A Phase 3, randomized, double-blind, efficacy and safety study comparing SAR442168 to placebo in participants with nonrelapsing secondary progressive multiple sclerosis

Published: 16-09-2020
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Primary: To determine the efficacy of SAR442168 compared to placebo in delaying disability progression in nrSPMSSecondary: 1. To evaluate safety, tolerability, and efficacy of SAR442168 compared to placebo on clinical endpoints, MRI lesions,...

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

Summary

ID

NL-OMON54474

Source
ToetsingOnline

Brief title
HERCULES

Condition

- Demyelinating disorders

Synonym
demyelinating disease, Multiple sclerosis

Research involving
Human

Sponsors and support

Primary sponsor: Sanofi B.V.
Source(s) of monetary or material Support: Genzyme Europe B.V.

Intervention

Keyword: autoimmune disease, Bruton's tyrosin kinase inhibitor, Multiple sclerosis, SPMS

Outcome measures

Primary outcome

The primary efficacy endpoint is the time to onset of CDP (confirmed for at

least 6 months) assessed by the EDSS score.

Secondary outcome

The secondary endpoints from time to event will be analyzed in a similar manner

to the primary efficacy endpoint.

• Time to start of composite CDP

• Time to start of 3 months CDP

• Time to CDI

• Total number of new and / or growing hyperintense T2 lesions using MRI

• Percentage change in brain volume loss using MRI

• Change in cognitive function using the SDMT

• Change in the score on the "quality of life" questionnaire

• Adverse reactions (AEs), serious adverse events (SAEs), safety results on

MRI, and possible clinically significant abnormalities in laboratory results,

on electrocardiogram (ECG) or in vital signs during the study period.

Study description

Background summary

The Bruton's tyrosine kinase (BTK) pathway is critical for signaling in B lymphocytes and myeloid cells including the central nervous system (CNS) microglia. Each of these cell types is involved in the pathophysiology of multiple sclerosis (MS).
SAR442168, a CNS penetrant BTK inhibitor, has the potential for a dual mechanism of action by modulation and subsequently inhibition of antigen-induced B cell activation responsible for inflammation and by modulating macrophages and poorly adapted microglial cells linked to neuro -inflammation in the brain and spinal cord.

Even the most recent high-efficiency disease modifying therapies primarily work on adaptive immunity in the periphery with only a modest or temporary ability to stop neuro-inflammatory and neurodegenerative processes and stop disease progression

Chronic disability accumulation remains a significant, unfulfilled problem for people with MS. Individuals with progressive disease, including secondary progressive MS (SPMS), need treatment to reduce disability accumulation.The recent approval of siponimod reflects the perception that this type of drug reduced acute inflammatory activity rather than directly reducing "progression independent of relapse activity (PIRA)".

In a phase 2 dose-finding study involving participants with relapsing MS (RMS) (DRI15928), SAR442168 was shown to reach pharmacologically relevant concentrations in cerebrospinal fluid (CSF) with the potential to inhibit microgliocytes and infiltrating macrophages from the bone marrow, which are believed to be responsible for stimulating neuro-inflammation linked to disease progression.

Study objective

Primary: To determine the efficacy of SAR442168 compared to placebo in delaying disability progression in nrSPMS

Secondary:
1. To evaluate safety, tolerability, and efficacy of SAR442168 compared to placebo on clinical endpoints, MRI lesions, cognitive performance, physical function, and quality of life
2. To evaluate the pharmacokinetics and pharmacodynamics of SAR442168.

Study design

A Phase 3, randomized, double-blind, 2-arm, placebo-controlled, parallel group, multicenter, event-driven (6-month CDP) trial with a variable treatment duration ranging from approximately 24 to 48 months in participants with nrSPMS.

Intervention

Enrolled participants will be randomly assigned in a 2: 1 ratio to 60 mg oral SAR442168 (obtained from dose determination study DRI15928) or placebo corresponding daily.
Randomisation will be stratified for absence / presence of gadolinium (Gd) enhancing T1 lesions at baseline (number of Gd enhancing lesions = 0 versus >=1) and geographical origin (US versus non-US).

Study burden and risks

Risks related to blood sampling / MRI and side effects of the study drug and contrast medium.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

*previous diagnosis of RRMS in accordance with the 2017 revised McDonald criteria
*18 to 60 year old male or female with nrSPMS
*Demonstrated active disability progression since last year
*EDSS (at screening) of 3 (minimal disability) to 6.5 points (use of intermittent or unilateral assistance to walk about 100 meters)
*Without:
-Relapse in last 24 months
-Recent use of MS treatments
*If female of childbearing potential:
--not pregnant or breastfeeding, and agrees to use acceptable contraceptive method during the intervention period (at a minimum until after the last IMP dose)

Exclusion criteria

-History of infection or at risk for infection
-Presence of psychiatric disturbance or substance abuse
-Excess bleeding risk or use of antiplatelets/anticoagulants
-Significant other concomitant illness/short life expectancy
-Confirmed laboratory or ECG abnormalities, during the screening visit, deemed by the investigator to be clinically significant.
-Conditions that would adversely affect participation in study or make primary efficacy endpoint
-Receiving strong inducers or inhibitors of cytochrome P450 3A (CYP3A) or CYP2C8 hepatic enzymes
-Receiving anticoagulant/antiplatelet therapies
-Sensitivity to study interventions, or drug or other allergy that, per Investigator, contraindicates participation in the study.
-Previously exposed to any BTK inhibitor, including SAR442168.
-Taken other investigational drugs within 3 months or 5 half-lives, whichever is longer, before SCR.
-Contraindication for MRI (People with contraindication to gadolinium (Gd) can be enrolled but cannot receive Gd during MRI scan.)
-Institutionalized because of regulatory or legal order; prisoners or participants who are legally institutionalized.
-Any country-related regulation that would prevent entering the study, if

applicable.
-Not suitable for participation, whatever the reason, as judged by Investigator, including medical or clinical conditions, or participants potentially at risk of noncompliance to study procedures or not able to follow protocol assessments
-Dependent on Sponsor or Investigator
-Employees of study site or directly involved in conduct of study, or immediate family members of such individuals.
-Any other situation during study course that may raise ethics considerations.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	10-06-2021
Enrollment:	10
Type:	Actual

Ethics review

Approved WMO

Date:	16-09-2020
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	23-12-2020
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-02-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-03-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-07-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-08-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-09-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-10-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-01-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-03-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	23-05-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-07-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-08-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	31-08-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-09-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-09-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-11-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-02-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-04-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	05-05-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-08-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-02-2024
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-02-2024
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2020-000647-30-NL
CCMO	NL73813.029.20
Other	U1111-1246-7768