A Phase 2b dose-finding study for SAR442168, a Bruton's tyrosine kinase inhibitor, in participants with relapsing multiple sclerosis

Published: 23-01-2019
Last updated: 09-04-2024

Primary: - To determine the dose-response relationship for SAR442168 to reduce the number of new active brain lesions. Secondary: - To evaluate efficacy of SAR442168 on disease activity, assessed by clinical and imaging measures.- To evaluate the...

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

Summary

ID

NL-OMON48153

Source
ToetsingOnline

Brief title
DRI15928

Condition

- Demyelinating disorders

Synonym
demyelinating disease, Multiple sclerosis

Research involving
Human

Sponsors and support

Primary sponsor: Sanofi-aventis

Source(s) of monetary or material Support: Sanofi

Intervention

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

Outcome measures

Primary outcome

Number of new Gd-enhancing T1-hyperintense lesions at the end of 12 weeks of SAR442168 treatment as detected by brain MRI.

Secondary outcome

- Number of new or enlarging T2 lesions at the end of 12 weeks of SAR442168 treatment

- Number of Gd-enhancing T1-hyperintense lesions at the end of 12 weeks of SAR442168 treatment

- Adverse events (AEs), serious adverse events (SAEs), potentially clinically significant abnormalities in laboratory tests, electrocardiogram (ECG), or vital signs during the study period

Study description

Background summary

The Bruton's tyrosine kinase (BTK) pathway is critical to signaling in B lymphocytes and myeloid cells including central nervous system (CNS) microglia. Each of these cell types has been implicated in the pathophysiology of multiple sclerosis (MS). Accordingly, SAR442168, a CNS-penetrant BTK inhibitor has the potential for a dual mechanism of action by inhibiting antigen-induced B-cell activation responsible for inflammation and by modulating maladaptive microglial cells linked to neuroinflammation in the brain and spinal cord. There is still a significant unmet need for therapies that target neuroinflammation in the CNS with a goal of halting long-term disability and neurodegeneration in people with relapsing multiple sclerosis (RMS), and also

in progressive forms of the disease (primary progressive multiple sclerosis [PPMS] and secondary progressive multiple sclerosis [SPMS]). Even the most recent high-efficacy disease-modifying therapies act mainly on adaptive immunity in the periphery with only modest or temporary ability to halt neuroinflammatory and neurodegenerative processes and stop disease progression, as also demonstrated by recent studies in progressive MS.

Study objective

Primary:
- To determine the dose-response relationship for SAR442168 to reduce the number of new active brain lesions.

Secondary:
- To evaluate efficacy of SAR442168 on disease activity, assessed by clinical and imaging measures.
- To evaluate the safety and tolerability of SAR442168.

Study design

A Phase 2, randomized, double-blind, placebo-controlled, cross-over, dose-ranging study to investigate the MRI efficacy and the safety of 12 weeks administration of SAR442168

Intervention

Bruton's tyrosine kinase inhibitor, up to four tablets daily to achieve 5, 15, 30 or 60mg daily doses depending on the cohort and arm the patient is randomized to. This is given in tablet form and the route of administration is oral. Patients will take the medication for 12 weeks and will take placebo 4 weeks before or after the treatment period.

Study burden and risks

Risks and burdens related to blood collection, study procedures and possible adverse events of study medication.

Contacts

Public
Sanofi-aventis

Paasheuvelweg 25
Amsterdam 1105 BP

NL
Scientific
Sanofi-aventis

Paasheuvelweg 25
Amsterdam 1105 BP
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- The participant must be 18 to 55 years of age, inclusive, at the time of signing the informed consent.
- The participant must have been diagnosed with RMS according to the 2017 revision of the McDonald diagnostic criteria.
- The participant must have at least 1 documented relapse within the previous year, *2 documented relapses within the previous 2 years, or *1 active Gd-enhancing brain lesion on an MRI scan in the past 6 months and prior to screening.
- A female participant must use a double contraception method including a highly effective method of birth control, except if she has undergone sterilization at least 3 months earlier or is postmenopausal. Menopause is defined as being amenorrheic for *2 years with serum follicle-stimulating hormone (FSH) level >30 UI/L.
- Male participants, whose partners are of childbearing potential (including breastfeeding women), must accept to use, during sexual intercourse, a double contraceptive method according to the following algorithm: (condom) plus (intrauterine device or hormonal contraceptive) from inclusion up to 3 months after the last dose.
- Male participants whose partners are pregnant must use, during sexual intercourse, a condom from inclusion up to 3 months after the last dose.
- Male participants must have agreed not to donate sperm from the inclusion up to 3 months after the last dose.

Exclusion criteria

- The participant has been diagnosed with PPMS according to the 2017 revision of the McDonald diagnostic criteria or with non-relapsing SPMS.
- The participant has conditions or situations that would adversely affect participation in this study, including but not limited to: A short life expectancy due to pre-existing health condition(s) as determined by their treating neurologist; Medical condition(s) or concomitant disease(s) making them nonevaluable for the primary efficacy endpoint or that would adversely affect participation in this study, as judged by the Investigator; A requirement for concomitant treatment that could bias the primary evaluation; Contraindication for MRI, ie, presence of pacemaker, metallic implants in high-risk areas (ie, artificial heart valves, aneurysm/vessel clips), presence of metallic material
(eg, shrapnel) in high risk areas, known history of allergy to any contrast medium, or history of claustrophobia that would prevent completion of all protocol-scheduled MRI; Contraindications to use MRI Gd contrast-enhancing preparations.
- The participant has a history of or currently has concomitant medical or clinical conditions that would adversely affect participation in this study, including but not limited to: A history of T-lymphocyte or T-lymphocyte-receptor vaccination, transplantation and/or antirejection therapy; A history of diagnosis of progressive multifocal leukoencephalopathy (PML) or evidence of findings suggestive of PML on the baseline MRI; A history of infection with the human immunodeficiency virus; A history of active or latent tuberculosis; Any other active infections that would adversely affect participation or IMP administration in this study, as judged by the Investigator; A history of malignancy within 10 years prior to the first screening visit, except effectively treated carcinoma in situ of the cervix or adequately treated non-metastatic squamous or basal cell carcinoma of the skin; A history of alcohol or drug abuse within 1 year prior to the first screening visit; A history of any psychiatric disease, behavioral condition, or depression requiring hospitalization within 2 years prior to the first screening visit; Presence of any screening laboratory or ECG values outside normal limits that are considered in the Investigator*s judgment to be clinically significant; Presence of liver injury defined as underlying hepatobiliary disease or screening alanine aminotransferase (ALT) >3 x upper limit of normal (ULN).
- At screening, the participant is positive for hepatitis B surface antigen and/or hepatitis B core antibody and/or is positive for hepatitis C antibody.
- The participant has any of the following: A bleeding disorder or known platelet dysfunction at any time prior to the first screening visit; A platelet count <150 000/*L at the screening visit.
- The participant has a lymphocyte count less than the lower limit of normal (LLN) at the screening visit.
- The participant has received any live (attenuated) vaccine within 2 months before the first treatment visit.
- The participant has received any of the following medications/treatments within the specified time frame before any baseline assessment (no wash-out is required forinterferons beta or glatiramer acetate treatments):
-Systemic corticosteroids, adrenocorticotropic hormone 1 month prior to screening MRI scan
-Dimethyl fumarate 1 month prior to randomization
-Intravenous (IV) immunoglobulin, fingolimod, natalizumab 2 months prior to randomization

-Teriflunomide 2 years prior to randomization or 1 month prior to randomization if participant undergoes an accelerated elimination procedure and hasdocumented teriflunomide plasma level below 0.02 mg/L before randomization
-B-cell-depleting therapies such as ocrelizumab and rituximab 6 months prior to randomization or until return of B-cell counts to normal levels, whichever is longer
-Mildly to moderately immunosuppressive/chemotherapeutic medications such azathioprine and methotrexate 6 months prior to randomization
-Highly immunosuppressive/chemotherapeutic medications: mitoxantrone up to 120 mg/m2 body surface area, cyclophosphamide, cladribine 2 years prior to randomization
- Alemtuzumab 4 years prior to randomization
- Lymphoid irradiation, bone marrow transplantation, mitoxantrone (with evidence of cardiotoxicity following treatment, or cumulative lifetime dose >120 mg/m2), other strongly immunosuppressive treatments with very long-lasting effects Any time
- The participant is receiving strong inducers or inhibitors of CYP3A or CYP2C8 hepatic enzymes as listed in the Appendix 7.
- The participant is receiving anticoagulant/antiplatelet therapies
- The participant has an EDSS score >5.5 at the first screening visit.
- The participant has had a relapse in the 30 days prior to randomization.
- The participant is pregnant or a breastfeeding woman.
- The participant has any of the following within 4 weeks of the first screening visit: Fever (*38°C); Persistent chronic or active recurring infection requiring treatment with antibiotics, antivirals, or antifungals
- The participant has a documented history of attempted suicide over the 6 months prior to the screening visit, presents with suicidal ideation of category 4 or 5 on the Columbia Suicide Severity Rating Scale (C-SSRS) during the study, OR if in the Investigator's judgment, the participant is at risk for a suicide attempt.
- The participant has had major surgery within 4 weeks prior to the first screening visit, which could affect participant*s safety or affect immune response (as judged by the Investigator) or has planned any elective surgery during the course of the study.
- The participant has a history or presence of significant other concomitant illness according to the Investigator*s judgment such as, but not limited to cardiovascular renal, neurological, endocrinological, gastrointestinal, hepatic, metabolic, pulmonary, or lymphatic disease that would adversely affect participation in this study.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Crossover
Masking:	Double blinded (masking used)

Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	17-07-2019
Enrollment:	5
Type:	Actual

Ethics review

Approved WMO Date:	23-01-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-05-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-07-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-07-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-08-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-08-2019
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	EUCTR2018-003927-12-NL
CCMO	NL67984.029.19
Other	U1111-1220-0572