A Phase III, Multicenter, Randomized, Parallel Group, Double Blind, Double Dummy, Active Controlled Study of Evobrutinib Compared with Teriflunomide, in Participants with Relapsing Multiple Sclerosis to Evaluate Efficacy and Safety.

Published: 10-06-2020
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Main objective:To demonstrate superior efficacy with evobrutinib compared to Teriflunomide in terms of Annualized Relapse Rate (ARR) Secondary objectives:a.To demonstrate the efficacy of evobrutinib relative to that of Teriflunomide on disability...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Movement disorders (incl parkinsonism)
Study type	Observational invasive

Summary

ID

NL-OMON54887

Source
ToetsingOnline

Brief title
MS200527_0080

Condition

- Movement disorders (incl parkinsonism)

Synonym
Relapsing Multiple Sclerosis (RMS)

Research involving
Human

Sponsors and support

Primary sponsor: Merck Healthcare KGaA
Source(s) of monetary or material Support: the pharmaceutical industry

Intervention

Keyword: Evobrutinib, phase III, Relapsing Multiple Sclerosis, Teriflunomide

Outcome measures

Primary outcome

ARR based on qualified relapses at Week 96 in participants with RMS

Secondary outcome

a. Time to first occurrence of 12-week confirmed disability progression (CDP)

as measured by the Expanded Disability Status Scale (EDSS) over 96 weeks

b.Time to first occurrence of 24-week CDP as measured by EDSS over 96 weeks

c.Change from Baseline (CFB) in Patient Reported Outcomes Measurement

Information System [PROMIS] PF score at 96 weeks

d.CFB in PROMIS Fatigue score at 96 weeks

e.Total number of T1 Gd+ lesions based on assessments at Week 24, Week 48, and

Week 96.

f. Total number of new or enlarging T2 lesions based on assessments at Week 24,

Week 48, and Week 96

g.Safety as assessed by the nature, severity, and occurrence of adverse events

(AEs) and adverse events of special interest (AESIs); vital signs;

electrocardiograms (ECGs); absolute concentrations and change from Baseline in

immunoglobulin (Ig) levels; and clinical laboratory safety parameters up to

Week 108

h. OLE period:

*Efficacy and HRQoL endpoints at Weeks 48, 96, and 144

oARR, based on protocol-defined qualified relapses

oChange from Baseline in PROMIS PF score

oChange from Baseline in PROMIS fatigue score

oChange from Baseline in Medical Outcomes Study 36 Item Short Form Health Survey (SF-36v2)

*Efficacy and HRQoL endpoints over 144 weeks

oTime to first occurrence of 12-week confirmed EDSS progression over 144 weeks

oTime to first occurrence of 24-week confirmed EDSS progression over 144 weeks

oTime to first occurrence of 12-week confirmed PF deterioration compared to Baseline over 144 weeks

*Efficacy endpoints at Weeks 24, 48, 96, and 144

oTotal number of new or enlarging T2 lesions

oTotal number of T1 Gd+ lesions

*Safety as assessed by the nature, severity, and occurrence of AEs and AESIs; vital signs; ECGs; absolute concentrations and change from Baseline in Ig levels; clinical laboratory safety parameters up to Week 144

* Changes in fluid biomarker levels between treatment groups

* Correlations between levels in fluid biomarkers, gene expression and MRI changes, and clinical outcomes measured by SDMT, EDSS, 9HPT, T25-FW and relapses

Study description

Background summary

Currently there is no cure for MS, but the course of the disease can be altered favorably with disease-modifying drugs (DMDs) with varying levels of efficacy, and distinct safety and tolerability profiles. Despite the recent approvals of newer therapies for the treatment of MS, there remains an unmet need for highly effective and well-tolerated therapies for patients with MS at all stages of the disease. Early treatment with a highly efficacious and safer DMD could be advantageous for long term quality of life for MS patients and might slow the process of brain atrophy, which accompanies axonal damage and loss of gray and white matter. Since B cell depletion studies have shown that antibody independent B cell functions play an important role in MS pathogenesis and an altered innate immune system contributes to disability progression and repair in MS, evobrutinib may offer advantages over current approved DMDs. Evobrutinib is a highly specific, oral inhibitor of BTK that inhibits B cell activation and B cell/T cell interaction, decreasing plasma cell formation and autoantibody production.

Study objective

Main objective:
To demonstrate superior efficacy with evobrutinib compared to Teriflunomide in terms of Annualized Relapse Rate (ARR)

Secondary objectives:
a.To demonstrate the efficacy of evobrutinib relative to that of Teriflunomide on disability progression
b.To demonstrate the efficacy of evobrutinib relative to that of Teriflunomide on patient reported symptoms and functional status
c.To demonstrate the efficacy of evobrutinib relative to that of Teriflunomideon magnetic resonance imaging (MRI) lesion parameters
d.To characterize the safety and tolerability of evobrutinib.
e. OLE period: To evaluate the long-term safety, efficacy, and HRQoL of evobrutinib for an additional up to 144 weeks.

Study design

A Phase III, Multicenter, Randomized, Parallel Group, Double Blind, Double Dummy, Active Controlled Study in participants with relapsing multiple sclerosis

Study burden and risks

Evobrutinib inhibits activation of B cells via the B cell receptor, decreasing plasma cell formation and autoantibody production. Also, evobrutinib shows inhibition of myeloid cell activation by immune complexes. In addition, evobrutinib inhibits activation of myeloid cells by immune complexes via Fc receptors as well as the differentiation of proinflammatory macrophages. Thus, evobrutinib may be suitable for the treatment of multiple sclerosis (MS). Considering the unmet medical need in MS patients, reduction of MS activities (decreased in the number of Gd+ T1 lesions and lower ARR compared with placebo), convenience of an oral therapy and the measures put in place to mitigate the important identified and important potential risks, the benefit-risk of evobrutinib 45 mg twice daily supports continued clinical development of evobrutinib in this population.

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

- 18 years to 55 years female and male participants
- Participants are diagnosed with RMS (relapsing-remitting multiple sclerosis [RRMS] or secondary progressive multiple sclerosis [SPMS] with relapses) in accordance with 2017 Revised McDonald criteria
(Thompson 2018)
- Participants with one or more documented relapses within the 2 years before Screening with either: a. one relapse which occurred within the last year prior to randomization, OR b. the presence of at least 1
gadolinium-enhancing (Gd+) T1 lesion within 6 months prior to randomization
- Participants have Expanded Disability Status Scale (EDSS) score of 0 to 5.5 at Screening and Baseline (Day 1). Participants with an EDSS score <<= 2 at Screening and Baseline (Day 1) are only eligible for participation if their disease duration (time since onset of symptoms) is no more than 10 years
- Participants are neurologically stable for ><= 30 days prior to both screening and baseline
- Female participants must be neither pregnant nor breast-feeding or must lack child-bearing potential (as defined by either: post-menopausal or surgically sterile), or use an effective method of contraception for the duration of the study and at least 2 years after study intervention due to the long elimination period for teriflunomide of 2 years, unless the participant undergoes an accelerated elimination procedure - Male participants must refrain from donating sperm and/or abstain from intercourse with women of child-bearing potential or use an effective method of contraception for the duration of the study and at least 2 years after study intervention due to the long elimination period for teriflunomide of 2 years, unless the participant undergoes an accelerated elimination procedure
- Participants have given written informed consent prior to any study related procedure
- Other protocol defined inclusion criteria could apply.

Exclusion criteria

- Participants diagnosed with Progressive MS, in accordance with the 2017 Revised McDonald criteria as follows: a). Participants with Primary Progressive MS. b) Participants with secondary progressive MS without evidence of relapse.
- Disease duration more than (>) 10 years in participants with an EDSS =< 2.0 at screening.
- Immunologic disorder other than MS, or any other condition requiring oral, intravenous (IV) , intramuscular, or intra-articular corticosteroid therapy, with the exception of well-controlled Type 2 Diabetes mellitus or well controlled thyroid disease.
-Other protocol defined exclusion criteria could apply.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-10-2020
Enrollment:	8
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO

Date:	10-06-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	01-10-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-11-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	26-11-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	09-04-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-06-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	29-07-2021
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	EUCTR2019-004972-20-NL
CCMO	NL73999.056.20