A Study of Respiratory Muscle Strength, including Effort-Independent Measures, in Subjects with Late-Onset Pompe Disease

Published: 15-02-2016
Last updated: 14-04-2024

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Ethical review	Approved WMO
Status	Pending
Health condition type	Muscle disorders
Study type	Observational non invasive

Summary

ID

NL-OMON43764

Source
ToetsingOnline

Brief title
BMN701-201

Condition

- Muscle disorders

Synonym
Late-onset Pompe disease

Research involving
Human

Sponsors and support

Primary sponsor: BioMarin Pharmaceutical Inc.

Source(s) of monetary or material Support: Sponsor: Biomarin

Intervention

Keyword: Late-onset Pompe disease, Respiratory Muscle Strength

Outcome measures

Primary outcome

The primary objective of this study is to compare respiratory muscle strength

values obtained using volitional techniques with values obtained using

non-volitional techniques

Secondary outcome

The secondary objective is to compare the change for these two sets of values

after 24 weeks in subjects treated or not treated with BMN 701.

Study description

Background summary

Progressive respiratory failure is the most frequent cause of death in late-onset Pompe disease. The Phase 1/2 study (POM-001) of BMN 701 treatment with 20 mg/kg every other week resulted in substantial improvement in maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) as well as improvement in other measures of respiratory function and in 6-minute walk test (6MWT) distance. As a result, a Phase 3 study (701-301) was undertaken to determine whether BMN 701 can improve measures of respiratory muscle strength in late-onset Pompe disease patients previously treated with commercial recombinant human GAA (rhGAA). The primary endpoint of the Phase 3 study is MIP; one of the secondary endpoints is MEP; one of the exploratory endpoints is sniff nasal inspiratory pressure (SNIP).
Given that MIP, MEP, and SNIP, like other measures of respiratory strength or function, depend on the patient making his/her best effort, it is possible these values may increase through factors other than improvement in respiratory muscle contractility. Such factors may include subject aptitude, motivation, cooperation, or practice. Therefore, to substantiate improvement in effort-dependent test results following BMN 701 treatment in Study 701-301, this study (701-201) will use the non-volitional technique of magnetic nerve

stimulation to measure diaphragmatic muscle strength to compare with volitional techniques to measure respiratory muscle strength.
Magnetic nerve stimulation involves a rapidly changing magnetic field emanating from a coil placed on the skin that simultaneously depolarizes bilateral phrenic or thoracic nerve motor axons, causing a brief maximal diaphragmatic contraction, termed a *twitch.* Twitch magnitude is measured as a transdiaphragmatic pressure (TDP). Measuring diaphragmatic twitch pressure (TwPdi) and twitch gastric pressure (TwPga) via esophageal (Poes) and gastric (Pga) pressure balloons provides an objective (effort-independent) measure of treatment effect.
To assure accurate assessment of respiratory muscle strength, which varies with lung volume, this study will assess lung volume by whole-body plethysmography. Because respiratory muscle weakness may compromise gas exchange, this study will measure the carbon monoxide transfer factor (TLCO) to determine the lung*s ability to transfer a tracer gas, carbon monoxide, from alveolus to blood stream. To evaluate BMN 701 treatment effect more comprehensively and to correlate findings with MIP, MEP, and SNIP measurements in Study 701-301, respiratory measures also will include MIP, MEP, SNIP, sniff esophageal pressure (Poes), sniff diaphragmatic pressure (Pdi), and cough gastric pressure (Pga). To assess ease of lung inflation, this study will measure dynamic lung compliance, the ability of alveoli and lung tissue to expand during inspiration. Phrenic and thoracic nerve stimulation will provide effort-independent respiratory muscle strength by measuring diaphragmatic TwPdi and TwPga via esophageal and gastric pressure balloons, respectively.
To optimize enrollment for a meaningful comparison of volitional and non-volitional tests of respiratory muscle strength in patients with late-onset Pompe disease (primary objective), the study population may include subjects enrolled in Study 701-301 (switched from commercial rhGAA to BMN 701), subjects enrolled in Study POM-002 (receiving BMN 701), Study 701-901 (untreated or receiving commercial rhGAA), and/or late-onset Pompe disease patients enrolled in no other study (untreated or receiving commercial rhGAA). Change in these test results after 24 weeks (secondary objective) in subjects not receiving BMN 701 (whether receiving commercial rhGAA or not) will reflect the natural history of the disease in terms of volitional and non-volitional measures.
Studies POM-002 (N=22), 701-901 (N=100), and 701-301 (N=50) are studies in patients with late-onset Pompe disease. Study POM-002 is an extension of POM-001 to evaluate longer-term BMN 701 safety and preliminary efficacy. Study 701-901 is a prospective, noninterventional, observational study in adults treated or untreated with commercial rhGAA. Study 701-301 is a Phase 3 study of BMN 701 safety and efficacy in patients switched from commercial rhGAA to BMN 701.

Study objective

The primary objective of this study is to compare respiratory muscle strength values obtained using volitional techniques with values obtained using non-volitional techniques. The secondary objective is to compare the change for

these two sets of values after 24 weeks in subjects treated or not treated with BMN 701.

Study design

Following informed consent, approximately 5 to 15 subjects will enter this single-arm respiratory study at sites specializing in respiratory assessment. The study will test respiratory muscle strength initially and again after 24 weeks in subjects treated or not treated with BMN 701 by effort-dependent and effort-independent techniques. Phrenic and thoracic nerve stimulation will provide effort-independent (non-volitional) respiratory muscle strength by measuring diaphragmatic TwPdi and TwPga via esophageal (to obtain Poes) and gastric (to obtain Pga) pressure balloons.
This study consists of two visits and a follow-up:
* First Visit is after study entry criteria are met. For subjects enrolled in Study 701-301, the First Visit is after all Study 701-301 entry criteria are met and before the Week 4 infusion.
* Last Visit
* is 24 ±3 weeks after the First Visit.
Follow-Up
Pulmonary measures at each study visit will include lung volume by whole-body plethysmography (unless precluded by mobility issues), carbon monoxide gas transfer, volitional measures of respiratory muscle strength (MIP, MEP, SNIP, sniff Poes, sniff Pdi, and cough Pga), non-volitional measures of respiratory muscle strength (TwPdi and TwPga), and dynamic lung compliance.

Study burden and risks

There is no study drug admission involved in this study and no study procedure is experimental. Although some of these tests are very specialized, all are performed as part of the clinical evaluation of some patients with respiratory muscle function abnormalities due to neuromuscular disease such as Pompe disease.
There is a risk the patiënt may feel bad from a study procedure. Some of these risks are listed below but doctors and study sponsors cannot know all risks that may occur. These vary from person to person.
Blood Pressure: A rubber cuff will squeeze one arm and may make you feel funny, like your hand is asleep.
Nose Tubes: Swallowing the tubes may cause some discomfort. Local anesthetic is used in the nose and back of the throat to reduce any discomfort. Although unlikely, a sore throat, nose bleed, or sinusitis may result.
Breathing Tests: Blowing into the mouthpiece may make you feel dizzy or light-headed so these tests are done with you seated in a chair. Inhaling carbon dioxide temporarily will increase your breathing rate, which may be a little alarming but does not last long. When the nerves are stimulated, you may feel a strange sensation like a big hiccup and feel a strong twitch in your arm

and leg muscles but it is not dangerous.

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

* Willing and able to provide written informed consent, after the nature of the study has been explained, and prior to any study-related procedures
* Documented diagnosis with late-onset Pompe disease based on GAA gene mutations and/or endogenous GAA activity <75% of the lower limit of the normal adult range reported by the testing laboratory, assessed by dried blood spot, whole-blood, skin fibroblasts, or muscle biopsy
* At least 18 years of age at study entry
* Willing and able to comply with all study procedures

Exclusion criteria

* Requires ventilatory support while awake and in the upright position. Subjects who require night time ventilator support may only enroll upon obtaining approval from the sponsor.
* Concurrent disease, medical condition, or extenuating circumstance that, in the opinion of the investigator, might compromise patient wellbeing,
study completion, or data collection.
- subjects with a diagnosis of asthma, chronic obstructive pulmonary disease, emphysema, or any other condition that may manifest with airway obstruction should be excluded, unless the subject has an FEV1/FVC ratio > 0.80 on spirometry (in another study or elsewhere) performed within 3 months in this study.
* Swallowing difficulty precluding balloon catheter placement (eg, esophageal strictures)
* Allergy to tools or procedures used for respiratory muscle testing
* Implanted ferrous metals (eg, cardiac pacemakers)
* Subjects taking medication for the treatment of obstructive lung disease (including, but not limited to, systemic or inhaled beta agonists, inhaled corticosteroids, or inhaled anticholinergic/anti-muscarinic agents) may not be enrolled in this study.
* Subjects who are pregnant, planning to become pregnant, or unable/unwilling to use effective contraception (as evaluated by the principal investigator) for the duration of the study.

Study design

Design

Study phase:	4
Study type:	Observational non invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	31-03-2015
Enrollment:	5

Type:	Anticipated

Ethics review

Approved WMO Date:	15-02-2016
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	24-05-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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
CCMO	NL51709.091.15