Extension of the CBYM338B2203 phase IIb/III study to evaluate the long-term efficacy, safety and tolerability of intravenous BYM338 in patients with sporadic inclusion body myositis

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Main Objective:To evaluate the long-term safety and tolerability of BYM338 in the treatment of sIBM and to further evaluate the effect of three BYM338dose regimens against placebo in increasing the distance traveled as measured by the 6 Minute...

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

Summary

ID

NL-OMON42420

Source
ToetsingOnline

Brief title
CBYM338B2203E1

Condition

- Muscle disorders

Synonym
sporadic inclusion body myositis

Research involving
Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: Novartis Pharma B.V. (sponsor/verrichter van dit onderzoek)

Intervention

Keyword: body, BYM338, inclusion, myositis

Outcome measures

Primary outcome

- Safety and tolerabilty of different i.v. BYM338 doses

- Change from baseline in 6 Minute Walking Distance Test (6MWD)

Secondary outcome

* To describe the long-term evolution of quadriceps muscle strength using

quadriceps Quantitative Muscle Testing (QMT)

* To describe physical function reported by patients using the Sporadic

Inclusion Body Myositis Functional Assessment (sIFA)

* To report the incidence of self-reported falls and self-reported injurious

falls (falls that result in any subject injury) which are a subset of all

self-reported falls

* To describe physical performance using the Short Physical Performance Battery

(SPPB)

* To characterize muscle changes using magnetic resonance imaging (MRI) from a

subset of patients

* To investigate the development of immunogenicity against BYM338

Study description

Background summary

Inclusion-body myositis inclusion-body myositis (sIBM) is a very rare disease. The estimated prevalence is 15-71 per milliorn for all ages, and 51 per million over age 50. Men are more often affected than women (2:1). The etiology is unknown. sIBM is refractory to any treatments despite evidence of possibly secondary degenerative and inflammatory features.
The disease is characterized by the insidious and asymmetric onset of proximal and distal muscle weakness. Lower extremity complaints come typically in the form of difficulty arising from chairs, and walking upstairs or downstairs. As the disease progresses, lower extremity weakness leads to frequent falls. In addition there is early onset of hand and finger weakness which eventually impairs activities of daily living (e.g. writing, feeding, bathing, dressing, brushing teeth). Of other important symptoms, dysphagia occurs in at least 40% of patients due to esophageal and pharyngeal muscle involvement. Disease progression is relatively slow but virtually all patients with sIBM require a wheelchair, by about ten years of onset.
No treatments have been found to slow or reverse the progression of muscle weakness in sIBM. Patients with sIBM have not demonstrated a clinically meaningful response to agents used traditionally to treat inflammatory myopathies, including corticosteroids, methotrexate, azathioprine or cyclophosphamide. Intravenous immunoglobulin is used off label in some centers, but there is no evidence to support its longterm effectiveness. Similar overall conclusions can be drawn on the efficacy of different immunotherapies such as the anti-T lymphocyte inhibitor, the anti-TNF medication (etanercept) and beta-inteferon 1A. Oxandrolone is still in an explorative phase and further data are required before reaching conclusions on its potential benefits. Therefore, there is currently a clear, unmet medical need in the
treatment of patients with sIBM.
Myostatin, a member of the TGF-13 family, is a protein that negatively regulates skeletal muscle mass. Inhibition of myostatin increases muscle mass and strength. BYM338 is a fully human monoclonal antibody developed to bind competitively to activin receptor type II B with greater affinity than myostatin and activin, its natural ligands. BYM338 is formulated for both i.v. and s.c. administration.
Since sIBM causes dramatic skeletal muscle atrophy, treatments that target atrophy pathways in muscle, like BYM338, may be effective in this disease. Data from study CBYM338X2205 on 14 patients with sIBM (11 active, 3 placebo) showed statistically significant increases in BYM338 relative to placebo for both muscle volume and Lean body mass after a single dose of BYM338 30 mg/kg i.v. was administered.

This extension trial is designed to provide additional placebo-controlled data

(Treatment Period 1) to further evaluate the efficacy, safety, and tolerability of three doses of BYM338 as well as long-term safety, tolerability, and efficacy data (Treatment Period 2) for patients who enroll from the core study (CBYM338B2203).

Study objective

Main Objective:
To evaluate the long-term safety and tolerability of BYM338 in the treatment of sIBM and to further evaluate the effect of three BYM338 dose regimens against placebo in increasing the distance traveled as measured by the 6 Minute Walking Distance Test (6MWD).

Secondary Objectives:
- To describe the long-term evolution of quadriceps muscle strength using quadriceps Quantitative Muscle Testing (QMT)
- To describe physical function reported by patients using the Sporadic Inclusion Body Myositis Functional Assessment (sIFA)
- To report the incidence of self-reported falls and self-reported injurious falls (falls that result in any subject injury) which are a subset of all selfreported falls
- To describe physical performance using the Short Physical Performance Battery (SPPB)
- To characterize muscle changes using magnetic resonance imaging (MRI) from a subset of patients
- To investigate the development of immunogenicity against BYM338

Study design

The extension study consists of a Screening epoch, during which patient eligibility will be assessed, followed by a Treatment Period 1 epoch, which is double-blind and placebo-controlled (according to randomisation used in Corestudy), and a Treatment Period 2 epoch, which is open-label. A Post-treatment Follow-up epoch is also provided for patients who discontinue prematurely.
Treatmentperiod 1:
BYM338 1 mg/kg i.v.: every 4 weeks
BYM338 3 mg/kg i.v.: every 4 weeks
BYM338 10 mg/kg i.v.: every 4 weeks
Placebo: every 4 weeks
Duration: max 1 year

Treatmentperiod 2:
BYM33 optimal dosing, depending on the results from the corestudie, i.v.: every 4 weeks
Duration: untill BYM338 will be commercially available on the Dutch market or

untill sponsor stops the study.

Posttreatment Follow up visits after 3 and 6 months of last dose will be applicable for subjects who duiscontinue the study prematurely.

240 patients.

DMC is in place.

Intervention

BYM338 i.v. or placebo i.v. (treatment period 1).
BYM338 i.v. (treatment period 2)

Study burden and risks

Risk: adverse events studymedication and risk study procedures.

Burden:
Studyduration 2 years, visits 4-weekly. Duration 1-4 hours per visit.

26 i.v. infusions (100 ml), duration 30 min minimal.

Every visit (as of week 4):
* Columbia Suicide Rating Scale.
* Weight
* Pregnancytest (urine, when applicable)

At screening visit and Day 1, results of assessments done in the core study will be taken and these assessments are not extra performed in the context of this extension study and so not listed below.

Treatmentperiod 1:
* Physical examination (2x).
* Bloodpressure, heart rate and body temperature (2x)
* Blood collection, 20 ml per visit (2x).
* Evaluation muscle/physical activity (5x)
* 6 minute walktest (2x)
* Quadriceps strenght (2x)
* Pinch strength (2x)
* Short test battery balance, speed, getting up from a chair (2x)
* ECG (5x)
* Questionnaire ((Dietary assessment Nutrition Status (PIQ)): 5x
* Questionnaires (severity of symptoms, dysphagia, quality of life) (2x)

Treatmentperiod 2:

* Physical examination (3x).
* Bloodpressure and heart rate (3x)
* Body temperature (3x)
* Blood collection, 20 ml per visit (2x).
* Evaluation muscle/physical activity (4x)
* 6 minute walktest (1x)
* Quadriceps strenght (1x)
* Pinch strength (1x)
* Short test battery balance, speed, getting up from a chair (1x)
* ECG (3x)
* Questionnaire ((Dietary assessment Nutrition Status (PIQ)): 4x
* Questionnaires (severity of symptoms, dysphagia, quality of life) (1x)

Throughout study period:
* Diary (number of falls)

Optional substudy:
MRI (2x during total duration study)

Contacts

Public
Novartis

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Arnhem 6824 DP
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Scientific
Novartis

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Patients who completed the core study
- Written informed consent must be obtained before any extension study assessment is performed
- Able to communicate well with the investigator
- Willing to participate for the entire duration of the extension study with commitment to follow study requirements and procedures

Exclusion criteria

- Women who are pregnant
- Women of child-bearing potential unless they are using highly effective methods of contraception during dosing and for 6 months after the last BYM338 dose
- Current use of prohibited treatments
- History of severe hypersensitivity reaction in the core study
- History of adverse event(s) (including those from the core study) prior to the start of study drug in the extension study that, in the judgment of the investigator, taking into account the subject's overall status, prevent the subject from entering the extension study
- Clinically significant abnormal liver function tests
- Any medical condition or laboratory finding which, in the opinion of the investigator may interfere with participation in the study, might confound the results of the study, or pose an additional safety risk in administering BYM338

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):	03-11-2015
Enrollment:	18
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	BYM338
Generic name:	BYM338

Ethics review

Approved WMO Date:	17-08-2015
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-10-2015
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-10-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	30-10-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-12-2015

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-01-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-12-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-12-2016
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	EUCTR2015-001411-12-NL
CCMO	NL54491.018.15