A PHASE III MULTICENTER, RANDOMIZED, DOUBLE-BLIND, DOUBLE-DUMMY, PARALLEL-GROUP STUDY TO EVALUATE THE EFFICACY AND SAFETY OF FENEBRUTINIB COMPARED WITH TERIFLUNOMIDE IN ADULT PATIENTS WITH RELAPSING MULTIPLE SCLEROSIS

Published: 16-11-2020
Last updated: 08-04-2024

The goal of the fenebrutinib development program in MS is to evaluate the benefits and risks of fenebrutinib treatment across the spectrum of patients with MS. Based on the existing toxicology, pharmacology, and clinical experience with fenebrutinib...

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

Summary

ID

NL-OMON54410

Source
ToetsingOnline

Brief title
Fenhance - GN41851

Condition

- Demyelinating disorders

Synonym
Relapsing Multiple Sclerosis, RMS

Research involving
Human

Sponsors and support

Primary sponsor: Roche Nederland B.V.
Source(s) of monetary or material Support: F. Hoffman-La Roche

Intervention

Keyword: double blind, Fenebrutinib, relapsing MS, Teriflunomide

Outcome measures

Primary outcome

The primary efficacy objective for this study is to evaluate the efficacy of fenebrutinib compared with teriflunomide on the basis of the primary endpoint of Annualized Relapse Rate (see Section 4.5.11 for protocol-defined relapse).

A detailed description of the primary estimands is provided in Sections 2.1.1 and 6.4.1.

Secondary outcome

The secondary efficacy objective for this study is to evaluate the efficacy of fenebrutinib treatment compared with teriflunomide on the basis of the following endpoints:

* Time to onset of composite 12-week confirmed disability progression (cCDP12), defined as the time from baseline to the first occurrence of a progression event according to at least one of the following three criteria; must be confirmed at a regularly scheduled visit that is at least 12 weeks after the initial disability progression:

- An increase from baseline in EDSS score of >=1.0 point in patients with

a baseline EDSS score of <= 5.5 or an increase of >= 0.5 points in

patients with a baseline EDSS score of > 5.5 (confirmed disability

progression [CDP])

- >= 20% increase from baseline in the T25FWT

- >= 20% increase from baseline in time to complete the 9-HPT

* Time to onset of 24-week CDP (CDP24)

* Total number of T1Gd+ lesions as detected by MRI

* Total number of new and/or enlarging T2-weighted lesions as detected by MRI

* Rate of percent change in total brain volume from Week 24 as assessed by MRI

* Change in patient-reported physical impacts of MS, as measured by the

Multiple Sclerosis Impact Scale (29-Item), Version 2 (MSIS-29 v2) physical

scale)

* Time to onset of 12-week confirmed 4-point worsening in Symbol Digit

Modalities Test (SDMT) score

* Change from baseline to Week 48 in the concentration of serum neurofilament

light chain (NfL)

The secondary endpoints above do not reflect order of statistical hierarchy.

Study description

Background summary

Multiple sclerosis (MS) is a chronic, inflammatory, demyelinating, and degenerative disease of the CNS that affects approximately 900,000 people in the United States (Wallin et al. 2019) and 2.3 million people worldwide (GBD 2016 Multiple Sclerosis Collaborators 2019).
Currently, the quantitative relationship between 90% inhibition of BTK and proposed clinical endpoint (i.e., ARR) in MS is unknown. The role of BTK

inhibition in MS has been established by the results from two Phase II randomized clinical trials, one study (NCT02975349) evaluated the safety and efficacy of evobrutinib in patients with RMS (Clinicaltrials.gov 2016; Montalban et al. 2019) and one study (NCT03889639) evaluated SAR442168 in patients with RMS (Clinicaltrials.gov 2020; Sanofi Virtual Scientific Meeting 2020). Given the similar mechanism of action, the results of these Phase II trials suggest that fenebrutinib will have a positive treatment effect on MS pathophysiology and thus support further study of this BTK inhibitor (fenebrutinib) in MS. See section 1 of the protocol.

Study objective

The goal of the fenebrutinib development program in MS is to evaluate the benefits and risks of fenebrutinib treatment across the spectrum of patients with MS. Based on the existing toxicology, pharmacology, and clinical experience with fenebrutinib 200 mg BID in other autoimmune diseases combined with the efficacy observed in patients with MS with other BTK inhibitors, the potential effect on DA and progression biology together with the favorable safety profile in other autoimmune indications provides a reasonable expectation that evaluating fenebrutinib in patients with MS will result in a favorable benefit-risk assessment.

Study design

Study GN41851 is a Phase III, randomized, multicenter, double-blind, double-dummy, parallel-group study to evaluate the efficacy and safety of fenebrutinib compared with teriflunomide in adult patients with RRMS and active secondary progressive MS, collectively referred to as RMS. All eligible patients will be randomized 1:1 through an interactive voice or web-based response system (IxRS) to either one of two arms:
* Fenebrutinib treatment arm: fenebrutinib (200 mg by mouth [PO] BID) with teriflunomide-matching placebo
* Teriflunomide treatment arm: teriflunomide (14 mg PO QD) with fenebrutinib-matching placebo in a blinded fashion

Intervention

This study will consist of the following phases:
* Screening phase
* Double-blind treatment (DBT) phase
* Post-DBT*safety follow-up (post-DBT*SFU) phase
* Optional open-label extension (OLE) phase
* OLE safety follow-up (OLE-SFU) phase

Details for each study phase can be found in Sections 3.1.2, 3.1.3, 3.1.5, and 3.1.6. The study duration will vary for each patient as a result of the primary analysis being event driven.

Double-blind treatment (DBT) phase:
Patients will either receive fenebrutinib 200 mg PO BID with teriflunomide-matching placebo or to teriflunomide 14 mg PO QD with fenebrutinib- matching placebo in the DBT phase. Every 2 weeks for the first 16 weeks, then every 4 weeks until week 24 and every 12 weeks thereafter patients must visit the site. Semi-structured telephone interviews will be conducted during the DBT phase every 6 weeks (+- 3 days) between study visits.

Study burden and risks

The general burden for the patient consists, among others things, coming to hospital on regular basis (every 2 weeks first 16 weeks, then every 4 weeks until week 24, after this every 12 weeks) and blood sampling (each visit) and various test and interviews.
The patients need to take the drug daily and keep record of this. IMP may lead to various adverse events.

Contacts

Public
Roche Nederland B.V.

Beneluxlaan 2a
Woerden 3446 GR
NL
Scientific
Roche Nederland B.V.

Beneluxlaan 2a
Woerden 3446 GR
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

• Age 18-55 years
• Expanded Disability Status Scale score (EDSS) of 0.0-5.5 at screening
• A diagnosis of RMS in accordance with the revised 2017 McDonald Criteria
• Neurologically stable for at least 30 days prior to randomization and baseline assessments
• Ability to complete the 9-HPT for each hand in < 240 seconds
• Ability to perform the timed 25-Foot Walk Test in < 150 seconds
• For women of childbearing potential: agreement to remain abstinent or use contraception, and agreement to refrain from donating eggs, women must remain abstinent or use contraceptive methods with a failure rate of < 1% per year during the treatment period, for 8 weeks after the final dose of study medication, and until the teriflunomide elimination protocol is completed
• For men: agreement to remain abstinent or use a condom, and agreement to refrain from donating sperm, with a female partner of childbearing potential or pregnant female partner, men must remain abstinent or use a condom during the treatment phase, for 8 weeks after the final dose of study drug, and until completion of the teriflunomide elimination protocol. Men must also refrain from donating sperm during this same period.
See 4.1.1 of the protocol for all inclusion criteria

Exclusion criteria

• A diagnosis of PPMS or non-active SPMS
• Disease duration of > 10 years from the onset of symptoms and an EDSS score at screening < 2.0
• Any known or suspected active infection at screening or baseline, or any major episode of infection requiring hospitalization or treatment with IV anti-microbials within 8 weeks prior to and during screening or treatment with oral anti-microbials within 2 weeks prior to and during screening. Onychomycosis is not exclusionary unless it is being treated with systemic therapy.
• History of cancer including hematologic malignancy and solid tumors within 10 years of screening.
• Known presence of other neurological disorders that could interfere with the diagnosis of MS or assessments of efficacy or safety during the study, clinically significant cardiovascular, psychiatric, pulmonary, renal, hepatic, endocrine, metabolic or gastrointestinal disease
• Any concomitant disease that may require chronic treatment with systemic corticosteroids, immunosuppressants during the course of the study.

• History of alcohol or other drug abuse within 12 months prior to screening
• Any previous treatment with immunomodulatory or immunosuppressive medication without an appropriate washout period
• Receipt of a live or live-attenuated vaccine within 6 weeks prior to randomization
• Female participants who are pregnant or breastfeeding or intending to become pregnant during the study or 8 weeks (with accelerated teriflunomide elimination procedure (ATEP)) after final dose of study drug
• Male participants intending to father a child during the study or 8 weeks (with ATEP) after final dose of study drug
• Presence of cirrhosis (Child-Pugh Class C) or Gilbert's Syndrome

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	31-10-2022
Enrollment:	4
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Aubagio
Generic name:	Teriflunomide
Registration:	Yes - NL outside intended use

Product type:	Medicine
Brand name:	fenebrutinib
Generic name:	fenebrutinib

Ethics review

Approved WMO Date:	16-11-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-02-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-03-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	24-04-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	07-07-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-08-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO	

Date:	09-10-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-10-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	28-02-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	30-03-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	26-05-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	07-12-2023
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	EUCTR2019-004857-10-NL
ClinicalTrials.gov	NCT04586010
CCMO	NL75413.056.20