Sponsor: Sanofi **Drug substance(s):** SAR443820	**Study Identifiers:** WHO: U1111-1263-5766 IND: 151444 EudraCT: 2021-004156-42 NCT: NCT05237284 **Study code:** ACT16970

Title of the study:

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

Study center(s):

This study was conducted at 62 centers that enrolled at least 1 participant in 13 countries (Belgium, Canada, China, France, Germany, Italy, Japan, Netherlands, Spain, Sweden, Poland, United Kingdom, and United States of America).

Study period:

Study initiation date: 13 April 2022 (first signed informed consent)

Cut-off data of data (final analysis): 07 March 2024

Study Status: Terminated. The study was terminated as its Part A did not meet the primary endpoint.

Phase of development: Phase 2

Objectives:

Part A

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)

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)
- To assess the pharmacodynamic (PD) effect of SAR443820 compared to placebo on a key disease biomarker
- To assess the safety and tolerability of SAR443820 compared to placebo
- To assess the pharmacokinetics (PK) of SAR443820

Part B

Primary

- To assess the long-term effects of SAR443820 on function and survival

Secondary

- To assess the long-term effects of SAR443820 on disease progression, survival, respiratory function, and quality of life (QoL)
- To assess the long-term effect of SAR443820 on a key disease biomarker
- To assess the long-term safety and tolerability of SAR443820
- To assess the pharmacokinetics (PK) of SAR443820

Methodology:

ACT16970 was 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 ALS, followed by an open label extension.

Study ACT16970 consisted of 2 parts (A and B).

Part A was a 24-week, double blind, placebo-controlled part, preceded by a screening period of up to 4 weeks before Day 1. On Day 1, participants were randomized in a ratio of 2:1 to receive either 20 mg BID SAR443820 or matching BID placebo. Randomization was stratified by the geographic region of the study site, 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 were to attend in-clinic study assessments for all visits up to Week 24. All participants who completed study intervention in Part A entered open-label extension (Part B) starting from Week 24. Participants who permanently discontinued study intervention or chose not to enter Part B had their follow up visit 2 weeks after the last dose of the study intervention. Participants who had permanently discontinued study intervention during Part A also had the option to remain in the study for follow up, however they would not receive any further study intervention.

Part B was an open-label, long-term extension of Part A, starting from Week 24 and continuing up to Week 104. In Part B, participants received 20 mg BID SAR443820, except those who had permanently discontinued study intervention in Part A and chose to remain in the study for follow-up. The study intervention assignment of participants at randomization in Part A remained blinded for Investigators, participants, and site personnel until the end of Part B unless there was a medical need to unblind individual study intervention assignment.

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

Number of study participants:

Out of 261 planned participants, 305 participants were eventually enrolled in Part A, including 203 participants in SAR443820 group, and 102 participants in placebo group (1 participant was randomized but not treated).

Part A was completed on 11 January 2024 (last participant last visit), with a total of 255 participants completing the study up to Week 24. This included 167 (82.3%) participants from the SAR443820 group and 88 (86.3%) participants from the placebo group. Out of these 255 participants, 242 participants completed Part A while still taking study intervention (155 [76.4%] participants from the SAR443820 group and 87 [85.3%] participants from the placebo group).

During the study, a risk of ALT increase/DILI for SAR443820 was identified. In response to this risk, IMP administration was paused immediately in Part B (study sites were notified on 05 December 2023). At that point in time, 230 participants had already entered Part B:

- a total of 215 participants (136 from the SAR443820 group and 79 from the placebo group, respectively) had entered Part B with study intervention;
- a total of 15 participants (all from SAR443820 group) had entered Part B without study intervention. They had stopped intervention during Part A and opted to stay in the study for follow-up.

The remaining 25 participants (16 and 9 participants from SAR443820 and placebo groups, respectively) entered Part B without any study intervention due to IMP administration pause.

At the time of study termination, 190 participants were in Part B.

All enrolled participants were included in the analyses. This synopsis presents key data collected up to data lock point of 07 March 2024.

Diagnosis and criteria for inclusion:

This study enrolled both male and female participants, ranging from 18 to 80 years of age inclusive, and with an early stage of 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

Study products

In Part A (24-week double blind period), participants were randomized to receive either 20 mg BID SAR443820 or BID matching placebo.

In Part B (80-week open-label period), participants were to receive 20 mg BID SAR443820 (until identified risk of ALT increase/DILI led to IMP immediate pause in Part B, as per amended protocol 05, dated 13 December 2023).

Duration of study intervention:

20 mg BID SAR443820 or BID matching placebo were administered in Part A for 24 weeks. In Part B, 20 mg BID SAR443820 was to be administered for 80 weeks (until identified risk of ALT increase/DILI led to IMP immediate pause in Part B, as per amended clinical trial protocol 05, dated 13 December 2023).

Criteria for evaluation:

Part A

Primary

- Change from baseline in the ALSFRS-R total score to Week 24

Secondary

- 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
- Change from baseline in serum neurofilament light chain (NfL) to Week 24
- 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
- Plasma concentration of SAR443820

Part B

Primary

- Combined assessment of the function and survival (CAFS) score at Week 52

Secondary

- 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
- Change from baseline in serum neurofilament light chain (NfL) to Week 52
- 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
- Plasma concentration of SAR443820

Statistical methods:

Analysis populations:

The Intent-to-treat population (ITT) consisted of all randomized participants. The modified ITT (mITT) population consisted of all randomized participants who either died or had available baseline and at least one post-baseline ALSFRS-R assessment. The safety population consisted of all randomized participants who received at least 1 dose (including partial dose) of the study intervention. The pharmacokinetic (PK) population consisted of all randomized participants who received at least 1 dose of the study intervention and had at least 1 PK assessment with adequate documentation of dosing and sampling dates and times.

Primary analysis for the primary endpoint in Part A:

The primary efficacy endpoint was the change from baseline in the Amyotrophic Lateral Sclerosis Functional Rating Scale Revised (ALSFRS-R) total score to Week 24. The primary endpoint was 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 there was less than 10 participants in a randomization strata level, then the corresponding factor was not included as a covariate in the MMRM model.

Primary analysis for the primary endpoint in Part B:
The primary endpoint in Part B was the combined assessment of function and survival (CAFS) at Week 52. The CAFS for each participant is the sum of all pairwise comparisons (+1, 0, -1) based on survival data and/or change from baseline in ALSFRS-R score to Week 52 (based on the last ALSFRS-R time-point available for both participants up to Week 52). CAFS score at Week 52 was analyzed in the mITT population using the Wilcoxon-Mann-Whitney test to compare mean scores between the study intervention groups at Week 52.

Analysis of secondary efficacy endpoints:

For Part A, secondary efficacy endpoints included the CAFS at Week 24, change from baseline in SVC, ALSAQ-5, and muscle strength (HDD and grip strength analyzed separately) to Week 24. CAFS at Week 24 was analyzed using the similar statistical method as used for CAFS at Week 52 in Part B using the mITT population. The other continuous secondary endpoints in Part A were analyzed using similar statistical methods as those used for the primary analysis of the change from baseline in ALSFRS-R total score to Week 24 in Part A using the ITT population, except that baseline ALSFRS-R total score was replaced by the baseline value of the corresponding endpoint.

For Part B, secondary efficacy endpoints included the CAFS at Week 76 and 104, change from baseline in ALSFRS-R total score, SVC, serum neurofilament light chain, in ALSAQ-5 to Week 52, Week 76, and Week 104, time from baseline to death, and time from baseline to either death or permanent assisted ventilation, whichever comes first. Similar statistical method was used as for the primary endpoint (primary analysis for Part A) for continuous endpoints, except for CAFS at Week 76 and 104, for which similar method as for CAFS at Week 52 was used (primary analysis for primary endpoint of Part B).

A study-level multiplicity procedure was used to control the overall type I error rate for testing primary and secondary efficacy endpoints at a 2-sided significance level of 0.05.

Analysis of safety data:

All safety analyses were performed descriptively on the safety population and analyzed according to the intervention actually received. No statistical testing was performed for safety analyses.

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

Summary Results:

Demographic and other baseline characteristics:

Demographics and participant characteristics at baseline were balanced between intervention groups. The mean (SD) age of the randomized population was 56.9 (11.5) years, 28.9% of the population was 65 years or older.

A total of 183 (60.0%) male and 122 (40.0%) female participants were included in the study, most of them were White (195 [63.9%] participants) or Asian (78 [25.6%] participants). The median BMI was 24.27 kg/m2 with the majority of participants having a normal BMI. The use of non-investigational medications for ALS had similar distribution across the treatment groups.

The disease characteristics at baseline were generally balanced between intervention groups (less or equal to 10% difference between groups).

Overall, the most frequent ALS diagnosis types were clinically definite ALS for 125 (41.0%) participants, clinically probable ALS for 95 (31.1%) participants, and clinically probable ALS - laboratory-supported for 56 (18.4%) participants. The ALS onset region was bulbar for 61 (20.0%) participants and other for 244 (80.0%). The mean (SD) time since symptom onset was 1.14 (0.45) years overall (range: 0.2 to 2.0). The mean (SD) time since diagnosis was 0.47 (0.34) years overall (range: 0.0 to 1.7). The mean (SD) baseline ALSFRS-R total score was 36.06 (4.61) overall (range: 21.0 to 45.0). The mean (SD) ALSFRS-R pre-study decline rate per month was 0.97 (0.58) overall (range: 0.4 to 4.7). The mean (SD) baseline slow vital capacity was 81.10 (17.38) overall (range: 38.6 to 139.0).

Exposure:

Part A

The cumulative exposure was comparable in both groups (82.79 participant years and 44.59 participant years, in the SAR443820 group for SAR443820 exposure, and in the placebo group for placebo exposure, respectively), considering the 2:1 randomization. The median extent of IMP exposure (SAR443820 and placebo) was 168.0 days in both groups.

Part A + Part B

The cumulative exposure was 126.72 participant years and 21.66 participant years, in the SAR443820/SAR443820 group and in the placebo/SAR443820 group, respectively. The median extent of IMP exposure was 204.5 days and 85.0 days in the SAR443820/SAR443820 group and in the placebo/SAR443820 group, respectively.

Efficacy

Part A

Primary endpoint

The primary endpoint was not met: Mean (SD) changes from baseline in ALSFRS-R at Week 24 were similar in both the SAR443820 and the placebo groups (-6.1 [5.4] and -5.9 [5.9], respectively). No significant difference was found in least squares (LS) mean (95% CI) between the SAR443820 group (-6.730 [-7.484, -5.976]) and the placebo group (-6.317 [-7.362, -5.271]) (P=0.5289). In addition, no positive trend was observed from the SAR443820 group compared to the placebo group in change in ALSFRS-R score from baseline to Week 24 in the subgroup analyses.

Secondary endpoints

At Week 24:

• The mean (SD) CAFS scores were similar in the SAR44320 group (147.13 [83.06]) and in the placebo group (151.19 [90.71]) (nominal P=0.6999).

• The mean (SD) SVC had decreased when compared to baseline. This decrease was similar in both groups (-11.24 [13.35] and -13.43 [14.66] in the SAR443820 group and in the placebo group, respectively). Also, no difference was found in LS mean (95% CI) between the SAR443820 group (-13.163 [-15.215, -11.112]) and the placebo group (-13.583 [-16.376, -10.790]) (nominal P=0.8134).

• The mean (SD) in megascore (pertaining to muscle strength) had slightly decreased since baseline. The decrease was found similar for both groups and mean (SD) change from baseline was -0.495 (0.704) in the SAR443820 group and -0.498 (0.960) in the placebo group. In addition, no difference was found in LS mean (95% CI) between the SAR443820 group (-0.519 [-0.632, -0.406]) and the placebo group (-0.514 [-0.664, -0.365]) (nominal P=0.9565).

• There was a slight increase in ALSAQ-5 score, for both groups, and mean (SD) change from baseline was similar in the SAR443820 group (2.4 [3.1]) and in the placebo group (2.1 [3.1]). No difference was found in LS mean (95% CI) between the SAR443820 group (2.546 [2.057, 3.035]) and the placebo group (2.026 [1.358, 2.695]) (nominal P=0.2182).

• Mean (SD) changes from baseline to Week 24 in serum NfL were similar in the SAR443820 group (0.362 pg/mL [22.244 pg/mL]) and in the placebo group (0.682 pg/mL [39.923 pg/mL]). No difference was found in Week 24 LS geometric mean ratio to baseline (95% CI) between the SAR443820 group (0.994 [0.955, 1.034]) and the placebo group (1.035 [0.981, 1.092]) (nominal P=0.2356).

Part B

Cumulative Part A + Part B data, up to data lock point, did not reveal any difference in efficacy related primary (CAFS at Week 52: mean rank = 89.99 and 90.02 for SAR443820/SAR443820 and placebo/SAR443820, respectively, with nominal p-value=0.9988) and secondary endpoints between SAR443820/SAR443820 group and placebo/SAR443820 group. Since the study was prematurely terminated, results of Part B should be considered with caution due to small sample size.

Safety results:

Part A

• **TEAEs**: the percentage of participants with any TEAEs was higher in the SAR443820 group (171 [84.7%]) compared with the placebo group (80 [78.4%]).

- TEAEs were assessed as related to the IMP (by the Investigator) in a greater proportion of participants in SAR443820 group (73 [36.1%]) when compared to placebo group (19 [18.6%]).

- The 4 most frequently reported TEAEs in either intervention group by PT were: fall (44 [21.8%] participants in the SAR443820 group and 22 [21.6%] participants in the placebo group), hepatic enzyme increased (35 [17.3%], 2 [2.0%]), headache (25 [12.4%], 9 [8.8%]), and COVID-19 (21 [10.4%], 11 [10.8%]).

- The PT with notably higher TEAE incidence in the SAR443820 group compared with placebo group (with a difference of ⩾ 5%) was hepatic enzyme increased (35 [17.3%], 2 [2.0%]).

• **SAEs:** The incidence of treatment-emergent SAEs was similar in both the SAR443820 group (32 [15.8%]) and the placebo group (16 [15.7%]).

- Treatment-emergent SAEs were assessed as related to the IMP in 4 (2.0%) and 0 participants in the SAR443820 group and in the placebo group, respectively (3 [1.5%] participants with hepatic enzyme increased and 1 [0.5%] participant with DILI.

• **Deaths:** A total of 9 participants died during this study part (7 [3.5%] and 2 [2.0%] participants in the SAR443820 group and in the placebo group, respectively), in similar proportions across groups.

• **TEAEs leading to permanent treatment discontinuation:** TEAEs leading to permanent treatment discontinuation were reported with higher incidence in the SAR443820 group than in the placebo group (28 [13.9%] and 5 [4.9%] participants, respectively).

- The most frequently reported TEAEs leading to permanent treatment discontinuation (in ⩾2% of participants in either intervention group) at the PT level were hepatic enzyme increased (16 [7.9%] participants in the SAR443820 group and 1 [1.0%] participants in the placebo group).

• **AESIs:** AESIs were reported with higher incidence in the SAR443820 group than in the placebo group (44 [21.8%] and 4 [3.9%] participants, respectively).

- The most frequently reported AESIs (in ⩾2% of participants in either intervention group) at the PT level were hepatic enzyme increased (30 [14.9%] participants in the SAR443820 group and 2 [2.0%] participants in the placebo group), ALT increased (4 [2.0%], 1 [1.0%]), and hepatic function abnormal (4 [2.0%], no participant).

There were no clinically meaningful changes over time in red blood cells, platelets, coagulation, white blood cells, electrolytes, metabolism, renal function, and urinalysis observed throughout the course of the study. However, there were notable imbalances between the SAR443820 and placebo groups in liver function parameters, with increases in mean ALT and AST values in the SAR443820 group compared to the placebo group. The most frequently reported potentially clinically significant abnormalities (PCSAs) in the SAR443820 group were ALT >3 ULN, AST >3 ULN, and ALT >5 ULN, with notable imbalances in post-baseline rates between intervention groups for these parameters. There were a total of 3 Hy's Law cases reported (N=2 in Part A, N=1 in Part B).

Part A + Part B (while on SAR443820)

For Part A + Part B safety, results are displayed “while on SAR443820” cumulatively from the beginning of the study to the end of Part B by the time of database lock. They include participants who started receiving SAR443820 in Part A from the SAR443820/SAR443820 group as well as participants who switched to SAR443820 in Part B from the placebo/SAR443820 group.

• **TEAEs:** the percentage of participants with any TEAEs was higher in the SAR443820/SAR443820 group (183 [90.6%]) compared with the placebo/SAR443820 group (51 [64.6%]).

- The incidence of TEAEs considered to be related to IMP (as per Investigator) was higher in the SAR443820/SAR443820 group (83 [41.1%]) compared with placebo/SAR443820 group (23 [29.1%]).

- The 4 most frequently reported TEAEs in either intervention group by PT were: fall (53 [26.2%] participants in the SAR443820/SAR443820 group and 10 [12.7%] participants in the placebo/SAR443820 group), hepatic enzyme increased (41 [20.3%], 13 [16.5%]), headache (26 [12.9%], 3 [3.8%]), and COVID-19 (24 [11.9%], 3 [3.8%]).

- The PTs with notably higher TEAE incidence in the SAR443820/SAR443820 group compared with placebo/SAR443820 group (with a difference of ⩾5%) were fall (see above), headache (see above), diarrhoea (20 [9.9%] versus 1 [1.3%]), COVID-19 (see above), respiratory failure (15 [7.4%] versus no participants), dizziness (14 [6.9%] versus 1 [1.3%]), and fatigue (10 [5.0%] versus no participants).

• **SAEs:** treatment-emergent SAEs were reported in 66 (23.5%) participants, with higher incidence in the SAR443820/SAR443820 group (53 [26.2%]) compared with placebo/SAR443820 group (13 [16.5%]).

- Treatment-emergent SAEs were assessed as related to the IMP in 4 (2.0%) and 5 (6.3%) participants in the SAR443820/SAR443820 group and in the placebo/SAR443820 group, respectively: in SAR443820/SAR443820, 3 (1.5%) participants with hepatic enzyme increased and 1 (0.5%) with DILI. In placebo/SAR443820 group, 3 (3.8%) participants with hepatic enzyme increased, 1 (1.3%) with gastrointestinal infection, and 1 (1.3%) with urinary tract infection).

• **Deaths:** A total of 35 deaths occurred regardless of the study period: In Part A + Part B, a total of 16 deaths were reported (14 [6.9%] in the SAR443820/SAR443820 group and 2 [2.5%] in the placebo/SAR443820 group). Post-treatment, 9 (4.5%) deaths in the SAR443820 group and 10 (9.8%) in the placebo group were reported. Only one SAE resulting in death was assessed as related to the IMP, which was a gastrointestinal infection in a participant from the placebo/SAR443820 group.

• **TEAEs leading to permanent treatment discontinuation:** TEAEs leading to permanent treatment discontinuation (while on treatment) were reported in 46 (16.4%) participants overall, with higher incidence in the SAR443820/SAR443820 group (36 [17.8%]) compared with placebo/SAR443820 group (10 [12.7%]).

- The most frequently reported TEAEs leading to permanent treatment discontinuation (in ⩾2% of participants in either intervention group) at the PT level were: hepatic enzyme increased (18 [8.9%] participants in the SAR443820/SAR443820 group and 7 [8.9%] participants in the placebo/SAR443820 group), and respiratory failure (4 [2.0%], no participants).

• **AESIs:** AESIs were reported in 73 (26.0%) participants overall, with comparable proportion in the SAR443820/SAR443820 group (55 [27.2%]) and in the placebo/SAR443820 group (18 [22.8%]).

- The most frequently reported AESIs (in ⩾2% of participants in either intervention group) at the PT level were hepatic enzyme increased (35 [17.3%] participants in the SAR443820/SAR443820 group and 12 [15.2%] participants in the placebo/SAR443820 group), ALT increased (4 [2.0%], 1 [1.3%]), hepatic function abnormal (4 [2.0%], 1 [1.3%]), and pneumonia (4 [2.0%], no participant).

Issue date: 23-Jan-2025