A Prospective Natural History Study of the Progression of Physical Impairment, Activity Limitation and Quality of Life in Duchenne Muscular Dystrophy (DMD)

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•To characterize the natural history and progression of DMD to help inform the design of future studies•To capture biomarkers of safety and disease progression•To provide comparative data for the development of rare exons for which formal controlled…

Ethical review	Approved WMO
Status	Pending
Health condition type	Musculoskeletal and connective tissue disorders congenital
Study type	Observational invasive

Summary

ID

NL-OMON39538

Source
ToetsingOnline

Brief title
DMD Natural History

Condition

- Musculoskeletal and connective tissue disorders congenital
- Muscle disorders

Synonym
Duchenne Muscular Dystrophy (DMD), muscular dystrophy

Research involving
Human

Sponsors and support

Primary sponsor: Prosensa Therapeutics B.V.
Source(s) of monetary or material Support: GlaxoSmithKline,Prosensa Therapeutics B.V. (industry)

Intervention

Keyword: Duchenne Muscular Dystrophy, Natural History

Outcome measures

Primary outcome

This is an exploratory observational study with no formal statistical

hypotheses. All data will be summarised at each time point. In general,

categorical data will be presented using counts and percentages, whilst

continual variable will be presented using the mean, standard deviation,

median, minimum, maximum and number of patients.

Interim analyses will be conducted at yearly intervals during this study.

Secondary outcome

N/A

Study description

Background summary

Duchenne Muscular Dystrophy (DMD) is an inheritable (X-chromosome linked) lethal childhood disease with an incidence of approximately 1 in 3,500 newborn boys (Emery, 1993). DMD is caused by alterations in the gene coding for the protein dystrophin which leads to little or no dystrophin being produced. Dystrophin is essential for the integrity and functioning of muscle fibres (Hoffman EP, 1988).
First signs of muscle weakness typically occur before the age of 4 years and gradually progress to include skeletal muscles in the arms, legs and trunk. Over time, heart muscle and respiratory muscles are affected.
Even with more recent clinical interventions, such as glucocorticosteroid

treatment and ventilatory support, DMD patients are usually wheelchair-bound by their mid-teens and generally die in their twenties/early thirties.
Although specific treatments for DMD have not reached the clinic yet, the natural history of the disease has been changed by targeting known manifestations and complications. Specifically, corticosteroid, respiratory, cardiac, orthopaedic and rehabilitative interventions have led to improvements in function, quality of life, health and longevity. There will be further advances and more effective treatment of the underlying pathology of DMD, currently exon skipping with AONs seems to be the most promising.
In order to assess the clinical effectiveness of specific treatments it is vital to understand how the commonly used evaluations of DMD change over time as the boy grows and develops. Also, as treatments are developed for the rarer exon mutations, the number of boys that can be included in clinical trials will become very small and so reference to the natural history of the disease will be important in the bid to understand whether an intervention is effective or not.
A variety of outcome measures are in current use in ambulant and non-ambulant DMD boys. Outcome measures in ambulant boys which give high test-retest correlations include the 6 minute walking distance test (6MWD), timed functional tests (10 m walk/run, stair climb, stair descend and supine to stand) and muscle strength testing using hand-held myometry. Outcome measures in non-ambulatory boys have been less well studied and developed and include a variety of functional scales and measures of Quality of Life as well as assessments of upper limb muscle strength with myometry and also pulmonary function testing. In order to develop the most meaningful outcome measures it is important to understand how the measures change as the child grows and ages and these changes translate into quality of life. It will also be possible to study of the value of the outcome measures in predicting life altering events, such as the loss of independent ambulation. There are further novel developments on the application of serum biomarkers as an outcome, such as MMP-9, TIMP-1 and miRNA*s which appear to correlate with disease progression.
Finally, clinical trials in DMD patients require careful monitoring for safety, but many of the common blood parameters are not validated for DMD patients, in particular those related to inflammation, liver and kidney function. This study provides the opportunity to gain comprehensive background data essential for safe clinical trials in this population at a low burden.
Therefore the main purpose of this prospective natural history study is to expand the study of various outcome measures, particularly those for non-ambulant boys and those in younger boys. The information gained will in turn inform the design of future clinical trials.
The aim of the design of this protocol has been to minimize as far as possible the burden for each subject in participating in this study. The evaluations proposed do not differfrom those that are commonly used in DMD clinics in Europe and the USA. The intention is to gather more data on all of the measures in a natural history setting in order to contribute to the ongoing global efforts towards a consensus on the best measures to use to evaluate the

progression of DMD.

Study objective

•To characterize the natural history and progression of DMD to help inform the design of future studies
•To capture biomarkers of safety and disease progression
•To provide comparative data for the development of rare exons for which formal controlled trials are not feasible

Study design

This is a prospective study. All DMD patients that fulfil the inclusion/exclusion criteria are eligible although the study is weighted towards ambulant subjects aged 3 years or older. There will be 7 study visits - baseline, then at 6, 12, 18, 24, 30 and 36 months.
Subjects will be in the study for a maximum of 3 years.

Evaluations (for a schedule of procedures at each site visit: please see protocol appendix 1):

Completion of these evaluations will depend on age and ambulancy of the individual subjects:

For the ambulatant subjects at each visit:
•6 minute walking distance (6MWD) + accelerometry in centres where Locometrix is available
•Patient reported outcomes questionnaire - DMD FOS
•North Star Assessment
•Timed tests i.e. rise from floor, 10m walk/run, stair climb

In addition, for the very young subjects, ages 3 to approximately 5 yrs, there will likely be an assessment of their development and motor skills using an appropriate test or tests. The test/s to be used will be specified prior to recruitment of subjects aged 3-5 yrs.

For the non-ambulant subjects at each visit, measures to include:
•Egen Klassification - measures functional ability (transfer, standing etc)

For all subjects:
•Myometry - to measure muscle strength - at each visit
•Goniometry - to measure range of movement - at each visit
•Myotools i.e. moviplate, pinch and hand grip in centres with the equipment and training - at each visit
•Blood sampling at 4 time points: baseline, 12, 24 and 36 months (or when subject leaves the study). The samples will be frozen and stored at the central

lab for future analysis. Some biomarkers from the following list will be measured in the samples; MCP-1, Complement Factor C3, IL-6, CRP, cystatin C, E-selectin, ppVWF, GLDH, MMP-9, TIMP-1, micro RNAs.
•Urinalysis sampling at 4 time points i.e. at baseline then at 12, 24 and 36 months or when subject leaves study if before 24 months: glucose, albumin, protein, cystatin C, alpha1 microglobulin, KIM-1.
•ECG - if done at site, then it will be requested that the data is entered into theeCRF
•Echocardiogram - if an ECHO is done at site it will be requested that the data is entered into the eCRF
•Spirometry (FVC, FEV1, PCF and PF) - if done at site it will be requested that the data is entered into the eCRF
•Sniff pressure test (SNIP) - where required equipment is at site
•DEXA - if done at site it will be requested that the data is entered into the CRF
• Pulmonary function (appr. twice a year)
• PROM questionnaire (to asses ability to perform daily life activities)
• Performance Upper Limb

For all subjects at each visit:
•Asked about concomitant medication
•Assessment of illness/missed days at school/falls etc
•Assessment of *procedure related* events
•Vital signs
•Weight, height and BMI
•Physical examination including major events notable for disease progression
•Assessment of other treatments and/or hospital visits since last visit e.g. physiotherapy, surgery

Study burden and risks

The aim of the design of this protocol has been to minimize as far as possible the burden for each subject in participating in this study.
The evaluations proposed do not differ from those that are commonly used in DMD clinics in Europe and the USA and the visits are in line with routine patient management.
Some subjects, at some visits, may find it difficult to undertake/complete particular tasks as specified in the protocol. In these cases, the Investigator is asked, where appropriate, to enter any data generated and to record the reasons why the subject has not been able to undertake or complete the task in the e-CRF.
The intention is to gather more data on all of the measures in a natural history setting in order to contribute to the ongoing global efforts towards a consensus on the best measures to use to evaluate the progression of DMD.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

•Diagnosis of DMD resulting from a mutation in the DMD gene confirmed by a state of the art DNA diagnostic technique covering all DMD gene exons.
•Age 3 - 18 years
•Willing and able to comply with protocol requirements
•Life expectancy of at least 3 years
•Able to give informed assent and/or consent in writing signed by the subject and/or parent(s)/legal guardian (according to local regulations)

Exclusion criteria

•Current participation in a clinical study with an Investigational Medicinal Product(IMP)
•Participation within the previous 1 month in a clinical study with an IMP

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Other

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	31-08-2012
Enrollment:	30
Type:	Anticipated

Ethics review

Approved WMO

Date:	25-01-2013
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Approved WMO

Date:	27-08-2015
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	NL39422.091.12