A randomized, double-blind, placebo-controlled, multicenter, parallel group, dose-finding, pivotal, phase IIb/III study to evaluate the efficacy, safety and tolerability of intravenous BYM338 at 52 weeks on physical function, muscle strength, and mobility and additional long-term safety up to 2 years in patients with sporadic inclusion body myositis (CBYM338B2203)

Published: 20-12-2013
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Primary: to demonstrate that at least one dose regimen of BYM338 in sporadic inclusion body myositis patients will increase the distance traveled as measured by change from baseline at Week 52 of the 6 minute walking distance test relative to...

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

Summary

ID

NL-OMON41682

Source
ToetsingOnline

Brief title
CBYM338B2203

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 BV

Intervention

Keyword: body, BYM338, inclusion, myositis

Outcome measures

Primary outcome

6 minute walk test.

Secondary outcome

Quadriceps muscle strength, Sporadic Inclusion Body Myositis Functional

Assessment, falls, lean body mass, Short Physical Performance Battery. Adverse

events.

Study description

Background summary

Sporadic inclusion-body myositis (sIBM) is a very rare disease. The estimated prevalence is 15-71 per million 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-* 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.
The purpose of the present dose-finding study is to demonstrate that at least one dose regimen of BYM338 in sIBM patients improves physical function and mobility when compared to placebo after 52 weeks of treatment.

Study objective

Primary: to demonstrate that at least one dose regimen of BYM338 in sporadic inclusion body myositis patients will increase the distance traveled as measured by change from baseline at Week 52 of the 6 minute walking distance test relative to placebo.
Secondary: Quadriceps muscle strength, Sporadic Inclusion Body Myositis Functional Assessment, falls, lean body mass, Short Physical Performance Battery. Dose-reponse in 6 minute walk test. Safety and tolerability.
Several exploratory objectives (see protocol page 19).

Study design

Randomized, double blind, placebo controlled, phase II study.
Randomization (1:1:1:1) to
* BYM338 10 mg/kg i.v. infusion every 4 weeks
* BYM338 3 mg/kg i.v. infusion every 4 weeks
* BYM338 1 mg/kg i.v. infusion every 4 weeks
* Placebo, administered as i.v. infusion every 4 weeks
Treatment duration until the last patient has completed the week 48 evaluation.
Maximal treatment duration approx. 2 years.
Post-treatment follow-up 8 weeks after last dose of study medication.
240 patients.
A maximum of 20% of patients with baseline 6 minute walk distance >400 meters will be
randomized.
Independent Data Monitoring Committee.

Intervention

Treatment with BYM338 or placebo.

Study burden and risks

Risk: Adverse effects of study medication.
Burden: Study duration approx. 1-2 years. 18-31 visits. Duration 4-8 h.
13-26 i.v. infusions (100 mL), duration at least 30 min.
Every visit:
* Physical examination.
* Columbia Suicide Rating Scale.
Every visit 1st year and every 12 weeks thereafter:
* Blood draw, 20-30 ml per occasion.
Every 8 weeks:
* Evaluation muscle strength
* 6 minute walk test
* Quadriceps strength
* Hand grip strength
* Short test battery balance, speed, getting up from a chair.
Every 12 weeks:
* ECG
* DEXA scan (approx. 0,02 mSv per occasion)
Every 24 weeks:
* Echocardiogram
* Videofluoroscopy (in case of dysphagia approx. 0,2 mSv (LUMC), c.q. 0,9 mSv (AMC))
Every 8-24 weeks:
* Questionnaires (severity of symptoms, dysphagia, quality of life)

Full study period:
* Diary (number of falls)
Optional:
* Blood and urine sampling pharmacogenetics, biomarkers. 12 blood samples (27-35 ml) during treatment period.

Contacts

Public
Novartis

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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

* Male and female patients with sporadic inclusion body myositis, 36-85 years of age.
* Must not be wheel-chair bound (intermittent use of wheelchair is allowed) at both screening and baseline visits, as defined by a 6MWD score >1 meter.

Exclusion criteria

* Any active chronic non-sIBM condition associated with cachexia or muscle atrophy or that limits mobility as a result of respiratory function. See protocol page 31 for details.
* Uncontrolled diabetes mellitus (i.e. HbA1C *9.0 mmol/l) and/or any other uncontrolled endocrine disease.
* History of a hip fracture in the last 6 months or has undergone surgery for a hip or knee prosthesis in the last 6 months.
* Abnormal scores in Columbia Suicide Severity Rating Scale. See protocol page 31 for details.
* Severe Vitamin D deficiency defined as 25-OH-vitamin D levels <23 nmol/mL at screening.
* Systolic blood pressure >180 or <90 mm Hg or diastolic blood pressure >100 or <50 mmHg at screening.
* Use of prohibited systemic treatments, including VEGF inhibitors, within past 6 months prior to randomization or any therapies known to affect muscle mass. See protocol page 33 for details.
* Chronic corticosteroid use or history of systemic corticosteroid use for at least 90 days prior to randomization at a daily dose greater than or equal to 10 mg prednisone equivalent.
* Immunosuppressive therapy or antibody immunosuppressive therapy within the past 6 months or non-antibody therapy for autoimmune diseases within the past 3 months. See protocol page 33 for details.
* Known active infection or any major episode of infection within the past 8 weeks, any chronic infection. See protocol page 33 for details.
* Pregnant or lactating women.
* Women of child-bearing potential not using adequate contraception.

Study design

Design

Study phase:	2
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):	07-08-2014
Enrollment:	20
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	20-12-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-07-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-09-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-09-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-11-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	08-12-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	30-01-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-02-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-07-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-07-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-08-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-08-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-11-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-11-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	06-01-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-01-2016
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	EUCTR2013-000705-23-NL
ClinicalTrials.gov	NCT01925209
CCMO	NL46014.018.13