A Multicenter, Randomized, Placebo-Controlled, Double-Blind Phase 1b Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of SAR443060 in Subjects with Amyotrophic Lateral Sclerosis (ALS)

Published: 01-11-2018
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Double-blinded part:The primary objectives of the study are as follows:• To investigate the safety and tolerability of 28 days of oral doses of SAR443060 in subjects with ALS.The secondary objectives of the study are as follows: • To characterize…

Ethical review	Approved WMO
Status	Completed
Health condition type	Neuromuscular disorders
Study type	Interventional

Summary

ID

NL-OMON49740

Source
ToetsingOnline

Brief title
A study to investigate SAR443060 in patients with ALS

Condition

- Neuromuscular disorders

Synonym
Amyotrophic Lateral Sclerosis (ALS), motor neurone disease

Research involving
Human

Sponsors and support

Primary sponsor: Sanofi-aventis
Source(s) of monetary or material Support: Funded by sponsor: Denali Therapeutics Inc.

Intervention

Keyword: Amyotrophic Lateral Sclerosis (ALS), Neurodegeneration, Phase 1b, RIPK1 inhibitor

Outcome measures

Primary outcome

Safety and tolerability:

AEs, clinical laboratory evaluations (hematology, clinical chemistry,

urinalysis), 12 lead ECGs, vital sign measurements, and physical examinations.

Responses obtained from the Columbia-Suicide Severity Rating Scale (C-SSRS)

will also be used to derive a category for suicidality according to the

Columbia Classification of Suicide Assessment (C-CASA).

Secondary outcome

Pharmacokinetics:

Blood and CSF will be collected for the analysis of plasma and CSF

concentrations of SAR443060. The following endpoints may be determined for

SAR443060 in plasma following each treatment. They will be derived by

noncompartmental analysis of the plasma concentration-time data:

• Cmax

• AUC from time zero to 12 hours (AUC0-12h), AUC from time zero to the last

measured concentration above the limit of quantification (AUC0-last), and/or

AUC from time zero extrapolated to infinity (AUC0-*), as appropriate

• Tmax

• Terminal disposition rate constant (*z) with the respective t1/2

• Other parameters, including oral volume of distribution and oral clearance,

may be determined as appropriate.

• CSF-to-plasma ratios on Days 29 and 71

These parameters may also be determined for metabolites if appropriate.

Pharmacodynamics:

PD of SAR443060 is measured by RIPK1 pS166 in PBMCs from blood. Exploratory

biomarker assays for cytokines, lipids, and metabolomics may be explored in

PBMCs, plasma, urine, and CSF.

Exploratory Clinical:

• Clinical changes in the ALSFRS-R

Study description

Background summary

SAR443060 is a new experimental drug that is being developed as part of the treatment for ALS. The purpose of this study is to investigate how safe and tolerable the new experimental drug SAR443060 is, what its effects are when it is administered to patients with ALS and how the new experimental drug is absorbed and processed by the body.

Receptor-interacting protein kinase 1 (RIP1) is a serine/threonine kinase involved in the regulation of inflammation and cell death. In response to tumor

necrosis factor (TNF)-alpha signaling, RIP1 is activated, and in turn regulates activation of downstream targets, including RIPK3, mixed-lineage kinase domain-like (MLKL) and NF-kB. This signaling cascade initiates a number of cellular processes, including cytokine release, microglial activation, and necroptosis, a regulated form of cell death.

RIPK1 inhibition has been shown to reduce necroptotic cell death in several animal models, including a model of motor neuron cell death related to amyotrophic lateral sclerosis. Immunoblotting analysis of human ALS spinal cord samples has shown increased levels of RIPK1 to be present.

SAR443060 is a novel, potent and selective RIP1 kinase inhibitor that has favorable pharmacokinetic properties and good penetration across the blood brain barrier, allowing target inhibition in the central nervous system. As such, it is a potential therapeutic candidate for neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS).

Study objective

Double-blinded part:
The primary objectives of the study are as follows:
• To investigate the safety and tolerability of 28 days of oral doses of SAR443060 in subjects with ALS.
The secondary objectives of the study are as follows:
• To characterize the PK in plasma and CSF following oral doses of SAR443060.
• To characterize the PD and target engagement of SAR443060 using an assay for RIPK1 pS166 in PBMCs.
The exploratory objectives of the study are as follows:
• To measure changes in cytokines (such as monocyte chemoattractant protein 1 [MCP-1]), neurofilament light chain (NF L), and other inflammatory and neurodegenerative biomarkers in blood, urine, and CSF.
• To explore clinical changes in the revised Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS R).

Open Label Extension:
The primary objective of the OLE is as follows:
• To investigate the safety and tolerability of up to 12 months of oral doses of SAR443060 in subjects with ALS
The exploratory objectives of the OLE are as follows:
• To characterize the PD and target engagement of SAR443060 using an assay for RIPK1 pS166 in PBMCs
• To measure changes in cytokines (such as MCP-1), NF-L, p75ECD and other target- and disease-related (e.g., inflammatory and neurodegenerative) biomarkers in blood, CSF, and urine
• To explore clinical changes in the ALSFRS-R

Study design

This is a (potentially multicenter) randomized, placebo-controlled, double-blind, crossover design phase 1B study that will include up at least 16 and up to 26 subjects. There are two treatment periods. Subjects will be randomized 1:1 to receive either active or placebo treatment for 28 days BID for the first period and then cross over to the opposite treatment assignment for 28 days BID for the second period. There will be a 14-day washout period between the 2 treatment periods.

Subjects will be admitted to the research unit on days 1, 28, 42, and 70. Subjects will be confined to the unit for up to 3 days/2 nights at each admission. In between the subjects will visit the research unit once per week and will administer the study medication at home.

Open-Label Extension:
In the Netherlands, subjects who complete the double-blind study period through the FFU visit may be eligible to enter an OLE and receive dosing with SAR443060 for up to an additional 12 months.
Cumulative data from the ongoing safety review of 8 ALS subjects in the double-blind part of this study and data from the completed 3-month nonclinical toxicity support the initiation of the OLE.
Subjects who complete the double-blind study period more than 14 days before enrolling in the OLE will undergo baseline safety assessments to reassess eligibility prior to receiving SAR443060 in the OLE.

Intervention

SAR443060 (RIPK1 kinase inhibitor)

Study burden and risks

The burden for the participants includes the time investment for the briefing, screening, the occasions, and the follow-up visit. The occasion will consist of 12 days and 8 nights of confinement to the research units. Additionally the participants will visit the research unit 10 times for approximately 4 hour visits.

Blood, urine, CSF (3x) and DNA (1x) samples will be collected during the screening, the occasions and the follow-up visits. Participants will be requested to complete several questionnaires concerning their mental, physical and neurological status and will undergo physical examinations. Life-style restrictions concerning prescription medication, smoking, alcohol intake, strenuous activity and contraception will apply.

The risks of participation are primarily those associated with adverse

reactions to the study drug SAR443060 , which has been evaluated in over 57 healthy subjects (up to 400mg BID) and in 10 patients with ALS or Alzheimer's, and in nonclinical studies to characterize its safety profile. There have been no identified risks or adverse drug reactions to date from the evaluation of SAR443060 in healthy volunteers in Study DNLI-D-0001. Preclinical studies indicate that the immune system, red blood cells, platelets and skin are potential target organs/cell populations in human subjects participating in clinical studies. In nonclinical studies, these effects were observed in monkeys at relatively high exposures (1000mg/kg/d) that exceed those to be tested in human subjects (400mg/d) and are expected to be reversible and able to be monitored in a clinical setting. In the ongoing 3-month nonclinical toxicity study in cynomolgus monkeys, individual animals administered 40 and 200 mg/kg/d had moderate to severe reductions in both red cell mass and platelets. These are also expected to be reversible and able to be monitored in a clinical setting. The Phase 1b dose is 50 mg BID, and at this dose level, the anticipated exposure is expected to provide at least a 6-fold margin to potential risks for thrombocytopenia and anemia in the clinic.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Double-blinded part:
6) Diagnosis of laboratory-supported probable, probable, or definite (sporadic or familial) ALS according to the El Escorial World Federation of Neurology revised research diagnostic criteria (Ludolph et al. 2015;)
7) Less than 3 years since symptom onset
8) Forced vital capacity (FVC) >50% predicted measured within 30 days of screening
9) If subject is taking approved ALS treatments (riluzole and/or edaravone), doses must be stable for >=2 months prior to screening and subject is expected to stay on a stable regimen throughout the study.
11) Subjects must be able to swallow the study capsules.
Open Label Extension:
1) Successful completion of both periods of the double-blind, crossover part of this study within 12 months of anticipated first dose of OLE
2) Body weight of at least 45 kg
6) Stable prescription medications including riluzole and/or edaravone for >= 1 month. New prescription medications or changes to existing medications during this trial period are allowed with investigator discretion.
7) Subjects must either be able to swallow the study capsules (thickening agents to assist in swallowing are permitted) or have a G-tube in place and are able to administer study drug through G-tube either independently or with help via a caregiver.

Exclusion criteria

Double-blinded part:
1) Unstable or poorly controlled comorbid disease process of any organ system currently requiring active treatment or likely to require treatment adjustment during the study, as assessed by the investigator or Sponsor
2) History of a clinically significant non-ALS neurologic disorder (other than frontal temporal lobe dementia), including, but not limited to, muscular dystrophy, spinal stenosis, peripheral neuropathy, inherited neuropathies, AD, Parkinson*s disease, Lewy body dementia, vascular dementia, Huntington*s disease, epilepsy, stroke, multiple sclerosis, brain tumor, or brain infection or abscess
3) History of head trauma resulting in loss of consciousness or clinically

significant concussion within 1 year before screening, or any head trauma that resulted in permanent neurologic deficit
4) Clinical laboratory test values outside the normal range at screening, unless assessed by the investigator and CRO medical monitor as clinically acceptable or as specified in other exclusion criteria below
21) Use of or intention to use any prohibited prescription or over-the-counter (OTC) medication (including vitamin/mineral supplements and herbal medicines such as St. John*s Wort) that is a moderate to strong CYP3A inducer or inhibitor within 7 days or 5 half-lives (whichever is longer) of the first dose administration or anticipated use through the follow-up visit. Note: other medications are permitted if subject is on a stable regimen for at least 30 days before first dose administration. Nonsystemic medications (e.g., topical medications unlikely to achieve meaningful plasma exposure), subcutaneous lidocaine, paracetamol, and caffeine for treatment of post-LP headache, and medications needed to treat AEs and medical emergencies are permitted. Other medication may also be permitted if jointly agreed to by both investigator and Sponsor.
22) Use of anticoagulation, daily aspirin >100 mg, or anti-platelet medications within 5 half-lives before the first administration of study drug or anticipated need for these medications through the final follow-up visit. Note: the use of OTC nonsteroidal anti-inflammatory drugs (NSAIDs) at doses specified in the OTC drug label for less than 3 consecutive days is permitted.
23) History of bleeding disorders included but not limited to thrombocytopenia (defined as platelets <140,000/µL), von Willebrand disease, hemophilia, and other factor deficiencies
Open Label Extension:
1) Presence of laboratory abnormalities, physical examination findings, or AEs determined to be clinically significant by the investigator from the double-blind part of the study that have not resolved by the FFU visit
2) For subjects who completed the double-blind part of the study >14 days prior to start of OLE, presence of clinical laboratory test values outside the normal range at OLE screening, significant physical examination abnormalities, or persistent AEs from the double-blind part of the study, unless assessed by the investigator as clinically acceptable
3) New diagnosis of a clinically significant non-ALS neurologic disorder (other than frontal temporal lobe dementia), including, but not limited to: muscular dystrophy, spinal stenosis, peripheral neuropathy, inherited neuropathies, AD, Parkinson*s disease, Lewy body dementia, vascular dementia, Huntington*s disease, epilepsy, stroke, multiple sclerosis, brain tumor, or brain infection or abscess
4) Any diagnosis of new onset disease that was exclusionary in the randomized, double-blind part of the study. New onset spinal cord disease or other lumbar region abnormalities that may interfere with lumbar puncture (e.g., skin infection, structural abnormalities) will be allowed at the investigator*s discretion
10) Participation in any other investigational drug trial or use of investigational drug within 7 days or 5 half-lives (whichever is longer) prior

to OLE initiation, or planned use of investigational drugs during the OLE
12) Use of or intention to use any prohibited prescription or over-the-counter (OTC) medication (including vitamin/mineral supplements and herbal medicines such as St. John*s Wort) that is a moderate to strong CYP3A4/5 inducer or inhibitor within 7 days or 5 half-lives (whichever is longer) of the first dose administration or anticipated use through the follow-up visit. Note: other medications are permitted if subject is on a stable regimen for at least 30 days before first dose administration. Nonsystemic medications (e.g., topical medications unlikely to achieve meaningful plasma exposure), subcutaneous lidocaine, paracetamol, and caffeine for treatment of post-LP headache, and medications needed to treat AEs and medical emergencies are permitted. Other medication may also be permitted if jointly agreed to by both investigator and Sponsor.
13) Use of anticoagulation, daily aspirin >100 mg, or anti-platelet medications within 5 half-lives before the first administration of study drug or anticipated need for these medications through the final follow-up visit. Note: the use of OTC NSAIDs at doses specified in the OTC drug label for less than 3 consecutive days is permitted.
14) History of bleeding disorders included but not limited to thrombocytopenia (defined as platelets <140,000/µL), von Willebrand disease, hemophilia, and other factor deficiencies

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	07-12-2018
Enrollment:	16
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	SAR443060
Generic name:	N/A

Ethics review

Approved WMO Date:	01-11-2018
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-11-2018
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-01-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-01-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-02-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	14-08-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	19-08-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	28-11-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	05-12-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-02-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-02-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	05-03-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2018-003623-11-NL
ClinicalTrials.gov	NCT03757351
CCMO	NL67676.056.18

Study results

Date completed: 10-06-2020

Results posted: 19-04-2022

First publication
07-02-2021