A multicenter, randomized, double-blind, parallel-group, placebo-controlled variable treatment duration study evaluating the efficacy and safety of Siponimod (BAF312) in patients with secondary progressive multiple sclerosis followed by extended treatment with open-label BAF312(CBAF312A2304)

Published: 21-09-2012
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Primary Core: to demonstrate the efficacy of BAF312 relative to placebo in delaying the time to 3-month confirmed disability progression, measured by EDSS. Main secondary objectives Core: to demonstrate the efficacy in delaying the time to 3-month...

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

Summary

ID

NL-OMON53018

Source
ToetsingOnline

Brief title
CBAF312A2304 (Expand)

Condition

- Neurological disorders NEC

Synonym
MS, secondary progressive MS

Research involving
Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: Novartis Pharma BV

Intervention

Keyword: BAF312, multiple sclerosis, secondary progressive, siponimod

Outcome measures

Primary outcome

Expanded Disability Status Score (EDSS).

Secondary outcome

Timed 25-Foot walk (T25W), Nine Hole Peg Test (9-HPT), Paced Auditory Serial Addition Test (PASAT), MS Relapse, MRI, Symbol Digital Modalities Test (SDMT), Brief Visuospatial Memory Test-Revised (BVMT-R), Low Contract Visual Acuity (LCVA), adverse events, questionnaires QoL and Colombia Suicide Severity Rating, PK, pharmacogenomics (optional), biomarkers.

Study description

Background summary

For the treatment of secondary progressive MS mitoxantrone and interferon B-1b are being used. Mitoxantrone is approved for the treatment of SPMS in the Netherlands. However, there are no convincing data demonstrating the efficacy of mitoxantrone in SPMS patients without superimposed relapses and the risks associated with mitoxantrone (heart failure, leukemia) limit the use of the product. IFNβ-1b carries an indication for SPMS with active disease, evidenced by relapses. a considerable medical need remains to find therapies that will be

effective in delaying disability progression in patients with SPMS without relapses.
Fingolimod has been registered for very active relapsing-remitting MS.
Siponimod (BAF312) is a novel S1P receptor modulator that leads to the reduction of peripheral lymphocyte counts in blood. The mechanism of action is similar to that of the S1P receptor modulator fingolimod, but BAF312 belongs to a different chemical class. Whereas fingolimod acts as an agonist on four out of five S1P receptors (namely S1P1, S1P3, S1P4, and S1P5); BAF312 is a S1P1/S1P5-selective agonist. In contrast to fingolimod, BAF312 does not require a phosphorylation step in vivo. The half-life of BAF312 compared to fingolimod is shorter (approximately 30 h versus 200 h), therefore drug effects cease more rapidly after discontinuation. For example, 90% recovery of the baseline lymphocyte counts after treatment withdrawal from steady state conditions should be achieved in one week at a daily BAF312 dose of 2 mg. In contrast, in the case of fingolimod the return to 90% of the baseline lymphocyte counts after discontinuation of 0.5 mg fingolimod takes ~12 weeks. The BAF312 mode of action in MS is believed to include S1P1-mediated prevention of effector lymphocyte recirculation from lymphatic tissue to inflammatory lesions in the CNS. In addition, there may be direct beneficial effects in the CNS mediated by S1P1 and/or S1P5.
In this phase III study, effects of BAF312 (efficacy, safety and tolerability) will be compared to those of placebo, for up to maiximum 3 years. Placebo-controlled trials are considered to be ethical for those with forms of the disease lacking established effective treatment. This is followed by an open-label extension part; all patients treated ith BAF312 to investigate long-term safety and tolerability.

Study objective

Primary Core: to demonstrate the efficacy of BAF312 relative to placebo in delaying the time to 3-month confirmed disability progression, measured by EDSS.
Main secondary objectives Core: to demonstrate the efficacy in delaying the time to 3-month confirmed worsening of at least 20% from Baseline in the timed 25-foot walk test and in reducing the increase in T2 lesion volume from Baseline to the end of the study.

Extension: To evaluate the long-term safety and tolerability of BAF312

Study design

Multicenter, randomized, double-blind, parallel-group phase III study.
Discontinuation of current MS treatment (if any).
Core:
Randomization (2:1):
• BAF312 2 mg daily

• Placebo
In case of unacceptable reduction of lymphocytes: dose adjustment (once). In case of recurrence: temporary interruption of treatment.
Estimated treatment duration (depending of time of enrollment) approx. 23-36 months. Maximum: 36 months (3 years).
Followed by an open-label extension part; all patients treated ith BAF312 up to maximum of 7 years.

1530 patients.

Intervention

Core: Treatment with BAF312 or placebo. Extension: Treatment with BAF312.

Study burden and risks

Risks: Adverse effects of study medication.

Core:
Burden: Visits screening, day (D) 1,7,28, month (M) 3, thereafter every 3 M. Duration 1-8 h. Some visits: fasting.
(Nearly) every visit: physical examination, blood draw (screening 50 ml, others approx. 15 ml).
Pregnancy tests: every month (partly at home).
Ophthalmic examination: screening, M 3, thereafter every year (visual acuity every 6 M).
ECG: screening, D 1,7, M 3 thereafter every year.
Ambulant ECG monitoring during the first 6 treatment days.
Pulmonary function test: screening, M3, thereafter every year.
T25W: screening, D 1, thereafter every 3 M.
9-HPT: screening, M 3, thereafter every 3 M.
Other MS related tests: screening and every 6 M.
MRI brain: screening and every year.
CT/MRI lungs: screening and M 24.
Questionnaires: screening, D 28, M3, thereafter every 3 M.
Diary: Intake study medication and results pregnancy test at home.

Extension:
Visits Day 1,7, Month 1,3,6,9,12, then bi-annually, end of treatment visit, follow-up visit 1 month post-treatment. Duration: 1-8 hours per visit. Some visits: Patient should be fasting.
Physical Examination: Each visit.
EDSS: As of month 3 each visit.
Blood- and urine collection: (Nearly) each visit (not at Day 7 and Follow-up visit). ca. 25 ml blood per visit.
Dermatological Exam: Month 12, then yearly and at end of treatment visit.

Ophthalmologic Exam: Month 3,6,12, daarna jaarlijks en op end of treatment visit.
ECG: Day 1,7, Month 3,12, then yearly, at end of treatment and follow-up visit.
Pulmonary Function Test: Maand 3,6,12, then yearly, at end of treatment visit and follow-up visit.
T25W: Month 3,6,9,12, then each visit up to month 18 from then every year (not at follow-up visit).
SDMT: Month 6, as of month 12 each visit up to month 18 from then every year (not at follow-up visit).
MRI brain: Month 12, then 2-yearly and at end of treatment visit.
Completion Questionnaire(s): As of Month 1 each visit up to month 18 from then every year
Completion diary: Daily during treatment period.

Contacts

Public
Novartis

Raapopseweg 1
Arnhem 6824 LZ
NL
Scientific
Novartis

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NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

Core part:
• 18 to 60 years (inclusive).
• History of relapsing-remitting MS according to the 2010 Revised McDonald criteria.
• Secondary progressive course of MS.
• EDSS score of 3.0 to 6.5 (inclusive).
• Documented EDSS progression in the 2 years prior to study of >=1 point for patients with EDSS <6.0 at baseline, and >=0.5 point for patients with EDSS >=6.0 at baseline. Should documented EDSS scores not be available, a written summary of the clinical evidence of disability progression in the previous 2 years, and retrospective assessment of EDSS score from data up to 2 years prior to screening must be submitted for central review.
• No evidence of relapse or corticosteroid treatment within 3 months prior to randomization., Patients who completed the Core Part on:
* double-blind treatment
* open-label BAF312
* abbreviated schedule of assessments (with the exception of patients with BAF312-related AE or SAE)
are eligible to enter the extension part.

Exclusion criteria

• Active chronic disease (or stable but treated with immune therapy) of the immune system other than MS.
• Diagnosis of macular edema during pre-randomization phase (patients with a history of macular edema will be allowed to enter the study provided that they do not have macular edema at the ophthalmic examination at the Screening Visit).
• Negative for varicella-zoster virus IgG antibodies at Screening.
• Live or live-attenuated vaccines within 2 months prior to randomization.
• Have been treated with: BAF312, fingolimod within 2 months (M) or for more than 6 M, intravenous immunoglobulin within 2 M, dimethyl fumarate within 2 M, natalizumab within 6 M, immunosuppressive/chemotherapeutic medications within 6 M, cyclophosphamide within 12 M, rituximab, ofatumumab, ocrelizumab, cladribine within 24 M, mitoxantrone during previous 24 M or evidence of cardiotoxicity following mitoxantrone or a cumulative life-time dose of more than 60 mg/m2, teriflunomide within 2Y (unless teriflunomide plasma concentration is zero or without relevant biological significance) OR within 2W following successful accelerated elimination procedure as described in the product label
• Abnormalities in the Suicidal Ideation section of the eC-SSRS (see protocol for details)
• Homozygosity for CYP2C9*3 (will be tested at Screening), or refusal to test for CYP2C9*3 haplotype.

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:	Recruitment stopped
Start date (anticipated):	08-01-2013
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	siponimod
Generic name:	siponimod

Ethics review

Approved WMO Date:	21-09-2012
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-11-2012
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	16-04-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-05-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-07-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-08-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-08-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	30-08-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-10-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-11-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-02-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	19-02-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-06-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-07-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-08-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-10-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-05-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-05-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-07-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-09-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	09-10-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-10-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-12-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-12-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-12-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-02-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-03-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-05-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-06-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	19-07-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-07-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-08-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-09-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-10-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-05-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-06-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-12-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-01-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	29-07-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-08-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-10-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-12-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-02-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-07-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-07-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-09-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-09-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	02-07-2021
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:	18-07-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-08-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-09-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-11-2022
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
Other	EUCTR2012-003056-36-BG en NCT01665144
EudraCT	EUCTR2012-003056-36-NL
CCMO	NL42105.029.12