STATISTICAL ANALYSIS PLAN

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**
Compound number (INN/Trademark):	**SAR443820** **Not applicable**
Study phase:	**Phase 2**
Short Title:	**Phase 2 study for SAR443820 in participants with amyotrophic lateral sclerosis (ALS)** HIMALAYA
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VERSION HISTORY

This amended statistical analysis plan (SAP) for study ACT16970 is based on the Amended Clinical Trial Protocol 05 dated 13-Dec-2023. The first participant was randomized on 28-Apr-2022. The initial SAP V1 was approved before the interim analysis for futility was conducted. This amended SAP is approved before the first database lock.

Major changes in statistical analysis plan

SAP Version	Approval Date	Changes from Protocol Amendment	Rationale
1	28-Apr-2023	Disease duration (from first symptom onset to the screening visit) and the corresponding by-visit interaction are added as covariates in the Part A primary analysis model.	Based on clinical input
		[redacted]. Instead, each of the 5 dimensions will be included in the analysis.	Index score is not really used for regulatory/clinical development purposes
2	08-Jan-2024	MMRM will be applied to the complete datasets after multiple imputation instead of ANCOVA in the sensitivity analysis of the primary endpoint in Part A.	Based on FDA feedback
		[redacted]	Based on FDA feedback
		Update megascore derivation if there are missing measurements	Clarification
		Add the analysis of grip strength and its derivation	Clarification
Additional changes have been made to improve clarity and consistency.			

1 INTRODUCTION

1.1 STUDY DESIGN

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

Part A is a 24-week, double-blind, placebo-controlled part, preceded by a screening period of up to 4 weeks before Day 1. After a screening phase of up to 4 weeks, 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 (Asia, Europe or North America), region of ALS onset (bulbar or other areas), use of riluzole (yes or no), use of edaravone (yes or no), and use of the combination of sodium phenylbutyrate and taurursodiol (named Relyvrio in the USA and Albrioza in Canada) (yes or 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 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, which starts from Week 24 and continues up to Week 106. The study intervention assignment of participants at randomization in Part A will remain blinded to Investigators, participants, and site personnel until the end of 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 evaluation is made.

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 (Part B) and 2-week post-treatment follow-up period, with a maximum total study duration of 110 weeks.

1.2 OBJECTIVES AND ENDPOINTS

Table 1 - 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
[redacted]	
• [redacted] SAR443820 [redacted]	• [redacted]

Objectives	Endpoints
	[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]

Objectives	Endpoints
SAR443820	

1.2.1 Estimands

Primary estimands defined for main endpoints in Part A are summarized in below Table 2. More details are provided in Section 3.

For all these estimands, the comparison of interest will be the comparison of SAR443820 vs. placebo.

Table 2 - Summary of primary estimand for main endpoints

Endpoint Category (estimand)	Estimands			
	Endpoint	**Population**	**Intercurrent event(s) handling strategy**	**Population-level summary (Analysis and missing data handling)**
Primary objective: 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)				
Primary endpoint (treatment policy)	Change from baseline in the ALSFRS-R total score to Week 24	ITT	Permanent study intervention discontinuation before Week 24 – regardless of treatment discontinuation (treatment policy)	The primary endpoint will be analyzed using MMRM with change from baseline in ALSFRS-R total score up to Week 24 as response variable, and treatment, visit, 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 or no), treatment-by-visit interaction, disease duration (from first symptom onset to the screening visit), baseline ALSFRS-R score, baseline NfL, disease duration-by-visit interaction, baseline NfL-by-visit interaction and baseline ALSFRS-R score-by-visit interaction as covariates. All available data will be used, and missing data will be handled by MMRM based on missing at random assumption.
Secondary endpoints (treatment policy)	Combined assessment of the function and survival (CAFS) score at Week 24	mITT	Permanent study intervention discontinuation before Week 24 – regardless of treatment discontinuation (treatment policy)	CAFS at Week 24 will be analyzed using the Wilcoxon-Mann-Whitney test to compare mean scores between the treatment groups at Week 24.
	Change from baseline in slow vital capacity (SVC) (muscle strength, Amyotrophic Lateral Sclerosis Assessment Questionnaire (ALSAQ-5), serum neurofilament light chain (NfL)) to Week 24	ITT	Permanent study intervention discontinuation before Week 24 – regardless of treatment discontinuation (treatment policy)	These secondary endpoints will be analyzed using MMRM with change from baseline value up to Week 24 as response variable, and treatment, visit, 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 or no), treatment-by-visit interaction, disease duration (from first symptom onset to the screening visit), baseline value of the endpoint, baseline NfL (if different from the baseline value of the endpoint), disease duration-by-visit interaction, baseline value of the endpoint-by-visit interaction and

Endpoint Category (estimand)	Estimands			
	Endpoint	Population	Intercurrent event(s) handling strategy	Population-level summary (Analysis and missing data handling)
				baseline NfL-by-visit interaction (if different from the baseline value of the endpoint-by-visit interaction) as covariates. All available data will be used, and missing data will be handled by MMRM based on missing at random assumption. For muscle strength data, if there is a missing value for one muscle measurement which continues to have the missing value through the final assessment (eg, at least 2 consecutive missing values up to the final assessment), then these missing values for this muscle measurement will be imputed as zero; all the other missing values will not be imputed.

2 ANALYSIS POPULATIONS

The following populations for analyses are defined.

Table 3 - 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 have taken at least 1 dose of study intervention.
Intent-to-treat (ITT)	All randomized participants. Participants will be analyzed according to the intervention allocated by randomization.
Modified Intent-to-treat (mITT)	All randomized participants who either died or have available baseline and at least one post-baseline ALSFRS-R assessment
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 analysed according to the intervention they actually received.

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

Participants exposed to study intervention before or without being randomized will not be considered randomized and will not be included in any analysis population. The safety experience of these participants will be reported separately.

Randomized participants for whom it is unclear whether they took the study intervention will be considered as exposed and will be included in the safety population as randomized.

For any participant randomized more than once, only the data associated with the first randomization (except if the first randomization is done by error) will be used in any analysis population. The safety experience associated with any later randomization will be reported separately.

For participants receiving more than one study intervention during the study, the intervention group for as-treated analyses will be SAR443820 20 mg BID.

3 STATISTICAL ANALYSES

3.1 GENERAL CONSIDERATIONS

In general, continuous data will be summarized using the number of observations available, mean, standard deviation (SD), median, interquartile range (Q1, Q3), minimum, and maximum. Categorical and ordinal data will be summarized using the count and percentage of participants. Efficacy data will be analyzed in the ITT population, except CAFS endpoints in Part A and Part B will be analyzed in the mITT population. Safety data will be analyzed in the safety population, unless specified otherwise.

In Part A, baseline values are defined as follows. 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 C-SSRS, the baseline value will be the worst assessment between the past 6 months evaluation at screening and the since last visit evaluation on Day 1. For the other efficacy and safety assessments, the baseline values are defined as the last available value prior to the first dose of study intervention. For participants randomized but not treated, the baseline value is defined as the last available value before randomization. Unless otherwise indicated, 2-sided p-values and 95% confidence intervals [CI(s)] will be provided for efficacy assessment of treatment differences. Unless otherwise specified, analyses will be performed by treatment group (and overall for baseline and demographics characteristics).

Efficacy analyses in Part B will be conducted accumulatively according to the treatment group allocated by randomization in Part A (ie, Placebo/SAR443820 versus SAR443820/SAR443820). Baseline values defined above for Part A will be used as the baseline in the efficacy analyses for Part B, unless otherwise noted. Safety analyses in Part B are stated in Section 3.6.

Observation period

The observation period for safety will be divided into 4 segments:

- The **pre-treatment period** is defined as the period up to first investigational medicinal product (IMP) administration.
- The **on-treatment period** (ie, treatment-emergent (TE) period) **for the Part A** is defined as the period from the first IMP administration to the earliest of 1) last IMP administration + 14 days, 2) first IMP in Part B, 3) death date, or 4) last contact date.
- The **on-treatment period** (ie, treatment-emergent (TE) period) **for the Part B** is defined as the period from the first IMP administration in Part B to the earliest of 1) last IMP administration + 14 days, 2) death date, or 3) last contact date.
- The **post-treatment period,** if applicable, is defined as the period from the end of the on-treatment period to the last contact date.

The on-study period is defined as the time from randomization until the end of the study defined as the last scheduled visit for those who completed the study and the end-of-study date collected

on electronic case report form (e-CRF) page "Completion of End of Study" for those who did not complete the study. If death is the end-of-study reason, date of death will be used.

3.2 PRIMARY ENDPOINT(S) ANALYSIS

The primary endpoint in Part A detailed in this section is change from baseline in the ALSFRS-R total score to Week 24.

The primary endpoint in Part B detailed in this section is CAFS score at Week 52.

3.2.1 Definition of endpoint(s)

Part A

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 (1). Good reliability between face-to-face and telephone administration of the ALSFRS-R has been demonstrated (2).

Part B

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. CAFS is used to compare each study participant's outcome to others in the trial in a series of pairwise comparisons, based on function and survival (3). For each pairwise comparison, a study participant is assigned a score and then the summed scores are ranked for all participants. To calculate a participant's CAFS, each participant is compared individually to all other participants in the trial. The summary score for each participant is the sum of the comparisons $(+1, 0, -1)$ against all other participants. For each pairwise comparison of patients, the participant who fares better earns a point, and the one who fares worse loses a point. In the case of a tie, no points are added or subtracted. If both participants die, the one surviving longer fared better; if only one survives then that participant fared better; and if both participants survive, the one with the smaller decline in ALSFRS-R from baseline fared better. If a participant discontinues early, comparison to each other participant uses time to death if the comparator died; otherwise, the comparison is based on the last ALSFRS-R time-point available for both participants. Once these scores have been calculated for all subjects, they are ranked, from lowest (died first) to highest (best ALSFRS-R outcome among those who survived), yielding the final CAFS score used as the endpoint. The average rank score is then calculated for each treatment group. A higher mean rank score indicates that participants in that treatment group, on average, fared better.

3.2.2 Main analytical approach

Part A

The primary endpoint in Part A will be analyzed with the estimand defined according to the following attributes:

- Endpoint: Change from baseline in the ALSFRS-R total score to Week 24
- Treatment condition: SAR443820 will be compared to placebo
- Analysis population: ITT population
- Intercurrent events (IE):
  - The IMP discontinuation IE will be handled with the treatment policy strategy; The primary endpoint will be assessed based on all assessments irrespective of the IMP discontinuation
- Population-level summary: The primary endpoint will be analyzed using MMRM with change from baseline in ALSFRS-R total score up to Week 24 as response variable, and treatment, visit, 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 or no), treatment-by-visit interaction, disease duration (from first symptom onset to the screening visit), baseline ALSFRS-R score, baseline NfL, disease duration-by-visit interaction, baseline NfL-by-visit interaction and baseline ALSFRS-R score-by-visit interaction as covariates. If less than 10 participants in a randomization strata level, then the corresponding factor will not be included as a covariate in the MMRM model.

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”) by inclusion of the OBSMARGINS option in the LSMEANS statement. Plots of least squares means (± standard error) over time will be provided.

This model will be implemented using the SAS MIXED procedure with an unstructured covariance 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. If this model fails to converge, the following variance-covariance structures will be tested in this order:

- Heterogeneous Toeplitz
- Heterogeneous AR(1)
- Heterogeneous CS
- Toeplitz

- AR(1)
- CS.

The first (co)variance structure yielding convergence will be used as the primary analysis. When a variance-covariance structure other than unstructured is used, the denominator degree of freedom will be estimated using the between within method (DDFM=BW in SAS PROC MIXED) (4).

We assume a priori that change from baseline in the ALSFRS-R total score to Week 24 are normally distributed. Given the large sample size, the impact of violation of normality should not be great. In order to assess the impact of deviation from the normality assumption, a sensitivity analysis using rank analysis of covariance (ANCOVA) with the same covariates as for the MMRM analysis except visit and related interaction terms, will be performed to test the significance of the treatment effect.

Part B

CAFS score at Week 52 will be analyzed in the mITT population using the Wilcoxon-Mann-Whitney test to compare mean scores between the treatment groups at Week 52.

3.2.3 Sensitivity analyses

[redacted]

[redacted]

[redacted] SAR443820 [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted].

3.2.4 Supplementary analyses for primary endpoint in Part A

To assess the treatment effect when the participants adhere to the study treatment as directed, the difference (SAR443820 vs placebo) in the mean change from baseline in the ALSFRS-R total score to Week 24 will be analyzed in the ITT population based on data collected during the treatment-emergent period for the Part A using the same model as primary analysis. ALSFRS-R total scores obtained after the IMP discontinuation will be considered as missing.

3.2.5 Subgroup analyses for primary endpoint in Part A

To assess the homogeneity of the treatment effect across various subgroups, analyses will be performed on the primary endpoint across the following subgroups (categories with fewer than

10% participants will be combined with other categories; for factors with only two categories, no subgroup analysis will be performed if fewer than 10% participants in one category):

- Geographic region (US, non-US)
- Region (Europe, North America, Asia)
- Age at screening (≤ 40, > 40 years)
- Sex (Male or Female)
- Race (White, Black or African American, Asian, Other)
- 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 or no)

The estimated treatment effect (SAR443820 versus placebo) for the primary endpoint will be provided, as well as the corresponding 95% CI, for each subgroup separately, using the same method as applied in the primary analysis. Forest plots of differences in treatment group means and corresponding 95% CIs comparing SAR443820 to placebo within each subgroup will be provided.

Treatment by subgroup interaction and its p-value will be derived from a MMRM with terms for treatment, visit, 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 or no), treatment-by-visit interaction, disease duration (from first symptom onset to the screening visit), baseline ALSFRS-R score, baseline NfL, disease duration-by-visit interaction, baseline ALSFRS-R score-by-visit interaction, baseline NfL-by-visit interaction, subgroup (if different than the aforementioned covariates), subgroup-by-treatment interaction as covariates. If a quantitative treatment by subgroup interaction is detected with nominal p-value <0.1 for any subgroup factor, a further investigation will be performed to evaluate possible qualitative interaction.

3.3 SECONDARY ENDPOINT(S) ANALYSIS

The secondary endpoints detailed in this section are as follows:

Part A

- CAFS at Week 24
- change from baseline in SVC to Week 24
- change from baseline in muscle strength to Week 24
  - change from baseline in megascore to Week 24
  - change from baseline in grip strength to Week 24

- change from baseline in ALSAQ-5 to Week 24
- change from baseline in serum NfL to Week 24

Part B

- CAFS 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 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 SVC to Week 52, Week 76, and Week 104
- change from baseline in ALSAQ-5 to Week 52, Week 76, and Week 104
- change from baseline in serum NfL to Week 52

Other secondary endpoints analyses are defined in Section 3.6.2 (AE, SAE), Section 3.6.3.1 (laboratory abnormalities), Section 3.7.1.1 (PK) and Section 3.7.1.2 (PD).

3.3.1 Secondary endpoint(s)

3.3.1.1 Definition of endpoint(s)

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 (7). The highest SVC score among all attempts will be used for analysis.

Muscle Strength

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 (HHD). 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 3rd trial will be performed, all the values will be recorded and the maximum value of the 3 trials will be accepted. The order of testing is standardized and should be the same for each session. Grip strength will be tested first, followed by the arms and then the legs.

HHD data will be analyzed by combined muscle groups named (megascores). To create a megascore, individual muscles will be standardized using table e-1 in (8), from which individual muscle means and SDs were calculated from 228 healthy people. Note that in (8), each muscle

strength was measured in lbs, so the corresponding mean and SD in table e-1 are transformed to kg by multiplying a constant 0.453592. Two decimal places are kept as in (8). The transformed table is provided below. Z scores for each muscle measurement will be calculated from these means and SDs by subtracting the corresponding mean and dividing by the corresponding SD. Individual Z scores will then be averaged to produce a total megascore including all available muscle groups. To handle the missing data, the derivation rule for primary analysis is determined as follows: If a participant has a missing value for one muscle measurement and continues to have the missing value through the final assessment (eg, at least 2 consecutive missing values up to the final assessment), then these missing values for this muscle measurement will be imputed as zero; all the other missing values will not be imputed.

Mean strength, standard deviation for all muscles in 228 normal volunteers (table e-1 in (8))

HHD	Mean (kg)	SD	HHD	Mean (kg)	SD
L shoulder flexion	13.48	4.20	R shoulder flexion	14.01	4.11
L elbow flexion	15.78	5.22	R elbow flexion	15.87	5.34
L elbow extension	12.80	3.96	R elbow extension	12.79	3.78
L wrist extension	11.35	3.96	R wrist extension	12.02	3.97
L hip flexion	19.90	7.19	R hip flexion	20.15	7.08
L knee flexion	16.65	5.96	R knee flexion	16.77	5.71
L knee extension	16.00	6.03	R knee extension	16.24	6.42
L ankle dorsiflexion	17.25	6.91	R ankle dorsiflexion	17.45	7.03
L first dorsal interosseous	5.07	1.74	R first dorsal interosseous	5.35	1.97

Each mean and SD are derived from the table e-1 in (8) by multiplying a constant 0.453592 to change the unit from lbs to kg.

Grip strength data will be analyzed by the scores collected from left hand and right hand respectively. To handle the missing data, the derivation rule for primary analysis is determined as follows: If a participant has a missing value at one visit and continues to have the missing value through the final assessment (eg, at least 2 consecutive missing values up to the final assessment), then these missing values will be imputed as zero; all the other missing values will not be imputed.

ALSAQ-5

The ALSAQ-5 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.

Serum NfL

Serum blood samples will be used to measure changes in NfL, a marker of neuronal injury. Levels of NfL in both cerebrospinal fluid 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. Only serum NfL will be measured in this study to reduce the collection burden on participants.

3.3.1.2 Main analytical approach

Treatment policy will be used for the analyses of all secondary endpoints in Part A and Part B as stated in Table 2.

CAFS

CAFS at Week 24, Week 76 and Week 104 will be analyzed in the same manner as that used to analyze the primary endpoint in Part B in Section 3.2.2.

Continuous Endpoints

Continuous endpoints include:

Part A

- change from baseline in SVC to Week 24
- change from baseline in muscle strength to Week 24
  - change from baseline in megascore to Week 24
  - change from baseline in grip strength to Week 24
- change from baseline in ALSAQ-5 to Week 24
- change from baseline in serum NfL to Week 24

Part B

- change from baseline in the ALSFRS-R total score to Week 52, Week 76, and Week 104
- change from baseline in SVC to Week 52, Week 76, and Week 104
- change from baseline in ALSAQ-5 to Week 52, Week 76, and Week 104
- change from baseline in serum NfL to Week 52

These continuous endpoints will be analyzed using the same manner as that used to analyze the primary endpoint in Part A in Section 3.2.2, except that baseline ALSFRS-R score will be replaced by the baseline value of the corresponding endpoint. Plots of least squares means (± standard error) over time will be provided. Plots of mean (±SD) and/or mean change (±SD) and/or median over time will also be provided. For NfL data, log transformation will be applied in

the MMRM model. The treatment difference will then be back-transformed to the original scale. The back-transformed LS means stand for geometric mean ratios compared to baseline, and the back-transformed LS means difference stands for ratio of the geometric mean ratios compared to baseline between SAR443820 and placebo. In order to assess the impact of deviation from the normality assumption, a sensitivity analysis using rank analysis of covariance (ANCOVA) with the same covariates as for the MMRM analysis except visit and related interaction terms, will be performed to provide the p-value for the comparison between the treatment groups.

Time-to-event endpoints

Time-to-event endpoints in Part B include:

- time from baseline to 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

For the time-to-event endpoints, baseline is defined as randomization. The time to event will be modeled by a Cox proportional hazards model. The covariates included in the model are treatment group, 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 or no), disease duration (from first symptom onset to the screening visit), baseline ALSFRS-R score and baseline NfL. The hazard ratio between SAR443820 and placebo, its 95% confidence interval and the p-value for comparing SAR443820 and placebo will be estimated from this model with robust variance estimation (9). Comparison between SAR443820 and placebo will also be assessed by a log-rank test stratified by 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 or no) and baseline NfL (< median baseline NfL or >= median baseline NfL). Kaplan-Meier (KM) plots of the cumulative incidence rate will be provided by treatment group to depict the course of occurrence of event over time. The proportion of participants with events at given time points (eg, Week 4, 8, 12, 16, 20, 24, etc.) and median time to event (if feasible) will be calculated using the KM estimates.

3.3.1.3 Sensitivity analyses

CAFS endpoints in Part A and Part B

To assess the impact of baseline characteristics in the comparison of CAFS scores between treatment groups, a sensitivity analysis using a similar rank ANCOVA model to adjust for baseline prognostic factors in the mITT population as mentioned in Section 3.2.3 will be performed at Week 24, Week 76 and Week 104, respectively.

[redacted]

[redacted]

3.4 TERTIARY/EXPLORATORY ENDPOINT(S) ANALYSIS

Tertiary/exploratory endpoints in Part A and Part B are listed in Table 1.

3.4.1 Definition of endpoint(s)

3.4.2 Main analytical approach

Missing data will not be imputed in the analysis of tertiary endpoints, nor will sensitivity or subgroup analyses be conducted.

For continuous endpoints, summary statistics including mean, standard deviation, median, interquartile range (Q1, Q3), minimum, and maximum will be provided for these continuous endpoints at scheduled visits in Part A and Part B. Only participants with baseline and post-baseline data will be summarized. Plots of mean (±SD) and/or mean change (±SD) and/or median over time will also be provided for better visualization. These continuous endpoints will also be analyzed using a similar MMRM approach as described for the primary endpoint in Part A in Section 3.2.2, except that the baseline ALSFRS-R score will be replaced by the baseline values of

the corresponding endpoint. In addition, for the change from baseline in maximum phonation time on [redacted], age, height, and gender will also be included in the MMRM model as covariates. Plots of least squares means (± standard error) over time will be provided.

Time-to-event endpoints will be analyzed using the same manner as that used to analyze the secondary time-to-event endpoints in Part B in Section 3.3.1.2.

[redacted]

3.4.3 Comparison with external control

A matched analysis using data from historical clinical trial database (for example, PROACT) as a control will be conducted to demonstrate the superiority of SAR443820 on slowing down disease progression and prolonging survival over 104 weeks of treatment period.

Matching procedure

1. Pre-matching filtering: The participants in the historical clinical trial database will be filtered by the following factors that match our trial eligibility criteria and duration:
   - Age 18 – 80 years, inclusive
   - First ALS symptom onset <= 2 years
   - Baseline SVC (%) >= 60%
   - Baseline ALSFRS-R decline rate >= 0.5/month

2. Propensity score matching: Propensity score matching seeks to balance the distributions of known prognostic covariates in treatment and control group to resemble what would occur had the treatment been randomly assigned. A logistic regression for the treatment group as the dependent variable is performed to obtain the propensity score with the abovementioned matching variables, using all the participants (planned for 174) randomized to the SAR443820 arm and the participants from the historical clinical trial database after filtering as described above. Each participant in the SAR443820 treated group will be matched 1:1 using the Mahalanobis distance to a participant in the historical clinical trial database. Matching will be performed with replacement.

   To assess the success of the matching procedure, summary statistics of baseline matching variables will be presented and compared between the two treatment groups before and after matching to assess post-match balance.

Post-matching statistical analysis

Once the matching is performed, the comparison between participants who were randomized to SAR443820 and placebo arm generated from the historical trial database will be provided for the following endpoints using the similar analyses models as described for the primary and secondary endpoints in Section 3.2.2 and Section 3.3.1.2.

- Combined assessment of function and survival (CAFS) score at Week 52, Week 76, and Week 104
- Change from baseline in 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 hour daily for >7 consecutive days) whichever comes first
- Time from baseline to the occurrence of death

3.5 MULTIPLICITY ISSUES

To control the Type 1 error rate for the study, a hierarchical testing procedure will be applied at a 2-sided 5% significance level for primary and selected secondary endpoints in Part A, 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 in part A, a selective set of secondary endpoints in Part A will be tested following the hierarchical testing procedure shown below:

- CAFS score at Week 24
- Change from baseline in ALSAQ-5 to Week 24
- Change from baseline in serum NfL to Week 24
- Change from baseline in SVC to Week 24
- Change from baseline in megascore to Week 24

3.6 SAFETY ANALYSES

All safety analyses will be performed on the safety population as defined in Section 2, unless otherwise specified, using the following common rules:

- The analysis of the safety variables will be essentially descriptive, and no testing is planned.
- Safety data in participants who do not belong to the safety population (eg, exposed but not randomized) will be provided separately.

In Part A safety analysis, the safety analyses will be carried out with patients by the actual treatment received, irrespective of the treatment the patient has been randomized to.

Part A + Part B Safety Analyses

For categorical safety measures, such as AE, PCSA, shift summaries, data throughout both Part A and Part B will be summarized in three groups:

- Placebo/SAR443820 group includes participants who actually received placebo in Part A and SAR443820 in Part B. For participants in this group, only the data during SAR443820 exposure in Part B will be summarized. The baseline will be defined as the last available value prior to the first dose of SAR443820 in Part B.
- SAR443820/SAR443820 group includes participants who actually received SAR443820 in Part A, regardless of whether they entered Part B. For participants in this group, all data during SAR443820 exposure will be summarized. The baseline will be defined as the last available value prior to the first dose of the study intervention (same baseline defined for Part A in Section 3.1).
- Overall SAR443820 group includes participants from Placebo/SAR443820 group and SAR443820/SAR443820 group.

For continuous safety measures collected at longitudinal time point, such as labs and vital signs, data throughout both Part A and Part B will be summarized in two groups:

- Placebo/SAR443820 group includes participants who actually received placebo in Part A, regardless of whether they entered Part B. For participants in this group, all data during the on-treatment period of Part A and Part B will be summarized at each

protocol scheduled visit. The baseline will be defined as the last available value prior to the first dose of study intervention (same baseline defined for Part A in Section 3.1).

- SAR443820/SAR443820 group includes participants who actually received SAR443820 in Part A, regardless of whether they entered Part B. For participants in this group, all data during the on-treatment period of Part A and Part B will be summarized at each protocol scheduled visit. The baseline will be defined as the last available value prior to the first dose of study intervention (same baseline defined for Part A in Section 3.1).

3.6.1 Extent of exposure

The extent of IMP exposure will be assessed by the duration of IMP exposure and summarized within the safety population.

Duration of IMP exposure

Duration of IMP exposure in Part A is defined as last IMP administration date in Part A – first IMP administration date + 1 day, regardless of unplanned intermittent discontinuations. If the date of the last dose of IMP in Part A is missing, the duration of IMP exposure in Part A will be left as missing.

Duration of cumulative SAR443820 exposure in Part A + Part B is defined as last dose date of SAR443820 – first dose date of SAR443820 + 1 day, regardless of unplanned intermittent discontinuations. If the last dose date of SAR443820 is missing, this duration will be left as missing.

Duration of IMP exposure in Part A will be summarized quantitatively and categorically by the treatment group participants actually received in Part A (Placebo versus SAR443820):

- > 0 and ≤ 4 weeks
- > 4 and ≤ 8 weeks
- > 8 and ≤ 12 weeks
- > 12 and ≤ 16 weeks
- > 16 and ≤ 20 weeks
- > 20 and ≤ 24 weeks
- > 24 weeks

Duration of cumulative SAR443820 exposure in Part A + Part B will also be summarized quantitatively and categorically by actual treatment group (Placebo/SAR443820, SAR443820/SAR443820 and overall) within the safety population:

- > 0 and ≤ 4 weeks

- > 4 and ≤ 8 weeks
- > 8 and ≤ 12 weeks
- > 12 and ≤ 16 weeks
- > 16 and ≤ 20 weeks
- > 20 and ≤ 24 weeks
- > 24 and ≤ 52 weeks
- > 52 and ≤ 76 weeks
- > 76 and ≤ 104 weeks
- > 104 weeks

Additionally, the cumulative duration of treatment exposure (expressed in participant-years) will be provided for Part A and Part A + Part B separately.

Treatment compliance

A given administration will be considered noncompliant if the participant did not take the number of administrations as required by the protocol. No imputation will be made for participants with missing or incomplete data.

Percentage of treatment compliance for a participant will be defined as the number of administrations that the participant was compliant divided by the total number of administrations that the participant was planned to take from the first administration of IMP up to the actual last administration of IMP.

Treatment compliance will be summarized quantitatively and categorically (<80%, ≥80%) for Part A and Part A + Part B using the similar format as stated above for exposure.

3.6.2 Adverse events

General common rules for adverse events

All adverse events (AEs) will be coded to a lower-level term (LLT), preferred term (PT), high-level term (HLT), high-level group term (HLGT), and associated primary system organ class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA) version currently in effect at Sanofi at the time of database lock.

The AEs will be analyzed in the following 4 categories:

- Pre-treatment AEs: AEs that developed, worsened or became serious during the pre-treatment period.
- Treatment-emergent adverse events (TEAE)s for Part A: AEs that developed, worsened or became serious during the on-treatment period for Part A

- Treatment-emergent adverse events (TEAE)s for Part B: AEs that developed, worsened or became serious during the on-treatment period for Part B
- Post-treatment AEs: AEs that developed, worsened or became serious during the post-treatment period

Similarly, if occurring, deaths will be analyzed in the pre-treatment, treatment-emergent, and post-treatment periods.

The primary AE analyses will be on TEAEs. Pre-treatment and post-treatment AEs will be described separately.

An AE with incomplete or missing date/time of onset (occurrence, worsening, or becoming serious) will be classified as a TEAE unless there is definitive information to determine it is a pre-treatment or a post-treatment AE.

If the assessment of the relationship to IMP is missing for an AE, this AE will be assumed as related to IMP. Missing severity will be left as missing.

Multiple occurrences of the same event in the same participant will be counted only once in the tables within a treatment period, using the maximum (worst) severity by treatment phase.

The AE tables will be sorted as indicated in Table 4.

Table 4 - Sorting of AE tables

AE presentation	Sorting rules
SOC and PT	By the internationally agreed SOC order and decreasing frequency of PTs[a]
AESI category and PT	By AESI category (protocol order) and decreasing frequency of PTs[a]
PT	By decreasing frequency of PTs[a]

a Sorting will be based on the SAR443820 treatment group incidence, alphabetic order in case of equal frequency.

Analysis of all adverse events in Part A and Part A + Part B

The overview of TEAE will be generated presenting the number (%) of participants with:

- Any TEAE
- Any severe TEAE
- Any treatment-emergent SAE
- TEAE leading to death
- Any TEAE leading to permanent intervention discontinuation of IMP
- Any treatment-emergent AESI
- Any TEAE considered by the investigator as related to IMP

An additional overview summary including the number and rate of events will be provided.

The AE summaries of Table 5 will be generated with number (%) of participants experiencing at least one event.

Listings of SAEs from randomized participants, AEs from participants who are treated but not randomized, AEs leading to treatment/study discontinuation and severe AEs will be provided.

Table 5 - Analyses of adverse events

Type of AE	MedDRA levels
All TEAEs	Primary SOC and PT
Common TEAE (≥2% in any group)	PT
TEAEs related to IMP as per Investigator's judgment	Primary SOC and PT
	PT
TEAE by maximal intensity	Primary SOC and PT
Treatment emergent SAEs	Primary SOC and PT
	PT
Treatment emergent SAEs related to IMP as per Investigator's judgment	Primary SOC and PT
Treatment emergent AESIs	AESI category and PT
TEAEs leading to permanent intervention discontinuation	Primary SOC and PT
	PT
TEAEs leading to death[b]	Primary SOC and PT
Pretreatment AEs	Overview[a]
	Primary SOC and PT
Post-treatment AEs	Overview[a]
	Primary SOC and PT

a Will include the following AE categories: any AEs, any serious AEs, any AEs leading to death, any AEs leading to permanent intervention discontinuation
b Death as an outcome of the AE as reported by the Investigator in the AE page

Analysis of deaths in Part A and Part A + Part B

In addition to the analyses of deaths included in Table 5, the number (%) of participants in the following categories will be provided:

- Deaths during the treatment-emergent period and post-treatment period
- Deaths in non-randomized participants or randomized but not treated participants

Analysis of adverse events of special interest (AESIs) in Part A and Part A + Part B

Adverse events of special interest (AESIs) will be selected for analyses as indicated in Table 6. Number (%) of participants experiencing at least one event will be provided for each event of interest. Tables will be sorted as indicated in Table 4. A listing of AESIs will also be provided.

Table 6 - Selections for AESIs

AESIs	Selection
Pregnancy of a female participant or female partner of a male participant	Dedicated CRF page (AECAT="PREGNANCY DATA")
Symptomatic overdose (serious or non-serious) with IMP	Dedicated CRF page (AECAT="OVERDOSE DATA"; must be symptomatic and AESI marked "Y"
Convulsions	CMQsn00079 for selection and AESI marked "Y"
Serious infections meeting SAE definitions criteria	SOC of Infections and Infestations, both AESER and AESI marked "Y"
Increase in ALT > 3 x ULN	Dedicated CRF page (AECAT="ALT INCREASE DATA") and AESI marked "Y"

3.6.3 Additional safety assessments

3.6.3.1 Laboratory variables, vital signs and electrocardiograms (ECGs)

The following laboratory variables, vital signs and electrocardiogram (ECG) variables will be analyzed. They will be converted into standard international units and conventional unit, if applicable.

- Hematology:
  - Red blood cells and platelets and coagulation: hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, red blood cell count, platelet count
  - White blood cells: white blood cell count, neutrophils, lymphocytes, monocytes, basophils, eosinophils
- Clinical chemistry:
  - Metabolism: glucose, total protein, albumin, creatine phosphokinase
  - Electrolytes: sodium, potassium, calcium
  - Renal function: creatinine, blood urea nitrogen
  - Liver function: alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total and direct bilirubin
  - Pregnancy test: Serum β-human chorionic gonadotropin (all female participants)

  - Hepatitis screen: human immunodeficiency virus antibody, hepatitis B surface antigen, hepatitis C virus antibody
- Urinalysis:
  - Urinalysis for quantitative analysis: pH, specific gravity, proteins, glucose, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase (by dipstick)
- Vital signs: heart rate, systolic and diastolic blood pressure, weight, respiratory rate, temperature
- ECG variables: heart rate, PR, QRS, QT, and corrected QTc (according to Bazett and Fridericia)

Data below the lower limit of quantitation/detection limit (LLOQ) will be replaced by half of the LLOQ, data above the upper limit of quantification (ULOQ)will be replaced by ULOQ value for quantitative analysis.

Quantitative analyses

When relevant, for laboratory variables, vital signs and ECG variables above, descriptive statistics for results and changes from baseline will be provided for each analysis visit window during the on-treatment period for Part A and Part A + Part B. These analyses will be performed using central measurements only (when available) for laboratory variables.

For each laboratory parameter, vital sign parameter and ECG parameter, mean changes from baseline with the corresponding standard error will be plotted over time.

Analyses according to 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. For parameters for which no PCSA criteria are defined, similar analyses will be done using the normal range, if applicable.

Analyses according to PCSA (normal range) 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 above, the incidence of participants with at least one PCSA during the on-treatment period for Part A and Part A + Part B will be summarized regardless of the baseline level and according to the following baseline status categories:

- Normal/missing
- Abnormal according to PCSA (normal range) criterion or criteria

Additional analyses for drug-induced liver injury

The following additional analyses will be performed for drug-induced liver injury in Part A and Part A + Part B:

- Time to onset of the initial alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevation (>3 x ULN) and total bilirubin elevation (>2 x ULN) during the treatment-emergent period will be analyzed using Kaplan-Meier method.
- A graph of the distribution of peak values of ALT versus peak values of total bilirubin during the treatment-emergent period will be provided.
- For each liver function test (eg, ALT), participants having experienced a PCSA (eg, ALT >5 ULN) will be summarized using the following categories: Returned to baseline PCSA status (or returned to value ≤ ULN in case of missing baseline) before last IMP dose, Returned to baseline PCSA status after last IMP dose, Never returned to baseline PCSA status, No assessment after elevation. This summary will be performed by categories of elevation (ALT >3, >5, >10, >20 ULN).

3.6.3.2 Analysis of suicidality assessment

The number (%) of participants with suicidal ideation, suicidal behavior, and self-injurious behavior without suicidal intent based on the C-SSRS during treatment will be summarized. A shift table for baseline versus during treatment responses in Part A and Part A + Part B will be provided according to the categories of no suicidal ideation or behavior, suicidal ideation and suicidal behavior.

3.7 OTHER ANALYSES

3.7.1 Other variables and/or parameters

3.7.1.1 Pharmacokinetic (PK) analyses

Plasma concentration of SAR443820 will be summarized in the PK population using arithmetic and geometric means, standard deviation, standard error of the mean, coefficient of variation, minimum, median and maximum per sampling time. For drug-treated participants, where concentration values are below the lower limit of quantification (LLOQ), one-half of the LLOQ will be used. Values will be expressed in the tables with no more than three decimal places. These analyses will be performed for all participants received SAR443820 and by baseline body weight (by quartiles).

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

3.7.1.2 Pharmacodynamic (PD) analyses

PD parameters include NfL, chitinase-3-like protein-1, a selected panel of cytokines and chemokines in serum, soluble triggering receptor expressed on myeloid cells-2 in plasma and extracellular domain of p75 in urine. NfL data will be analyzed under secondary endpoints as described in Section 3.3.1.2. The rest of PD parameters will be summarized in Part A by actual treatment group in the safety population using the following descriptive statistics: mean, geometric mean, median, standard deviation, coefficient of variation, minimum, and maximum.

The corresponding change from baseline values will also be provided. Plots of mean (±SD) and/or mean change (±SD) over time will also be provided for better visualization.

3.7.1.3 PK/PD analysis

Exploratory exposure response analysis will be provided in a standalone report. The documentation of the methods of analysis will be described in a standalone plan.

3.8 INTERIM ANALYSES

A nonbinding interim analysis (IA) for futility may be conducted when approximately 40% of the participants complete Part A, the double-blind placebo-controlled period, or discontinue the study before Week 24. 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 (not involved with the conduct of the study), will conduct this 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, a prespecified limited number of the Sponsor's senior management team will 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 will be provided in the DMC SAP.

When all participants complete Part A, which is the 24 weeks of double-blind treatment period, or discontinue from the study before Week 24 (ie, last participant last visit for Part A), the final confirmatory analyses for Part A will be performed from the database lock for Part A, and the results will be provided in a study report.

For Part (open label, long-term extension period), interim analyses/reports may be prepared to support regulatory submission or other purpose.

When all participants complete Part B or discontinue from the study before the end of Part B (ie, last participant last visit for Part B), the final analyses for the entire study period will be conducted and the final clinical study report will be generated.

3.9 CHANGES TO PROTOCOL-PLANNED ANALYSES

This section summarizes major statistical changes in the protocol amendment(s).

Major statistical changes in protocol amendment(s)

Amendment Number	Approval Date	Changes	Rationale
2	02-Dec-2022	In MMRM model for change from baseline in continuous endpoints, baseline NfL (if different from the baseline value of the endpoint), use of the combination	Clarification of the terms in MMRM model

Amendment Number	Approval Date	Changes	Rationale
		of sodium phenylbutyrate and taurursodiol (yes vs no), baseline NfL-by-visit interaction (if different from the baseline value of the endpoint-by-visit interaction), baseline value of the endpoint-by-visit interaction are also included, while randomization strata-by-visit interaction is removed.	
5	13-Dec-2023	In MMRM for change from baseline in continuous endpoints, disease duration (first symptom onset to screening visit) and disease duration by visit interaction are also included	Clarification of the terms in MMRM model

4 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.

5 SUPPORTING DOCUMENTATION

5.1 APPENDIX 1 LIST OF ABBREVIATIONS

AE:	adverse event
AESIs:	adverse events of special interest
ALSAQ-5:	Amyotrophic Lateral Sclerosis Assessment Questionnaire
ALT:	alanine aminotransferase
ANCOVA:	analysis of covariance
ATC:	anatomic therapeutic category
ECG:	electrocardiogram
EU:	Europe
HDD:	handheld dynamometer
HLT:	high level term
IMP:	investigational medicinal product
ITT:	intent-to-treat
LLOQ:	lower limit of quantification
LLT:	lower-level term
MedDRA:	medical dictionary for regulatory activities
mITT:	modified intent-to-treat
NfL:	serum neurofilament light chain
PCSA:	potentially clinically significant abnormality
PK:	pharmacokinetic
PT:	preferred term
ROW:	rest of the world
SAP:	statistical analysis plan
SD:	standard deviation
SOC:	system organ class
TE:	treatment-emergent
TEAE:	treatment-emergent adverse event
WHO-DD:	World Health Organization-drug dictionary

5.2 APPENDIX 2 PARTICIPANT DISPOSITIONS

The number (%) of participants included in each of the analysis populations listed in Table 3 will be summarized.

Screened participants are those with a signed informed consent. Screen failures are defined as participants who consent to participate in the study but are not subsequently randomized. The number of screened participants will be summarized along with the number (%) of screen failures overall and by reasons.

The number (%) of participants in the following categories will be provided:

- Exposed but not randomized, if applicable
- Randomized
- Randomized but not exposed, if applicable
- Randomized and exposed
  - Completed the treatment period
  - Did not complete the treatment period including main reason for permanent intervention discontinuation and reason for intervention withdrawal by participant
- Completed the Part A study period
- Did not complete the Part A study period including main reason for study discontinuation
- Completed the Part B study period
- Did not complete the Part B study period including main reason for study discontinuation
- Status at last contact (alive, dead)

Reasons for permanent study intervention and study discontinuation, “adverse event” and “other reasons” will be split as related versus not related to COVID-19, if applicable.

For all categories of participants (except for screened and nonrandomized), percentages will be calculated using the number of randomized participants as the denominator.

In addition, the number (%) of participants screened, screened-failed, randomized, with permanent intervention discontinuation and with early study discontinuation for Part A/Part B study period will be provided by country and site. Listings of other reasons for treatment discontinuation, and participants who are exposed but not randomized will be provided.

Protocol deviations

Critical and major protocol deviations (automatic or manual) will be summarized in the randomized population as well as displayed separately as related versus not related to COVID-19 if applicable in Part A and Part A + Part B respectively. A listing of critical and major protocol deviations will be provided.

5.3 APPENDIX 3 DEMOGRAPHICS AND BASELINE CHARACTERISTICS, PRIOR OR CONCOMITANT MEDICATIONS

Demographics, baseline characteristics, medical surgical history

The following demographics and baseline characteristics, smoking and alcohol history, medical and surgical history and disease characteristics at baseline will be summarized using descriptive statistics in the randomized population.

Demographic and baseline characteristics include:

- age in years as quantitative variable and in categories (< 65, ≥ 65)
- gender (Male, Female)
- race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Multiple, Unknown, Not reported)
- ethnicity (Hispanic or Latino, not Hispanic or Latino, Unknown, Not reported)
- region (US, non-US; North America, Europe, Asia)
- weight in kg as a quantitative variable
- BMI in kg/m^2 as a quantitative variable and in categories (< 25, ≥ 25 to < 30, ≥ 30)

Smoking and alcohol habits:

- smoking history (Never, Current, Former)
- cessation prior to screening for Former smokers in months
- cigarettes per day for smokers
- frequency of alcohol drinking in the past 12 months (Never, Occasional, At least monthly, At least weekly, At least daily)
- Number of standard alcohol drinks on typical day when drinking (1 or 2, >2)

Disease characteristics at baseline include:

- ALS diagnosis type (possible, clinically probable ALS, clinically probable laboratory-supported, or clinically definite)
- initial disease onset location (bulbar, other)
- ALS disease duration (years) from first symptom onset to the screening visit
- time since diagnosis (years)
- ALSFRS-R total score
- ALSFRS-R pre-study slope defined as (48-ALSFRS-R score at the screening visit)/duration in months between the screening visit and disease onset)
- SVC

- use of Riluzole collected from IRT
- use of Edarovone collected from IRT
- use of the combination of sodium phenylbutyrate and taurursodiol collected from IRT
- use of Riluzole and Edarovone collected from IRT
- use of Riluzole and the combination of sodium phenylbutyrate and taurursodiol collected from IRT
- use of Edaravone and the combination of sodium phenylbutyrate and taurursodiol collected from IRT
- use of Edaravone and the combination of sodium phenylbutyrate and taurursodiol collected from IRT

Baseline safety and efficacy parameters (apart from those listed above) will be presented along with the safety and efficacy summaries.

Relevant medical and surgical history collected in the eCRF will be coded to a LLT, PT, HLT, HLGT, and associated primary SOC using the MedDRA version currently in effect at Sanofi at the time of database lock and will be summarized by primary SOC and HLT (internationally agreed SOC order and decreasing frequency of HLTs in the Overall group).

Prior or concomitant medications

All medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD) using the version currently in effect at Sanofi at the time of database lock.

- Prior medications are those the participant received prior to first IMP intake. Prior medications can be discontinued before first administration or can be ongoing during treatment period.
- Concomitant medications are any medications received by the participant concomitantly to the IMP during the on-treatment period.
- Post-treatment medications are those the participant received in the period running from the end of the concomitant medications period up to the end of the study, if applicable.
- A given medication can be classified as a prior medication and/or as a concomitant medication and/or as post-treatment medication. If it cannot be determined whether a given medication was taken prior or concomitantly or post, it will be considered as prior, concomitant, and post-treatment medication.

The prior, concomitant and post-treatment (if applicable) medications will be summarized for the randomized and exposed population, by anatomic and therapeutic level. Concomitant medications will be summarized the summary in Part A and Part A + Part B respectively. The summaries will be sorted by decreasing frequency of anatomic category (ATC) based on incidence in the SAR443820 group. In case of equal frequency, alphabetical order will be used. Participants will be counted once in each ATC category (anatomic or therapeutic) linked to the medication.

Any use of noninvestigational medicinal products (riluzole, edaravone, and the combination of sodium phenylbutyrate and taurursodiol, or any combinations of these medicinal products) will be summarized for the randomized and exposed population in Part A and Part A + Part B respectively.

5.4 APPENDIX 4 DATA HANDLING CONVENTIONS

Analysis windows for time points

The following analysis windows will decide how the scheduled and/or unscheduled visits will be used in the by-visit analyses of efficacy, safety, and PD variables.

A measurement (scheduled or unscheduled) will be used if it is available and measurement date is within the analysis window.

After applying these time windows, if multiple assessments are associated to the same time point, the closest from the targeted study day will be used. If the difference is a tie, the value after the targeted study day will be used. If multiple valid values exist within a same day, then the first value of the day will be selected.

If there is no measurement for a given parameter in an analysis window, data will be considered missing for the corresponding visit.

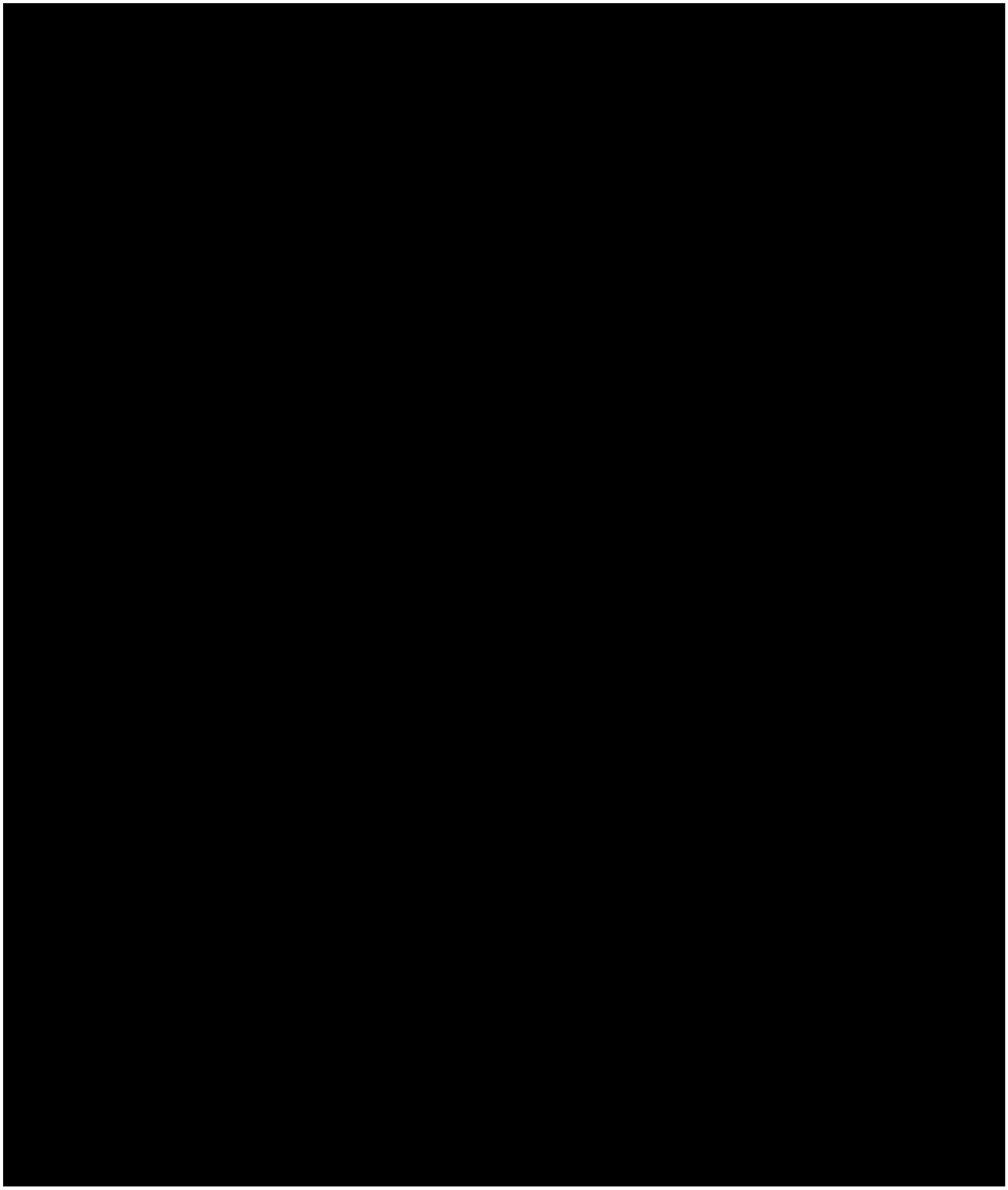
Table 7 - Analyses window definition of efficacy variables

Table 8 - Analyses window definition of safety variables

[redacted]

[redacted]

Table 9 - Analyses window definition of PD variables



Unscheduled visits

Unscheduled visit measurements of laboratory data, vital signs, and ECG will be used for computation of baseline, the last on-treatment value, analysis according to PCSAs, and the shift summaries for safety. They will also be included in the by-visit summaries (central lab only for laboratory) if they are re-allocated to scheduled visits based on the analysis windows defined above.

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