Participants with a positive hepatitis C antibody test due to prior resolved disease can be enrolled only if a confirmatory negative hepatitis C RNA test is obtained.

Other exclusions

E 18. Participants who are accommodated in an institution because of a regulatory or legal order; prisoners or participants who are legally institutionalized.

E 19. Participants who are employees of the clinical study site, other individuals directly involved in the conduct of the study, or immediate family members of such individuals (in conjunction with Section 1.61 of the International Council for Harmonisation (ICH)-Good Clinical Practice (GCP) Ordinance E6).

5.3 LIFESTYLE CONSIDERATIONS

5.3.1 Meals and dietary restrictions

Participants should be prohibited from consuming grapefruit or grapefruit juice (including pomelos, exotic citrus fruits, grapefruit hybrids, or fruit juices) from 5 days before the start of the study intervention until 2 days after the final dose.

PK samples can be collected at either fasting or non-fasting condition.

5.3.2 Caffeine, alcohol, and tobacco

The information of participant's regular use of alcohol and tobacco should be recorded in the electronic case report form (eCRF). During the entire study, participants should be warned not to consume substantial quantities of alcohol, defined as >14 grams (1 standard drink) per day in female participants or >28 grams (2 standard drinks) per day in male participants on a regular basis.

5.3.3 Activity

No special restrictions.

5.4 SCREEN FAILURES

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

When a participant does not meet the eligibility criteria but is likely to be eligible within the 4-week screening window after the initial screening visit, selected assessment(s), such as laboratory tests, can be repeated within the 4-week screening window as per the Investigator's medical judgment. The same initial consent form and study identification number will be applicable for the repeated assessments within the screening window.

Rescreening is allowed for participants who fail the initial screening at the Investigator's medical judgment for any manageable reasons that caused the initial screening failure. Participants who fail the initial screening may be rescreened up to 2 times during the study recruitment period. A new consent form will need to be signed and a new identification number will be issued for participants who undergo rescreening.

5.5 CRITERIA FOR TEMPORARILY DELAYING ENROLLMENT/RANDOMIZATION/ADMINISTRATION OF STUDY INTERVENTION ADMINISTRATION

During a regional or national emergency declared by a governmental agency, if the site is unable to adequately follow protocol-mandated procedures, contingency measures are proposed in Appendix 9 (Section 10.9).

6 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

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. In this study, the study intervention includes SAR443820 and placebo.

6.1 STUDY INTERVENTION(S) ADMINISTERED

Table 4 - Overview of study interventions administered

Intervention label	SAR443820	Placebo
Intervention name	SAR443820	Placebo
Type	Drug	Drug
Dose formulation	Tablet	Tablet
Unit dose strength(s)	20 mg	0 mg
Dosage level(s)	Twice daily	Twice daily
Route of administration	Oral	Oral
Use	Experimental	Experimental
IMP or NIMP	IMP	IMP
Packaging and labeling	Study Intervention will be provided in wallet blister packaging. Each wallet blister packaging will be labeled as required per country requirement.	Study Intervention will be provided in wallet blister packaging. Each wallet blister packaging will be labeled as required per country requirement.
Current/Former name(s) or alias(es)	SAR443820	Not Applicable

SAR443820 or matching placebo tablets are to be taken twice daily, 1 in the morning and 1 in the evening approximately 12 hours apart. The IMP tablet will be taken orally with approximately 100 mL of water for participants who can swallow tablets or with thickening agents to assist in swallowing for participants who develop swallowing difficulties during the study (tablets should be added to the thickening agents in their entirety and need to be taken immediately after mixing). For participants who have a gastrostomy tube (G-tube), the entire IMP tablet needs to be put in a glass with approximate 40 mL of water at ambient temperature, crushed roughly after approximately 10 minutes, and mixed manually for a few minutes before administration. The suspension will then be withdrawn with a syringe and administered through the G-tube, which will then be rinsed twice with approximately 40 mL of water and then 20 mL of water. The administration should take place within 15 minutes of suspension preparation. The IMP should be taken around the same time each day under the same condition (with or without food) throughout the study unless adjustment is specifically requested due to PK sampling at Day 1 and Week 2, Week 8, and Week 28 site visits.

SAR443820 or placebo may be supplied at the site or from the Investigator/site/Sponsor to the participant via a Sponsor-approved courier company if allowed by local regulations and agreed upon 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 Appendix 9 (Section 10.9).

6.1.1 Devices

Not applicable.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

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

SAR443820 and placebo tablets require no preparation and will be supplied to the study participants in labeled child-resistant wallets.

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 8.3.9).

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

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

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

- The study will be performed in a double-blind fashion for Part A. The placebo tablet will be identical to the SAR443820 tablet in appearance, quantity, taste, odor, and packaging.
- All participants will be centrally assigned to a randomized study intervention using an interactive response technology (IRT). Before the study is initiated, the login information and directions for the interactive web response system (IWRS) will be provided to each

site. The study intervention will be dispensed at the study visits summarized in the SoA. Returned IMP should not be redispensed to participants.

- A randomized participant is defined as a participant from the screened population who has been allocated to a randomized intervention regardless of whether the intervention was received or not. A participant cannot be randomized more than once in the study.
- The randomization in Part A is stratified by the geographic region of the study site, region of ALS onset (bulbar vs other areas), use of riluzole (yes vs no), use of edaravone (yes vs no) and use of the combination of sodium phenylbutyrate and taurursodiol (yes vs no).
- The Investigator, site staff, Sponsor monitoring team, and participants will remain blinded to the treatment assignment in Part A until the end of Part B. The sponsor study team, except Sponsor monitors, will be unblinded after database lock of Part A.
- The bioanalyst and the pharmacokineticist responsible for sample analysis and PK evaluation will be unblinded. However, they will agree not to disclose the randomization schedule or the individual unblinded analytical results before the official opening of the randomization schedule. Preliminary PK data, if needed and available during the study, will refer to means with descriptive statistics, and individual data will not be associated with any individual randomization numbers or participant numbers.
- This is a double-blind study in which participants/care providers/Investigators/outcomes assessors, etc. are blinded to the study intervention. The IRT will be programmed with blind-breaking instructions. In case of an emergency, the Investigator has the sole responsibility for determining if the unblinding of a participant's intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, he/she may, at his/her discretion, contact the Sponsor to discuss the situation prior to unblinding a participant's intervention assignment unless this could delay emergency treatment for the participant. If a participant's intervention assignment is unblinded, the Sponsor must be notified within 24 hours of this occurrence. The date and reason for the unblinding must be recorded.
- For regulatory reporting purposes, and if required by local health authorities, the Sponsor or designee will break the treatment code for all suspected unexpected serious adverse reactions (SUSARs) that are considered by the Investigator or Sponsor to be related to the study intervention.

6.4 STUDY INTERVENTION COMPLIANCE

- IMP accountability:
  - Intervention units are returned by the participant at each visit. In case of DTP process, the intervention units can be returned by the carrier (if defined in the contract)
  - The Investigator counts the number of tablets remaining in the returned packs, and fills in the Intervention Log Form
  - The Investigator records the dosing information on the appropriate page(s) of the eCRF
  - The monitor in charge of the study then checks the eCRF data by comparing them with the IMP which he/she has retrieved and intervention log forms

When participants are dosed at the site, they will receive the study intervention directly from the Investigator or designee, under medical supervision. The date and time of each dose administered in the site will be recorded in the source documents. The dose of the study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

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

A record of the quantity of SAR443820 and matching placebo dispensed to and administered by each participant must be maintained and reconciled with the study intervention and compliance records. The intervention start and stop dates, including dates for intervention delays and/or dose reductions, will also be recorded.

6.5 DOSE MODIFICATION

Dose modification is not foreseen in this study. The IMP treatment may need to be interrupted or permanently discontinued if deemed necessary due to an AE.

6.6 CONTINUED ACCESS TO INTERVENTION AFTER THE END OF THE STUDY

In addition to the 104 weeks of SAR443820 treatment in Part A and Part B of this trial, a separate, open-label, long-term safety follow-up study may be proposed for participants who complete this study if a positive benefit/risk ratio is confirmed in this trial. The details of the long-term study will be provided in a separate protocol.

6.7 TREATMENT OF OVERDOSE

For this study, overdose is defined as at least [redacted] mg IMP within 12 hours. Taking [redacted] mg IMP at the same time is considering a dosing error, but not an overdose as long as the participant skips the next dose.

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

In the event of an overdose, the Investigator should:

1. Closely monitor the participant for any AE/SAE and laboratory abnormalities until the IMP can no longer be detected systemically (at least 2 days). Provide supportive and symptomatic treatment as needed.
2. Evaluate the participant to determine whether study intervention should be interrupted or whether the dose should be reduced.
3. Obtain a plasma sample for PK analysis as soon as possible from the date of the last dose of the study intervention.
4. Document appropriately in the eCRF.
5. Contact the Sponsor as soon as possible.

6.8 CONCOMITANT THERAPY

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

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

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

Any concomitant therapy should be reported to the Investigator and recorded in the Concomitant Medications eCRF. The reported medications will be reviewed and evaluated by the Investigator or designee to determine whether they affect a participant's eligibility to participate or continue to participate in the study.

As of November 2022, riluzole and edaravone are currently approved treatment options for patients with ALS in the United States, Canada, China, and Japan, and edaravone is not currently approved in the EU. The combination of sodium phenylbutyrate and taurursodiol has been approved for ALS treatment in the USA and Canada. Although these agents have only moderate effects, they constitute the standard of care, along with various supportive care treatments. Participants are allowed to enter the study if they are either not receiving riluzole or receiving stable doses of riluzole for at least 4 weeks prior to the screening visit and are expected to continue riluzole treatment throughout the duration of the study, provided liver function tests meet the entry criteria. Participants are allowed to enter the study if they are either not receiving edaravone or receiving the standard schedule of edaravone treatment. Participants who are receiving edaravone must have completed at least 1 cycle of edaravone treatment before the screening visit and are expected to continue edaravone treatment throughout the duration of the study. Participants are allowed to enter the study if they either not receiving the combination of sodium phenylbutyrate and taurursodiol or receiving the standard schedule of the combination of sodium phenylbutyrate and taurursodiol treatment for at least 4 weeks prior to the screening visit and are expected to continue the combination of sodium phenylbutyrate and taurursodiol treatment throughout the duration of the study. Dosage changes or discontinuations of riluzole and/or edaravone and/or the combination of sodium phenylbutyrate and taurursodiol during the study period are only allowed if continued treatment of riluzole and/or edaravone and/or the combination of sodium phenylbutyrate and taurursodiol would risk the safety of participants as assessed by the Investigator. Initiation of riluzole and/or edaravone and/or the combination of sodium phenylbutyrate and taurursodiol treatment during Part A is not allowed. Initiation of riluzole and/or edaravone and/or the combination of sodium phenylbutyrate and taurursodiol treatment during Part B is allowed if considered absolutely necessary in the medical judgment of the Investigator. Participants with central IV lines, such as PICC, midline, or port-a-cath lines, will be excluded due to the concern of an increased risk of infection. Initiation of central intravenous lines is not allowed during Part A but is allowed during Part B if considered absolutely necessary in the medical judgment of the Investigator. Switching between IV and oral

formulation of edaravone in the countries where both formulations have been approved is allowed at any time during the study.

Based on in vitro results, SAR443820 is mainly metabolized by CYP3A4. A PK interaction with strong and moderate CYP3A4 inhibitors is [redacted] SAR443820 [redacted]. A PK interaction with strong CYP3A4 inducers is predicted to decrease the SAR443820 AUC. Therefore, concomitant medications or substances that are strong or moderate inhibitors or strong inducers of CYP3A4 (Appendix 10, Section 10.10, Table 8) are not allowed within the specified wash out period before the screening visit and for the duration of Part A and Part B.

The use of any live vaccine is prohibited within 14 days before the screening visit and during the study duration.

6.8.1 Rescue medicine

Not applicable.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

7.1.1 Permanent discontinuation

The study intervention should be continued whenever possible.

In rare instances, it may be necessary for a participant to permanently discontinue the study intervention.

In case of the following events, permanent discontinuation of the IMP is mandatory. This list is not intended to be exclusive.

- The Investigator or Sponsor determines it is in the best interest of the participant
- Occurrence of AEs or any other medical condition that, in the opinion of the Investigator or Sponsor, may jeopardize the participant's safety or data integrity. These include, but are not limited to, abnormal livers tests and meeting the stopping criteria (see Appendix 6 [Section 10.6])
- Noncompliance with the protocol, including the dosing regimen and visits
- Pregnancy of a female participant
- Any IMP discontinuation lasting longer than 2 weeks accumulative in Part A or 8 weeks accumulative in Part B
- Occurrence of convulsions
- Initiation of riluzole and/or edaravone and/or the combination of sodium phenylbutyrate and taurursodiol treatment during Part A

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

Handling of participants after permanent intervention discontinuation

If a participant is withdrawn from study intervention permanently, the Sponsor will be notified within 2 business days and the date and reason(s) for the withdrawal will be documented by the Investigator in the appropriate pages of the eCRF when considered as confirmed.

Participants who prematurely discontinue the IMP will be encouraged to complete the rest of study visits for safety and efficacy assessments up to and including the last scheduled visit (Week 106). A separate PK sample may be taken if appropriate. At a minimum, participants should complete an early discontinuation visit 2 weeks after the last IMP dosing. All withdrawn participants will be followed until resolution of all their AEs or until the unresolved AEs are judged by the Investigator or Sponsor to have stabilized (see Section 10.3.3).

7.1.2 Temporary discontinuation

Temporary intervention 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 (Appendix 9 [Section 10.9]). For all temporary intervention discontinuations, duration should be recorded by the Investigator in the appropriate pages of eCRF. Temporary discontinuation of study intervention is defined as stopping study intervention for a minimum of 1 day and a maximum of 2 weeks accumulative in Part A or 8 weeks accumulative in Part B.

Based on a data review and in accordance with DMC recommendations, the sites were instructed on 5th December 2023 to pause administration of SAR443820 in Part B (open-label extension) immediately. An early IMP discontinuation visit should happen 2 weeks after the last dose of IMP. All participants in Part B will be encouraged to continue follow-up visits, but no doses of SAR443820 should be administered. Participants who are in Part A, rollover to Part B for follow-up visits after completing Part A is encouraged, but without taking SAR443820 in Part B. An early IMP discontinuation visit should also happen 2 weeks after the last dose of IMP. The decision of whether resuming SAR443820 administration in Part B will be made based on DMC recommendation when Part A data is available and benefit risk ratio will be evaluated.

If a scheduled liver chemistry monitoring is missed during weekly assessments, an unscheduled assessment for liver chemistry monitoring should be completed within 3 days. If a participant is receiving IMP and is unable to comply with the monitoring schedule, but does not meet the permanent discontinuation criteria, the participant must stop IMP administration until liver chemistry monitoring can be completed.

7.1.2.1 Study intervention restart or rechallenge after temporary discontinuation of study intervention

Reinitiation of the study intervention will be done under close and appropriate clinical and/or laboratory monitoring once the Investigator has considered, according to his/her best medical judgment that the responsibility of the IMP in the occurrence of the concerned AE was unlikely to reoccur.

If the participant meets liver chemistry stopping criteria, do not restart/rechallenge the participant with study intervention unless:

- There is a clear, documented etiology for increase in ALT with no relationship to study drug.
- When the rechallenge criteria are met as described in Section 10.6.
- Ethics Committee and/or Institutional Review Board (IRB) approval is obtained, if required based on local practice

NOTE: If study intervention was interrupted for suspected intervention-induced liver injury, the participant should be informed of the risk of death, liver transplantation, hospitalization, and jaundice and reconsented before resumption of dosing. In case of confirmed drug-induced liver injury caused by the IMP, the rechallenge with the IMP is not permitted, and the participants must be permanently discontinued from IMP treatment.

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 9 (Section 10.9).

Refer to Appendix 6 (Section 10.6) for details on the restart/rechallenge process.

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, or compliance reasons. This is expected to be uncommon.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See SoA (Section 1.3) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- 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.

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

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

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

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

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

7.3 STUDY LEVEL STOPPING CRITERIA

The study may be stopped if any of the following criteria are met:

- Cancellation of or change in the drug development program per the discretion of the Sponsor.
- Emergence of AEs unknown to date or increased frequency and/or severity and/or a duration of known AEs that makes the benefit-risk for study continuation negative.

- The results of the interim data review meet no-go criteria as detailed in the Statistical Analysis Plan (SAP).
- Participant enrollment (evaluated after a reasonable amount of time) is unsatisfactory.

7.4 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 site 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.
- Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized, including those who did not get study intervention. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

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

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.
- Adherence to the study design requirements, including those specified in the SoA, 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, urine tests) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.
  - Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.
  - If onsite visits are not feasible (due to ALS progression, increased monitoring for AE follow-up), remote visits (eg, with home nurses, a home health vendor, a local clinic etc.) may be planned for the collection of safety and/or efficacy data.

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 9 (Section 10.9).

8.1 EFFICACY ASSESSMENTS

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

Key efficacy assessments will be measured by trained Investigator or rater. Same Investigator or rater is preferred to conduct the same assessment for individual participant at each visit, if possible.

8.1.1 ALSFRS-R

The ALSFRS-R is composed of 12 items across 4 subdomains of bodily function (bulbar, fine motor, gross motor, and breathing), with each item scored on an ordinal scale from 0 (total loss of function) to 4 (no loss of function). The total score of the ALSFRS-R ranges from 0 to 48, with a higher score indicating better function (23). Good reliability between face-to-face and telephone administration of the ALSFRS-R has been demonstrated (24).

8.1.2 Slow vital capacity (SVC)

SVC is measured in participants while they are in an upright position at least 3 trials per assessment or up to 5 trials when the highest and second highest of the first 3 measurements differ by 10% or more. SVC volumes are standardized to the percentage of the predicted normal value based on age, sex, and height (25). The highest SVC score among all attempts will be used for analysis.

8.1.3 Muscle strength measurement

The muscles measured in the study include upper-limb and lower-limb muscle groups.Bilateral hand grip will be measured using a grip dynamometer and all other muscles included in this study will be measured using a handheld dynamometer. For each muscle to be tested, 2 trials will be performed. If the variability of the 2 trials is 15% or less, values from both trials will be recorded and the higher score will be used for analysis. If the variability is greater than 15%, a 3 trial will be performed, all the values will be recorded and the maximum value of the 3 trials will be accepted. The order of muscle testing is standardized (26).

8.1.4 ALSAQ-5

The ALSAQ-5 is a PRO that consists of 5 items derived from the ALSAQ-40. The 5 items closely resemble those of the 5-dimension scores of the ALSAQ-40: eating and drinking; communication; activities of daily living/independence; physical mobility; and emotional functioning. The ALSAQ-5 has a recall period of the past 2 weeks and takes approximately 5 minutes to complete. Each item is scored on a 5-point Likert scale ranging from 0 (never) to 4 (always or cannot do at all) according to the frequency of a particular problem. Total scores range from 0 to 20, with higher scores indicative of greater physical and emotional limitations.

[redacted]

8.1.6 Survival

The survival endpoint will be defined as the time to death or permanent assisted ventilation (>22 hours a day for >7 consecutive days), whichever comes first. The CAFS is a combined endpoint that evaluates function and survival together to provide a more accurate indication of a treatment effect than independent analyses. Results from the ALSFRS-R and survival data will be used together to generate the CAFS scale.

[redacted]

[redacted]

8.2 SAFETY ASSESSMENTS

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

Planned time points for all safety assessments are provided in the SoA.

8.2.1 Physical examinations

- A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, neurological systems, skin and lymph node area systems. Height and weight will also be measured and recorded.
- A brief physical examination will include, at a minimum, assessments of the skin, lymph node areas, lungs, cardiovascular system, and abdomen (liver and spleen).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2 Neurological examinations

- A neurological examination will be performed and the results recorded. A complete neurological examination will include, at a minimum, assessments of mental status, cranial nerves, motor and sensory function, reflexes, coordination, and stance/gait.
- A brief neurological examination will include, at a minimum, assessments of assessments of cranial nerves, coordination/cerebellar function, reflexes, and motor function.
- Investigators should pay special attention to clinical signs related to previous neurological illnesses, including ALS.

8.2.3 Vital signs

- Oral, tympanic, axillary, or skin temperature, heart rate, respiratory rate, and blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.
- 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 (usually should be taken before blood collection for laboratory tests) will consist of 1 pulse and 3 blood pressure measurements (3 consecutive sitting blood pressure readings will be recorded at intervals of at least 1 minute). The average of the 3 blood pressure readings will be recorded. At Day 1 visit, postdose vital signs should be measured at least 10 minutes after the second PK sample collection (recommended to be measured within 10 to 30 minutes after the second PK sample collection).

8.2.4 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 QTc intervals.
- In case the ECG machine does not automatically calculate QTcF, manual calculation using following formula (QTcF=QT/RR1/3) or automatic website calculator (eg, https://reference.medscape.com/calculator/48/ecg-corrected-qt) is acceptable.
- ECGs and (longer) rhythm strips will be obtained locally.
- If a clinically significant finding is identified in the ECG (including, but not limited to changes from baseline in QTcF after enrollment), the Investigator or delegate will determine if the participant can continue in the study and if any change in participant management is needed including but not limited to referral to cardiology, and/or Holter monitor. The Investigator or delegate should perform the following tasks:
  - Review the ECG in a timely manner
  - Document the interpretation, sign and date it on ECG printout
  - Record your (or appropriate qualified physician) medical opinion (“normal” or “abnormal”) on the study participant´s records and in the eCRF
  - Assess for any symptoms of cardiac issues

- Each time when it is medically needed for clinical management of the study participant or/and in case of any safety concerns, additional ECG should be performed, and findings reported in the eCRF dedicated unscheduled visits ECG forms
- Clinically significant findings are to be checked with pre-existing medical history or/and, if appropriate, consider AE.

Please refer to (27) and (28) for definitions of heart failures classification.

8.2.5 Clinical safety laboratory assessments

- See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and to the SoA (Section 1.3) for the timing and frequency.
- The Investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents. Abnormal laboratory findings associated with the underlying disease are not considered clinically significant, unless judged by the Investigator to be more severe than expected for the participant's condition.
- All abnormal laboratory values that are considered by the Investigator as clinically significant during participation in the study or within 2 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.
  - If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified and the Sponsor notified.
  - All protocol-required laboratory tests, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).
  - If laboratory values from nonprotocol-specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the Investigator (eg, SAE or AE or dose modification), then the results must be recorded.

8.2.6 Pregnancy testing

For female participants of childbearing potential, a pregnancy test will be performed at each onsite visit during the whole study period. Additionally, monthly urine pregnancy tests will be provided directly to participants and self-conducted by them at home when not coinciding with a clinic visit. The study site staff will call the participants to remind them to conduct the monthly pregnancy tests and collect the results. A serum pregnancy test will be conducted at the screening visit, the last follow-up visit at Week 106, and the early discontinuation visit, and a urine pregnancy test will be performed for all other visits.

8.2.7 Suicidal ideation and behavior (SIB) risk monitoring

SAR443820 crosses the blood-brain barrier. Assessment of suicidal ideation and behavior/treatment-emergent suicidal ideation and behavior will be monitored during ACT16970

using the C-SSRS. For safety reasons, the C-SSRS will be administered throughout the study by the Investigator or delegated to an individual who is certified to administer the scale.

Study intervention administration must be interrupted if a participant scores "yes" on items 4 or 5 of the Suicidal Ideation Section of the C-SSRS or "yes" on any item of the Suicidal Behavior Section. A mental health professional will be consulted and will decide whether the study intervention can be restarted and if any additional risk mitigation strategies are required (eg, increased monitoring, antidepressant administration).

Participants being treated with the study intervention should be monitored appropriately and observed closely for suicidal ideation and behavior or any other unusual changes in behavior. Especially at the beginning and end of the course of treatment, consideration should be given to discontinuing the study medication in participants who experience signs of suicidal ideation or behavior following a risk assessment.

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

The definitions of AEs and SAEs can be found in Appendix 3 (Section 10.3). The definition of AESI is provided in Section 8.3.8.

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

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

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

8.3.1 Time period and frequency for collecting AE and SAE information

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

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

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

8.3.2 Method of detecting AEs and SAEs

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

8.3.3 Follow-up of AEs and SAEs

After the initial AE/AESI/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. At the prespecified study end-date, all SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.4). Further information on follow-up procedures is provided in Appendix 3 (Section 10.3).

8.3.4 Regulatory reporting requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/Independent Ethics Committee (IEC), and Investigators.
- Serious adverse events that are considered expected will be specified in IB.
- Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.
- An Investigator who receives an Investigator safety report describing an SAE, SUSAR or any other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements. It is the responsibility of the Sponsor to assess whether an event meets the criteria for a SUSAR, and therefore, is expedited to regulatory authorities.

8.3.5 Pregnancy

- Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study intervention and until the time period for postintervention contraception determined in Section 5.1.
- If a pregnancy is reported, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the pregnancy of a female participant or female partner of male participant after obtaining the necessary signed informed consent from the female partner.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.

- The participant or female partner of a male participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant or female partner of a male participant and the neonate, and the information will be forwarded to the Sponsor.
- Any poststudy pregnancy-related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section 8.3.4. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention.

8.3.6 Cardiovascular and death events

Since the risk of cardiovascular events is low based on preclinical and Phase 1 study results, cardiovascular events are not AESIs and will be reported per standard safety reporting and safety oversight practices (including a data review by the data monitoring committee [DMC]).

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

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

Respiratory function decline is a type of disease-related event (DRE). DREs are common in participants with ALS and can be serious/life threatening.

Because a decline in respiratory function, including respiratory failure, is typically associated with ALS, it will not be reported according to the standard process for expedited reporting of SAEs even though the event may meet the definition of an SAE. These events will be recorded within the eCRF. These DREs will be monitored by an independent DMC on a routine basis (See Section 10.1). Disease progression-related measures will not be recorded as AEs/SAsE, including ALSFRS-R, vital capacity results, and muscle strength results. Additionally, the scheduled events, eg, hospitalization for an elective procedure, including G-tube placement, are not considered SAEs since an elective or scheduled “procedure” or a “treatment” are not an untoward medical occurrence.

NOTE: However, if either of the following conditions applies, then the events must be recorded and reported as an AE/SAE (instead of a DRE):

- The event is, in the Investigator’s opinion, of greater intensity, frequency, or duration than expected for the individual participant.

OR

- The Investigator considers that there is a reasonable possibility that the event was related to study intervention.

8.3.8 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.

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

- Pregnancy of a female participant who has taken the IMP at least once as well as pregnancy occurring in a female partner of a male participant who has taken the IMP at least once during this study
  - Pregnancy will be qualified as an SAE only if it fulfills 1 of the seriousness criteria (see Appendix 3 [Section 10.3]).
  - In the event of pregnancy in a female participant, the IMP should be discontinued.
  - Follow-up of the pregnancy in a female participant or in a female partner of a male participant is mandatory until the outcome has been determined (See Appendix 4 [Section 10.4]).
- Symptomatic overdose (serious or nonserious) with IMP
  - An overdose (accidental or intentional) with the IMP is an event suspected by the Investigator or spontaneously notified by the participant (not based on a systematic pill count) and defined as at least 3 tablets of the IMP taken within 12 hours.
  - Note: An asymptomatic overdose has to be reported as a standard AE.
- Other project-specific AESIs
  - Convulsions.
  - Serious infections meeting SAE definitions criteria (please see Section 10.3.2 for SAE definitions).
  - Increase in ALT >3.0 × ULN (confirmed at retest): see the "Increase in ALT algorithm" flow chart in Appendix 6 (Section 10.6).

8.3.9 Guidelines for reporting product complaints

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

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

8.4 PHARMACOKINETICS

Whole blood samples will be collected for measurement of the plasma concentration of SAR443820 as specified in the SoA (Section 1.3), which is summarized in Table 5 below.

PK samples can be collected at either fasting or non-fasting condition.

Table 5 - Schedule of PK sampling

	Day 1*	Week 2	Week 8	Week 28
Before dose (within 1 hour predose)		X	X	X
After dose (15 minutes to 1 hour)	X			
After dose (1 hour to 3 hours)	X			
After dose (15 minutes to 3 hours)			X	

* At least 45 minutes between the 2 PK samples at Day 1.

The timing of sampling may be altered during the course of the study based on newly available data to ensure appropriate monitoring.

Instructions for the collection and handling of biological samples will be provided by the Sponsor or Sponsor's designee in a separate document. The actual date and time of each sample will be recorded.

Samples collected for analysis of the SAR443820 plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns raised during or after the study.

Pharmacokinetic samples will be tested by the Sponsor or Sponsor's designee.

Pharmacokinetic samples could be used for testing analytical method performance such as comparability and incurred sample reproducibility and for possible exploratory analysis of drug metabolites and biomarkers. The exploratory data will not be included in the study report but will be kept on file.

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

8.5 GENETICS AND/OR PHARMACOGENOMICS

An optional single blood collection for the isolation of DNA will be conducted in participants of Part A only if they provide informed consent for this collection. Analysis of DNA may include the identification of determinants of disease (mutations and genetic variation) or response to treatment.

8.6 BIOMARKERS

- Collection of biological samples for biomarker research is also part of this study. The following samples for biomarker research are required and will be collected from all participants in this study as specified in the SoA:
  - Blood, which will be used to isolate either serum or plasma components
  - Urine
- Samples will be tested for protocol-specific objectives to evaluate their association with the observed clinical responses to the IMP.
- Blood derivatives and urine collected during the study may be used for exploratory research, including development of PD assays and/or exploration of target- and disease-related exploratory biomarkers related to RIPK1 kinase inhibition, such as cytokines, lipids, metabolites, cellular markers, immune cell phenotypes, and other inflammatory and neurodegenerative biomarkers. Samples collected for biomarker analyses and their derivatives will be stored for a period of up to 5 years after the last participant last visit for potential reanalyses (see details in Section 8.9).

For China, please see Appendix 8 (Section 10.8) for details.

8.7 IMMUNOGENICITY ASSESSMENTS

Not applicable.

8.8 MEDICAL RESOURCE UTILIZATION AND HEALTH ECONOMICS

Medical resource utilization and health economics data, associated with medical encounters, will be collected by the Investigator and study-site personnel for all participants throughout the study. Protocol-mandated procedures, tests, and encounters are excluded. As there have been ample publications on [redacted] among participants with ALS, this study will focus on [redacted] data collection for the data elements that most significantly impact participants that may be used to further supplement health economic analyses, specifically walking aids and [redacted], during the study.

8.9 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. For example, additional biomarkers analyses related to RIPK1 and/or ALS biology, such as serum glial fibrillary acidic protein (GFAP), may be performed. 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 drug, the mechanism of action, and the disease or its associated conditions. Such research may include, but is not limited to, performing assessments on other proteins, lipids, or metabolites. This will also be limited to the purpose of addressing research questions related to the drug, the mechanism of action, the disease or its associated conditions. Additional consent will be collected if the participant opts in for the additional blood sample for DNA analysis.

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).

Samples consented for future research use 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. Samples from study participants who do not give consent for future research use will be held for up to 5 years until all testing and reporting related to the clinical study have been completed (Section 8.6).

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

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

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESIS

The null hypothesis for the primary efficacy endpoint of change from baseline in the ALSFRS-R total score to Week 24 is that there is no treatment difference between SAR443820 and placebo, and the alternative hypothesis is that there is a between-treatment difference.

To strongly control the Type 1 error rate for the study, a hierarchical testing procedure will be applied at a 2-sided 5% significance level, ie, each hypothesis will be formally tested only if the preceding one is significant at the 5% level. If SAR443820 is significant for the primary endpoint, a selective set of secondary endpoints will be tested following the hierarchical testing procedure. The complete list of the secondary endpoints that will be adjusted for multiplicity with their testing order will be detailed in the SAP prior to database lock or any interim analysis, if applicable.

The study will be declared positive if the null hypothesis for primary endpoint in Part A, change from baseline in the ALSFRS-R total score to Week 24 (end of Part A) for SAR443820 versus placebo is rejected in the primary analysis.

9.2 SAMPLE SIZE DETERMINATION

The proposed sample size (n = 261) provides an approximately 80% power to detect a 30% reduction in SAR443820 compared with placebo in the change of ALSFRS-R from baseline at Week 24, assuming a change of [redacted] points from baseline in ALSFRS-R in the placebo arm with a standard deviation of [redacted] points, and a 20% drop-out rate. Sample size is estimated via simulation with a 2-sided 5% significance level.

9.3 POPULATIONS FOR ANALYSES

The following populations for analyses are defined:

Table 6 - Populations for analyses

Population	Description
Screened	All participants who signed the ICF.
Randomized	All participants from the screened population who have been allocated to a randomized intervention by IRT regardless of whether the intervention was received.
Exposed	All screened participants who take at least 1 dose of the study intervention.
Intent-to-treat (ITT)	All randomized participants. Participants will be analyzed according to the intervention allocated by randomization.
Safety	All randomized participants who receive at least 1 dose (including partial dose) of the study intervention.
Pharmacokinetic (PK)	All randomized participants who receive at least 1 dose of the study intervention and have at least 1 PK assessment with adequate documentation of dosing and sampling dates and times. Participants will be analyzed according to the intervention they actually received.

ICF = informed consent form; IRT = interactive response technology; ITT = intent-to-treat; PK = pharmacokinetic

9.4 STATISTICAL ANALYSES

The SAP will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints in Part A and primary endpoint in Part B.

9.4.1 General considerations

The baseline values of NfL, CHI3L1, the cytokine and chemokine panel in serum, sTREM2 in plasma and $p75^{ECD}$ in urine, are defined as the average value from samples collected at the screening visit and at Day 1 prior to the first dose of the study intervention. For the other assessments, the baseline value is defined as the last nonmissing value before the first dose of study intervention.

Typically, continuous variables will be summarized by the mean, median, standard deviation (SD), first and third quartiles, minimum, and maximum; categorical variables will be summarized by the number and percentage of participants in each category. For estimates from statistical models for the primary and key secondary endpoints, estimates with the standard error (SE), 95% CI, and p-value will be determined.

9.4.2 Primary endpoint(s) in Part A

The primary efficacy endpoint is change from baseline in the ALSFRS-R total score to Week 24.

Estimands

The **primary estimand** will be the difference (SAR443820 vs placebo) in the mean change from baseline in the ALSFRS-R score estimated from baseline to Week 24 in the ITT population regardless of whether participants completed the treatment period. This estimand corresponds to a “treatment policy strategy” and will be using all available data and missing data will be not imputed.

The **secondary estimand** will be the difference (SAR443820 vs placebo) in the mean change from baseline in the ALSFRS-R score estimated in the ITT population during the treatment-emergent period. This estimand corresponds to a “while on treatment strategy.” This estimand will be considered for describing the effect of treatment as long as participants adhere to their randomized treatment.

Primary analysis

The primary analysis will be based on the primary estimand, which includes data collected for the primary endpoint for all participants included in the ITT population.

An MMRM will be fitted to change from baseline in the ALSFRS-R, which will include the fix effects of treatment (SAR443820 or placebo), visit (as a categorical variable), baseline ALSFRS-R score, baseline NfL, randomization strata of the geographic region of the study site, ALS onset region (bulbar or other areas), use of riluzole (yes or no), use of edaravone (yes or no),

use of the combination of sodium phenylbutyrate and taurursodiol (yes vs no), treatment-by-visit interaction, baseline NfL-by-visit interaction, and baseline ALSFRS-R score-by-visit interaction.

The least squares mean difference in the ALSFRS-R change from baseline at Week 24 between SAR443820 vs placebo, together with the p-value and the 95% CI for the difference, will be estimated from the MMRM model using weights for each stratum equal to the overall proportion of participants in each stratum (ie, "population weight").

This model will be implemented using the SAS MIXED procedure with an unstructured correlation matrix to model the within-participant errors. Parameters will be estimated using the restricted maximum likelihood method. The denominator degrees of freedom will be estimated using the Kenward-Roger approximation. This model will provide baseline adjusted least-squares means estimates at Week 24 for SAR443820 and placebo, together with their corresponding standard errors and CIs.

Subgroup analysis will be specified in the SAP.

9.4.3 Secondary endpoint(s) in Part A

The key secondary efficacy endpoints include the CAFS at Week 24, and change from baseline in SVC, change from baseline in muscle strength, ALSAQ-5, and serum NfL to Week 24. All secondary efficacy endpoints will be analyzed based on the ITT population.

For continuous variables, an MMRM approach under the MAR assumption will be used. This model will include the fixed effect of treatment (SAR443820 or placebo), visit as a categorical variable, baseline value of the endpoint, baseline NfL (if different from the baseline value of the enpoint), randomization strata of the geographic region of the study site, ALS onset region (bulbar or other areas), use of riluzole (yes or no), use of edaravone (yes or no), use of the combination of sodium phenylbutyrate and taurursodiol (yes vs no), treatment-by-visit interaction, and baseline value of the endpoint-by-visit interaction and baseline NfL-by-visit interaction (if different from the baseline value of the endpoint-by-visit interaction). The primary comparison of interest will be the difference between SAR443820 and placebo at Week 24, carried out using contrast within the treatment-by-time interaction term. Available data will be used for all secondary analyses.

To have strong control of the Type I error rate, a closed sequential testing approach will be used. The order of the secondary efficacy endpoints and all the details of sequential testing will be specified in the full SAP. The details of the analysis for other secondary endpoints will be outlined in the full SAP.

9.4.4 Primary endpoint in Part B

The primary endpoint in Part B is the CAFS at Week 52. The CAFS for each participant is the sum of all pairwise rankings based on survival data and change from baseline in ALSFRS-R score at Week 52 (15). The comparison of the CAFS will be conducted between the participants who are treated with SAR443820 and placebo in Part A. A Wilcoxon rank sum test will be used to compare these 2 groups. Different approaches handling missing data will be used in the sensitivity analysis and details will be described in the SAP.

9.4.5 Tertiary endpoints

Methods for analysis of tertiary endpoints will be included in the SAP. A matched analysis using data from the Phase 3 clinical trial for Ceftriaxone (NCT00349622) as a historical control might be conducted to demonstrate the superiority of SAR443820 on slowing down disease progression and prolonging survival over 104 weeks of treatment period.

9.4.6 Safety analysis

All safety analyses will be performed with the safety population. Safety summaries will be based on descriptive statistics, presented by treatment group. No statistical testing will be performed for safety analyses.

Safety analyses will be based on the reported AEs and other safety data, including clinical laboratory data, vital signs, and ECG. All AEs reported in the trial will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) with a version in effect at the time of the database lock.

9.4.6.1 Adverse events

General common rules for adverse events

The AEs that developed, worsened or became serious during the study observation period will be used for safety analysis. The safety observation period will be divided into 3 phases:

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

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

Summaries will be provided for all grades combined and for Grades ≥3 (including Grade 5). Missing grades, if any, will be included in the “all grades” category.

Analysis of all adverse events

Adverse event incidence table with the number and the percentage of participants with at least 1 event will be provided by treatment group for: all TEAEs, all treatment-emergent AESI (defined with a preferred term (PT) or a prespecified grouping), all treatment-emergent SAEs, all TEAEs leading to permanent treatment discontinuation and death. Multiple occurrences of the same event in the sample participant will be counted once in the summary.

Deaths will also be analyzed.

9.4.6.2 Laboratory variables, vital signs and electrocardiograms (ECGs)

Quantitative analyses

For laboratory variables, vital signs and ECG variables, descriptive statistics by treatment group for results and changes from baseline will be provided for each scheduled visit during the treatment period.

Analyses according to potential clinically significant abnormality (PCSA)

Potentially clinically significant abnormality (PCSA) analyses will be performed based on the PCSA list currently in effect at Sanofi at the time of the database lock.

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

For laboratory variables, vital signs and ECG variables, the incidence of participants with at least 1 PCSA during the treatment-emergent period will be summarized regardless of the baseline level and according to the following baseline status categories:

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

For ECG, the incidence of participants with at least 1 abnormal ECG during the treatment-emergent period will be summarized regardless of the baseline level and according to the following baseline status categories:

- Normal/missing
- Abnormal

9.4.6.3 Product complaints

Product complaints will be summarized in the safety population.

9.4.7 Other analysis

The population PK analyses will be presented separately from the main clinical study report (CSR).

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 9 (Section 10.9).

9.5 INTERIM ANALYSES

A nonbinding interim analysis for futility may be conducted when approximately 40% of the participants complete Part A, the double-blind placebo-controlled period. If both stopping criteria for change from baseline in the ALSFRS-R total score to Week 24 and change from baseline in NfL to Week 24 are met, the futility may be declared. An independent statistical group, external to the Sponsor, will conduct the IA and support the DMC activities. At the time of the IA, if the DMC recommends the study to continue, the Sponsor will be informed of the decision without receiving any unblinded results. Only if the DMC considers recommending the study to stop for futility, will a prespecified limited number of the Sponsor's senior management team be informed of the unblinded results. This limited Sponsor's senior management team will decide to stop or continue the study. No one involved in the conduct of the study will have access to the unblinded data. Interim analysis details, including the futility criteria and dissemination plan, will be provided in the SAP.

A second interim analysis will be performed when all patients complete the double-blind randomization period (from baseline to Week 24). An interim CSR containing all efficacy and safety results for Part A will be prepared.

An additional interim analysis during Part B may be performed at Sponsor's discretion.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1 Regulatory and ethical considerations

A) This study will be conducted in accordance with the protocol and with the following:
   - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and the applicable amendments and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
   - Applicable ICH-GCP Guidelines
   - Applicable laws and regulations (eg, data protection laws such as the General Data Protection Regulation - GDPR)

B) The protocol, protocol amendments, ICF, IB, IDFU, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.

C) 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.

D) Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

E) The Investigator will be responsible for the following:
   - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
   - Determining whether an incidental finding (as per Sanofi policy) should be returned to a participant and, if it meets the appropriate criteria, to ensure the finding is returned (an incidental finding is a previously undiagnosed medical condition that is discovered unintentionally and is unrelated to the aims of the study for which the tests are being performed). The following should be considered when determining the return of an incidental finding:
     - The return of such information to the study participant (and/or his/her designated healthcare professional, if so designated by the participant) is consistent with all applicable national, state, or regional laws and regulations in the country where the study is being conducted, and
     - The finding reveals a substantial risk of a serious health condition or has reproductive importance, AND has analytical validity, AND has clinical validity.
     - The participant in a clinical study has the right to opt out of being notified by the Investigator of such incidental findings. In the event that the participant has opted out of being notified and the finding has consequences for other individuals, eg, the

finding relates to a communicable disease, Investigators should seek independent ethical advice before determining next steps.
    - In case the participant has decided to opt out, the Investigator must record in the site medical files that she/he does not want to know about such findings.
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

As applicable, according to Directive 2001/20/EC, the Sponsor will be responsible for obtaining approval from the Competent Authorities of the EU Member States and/or Ethics Committees, as appropriate, for any amendments to the clinical trial that are deemed as "substantial" (ie*,* changes which are likely to have a significant impact on the safety or physical or mental integrity of the clinical trial participants or on the scientific value of the trial) prior to their implementation.

10.1.2 Financial disclosure

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

10.1.3 Informed consent process

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

- A copy of the ICF(s) must be provided to the participant or their legally authorized representative, where applicable.
- Please refer to Section 10.8.2 for participants from Germany.

Participants who are rescreened are required to sign a new ICF.

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

10.1.4 Data protection

All personal data collected and/or processed in relation to this study will be handled in compliance with all applicable Privacy & Data Protection laws and regulations, including the 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 they are required by regulatory agencies (eg, on Japanese population for the Pharmaceuticals and Medical Devices Agency in Japan). They will not be collected in the countries where this is prohibited by local regulation.

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor or its service providers will be identifiable only by the unique identifier; participant names or any information which would make the participant identifiable will not be transferred to the Sponsor.
- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with applicable data protection laws. The level of disclosure must also be explained to the participant as described in the informed consent.

- 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.
- 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 precontractual relationship. They may be communicated to any company of the Sanofi group ("Sanofi") or to Sanofi service providers, where needed.
- Personal data can be processed for other studies and projects. At any time, objection to processing can be made by contacting the Sanofi Data Protection Officer (link available at Sanofi.com).
- In case of refusal to the processing of personal data by or on behalf of Sanofi, it will be impossible to involve the professionals in any Sanofi study. In case the professionals have already been involved in a Sanofi study, they will not be able to object to the processing of their personal data as long as they are required to be processed by applicable regulations. The same rule applies in case the professionals are listed on a regulatory agencies disqualification list.
- Personal data can be communicated to the following recipients:
  - Personnel within Sanofi or partners or service providers involved in the study
  - Judicial, administrative and regulatory authorities, in order to comply with legal or regulatory requirements and/or to respond to specific requests or orders in the framework of judicial or administrative procedures. Contact details and identity may also be published on public websites in the interest of scientific research transparency
- Personal data may be transferred towards entities located outside the Economic European Area, in countries where the legislation does not necessarily offer the same level of data protection or in countries not recognized by the European Commission as offering an adequate level of protection. Those transfers are safeguarded by Sanofi in accordance with the requirement of European law including, notably:
  - The standard contractual clauses of the European Commission for transfers towards our partners and service providers
  - Sanofi's Binding Corporate Rules for intra-group transfers
- Professionals have the possibility to lodge a complaint with Sanofi leading Supervisory Authority, the "Commission Nationale de l'Informatique et des Libertés" (CNIL) or with any competent local regulatory authority.
- Personal data of professionals will be retained by Sanofi for up to thirty (30) years, unless further retention is required by applicable regulations.

- In order to facilitate the maintenance of Investigators personal data, especially if they contribute to studies sponsored by several pharmaceuticals companies, Sanofi participates in the Shared Investigator Platform (SIP) and in the TransCelerate Investigator Registry (IR) project (https://transceleratebiopharmainc.com/initiatives/investigator-registry/). Therefore, personal data will be securely shared by Sanofi with other pharmaceutical company members of the TransCelerate project. This sharing allows Investigators to keep their data up-to-date once for all across pharmaceutical companies participating in the project, with the right to object to the transfer of the data to the TransCelerate project.
- Professionals have the right to request the access to and the rectification of their personal data, as well as their erasure (where applicable) by contacting the Sanofi Data Protection Officer: Sanofi DPO - 54 rue La Boétie - 75008 PARIS - France (to contact Sanofi by email, visit https://www.sanofi.com/en/our-responsibility/sanofi-global-privacy-policy/contact).

10.1.5 Committee structure

10.1.5.1 Study Steering Committee

A study Steering Committee, composed of 5 experts in the field of ALS, will advise the Sponsor on the study design and conduct. In collaboration with the Sponsor, the committee will provide scientific leadership to the study to ensure that the highest standards are maintained. Details describing the committee processes and procedures are outlined in the Steering Committee charter.

10.1.5.2 Independent Data Monitoring Committee (DMC)

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

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

10.1.6 Dissemination of clinical study data

Study participants

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

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

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

Professionals involved in the study or in the drug development program

Sanofi undertakes the legal obligation to disclose the full name of the Investigator and his/her affiliated institute/ hospital's name and location on the China Trial Disclosure website as required by the National Medical Products Administration (NMPA) in its guidance "Drug Clinical Trial Registration and Information Disclosure Management Practice (Trial Implementation), requesting name disclosure of Chinese and foreign investigational sites and Investigators in any eligible clinical trial.

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

10.1.7 Data quality assurance

- All participant data relating to the study will be recorded on printed or eCRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF. The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Quality tolerance limits (QTLs) will be predefined to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined parameters will be monitored during the study, and important deviations from the QTLs and remedial actions taken will be summarized in the CSR.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or onsite monitoring) are provided in separate study documents.

- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).
- 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 case report form (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 the study manual.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH-GCP, and all applicable regulatory requirements.

10.1.9 Study and site start and closure

First act of recruitment

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

The first act of recruitment is the first site open and will be the study start date.

Study/Site termination

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

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

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

- For study termination:
  - Information on the product leads to doubt as to the benefit/risk ratio
  - Discontinuation of further study intervention development
- For site termination:
  - Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
  - Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the Investigator
  - Total number of participants included earlier than expected

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

10.1.10 Publication policy

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

10.2 APPENDIX 2: CLINICAL LABORATORY TESTS

- The tests detailed in Table 7 will be performed by the central laboratory.
- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be recorded.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Table 7 - Protocol-required laboratory tests

Laboratory tests	Parameters
Hematology	
	Platelet count
	Red blood cell (RBC) count
	Hemoglobin
	Hematocrit
	RBC indices:
	Mean corpuscle volume (MCV)
	Mean corpuscle hemoglobin (MCH)
	%Reticulocytes
	White blood cell (WBC) count with differential:
	Neutrophils
	Lymphocytes
	Monocytes
	Eosinophils
	Basophils
Clinical chemistry[a]	
	Blood urea nitrogen (BUN)
	Creatinine
	Glucose[b]
	Potassium
	Sodium
	Calcium
	Aspartate aminotransferase (AST)/ Serum glutamic-oxaloacetic transaminase (SGOT)
	Alanine aminotransferase (ALT)/ Serum glutamic-pyruvic transaminase (SGPT)
	Alkaline phosphatase[c]
	Albumin
	Creatine phosphokinase (at screening visit only)
	Total and direct bilirubin
	Total protein
Routine urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal)
Pregnancy testing	• Serum or highly sensitive urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[d]

Laboratory tests	Parameters
Other screening tests	• Follicle-stimulating hormone (FSH) and estradiol (as needed in women of non-childbearing potential only) • Serology (human immunodeficiency virus [HIV] antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody or specify other tests) • All study-required laboratory tests will be performed by a central laboratory.

NOTES :

a Details of liver chemistry stopping criteria and required actions and follow-up are given in Appendix 6 (Section 10.6) [Liver and other safety. Suggested actions and follow-up assessments [and study intervention rechallenge guidelines]. All events of ALT >3 × ULN, which may indicate liver injury, must be reported to Sponsor in an expedited manner (refer to the section on AESIs [Section 8.3.8]). Clinical laboratory findings of ALT >3 ULN and bilirubin >2 × ULN (>35% direct bilirubin), which may suggest severe liver injury (possible Hy's Law), must be reported to Sponsor in an expedited manner.

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

c If alkaline phosphatase is elevated, consider fractionating.

d Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

Investigators must document their review of each laboratory safety report.

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

10.3.1 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a 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.

Definition of unsolicited and solicited AE

- An unsolicited AE is an AE that was not solicited using a participant diary and that is communicated by a participant who has signed the informed consent. Unsolicited AEs include serious and non-serious AEs.
- Potential unsolicited AEs may be medically attended (ie, symptoms or illnesses requiring a hospitalization, or emergency room visit, or visit to/by a health care provider). The participants will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of participant concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records.
- Unsolicited AEs that are not medically attended nor perceived as a concern by participant will be collected during interview with the participants and by review of available medical records at the next visit.
- Solicited AEs are predefined systemic events for which the participant is specifically questioned.

Events meeting the AE definition

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

Events NOT meeting the AE definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant’s condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant’s condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2 Definition of SAE

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

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

D) Results in persistent or significant disability/incapacity

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

E) Is a congenital anomaly/birth defect

F) Is a suspected transmission of any infectious agent via an authorized medicinal product

G) Other situations:

- Medical or scientific judgment should be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.
  - Note: The following list of medically important events is intended to serve as a guideline for determining which condition has to be considered as a medically important event. The list is not intended to be exhaustive:
- Intensive treatment in an emergency room or at home for:
  - Allergic bronchospasm
  - Blood dyscrasias (ie, agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia, etc)
  - Convulsions

- Development of drug dependence or drug abuse
- ALT >3 × ULN + total bilirubin >2 × ULN or asymptomatic ALT increase >10 × ULN
- Suicide attempt or any event suggestive of suicidality
- Syncope, loss of consciousness (except if documented as a consequence of blood sampling)
- Bullous cutaneous eruptions

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

AE and SAE recording

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

Assessment of intensity

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

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

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

Assessment of causality

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than that a relationship cannot be ruled out.

- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The Investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to the Sponsor'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 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

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

10.3.4 Reporting of SAEs

SAE reporting to the Sponsor via an electronic data collection tool

- The primary mechanism for reporting an SAE to the Sponsor's representative will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.

- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the Sponsor's representative by telephone.
- Contacts for SAE reporting can be found in the Investigator Study File.

SAE reporting to the Sponsor via paper data collection tool

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

10.4 APPENDIX 4: CONTRACEPTIVE AND BARRIER GUIDANCE

10.4.1 Definitions

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

- A postmenopausal state is defined as the period of time after a woman has experienced no menses for 12 consecutive months without an alternative medical cause.
- A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT).
- Females on HRT and whose menopausal status is in doubt will be required to use 1 of the nonestrogen hormonal highly effective contraception methods if they want to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Permanent sterilization methods include:

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

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

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

10.4.2 Contraception guidance

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

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:

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

- Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)[c]
- Bilateral tubal occlusion
- Documented azoospermic partner (vasectomized or due to a medical cause)
  Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
  Note: Documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

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

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c]
  - oral
  - intravaginal
  - transdermal
  - injectable
- Progestogen-only hormone contraception associated with inhibition of ovulation[c]
  - oral
  - injectable
- Sexual abstinence
  Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

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

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

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

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

For male study participants whose partner is a WOCBP, a barrier method, ie, a male condom or a female barrier contraceptive (eg, a cervical cap, diaphragm or sponge), in combination with a spermicide, is acceptable in this study. Male participants should be advised of the benefit for a female partner who is a WOCBP to use a highly effective method of contraception.

COLLECTION OF PREGNANCY INFORMATION:

Male participants with partners who could 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 the IMP.
- 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 could become pregnant

- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial 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 for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at 22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any poststudy pregnancy related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section 8.3.4. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue the study intervention or be withdrawn from the study.

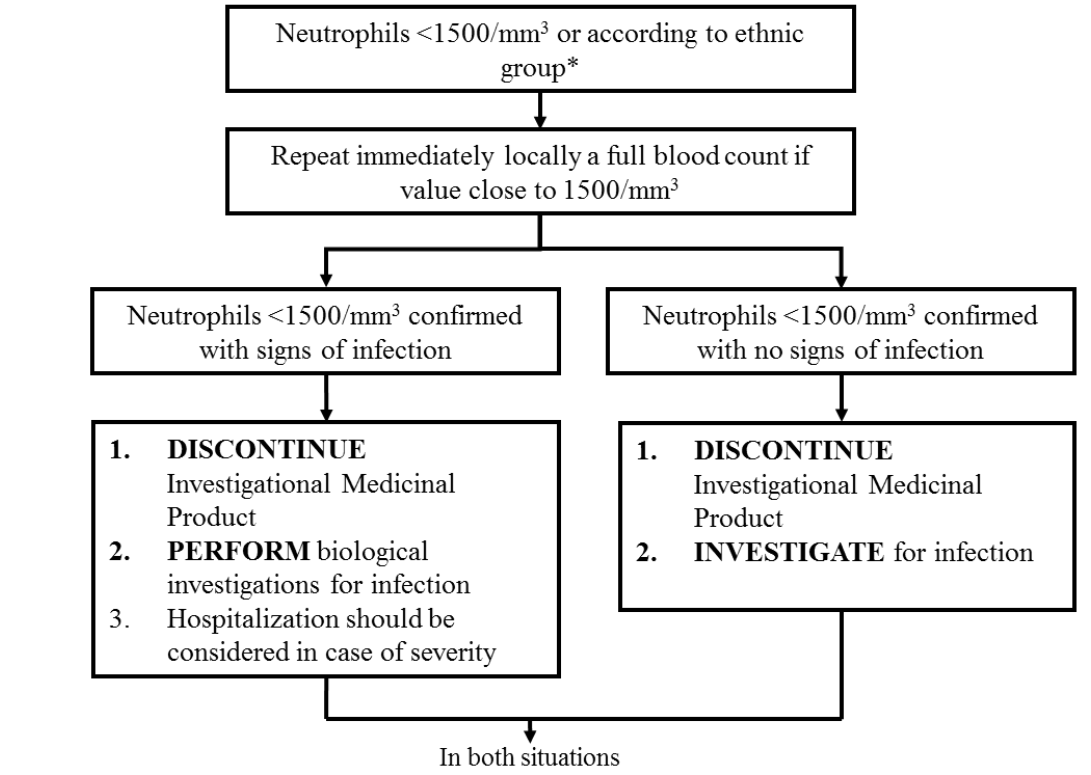
10.5 APPENDIX 5: GENETICS

Please refer to Section 8.5 for related information on an optional single blood collection for the isolation of DNA.

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

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

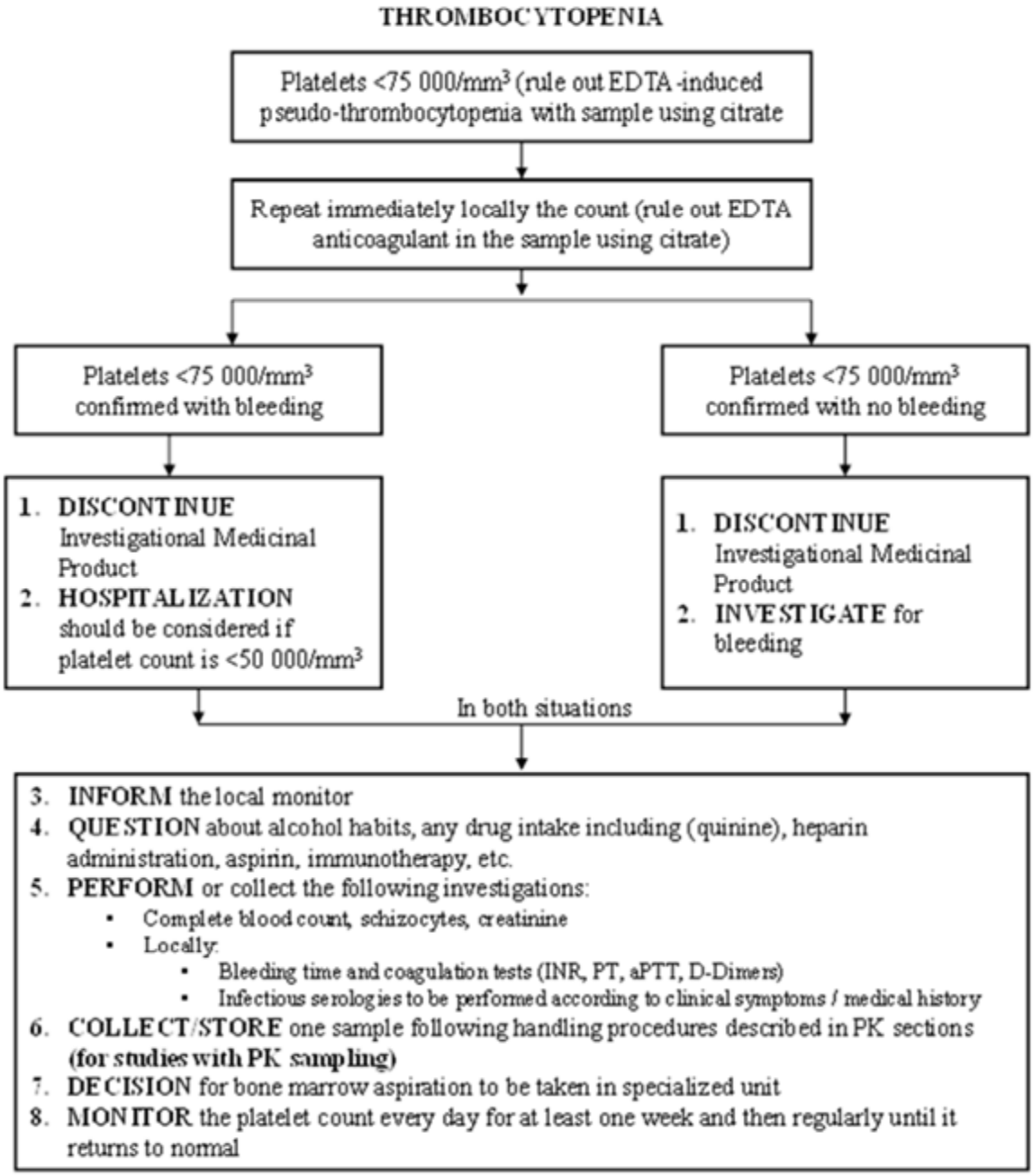
NEUTROPENIA



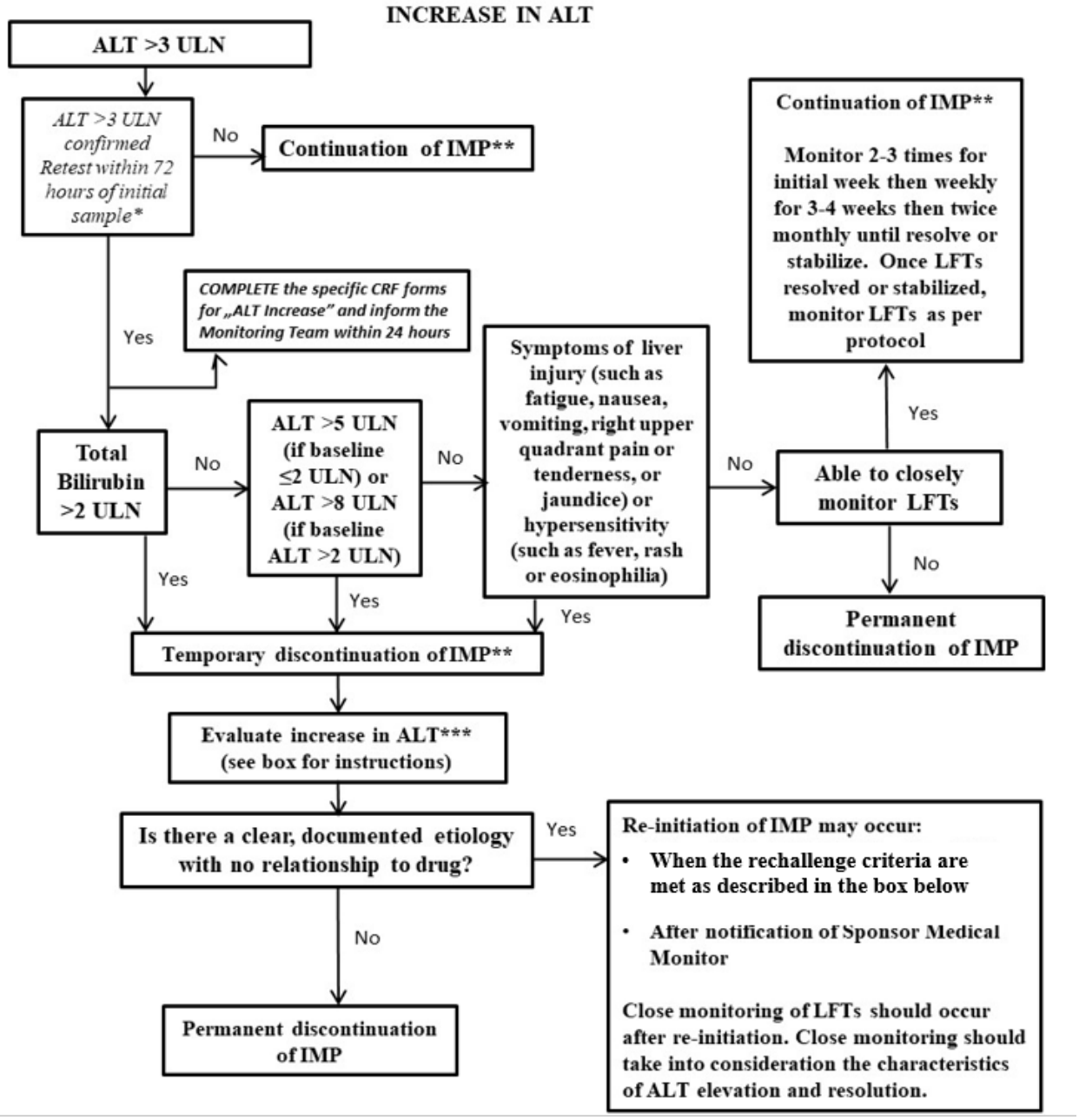
3. **INFORM** the local monitor
4. **INVESTIGATE** previous treatments particularly long-term, even a long time ago, exposure to toxic agents, e.g., benzene, X-rays, etc.
5. **PERFORM** and collect the following investigations (results):
   - RBC and platelet counts, Absolute Neutrophil Count (ANC)
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

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

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



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

** Unless a protocol-defined criterion for permanent discontinuation is met.

*** See box below

Note:

• "Baseline" refers to ALT sampled at baseline visit; or if baseline value unavailable, to the latest ALT sampled before the baseline visit. The algorithm does not apply to the instances of increase in ALT during screening.

• See Section 10.3 for guidance on safety reporting.

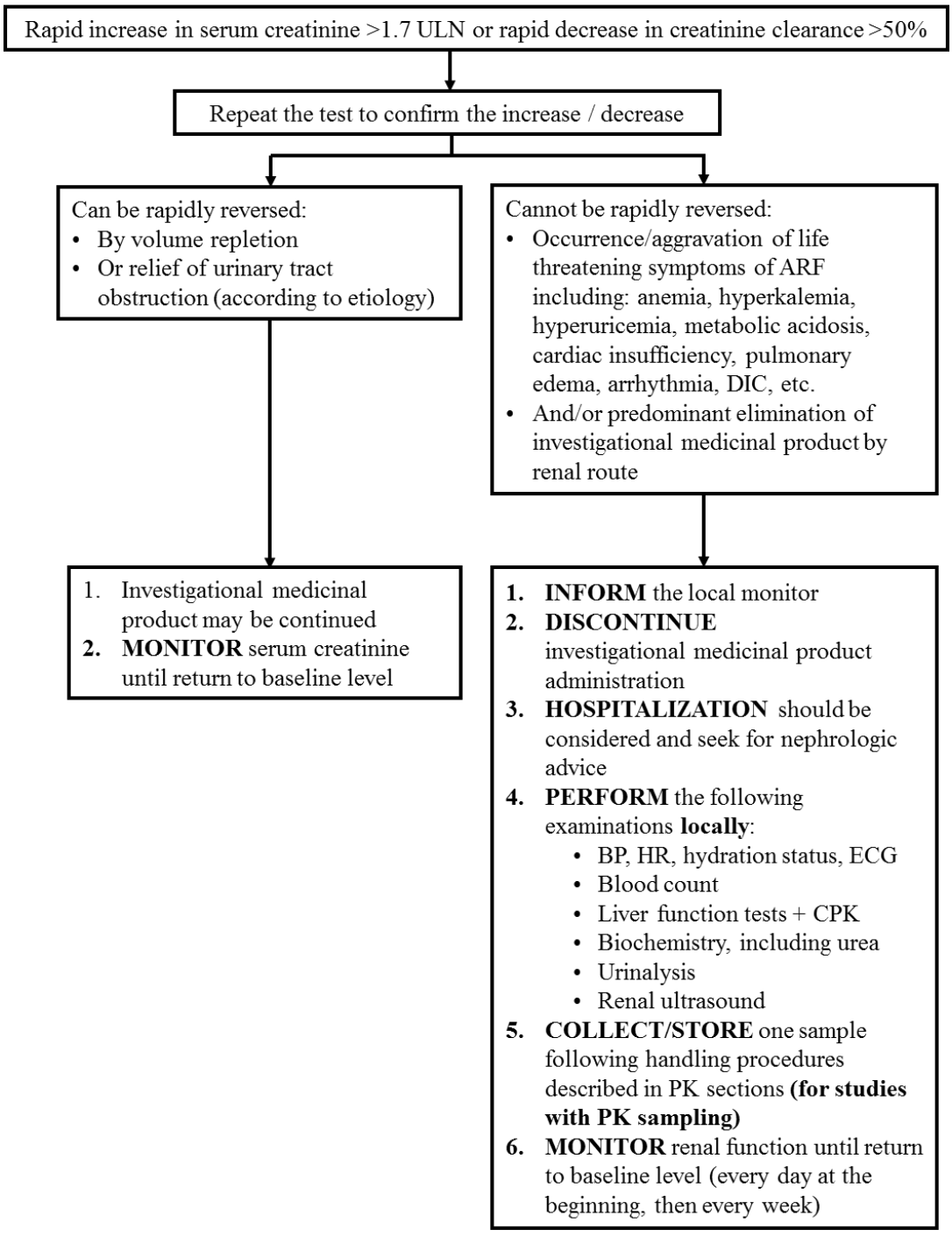
In ANY CONFIRMED CASE of ALT >5 × ULN, the following steps are REQUIRED (recommended for ALT between 3 - 5 × ULN, as clinically indicated):

- **INFORM** the Site Monitor who will forward the information to the Study Manager
- **INVESTIGATE** specifically for malaise with or without loss of consciousness, dizziness, and/or hypotension and/or episode of arrhythmia in the previous 72 hours; rule out muscular injury
- INVESTIGATE if any recent alcohol use or travel
- INVESTIGATE if any use of non-prescription medications including herbal or dietary supplements
- **PERFORM** the following tests:
- Liver function test (LFT): AST, ALT, alkaline phosphatase, total and conjugated bilirubin, gamma-glutamyl transferase, and prothrombin time (PT)/international normalized ratio (INR)
- CPK, serum creatinine, complete blood count
- Anti-Hepatitis A virus IgM, Hepatitis B surface antigen, anti-Hepatitis B core IgM, (Hepatitis B virus-DNA if clinically indicated), anti-Hepatitis C virus (HCV) and HCV RNA, and anti-Hepatitis E virus IgM antibodies
- Auto-antibodies: antinuclear, antineutrophil cytoplasmic antibodies, anti-double stranded DNA, anti-smooth muscle, anti-liver kidney microsome, anti-mitochondrial
- Evaluate recent infection with Epstein-Barr virus, cytomegalovirus, herpes viruses. Depending on the clinical context, consider testing for toxoplasma
- Iron, ferritin, transferrin saturation
- **Collect and freeze** serum sample (5 mL × 2)
- Collect and store one PK sample following the instructions in the central laboratory manual
- Hepatobiliary ultrasonography is mandatory (and other imaging investigations, as indicated).
- **CONSIDER** DNA test for Gilbert's disease if clinically indicated
- **CONSIDER** consulting with a hepatologist (mandatory if ALT >8 x ULN or is associated with elevated bilirubin)
- **CONSIDER** patient hospitalization if INR >2 (or PT <50%) and/or CNS disturbances suggesting hepatic encephalopathy
- MONITOR LFTs after permanent discontinuation of IMP:

- Monitor as closely as possible (every 2-3 days) every week until ALT is down-trending, then every week until ALT is < 2 × ULN, and then every scheduled visit.
- This frequent LFT monitoring may be done through central or local lab, or via home visit (depending on the Investigator's assessment and/or local regulatory requirements).

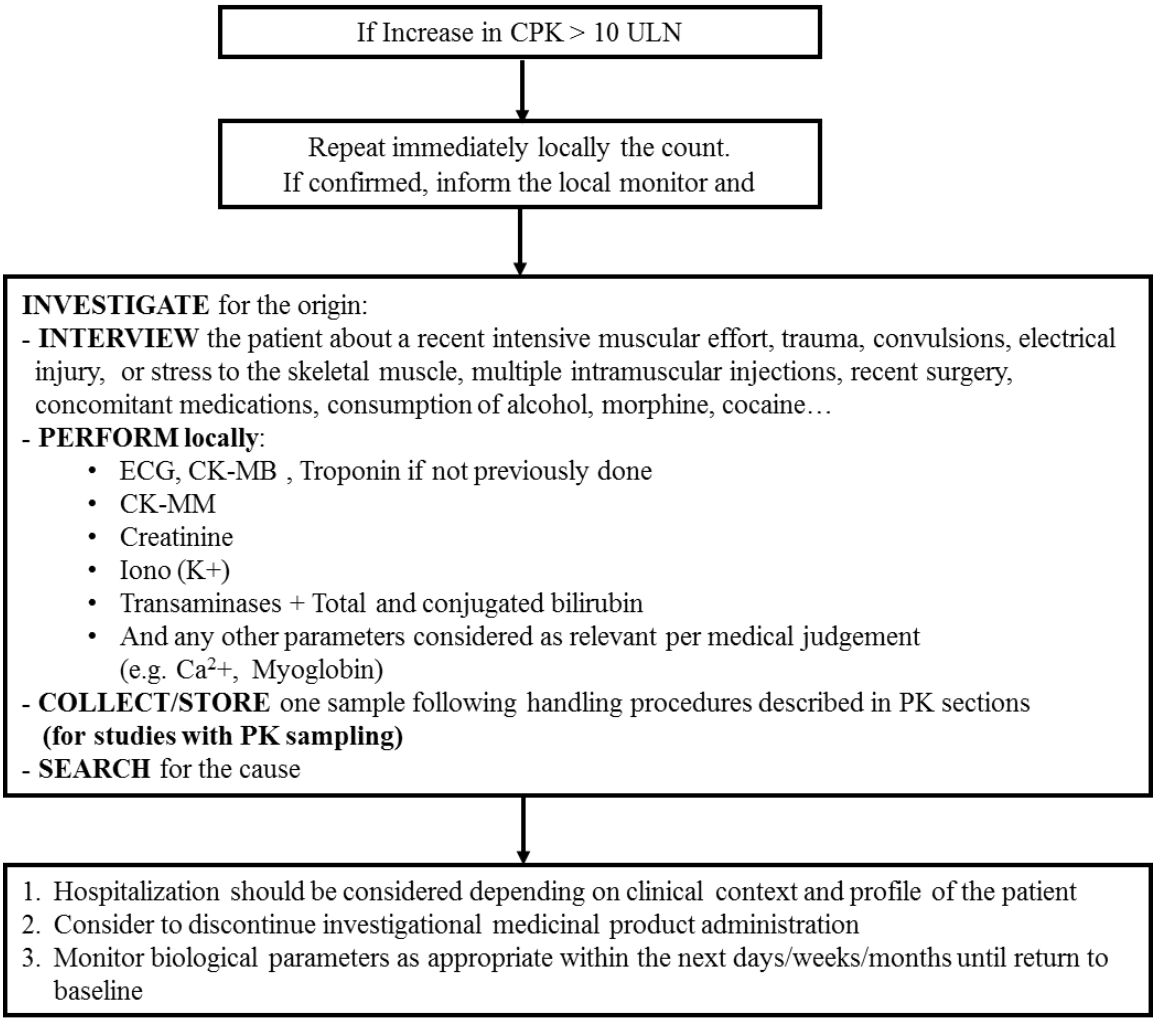
  - **Rechallenge**: Reinitiation of the study drug can only be considered when the ALT and AST both decrease below 2 × ULN (if baseline ALT ≤2 x ULN) or below baseline levels (if baseline ALT > 2 × ULN) and there is no clinical contraindication. In case the Investigator decides to restart the study drug, it is recommended that ALT/AST be assessed weekly for the first month and then monthly for the second and third months. The occurrence of new elevation above 3 × ULN for the ALT or AST values will lead to permanent discontinuation of the study drug. If liver injury is confirmed and determined to be related to the IMP, the rechallenge with the IMP is not permitted, and the participants must be permanently discontinued from IMP treatment.

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



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

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



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

10.7 APPENDIX 7: AES, ADES, SAES, SADES, USADES AND DEVICE DEFICIENCIES: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING IN MEDICAL DEVICE STUDIES

Not applicable.

10.8 APPENDIX 8: COUNTRY-SPECIFIC REQUIREMENTS

The primary objectives and endpoints for both study parts will be unchanged for participants in China. The [redacted] and urine p75ECD will not be measured in China.

10.8.1 China

10.8.1.1 Study objectives and endpoints

Part A

Objectives	Endpoints
Primary	
• To assess the effect of SAR443820 compared to placebo in reducing ALS progression as measured by Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS-R)	• Change from baseline in the ALSFRS-R total score to Week 24
Secondary	
• To assess the effect of SAR443820 compared to placebo on a combined assessment of function and survival, respiratory function, muscle strength, and quality of life (QoL)	• Combined assessment of the function and survival (CAFS) score at Week 24 • Change from baseline in slow vital capacity (SVC) to Week 24 • Change from baseline in muscle strength to Week 24 • Change from baseline in Amyotrophic Lateral Sclerosis Assessment Questionnaire (ALSAQ-5) to Week 24
• To assess the pharmacodynamic (PD) effect of SAR443820 compared to placebo on a key disease biomarker	• Change from baseline in serum neurofilament light chain (NfL) to Week 24
• To assess the safety and tolerability of SAR443820 compared to placebo	• Incidence of adverse events (AE), serious adverse events (SAE), treatment-emergent adverse events (TEAE), potentially clinically significant abnormalities (PCSA) in laboratory tests, electrocardiogram (ECG), and vital signs over 24 weeks
• To assess the pharmacokinetics (PK) of SAR443820	• Plasma concentration of SAR443820
Tertiary	
[redacted]	[redacted]
• To assess the effects of SAR443820 compared to placebo on other neurodegeneration and inflammation biomarkers	• Change from baseline in soluble triggering receptor expressed on myeloid cells-2 (sTREM2) in plasma, chitinase-3-like protein-1 (CHI3L1), and a selected panel of cytokines and chemokines in serum to Week 24

Part B

Objectives	Endpoints
Primary	
• To assess the long-term effects of SAR443820 on function and survival	• Combined assessment of the function and survival (CAFS) score at Week 52
Secondary	
• To assess the long-term effects of SAR443820 on disease progression, survival, respiratory function, and quality of life (QoL)	• Combined assessment of the function and survival (CAFS) score at Week 76 and Week 104 • Change from baseline in the ALSFRS-R total score to Week 52, Week 76, and Week 104 • Time from baseline to the occurrence of either death or permanent assisted ventilation (>22 hours daily for >7 consecutive days), whichever comes first • Time from baseline to the occurrence of death • Change from baseline in slow vital capacity (SVC) to Week 52, Week 76, and Week 104 • Change from baseline in Amyotrophic Lateral Sclerosis Assessment Questionnaire (ALSAQ-5) to Week 52, Week 76, and Week 104
• To assess the long-term effect of SAR443820 on a key disease biomarker	• Change from baseline in serum neurofilament light chain (NfL) to Week 52
• To assess the long-term safety and tolerability of SAR443820	• Incidence of adverse events (AE), serious adverse events (SAE), treatment-emergent adverse events (TEAE), potentially clinically significant abnormalities (PCSA) in laboratory tests, electrocardiogram (ECG), and vital signs during Part B
• To assess the pharmacokinetics (PK) of SAR443820	• Plasma concentration of SAR443820
Tertiary	
[redacted] SAR443820 [redacted]	[redacted]
[redacted] SAR443820 [redacted]	[redacted]

The content of this section supersedes the content in Section 3 for the study conducted in China.

10.8.1.2 Sample storage and disposition of samples after study completion

Blood samples for storage to support additional tertiary objectives beyond those in the study protocol will not be collected for participants in China.

All samples from participants in China will be disposed of following completion of the CSR.

10.8.2 Germany

Informed consent process: All references to "legally authorized representative" are not applicable in Germany; only participants who can give written consent themselves are included in the study. References to "legally authorized representative" are found in Section 8.3 and Section 10.1.3.

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

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

The following contingencies may be implemented for the duration of the emergency (after Sponsor agreement is obtained).

Study intervention

The following contingencies may be implemented to make clinical supplies available to the participant for the duration of the emergency:

- DTP supply of the IMP from the PI/site/Sponsor where allowed by local regulations and agreed upon by the participant.

If a participant has to stop the IMP due to a regional or national emergency (eg, coronavirus disease-2019 [COVID-19]), reinitiation of the study intervention will be done under close and appropriate clinical/and or laboratory monitoring and following the instructions provided in Section 7.1.2.

Study assessments and procedures

During the emergency, if the site will be unable to adequately follow protocol-mandated procedures, alternative treatment outside the clinical trial should be proposed, and screening/enrollment/administration of the study intervention may be temporarily delayed.

Attempts should be made to perform all assessments in accordance with the approved protocol to the fullest 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.

The following procedures are to be considered in the event of a regional or national emergency declared by a governmental agency:

- If onsite visits are not possible, remote visits (eg, with home nurses, a home health vendor, etc.) may be planned for the collection of possible safety and/or efficacy data, including 1) collection of samples for screening and clinical safety analyses, 2) ECG and vital signs assessments, 3) AEs, and 4) phone-based ALSFRS-R.
- If onsite visits are not possible, visit windows may be extended for assessments of safety and/or efficacy data that cannot be obtained remotely.
- Use of local site or laboratory locations may be allowed when central laboratory assessments cannot be performed due to a government declared national emergency.

Statistical analyses

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 of the emergency on efficacy (eg, missing data due to the emergency) and safety will be detailed in the SAP.

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 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 laboratories).

10.10 APPENDIX 10: STRONG AND MODERATE CYP3A4 INHIBITORS AND STRONG CYP3A4 INDUCERS

Table 8 - Strong and moderate CYP3A4 inhibitors and strong CYP3A4 inducers

Reason for exclusion	Compound (INN)	Therapeutic class	Wash out period (day)
Strong CYP3A4 inducer	Apalutamide	Antiandrogens	21
	Avasimibe	Other antilipemics	5
	Phenobarbital	Anticonvulsant	20
	Phenytoin	Anticonvulsant	14
	Rifampin	Antibiotics	14
	Rifapentine	Antibiotics	14
	St John's wort	Herbal medicine	14
	Carbamazepine	Anticonvulsant	14
	Enzalutamide	Antiandrogens	14
	Ivosidenib	Cancer treatment	19
	Lumacaftor	Cystic fibrosis treatment	14
	Mitotane	Other antineoplastics	90

Reason for exclusion	Compound (INN)	Therapeutic class	Wash out period (day)
Strong or moderate CYP3A4 inhibitor	ACT-539313	Hypnotic	2
	ACT17882	Renin inhibitor	5
	Amprenavir	Protease inhibitor	10
	Aprepitant	Antiemetics	3
	Atazanavir, atazanavir/ritonavir	Protease inhibitor	9
	Berotralstat	Cardiovascular drug	20
	Boceprevir	Antiviral	8
	Casopitant	Antiemetics	11
	Cenotavir/ritonavir	Antiviral	9
	Ceritinib	Kinase inhibitor	10
	Cimetidine	H-2 receptor antagonist	8
	Ciprofloxacin	Antibiotics	1
	Clarithromycin	Antibiotics	8
	Cobicistat	None	8
	Conivaptan	Diuretics	9
	Crizotinib	Kinase inhibitor	16
	Danoprevir/ritonavir	Antiviral	9
	Darunavir, darunavir/ritonavir	Protease inhibitor	11
	Diltiazem	Calcium channel blocker	8
	Dronedarone	Antiarrhythmic	14
	Duvelisib	Kinase Inhibitor	9
	Elvitegravir/ritonavir	AIDS treatment	10
	Erythromycin	Antibiotic	8
	Faldaprevir	Antiviral	15
	Fedratinib	Kinase inhibitor	31
	FK1706	Central nervous system agent	15
	Fluconazole	Antifungal	7
	Grapefruit juice	N/A	9
	Idelalisib	Kinase inhibitor	2
	Imatinib	Antineoplastic agent	12
	Indinavir, indinavir/ritonavir	Protease inhibitor	9
	Isavuconazole	Antifungal	27
	Istradefylline	Antiparkinsonian	25
	Itraconazole	Antifungal	12
	Josamycin	Antibiotic	1
	Ketoconazole	Antifungal	8
	LCL161	Cancer treatment	2
	Lefamulin	Antibiotic	2
	Letermovir	Antiviral	10
	Lonafarnib	Other	9
	Lopinavir, lopinavir/ritonavir	Protease inhibitor	9
	Mibefradil	Calcium channel blocker	12
	Mifepristone	Antiprogestins	25

Reason for exclusion	Compound (INN)	Therapeutic class	Wash out period (day)
	Nefazodone	Antidepressant	8
	Nelfinavir	Protease inhibitor	9
	Netupitant	Antiemetic	20
	Nilotinib	Kinase inhibitor	11
	Nirmatrelvir/ritonavir	Antiviral	9
	Posaconazole	Antifungal	14
	Ravuconazole	Antifungal	40
	Ribociclib	Kinase inhibitor	14
	Ritonavir	Protease inhibitor	9
	Saquinavir, saquinavir/ritonavir	Protease inhibitor	10
	Schisandra sphenanthera	Herbal medicine	21
	Telaprevir	Antiviral	10
	Telithromycin	Antibiotic	10
	Tipranavir/ritonavir	Protease inhibitor	9
	Tofisopam	Benzodiazepine	8
	Troleandomycin	Antibiotic	8
	Tucatinib	Kinase Inhibitor	9
	Verapamil	Calcium channel blocker	8
	Voriconazole	Antifungal	8
	Voxelotor	Hemoglobin inhibitor	8

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

10.11 APPENDIX 11: BLOOD VOLUME DETAILS

Part A

	Screening (mL)	Day 1 (mL)	Week 2 (mL)	Week 4 (mL)	Week 6 (mL)	DNA Sampling#* (mL)	Week 8 (mL)	Week 10 (mL)	Week 12 (mL)	Week 16 (mL)	Week 20 (mL)	Week 21 (mL)	Week 22 (mL)	Week 23 (mL)	Week 24 (mL)	E/D* visit (unscheduled) (mL)
China	24.5	26.5	7.5	5.5	2.5	NA	16.5	2.5	2.5	12.5	2.5	2.5	2.5	2.5	12.5	12.5
Other countries	26	26.5	7.5	5.5	2.5	2	16.5	2.5	2.5	12.5	2.5	2.5	2.5	2.5	12.5	12.5

Part B

	Week 28 (mL)	Week 30 (mL)	Week 32 (mL)	Week 34 (mL)	Week 36 (mL)	Week 40 (mL)	Week 44 (mL)	Week 52 (mL)	Week 64 (mL)	Week 76 (mL)	Week 88 (mL)	Week 104 (mL)	Last follow-up visit (mL)	E/D* visit (unscheduled) (mL)
All regions	11	2.5	2.5	2.5	9	2.5	9	9	5.5	5.5	5.5	5.5	5.5	9

Abbreviations: DNA: deoxyribonucleic acid; E/D: early discontinuation; NA: not applicable.
#Optional visit; can be performed at Week 2 or Week 4.
*Optional or unscheduled visit; not counted in the total blood volume.

Total blood volume including all required visits is approximately 202 mL in China and 198.5 mL in all other countries. Please note that there might be some additional blood withdrawal due to additional visit(s), retesting, or safety-related testing.

10.12 APPENDIX 12: ABBREVIATIONS

AD:	Alzheimer's disease
AE:	adverse event
AESI:	adverse event of special interest
ALS:	amyotrophic lateral sclerosis
ALSAQ-5:	Amyotrophic Lateral Sclerosis Assessment Scales - 5 items
ALSFRS-R:	Amyotrophic Lateral Sclerosis Functional Rating Scale Revised
ALT:	alanine aminotransferase
AST:	aspartate aminotransferase
AUC:	area under the curve
BID:	twice daily
BMI:	body mass index
CAFS:	combined assessment of function and survival
CHI3L1:	Chitinase-3-like protein 1
CI:	confidence interval
Cmax:	maximum plasma concentration
CNS:	central nervous system
CPK:	creatine phosphokinase
CSF:	cerebrospinal fluid
CSICF:	Core Study Informed Consent Form
CSR:	clinical study report
C-SSRS:	Columbia Suicide Severity Rating Scale
CYP:	cytochrome P450
DMC:	data monitoring committee
DRE:	disease-related event
DTP:	direct-to-patient
ECG:	electrocardiogram
eCRF:	electronic case report form
[redacted]	
[redacted]	
FDA:	Food and Drug Administration
FSH:	follicle-stimulating hormone
GCP:	Good Clinical Practice
GFAP:	glial fibrillary acidic protein
G-tube:	gastrostomy tube
HBcAb:	hepatitis B core antibodies
HBsAg:	Hepatitis B surface antigen
[redacted]	
HCV:	Hepatitis C virus
HIV:	human immunodeficiency virus
HRT:	hormonal replacement therapy
IB:	Investigator’s Brochure

ICF:	informed consent form
ICH:	International Council for Harmonisation
IEC:	Independent Ethics Committee
IMP:	investigational medicinal product
INR:	International normalized ratio
IP-10:	interferon gamma-induced protein-10
IRB:	Institutional Review Board
IRT:	interactive response technology
ITT:	intent-to-treat
IV:	intravenous
LFT:	Liver function test
MAD:	multiple ascending dose
MAR:	missing at random
MCP:	monocyte chemoattractant protein
MIP:	macrophage inflammatory protein
MLKL:	mixed lineage kinase domain-like pseudokinase
MMRM:	mixed-effect model with repeated measures
MS:	multiple sclerosis
NfL:	neurofilament light chain
NIMP:	noninvestigational medicinal product
NOAEL:	no-observed-adverse-effect-level
OPTN:	optineurin
p75ECD:	extracellular domain p75
PBMC:	peripheral blood mononuclear cell
PBPK:	physiological-based pharmacokinetic modeling and simulation
PCSA:	potentially clinically significant abnormality
PD:	pharmacodynamic
PICC:	peripherally inserted central catheter
PK:	pharmacokinetic
PRO:	patient-reported outcome
PT:	preferred term
PT:	Prothrombin Time
QoL:	quality of life
QTLs:	Quality tolerance limits
RIPK1:	receptor-interacting serine/threonine-protein kinase 1
RIPK3:	receptor-interacting serine/threonine-protein kinase 3
SAD:	single ascending dose
SAE:	serious adverse event
SAP:	Statistical Analysis Plan
SD:	standard deviation
SE:	standard error
SoA:	schedule of assessments
sTREM2:	soluble triggering receptor expressed on myeloid cells 2
SUSAR:	suspected unexpected serious adverse reaction
SVC:	slow vital capacity

TARC:	thymus- and activation-regulated chemokine
TBK1:	TANK-binding kinase 1
TEAE:	treatment-emergent adverse event
TNF-α:	tumor necrosis factor alpha
ULN:	upper limit of normal
USA:	United States of America
VAS:	visual analog scale
WOCBP:	woman of childbearing potential

10.13 APPENDIX 13: PROTOCOL AMENDMENT HISTORY

10.13.1 Amended protocol 04 (12 May 2023)

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

OVERALL RATIONALE FOR THE AMENDMENT

The main purpose of the protocol amendment 04 is to increase liver enzyme monitoring frequency to allow earlier detection of liver enzyme abnormality, if it occurs, and optimize our understanding on the safety profile of SAR443820.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis, 1.2 Schema, 1.3.1 Part A, 1.3.2 Part B, 4.1 Overall Design	Added 5 visits which include a liver chemistry test at each visit following visit (Week 6, Week 10 in Part A and at Week 30, Week 34 and Week 40 in Part B). Blood samples can also be collected at home and can be tested at the central or local lab.	To detect ALT increase early if it occurs and optimize our understanding on the safety profile of SAR443820
1.3.1 Part A, 1.3.2 Part B	New footnotes were added	To further describe parameters of assessment in the added visits
10.11 Appendix 11 Blood volume details Part A Part B	Blood volume updated due to increased visits in Part A (Week 6 and Week 10) and Part B (Week 30, Week 34 and Week 40)	To detect ALT increase early if it occurs and optimize our understanding on the safety profile of SAR443820
10.13 Appendix 13: Protocol amendment history	Order of appearance of amended protocols has been rearranged from newest to oldest	Internal compliance rules

Section # and Name	Description of Change	Brief Rationale
Protocol amendment Summary of Changes	Summary of changes pertaining amendment 03 were moved to appendices	Internal compliance rules

10.13.2 Amended protocol 03 (06 March 2023)

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.

OVERALL RATIONALE FOR THE AMENDMENT

The main purpose of the protocol amendment 03 is to include an additional liver laboratory monitoring at Week 12 in Part A and at Week 32 in Part B. Blood samples can also be collected at home and can be tested at the central or local lab. Also, an additional blood sample will be collected at baseline, which will be stored and may be used for future analysis, if needed, in case of an AE/SAE during the study.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis, 1.2 Schema, 1.3.1 Part A, 1.3.2 Part B, 4.1 Overall Design	Updated Week 12 from phone call to site visit and added a liver chemistry test at Week 12 visit. Added a site visit at Week 32 which includes a liver chemistry test. Added instructions on sample collecting, testing and results reporting at Week 12 and Week 32 visits and updated the respective footnotes. Updated the study schema to modify Week 12 visit and added Week 32 visit.	To increase liver monitoring as related to a Suspected Unexpected Serious Adverse Reaction (SUSAR) case of ALT and bilirubin increase
1.3.1 Part A, 10.11 Appendix 11: Blood Volume Details	Added blood sample for archiving at baseline visit and updated the total blood volume details to include changes/addition for baseline, Week 12, and Week 32 visits.	Save the sample before IMP initiation for future analysis if needed in case of an AE/SAE during the study.
6.8 Concomitant Therapy	Updated the text to reflect that concomitant medications or substances that are strong or moderate inhibitors or strong inducers of CYP3A4 are not allowed within the specified wash out period, in stead of “5 half lives” as mentioned previously	Correction
8 Study Assessments and Procedures	Added below text: • If onsite visits are not feasible (due to ALS progression, increased monitoring for AE follow-up, etc.), remote visits (eg, with home nurses, a home health vendor, a local clinic) may be planned for the collection of safety and/or efficacy data.	To provide flexibility of assessment when it is not feasible for participants to conduct site visits
8.9 Use of Biological Samples and Data for Future Research	Added an example of future research	Clarification

Section # and Name	Description of Change	Brief Rationale
10.1.6 Dissemination of Clinical Study Data	Replaced clinicaltrialregister (eu.ctr) by euclinicaltrials.eu, and clinicalstudydatarequest.com by vivli.org.	Administrative change
10.6 Appendix 6: Liver and Other Safety: Actions and Follow-Up Assessments	Updated the appendix heading from: Appendix 6: Liver and other Safety: Suggested Actions and Follow-Up Assessments and Study Intervention Rechallenge Guidelines To: Appendix 6: Liver and Other Safety: Actions and Follow-Up Assessments	To clarify that it is required to follow the procedure described in this appendix.
	Updated the algorithm graphical chart with increased frequency of ALT monitoring after ALT increase and updated the guidance text	To ensure all listed tests for etiology analysis of ALT increase will be conducted and to increase the frequency of liver function monitoring after ALT increase.
10.8.2 Germany	Added new sub-section and text to reflect that adult patients would be eligible for study only if they are able to give written consent themselves And added cross reference to this sub-section in Section 10.1.3	Update of local process
10.9 Appendix 9: Contingency Measures for A Regional or National Emergency that is Declared by A Governmental Agency	Added below text: For European countries contingency measures are currently only applicable for the COVID-19 pandemic.	Update of local process
10.10 Appendix 10: Strong and moderate CYP3A4 inhibitors and strong CYP3A4 inducers	Added cenotavir/ritonavir and nirmatrelvir/ritonavir in the list of CYP3A4 inhibitors. Modified the washout period of medications which are mechanism based CYP3A4 inhibitors	To update the list and correct the washout period of the medications
Throughout	Minor grammatical, stylistic, and minor typographical error corrections	Editorial changes

10.13.3 Amended protocol 02 (02 December 2022)

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

OVERALL RATIONALE FOR THE AMENDMENT

The main purpose of the protocol amendment 02 is to include the combination of sodium phenylbutyrate and taurursodiol (named Relyvrio® in the United States of America [USA] and Albrioza® in Canada) and oral edaravone as standard of care for ALS in countries where they have been approved. Some editorial and operational modifications are made.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Synopsis	Route of administration for edaravone is changed from "intravenous" to:" intravenous (IV) or oral"	Adding the oral formulation as it has been approved in the United States of America and China
Synopsis, Section 3 Objectives and Endpoints, Section 10.8.1.1 Study objectives and endpoints	In part B, deleting the text "before Week 52, Week 76, and Week 104" for the endpoints: time from baseline to the occurrence of either death or permanent assisted ventilation (>22 hours daily for >7 consecutive days), whichever comes first, time from baseline to the occurrence of death, time from baseline to the installation of a gastrostomy tube (G-tube)	To use all available data up to the time of cutoff
Synopsis, Section 1.3.1 Schedule of Activities. Part A, Section 2.2 Background, Section 4.1 Overall design, Section 5.1 Inclusion criteria, Section 6.3 Measures to minimize bias: randomization and blinding, Section 6.8 Concomitant therapy, Section 7.1.1 Permanent discontinuation, Section 9.4.2 Primary endpoint(s) in Part A, Section 9.4.3 Secondary endpoint(s) in Part A	The texts for noninvestigational medicinal products are changed to include the combination of sodium phenylbutyrate and taurursodiol (taurursodiol is also known as ursodoxicoltaurine).	The combination of sodium phenylbutyrate and taurursodiol is included as a standard of care for ALS in countries where it has been approved
Synopsis, Section 9.4.2 Primary endpoint(s) in Part A	The sentence "The model will also include a random intercept and slope" is deleted	Clarification of terms in the MMRM model
Synopsis, Section 9.4.3 Secondary endpoint(s) in Part A	For the main secondary endpoints in Part A, the text for continuous variables is changed to include baseline NfL (if different from the baseline value of the endpoint), use of the combination of sodium phenylbutyrate and taurursodiol, baseline value of endpoint-by-visit interaction, and baseline NfL-by-visit interaction (if different from the baseline value of the endpoint-by-visit interaction).	Clarification of terms in the MMRM model
Synopsis, Section 9.4.2 Primary endpoint(s) in Part A, Section 9.4.3 Secondary endpoint(s) in Part A	For the primary analysis, the text for the mixed effect model with repeated measure is changed to include baseline neurofilament light chain (NfL), use of the combination of sodium phenylbutyrate and taurursodiol, baseline NfL-by-visit interaction and ALSFRS-R score-by-visit interaction	Clarification of terms in the MMRM model
Section 1.3. Schedule of Activities.	Dates of visits are corrected in the way how it is calculated during intervention period, Part A and Part B	Align with actual calculation of the dates for visits during intervention period (Part A and Part B)
	IMP is added to the text "Early IMP discontinuation visit"	Editorial clarification

Section # and Name	Description of Change	Brief Rationale
Section 2.3.1 Risk assessment	Added potential risk of effects on pregnancy maintenance and embryo-fetal toxicity	To align the wording of the protocol with the IB edition 6 dated 15 June 2022, where this risk was already included.
Section 5.1 Inclusion criteria	Inclusion criterion I 09 is changed. The text: “at the screening visit” is added to the sentence: “Participants with a body weight no less than 45 kg and body mass index (BMI) no less than 18.0 kg/m2 at the screening visit.”	Clarification of body weight and BMI assessments at the screening visit for inclusion into the study
Section 5.2 Exclusion criteria	Exclusion criterion E12 is changed. The text “and/or” is changed to “or” in the sentence: “sodium phenylbutyrate or taurursodiol”	The combination of sodium phenylbutyrate and taurursodiol is now allowed
	In Exclusion criterion E16, HgBsAb is corrected to HBsAb	Typo
Section 6.8 Concomitant therapy	The text “prior to the screening visit” is added to the sentence: “Participants are allowed to enter the study if they are either not receiving riluzole or receiving stable doses of riluzole for at least 4 weeks prior to the screening visit”	Clarification of participants treated with riluzole who may enter the study
	The text “Switching between IV and oral formulation of edaravone in the countries where both formulations have been approved is allowed at any time during the study.” is added	Clarification on the route of administration for edaravone
Appendix 13 Section 10.13	Updated to include the amendment history of amended protocol 01	To refer to previous amended protocol
Throughout the document	Other minor editorial changes (eg, grammatical, stylistic, and minor typographical corrections).	To increase the clarity or consistency of the protocol.

10.13.4 Amended protocol 01 (07 April 2022)

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

OVERALL RATIONALE FOR THE AMENDMENT

The main purpose of the protocol amendment 01 is to provide monthly pregnancy test for female participants of childbearing potential, to modify the criterion for IMP reinitiation, and to address health authority requests.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Title Page	Updated IND number from: 15444 To: 151444.	Error correction
Title Page	Updated NCT number as NCT05237284.	Update
1.1 Synopsis (Main Secondary; endpoints in Part A); 3 Objectives and Endpoints (Part A); 9.4.3 Secondary endpoint(s) in Part A; 10.8.1.1 Study objectives and endpoints (Part A)	Clarify the secondary endpoint, muscle strength will be analyzed as the change from baseline to Week 24.	Clarification
1.1 Synopsis (Brief summary and Intervention groups and duration); 4.1 Overall design; Part A	Reworded to clarify that All ongoing participants in Part A will rollover to Part B.	To clarify the request for participants to rollover from Part A to Part B
1.1 Synopsis (Brief summary); 4.1 Overall design; Part B	Reworded to clarify that participants who permanently discontinue IMP in Part A will not receive SAR443820 in Part B.	Clarification
1.1 Synopsis (Rationale); 2.1 Study Rationale	The text “In summary, both preclinical and clinical studies have affirmed RIPK1 is a key mediator of necroptosis and inflammatory pathways in ALS.” has been modified to “In summary, both preclinical and patient-derived data have suggested RIPK1 may be a key mediator of necroptosis and inflammatory pathways in ALS.”	To be specific on the evidence supporting the study rationale
1 .1 Synopsis (Intervention groups and duration); 2.3.3 Overall benefit/risk conclusion; 6.8 Concomitant therapy	Updated from “November 2021” to “April 2022” on the available standard of care.	Update
1.3 Schedule of Activities, Part A	Instruction on IMP dosing at Week 24 has been added in footnote a (Part A).	Clarification

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities Part A; 8.2.3 Vital signs	Footnote 'j' added and details in Section 8.2.3 was reworded to provide instruction on when vital signs will be measured after first dose of IMP on Day 1.	Clarification
1.3 Schedule of Activities, Part A and Part B	In footnote b (Part A) and footnote c (Part B), 'discontinue from the study early' has been replaced by 'prematurely discontinue IMP'.	To clarify the participants who are required to take early discontinuation visit
1.3 Schedule of Activities, Part A and Part B; 8.2.6 Pregnancy testing	New footnote 'o' (Part A) and footnote 'l' (Part B) have been added to include instructions on pregnancy test.	To increase pregnancy test frequency to monthly since complete definite embryo-fetal study results are not available yet
1.3 Schedule of Activities, Part A	Procedure 'HHD'was replaced with 'Muscle strength' and a new footnote 'q' (Part A) have been added to include instructions on measuring muscle strength.	Adding hand grip in the muscle strength measurement
2 .3.1 Table 1 Risk assessment	Summary of data/rationale for risk related to convulsion was updated to include following text: No convulsions have been observed up to the dose level of [redacted] mg/kg/day in both the 3-month and 9-month studies.	Preclinical data update
	Mitigation strategy for convulsion was updated to include The following text: participants weighing <45 kg.	Clarification
	Summary of data/rationale for risk related to Immunomodulatory Effects was updated to include "9-month" for the nonhuman primate studies.	Preclinical data update
2.3.3 Overall benefit/risk conclusion	[redacted]	Updated with reference to completed first-in-human Phase 1 study result
3 Objectives and Endpoints, Part B	'Week 102' has been corrected to 'Week 104'.	Correction of typographical error
5.2 Exclusion Criteria	The following text has been added to E 03: "other causes of neuromuscular weakness"	Clarification
	The following text has been added to E 12: "(eg, sodium phenylbutyrate and/or taurursodiol)".	Clarification
5.3.1 Meals and dietary restrictions	Information was updated to clarify that participants should be prohibited from consuming grapefruit and grapefruit juices from 5 days before the start of the study intervention until 2 days after the final dose.	To avoid effect of grapefruit on SAR443820 metabolism as SAR443820 is mainly metabolized by CYP3A4 and grapefruit is a strong inhibitor of CYP3A4
6.1 Study Intervention(s) Administered	The instruction on drug administration has been modified to add details on the volume of water to use and how to mix the tablet with water.	To keep the instruction on drug administration

Section # and Name	Description of Change	Brief Rationale
		consistent between protocol and pharmacy manual
7.1.1 Permanent Discontinuation	Initiation of riluzole and/or edaravone during Part A was added as one of the criteria for study discontinuation.	To emphasize the criteria of study discontinuation
	The text in "Handling of participants after permanent intervention discontinuation" was updated to clarify that participants who prematurely discontinue the IMP will be encouraged to continue the rest of study visits for safety and efficacy assessments up to the last scheduled visit.	To be aligned with the intent-to-treat (ITT) analysis strategy
7.1.2.1 Study intervention restart or rechallenge after temporary discontinuation of study intervention	Any content related to the request of Sponsor approval to restart/rechallenge IMP has been deleted	To be aligned with ICH GCP guidance that investigator is responsible for all trial-related medical decisions
	If required "based on local practice" has been added after "Ethics Committee and/or Institutional Review Board (IRB) approval is obtained"	To provide flexibility on the request of IRB approval
	"In case of confirmed liver injury caused by the IMP, the rechallenge with the IMP is not permitted and the participants must be permanently discontinued from IMP treatment." has been added.	To emphasize confirmed IMP-induced liver injury will lead to permanent discontinuation of IMP
8.1.3 Muscle strength measurement	Heading title for Section 8.1.3 updated from "Handheld dynamometry (HHD)" to "Muscle strength measurement and the following text of "Bilateral hand grip will be measured using a grip dynamometer and all other muscles included in this study will be measured using a handheld dynamometer." was added	Adding hand grip in the muscle strength measurement
8.3.7 Disease-related events and/or disease-related outcomes not qualifying as AEs or SAEs	Disease-related events and disease-related outcomes have been defined and examples provided.	Clarification
8.3.8 Adverse event of special interest	The criterion of overdose has been updated.	Correction of error
	Reworded to clarify two AESI: serious infection and ALT increase.	Clarification
8.5 Genetics and/or pharmacogenomics	Added following text for an optional blood collection for isolation of DNA: "single".	Clarification
8.6 Biomarkers	Sample storage period was updated from '15 years' to '5 years' when the samples will be used only for clinical study related testing.	To clarify how long the sample will be stored for the clinical study related testing
8.9 Use Of Biological Samples And Data For Future Research	Reworded to clarify the purpose of future research.	Clarification
9.1 Statistical Hypothesis	Added new section to explain the statistical hypothesis.	To provide clarity on statistical hypothesis based

Section # and Name	Description of Change	Brief Rationale
		on request from Pharmaceuticals and Medical Devices Agency in Japan
	"The study will be declared positive if the null hypothesis for the primary endpoint in Part A change from baseline in the ALSFRS-R total score to Week 24 (end of Part A) for SAR443820 versus placebo is rejected in the primary analysis." has been added.	To add declaration of success
9.5 Interim Analyses	Added text to clarify when interim analysis will be conducted.	To provide clarity on interim analysis
10.1.7 Data quality assurance	Added description on how quality tolerance limits (QTLs) will be managed in the study.	Clarification
10.6 Appendix 6	Instructions on ALT increase have been added following the "Increase in ALT algorithm".	To provide detailed instruction on ALT increase
10.11 Appendix 11	Added a new appendix for blood volume details.	Clarification
Throughout the document	Editorial changes.	Grammatical corrections

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