A Phase 3, randomized, double-blind efficacy and safety study comparing SAR442168 to teriflunomide (Aubagio®) in participants with relapsing forms of multiple sclerosis.

Published: 10-09-2020
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Primary: To determine the efficacy of SAR442168 compared to a daily dose of 14 mgteriflunomide (Aubagio) in decreasing relapses in RMS.Secondary:1. To evaluate safety, tolerability, and efficacy of SAR442168 compared to placebo on clinical endpoints...

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

Summary

ID

NL-OMON53998

Source
ToetsingOnline

Brief title
GEMINI-2

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, RMS

Outcome measures

Primary outcome

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

least 6 months) assessed by the annualized adjudicated relapse rate(AARR).

Secondary outcome

The secondary endpoints from time to event will be analysed 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

The ability of SAR442168 to reduce formation of new, active brain lesions in MS was assessed in a Phase 2b dose-finding trial in participants with RMS (DRI15928). This radiographic outcome has been established as a highly reliable predictive biomarker for clinical efficacy in pivotal studies in MS including Phase 3 RMS studies.

Study objective

Primary: To determine the efficacy of SAR442168 compared to a daily dose of 14 mg
teriflunomide (Aubagio) in decreasing relapses in RMS.

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

This is a Phase 3, randomized, double-blind, double-dummy, 2-arm, active-controlled, parallel
group, multicenter, event-driven (6-month CDP (confirmed disability progression)) trial with a variable treatment duration ranging from approximately 18 to 36 months in participants with RMS.

Intervention

Participants will be randomly assigned at a 1:1 ratio to receive the 60 mg selected dose
(established from dose-finding Study DRI15928) of oral SAR442168 daily as well as a placebo to
match the teriflunomide tablet, or 14 mg oral teriflunomide as well as a placebo to match the
SAR442168 tablet daily. Randomization will be stratified by EDSS score at screening (<4 versus >=4) and geographic region (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

*18 to 55 year old male or female with RMS
*EDSS score of <= 5.5 points at screening
*At least 1 of the following prior to screening:
- >=1 documented relapse within the previous year OR
- >=2 documented relapses within the previous 2 years, OR
- >=1 documented Gd-enhancing brain lesion on an MRI scan within the previous year.

*Without:
-PPMS diagnosis
-Significant infection/at increased infection risk
-Significant psychiatric disease or substance abuse
-Excess bleeding risk or use of antiplatelets/anticoagulants
-Recent use of MS treatments
-Significant other concomitant illness/short life expectancy
*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)

Note. The initial clinical demyelinating episode of MS should be counted as a relapse for the
first 2 criteria.

Exclusion criteria

-Diagnose of PPMS
-History of infection or at risk for infection
-Presence of psychiatric disturbance or substance abuse
-Confirmed laboratory or ECG abnormalities, during the screening visit, deemed by the investigator to be clinically significant.
-Conditions that may predispose the participant to excessive bleeding
-Conditions that would adversely affect participation in study or make primary efficacy endpoint non-evaluable
-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.
-A relapse in the 30 days prior to randomization
-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:	Pending
Start date (anticipated):	01-01-2023
Enrollment:	1
Type:	Anticipated

Medical products/devices used

Product type:	Medicine

Brand name:	Aubagio
Generic name:	teriflunomide
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	10-09-2020
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-11-2020
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-12-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-12-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-03-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-03-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-06-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-06-2021

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-08-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-09-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-10-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-10-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-01-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-01-2022
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:	28-06-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-08-2022

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-11-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-11-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-02-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-03-2023
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:	12-09-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-12-2023
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:	01-03-2024
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	EUCTR2020-000644-55-NL
ClinicalTrials.gov	NCT04410978
CCMO	NL74113.029.20