A phase IIb, open-label study to assess the efficacy, safety, pharmacodynamics and pharmacokinetics of multiple subcutaneous doses of BMN 045 (previously known as PRO045) in subjects with Duchenne muscular dystrophy

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Primary objective:To assess the efficacy of BMN 045 after 48 weeks treatment in ambulant subjects with Duchenne muscular dystrophy.Secondary objectives:To assess the safety and tolerability of BMN 045 after 48 weeks of treatment in all study...

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

Summary

ID

NL-OMON43779

Source
ToetsingOnline

Brief title
PRO045-CLIN-01

Condition

- Muscle disorders
- Neuromuscular disorders

Synonym

Duchenne muscular dystrophy, Duchenne's disease

Research involving
Human

Sponsors and support

Primary sponsor: BioMarin Parmaceutical Inc.
Source(s) of monetary or material Support: BioMarin Pharmaceutical Inc.

Intervention

Keyword: BMN 045, Duchenne muscular dystrophy, Open-label, Phase IIb

Outcome measures

Primary outcome

Change from baseline in 6MWD after 48 weeks of treatment phase at selected

dose.

Secondary outcome

Efficacy (at all available study visits):

- Muscle function (North Star Ambulatory Assessment, Timed tests, 6MWD)

- Muscle strength (spirometry, handheld myometry)

- Performance of upper limb (PUL)

- DMD Functional Outcomes Questionnaire (DMD-FOS)

- Exploratory efficacy endpoints:

- Accelerometry

- Myotools (grip strength, key pinch, moviplate)

Safety parameters:

- Adverse events

- Local tolerability

- Laboratory assessments including:

- Routine biochemistry and haematology

- Urinalysis (routine parameters plus α1-microglobulin, microscopy) and 24-hour urine (additionally including protein electrophoresis, urine cystatin, KIM-1) and exploratory measurement of specific DMD protein biomarkers and micro RNAs

- Coagulation parameters (aPTT, PTT [INR], fibrinogen)

- Complement split products (C3a, SC5b-9, Bb)

- Pro-inflammatory markers (cytokines IL-6, TNF-α and chemokine MCP-1)

- Anti-dystrophin antibodies

- ECG parameters

- Vital signs (temperature, blood pressure, pulse rate, respiration rate)

- Echocardiography

- Physical examination and DEXA

- Standard renal ultrasound

Pharmacokinetic parameters

- BMN 045 levels in urine

- BMN 045 levels in muscle tissue

Pharmacodynamic parameters:

- Presence of (BMD-like) dystrophin expression after treatment (in muscle biopsy)

- Histological and immunological staining on cross-sections of muscle tissue

- Production of exon skip 45 mRNA (in muscle biopsy)

- Exploratory PD endpoints:

- Nuclear Magnetic Resonance imaging and spectroscopy (MRI and MRS)

- Exploratory biomarkers(e.g. TIMP, MMP-9, miR-1, miR-133)

Study description

Background summary

Duchenne muscular dystrophy (DMD) is a chromosome X-linked recessive muscle disorder, affecting 1/3500 newborn boys. Patients experience severe progressive muscle weakness and wasting, leading to early morbidity and mortality. 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 . Becker muscular dystrophy is also caused by mutations in the DMD gene, but these maintain the open reading frame, yield semi-functional dystrophin proteins, and result in a typically much milder phenotype and longer lifespan.
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 glucocorticosteroids and assisted ventilation have altered the natural course of DMD, there is still no effective treatment for the primary cause of the disease. A promising therapeutic strategy is treatment with antisense oligonucleotides that induce specific exon skipping during pre-mRNA splicing, aimed at reading frame correction and production of a Becker-like transcript. Although the functionality of the resulting protein may vary, this treatment could delay or even stop disease progression and improve remaining muscle function.
Exon skipping provides a mutation-specific, and thus personalized, therapeutic approach for DMD patients. As mutations cluster around exons 45 to 55, the skipping of one specific exon may be therapeutic for many patients with different mutations. The skipping of exon 45 applies to a subset of patients (~8%). Non-clinical studies on BMN 045 have shown its skipping efficiency, safety and favourable PK profile, and proof-of-concept for therapeutic exon 45 skipping therapy; inducing novel dystrophin production in cultured muscle cells from a DMD patient with a relevant mutation.
The aim of BioMarin Pharmaceutical's Inc. therapeutic strategy is to use RNA modulation (exon skipping) to change the severe form of the disease (DMD) into a milder form (BMD), in the expectation of a much improved outcome. The

clinical phenotype of BMD is variable and depends on the resulting levels of dystrophin and/or the functionality of the truncated protein. Cases have been described that are very severe and similar to DMD, others can be very mild (muscle cramps only) or even asymptomatic. Remarkably, very mild BMD patients have been described, who lack up to 67% of the central rod domain. This suggests, that despite large deletions, a partially functional dystrophin can be generated.

Study objective

Primary objective:
To assess the efficacy of BMN 045 after 48 weeks treatment in ambulant subjects with Duchenne muscular dystrophy.

Secondary objectives:
To assess the safety and tolerability of BMN 045 after 48 weeks of treatment in all study subjects with Duchenne muscular dystrophy including subjects from the dose-escalation phase of the study.
To determine the pharmacokinetics of BMN 045 at different dose levels after subcutaneous administration in subjects with Duchenne muscular dystrophy.
To assess the pharmacokinetics, bioavailability and safety of BMN 045 following single intravenous dose administration at different dose levels.
To assess the pharmacodynamics of BMN 045 at different dose levels after subcutaneous administration in subjects with Duchenne muscular dystrophy.
To assess trend in efficacy in all subjects with Duchenne Muscular Dystrophy not included in the primary objective after 48 weeks of treatment

Study design

This is a phase IIb, open-label, multiple-dose study. The study consists of two phases; a dose-escalation phase (with subsequent dose-titration) and a 48-week treatment phase.

Dose-escalation phase:
On the assumption that dose-limiting toxicities do not occur, the dose-escalation phase has the following design
Five groups of three subjects are planned. The BMN 045 starting doses for each group are 0.15 mg/kg (Group 1), 1 mg/kg (Group 2), 3 mg/kg (Group 3), 6 mg/kg (Group 4) and 9 mg/kg (Group 5). All doses will be administered by subcutaneous (SC) injection once per week.
Groups will be started sequentially and all three subjects in each group will ideally start dosing within the space of one week (the subjects within a group will each be separated by a minimum of 2 days for safety reasons). The safety data from at least the first 3 doses of BMN 045 for each subject in Group 1 will be reviewed by a Data and Safety Monitoring Board (DSMB) and assuming there are no safety concerns, Group 2 may be started (i.e. at a higher dose).

It is anticipated that, due to practical reasons, Group 2 will not start dosing until Group 1 has received at least 6 doses of BMN 045. Likewise, data from at least the first 3 doses of BMN 045 in Group 2 (plus all available data from Group 1) will be reviewed prior to starting Group 3, and similarly for Groups 4 and 5.
In parallel with starting the new dose groups, once a minimum of 12 weeks of dosing has been completed in Group 2 and assuming acceptable safety data, all subjects in Group 1 may have their dose increased (up-titrated) to the new dose level (i.e. from 0.15 mg/kg up to 1 mg/kg). Likewise, once a minimum of 12 weeks of dosing has completed in Group 3 and assuming acceptable safety data, all subjects in Groups 1 and 2 may have their dose up-titrated to the new dose level (i.e. from 1 mg/kg up to 3 mg/kg), and similarly for Group 4. It is therefore anticipated that all subjects will receive at least 18 weeks of dosing at their initial dose level, followed by at least 6 weeks of dosing at each subsequent dose level.
Finally, once 12 weeks of dosing has completed in Group 5 and assuming acceptable safety data, all subjects in Groups 1, 2, 3 and 4 may have their dose up-titrated to the new dose level (i.e. from 6 mg/kg up to 9 mg/kg).
All efficacy, safety, PD and PK data from all subjects collected up to Week 12 of Group 5 will be reviewed by the Sponsor and DSMB (all subjects will continue dosing whilst this review is ongoing).

48-week treatment phase:
At the end of the dose-escalation phase, a further 48 weeks of dosing for all subjects who participated in the escalation phase is planned in the treatment phase. In addition, a further group of 30 subjects will be recruited to enable methodologically valid assessment of the primary efficacy endpoint (6MWD) at the selected dose. The treatment phase will involve all subjects receiving the same dose regimen (either continuous or intermittent) which will be determined on the basis of emerging safety, tolerability, pharmacodynamic (PD) and pharmacokinetic (PK) data from the dose-escalation phase.

All 15 subjects participating in the dose-escalation phase will enter the 48-week treatment phase, but will not be included in the assessment of the primary efficacy endpoint. Subjects may continue at 9 mg/kg (or the maximum tolerated dose, if lower) for the 48 weeks, or alternatively the dose and or dosing regimen in the treatment phase may be chosen for all subjects based on emerging data as described previously. At the end of the 48 weeks, all subjects will stop dosing and will have a follow-up period of 21 weeks after the last administration of BMN 045 . Any subjects who withdraw will also enter the follow-up period (assuming consent is not withdrawn).

Dose-limiting toxicities:
If dose-limiting toxicities occur, the design will be modified depending on when the toxicities occur and the nature of the toxicities. Potential changes include:

If dose-limiting toxicity occurs in 1 of the 3 subjects in Group 1, a further 3 subjects may be recruited to this group (i.e. 6 subjects in total at 0.15 mg/kg BMN 045). If similar
dose-limiting toxicity occurs in 2 or more subjects at this dose level, the inclusion of any remaining new subjects planned at that dose level will be discontinued, and dose-escalation may be stopped after consultation with the DSMB.
If the dose-limiting toxicity in Group 1 occurs prior to dosing Group 2, then the start of Group 2 will be delayed until the new subjects in Group 1 have been dosed for at least the same time period as the original subjects were when the toxicity occurred. If dosing in Group 2 has already started, then the DSMB will be consulted to agree continuation of the study as planned, or down-titration of Group 2, following review of all relevant safety data. The same principle will apply to subsequent groups.

If dose-limiting toxicity occurs in 1 of the 3 subjects in Group 2 (and assuming none were observed in Group 1) and depending on the nature and/or timing of the event, and after discussions with the Medical Monitor and Sponsor, one of two possible scenarios will be implemented; 1) up to 3 subjects in Group 1 will be allowed to titrate up to this dose once Group 2 reaches 12 weeks of dosing (whilst any other subjects remain at the lower dose until it is confirmed that no further dose-limiting toxicities are observed in these new subjects within the timeframe of the initial dose-limiting toxicity), or 2) up to 3 new subjects may be recruited to Group 2 prior to escalating Group 1. If no further dose-limiting toxicities occur in the new subjects within 12 weeks, then Group 1 may be escalated as initially planned. The same principle will be applied to any dose-limiting toxicity occurring in 1 of 3 three subjects in Groups 3, 4 or 5, where either a maximum of 3 subjects from the combined lower dose group may be allowed to titrate to the higher dose, or 3 new subjects may be recruited. In the absence of further dose-limiting toxicities, the remaining subjects may then titrate to the higher dose following the appropriate time-window.

If more than one subject has a dose-limiting toxicity at any given dose level, dose-escalation and/or titration will be stopped after consultation with the DSMB.
If dose-escalation and/or titration is stopped due to dose-limiting toxicities at the highest dose level, the study may continue with subjects moved to (or kept at) a lower dose level and/or started on an intermittent dosing regimen, if deemed appropriate after consultation with the DSMB. The highest dose given, that was not associated with dose-limiting toxicity will be considered to be the maximum tolerated dose (MTD).
In the absence of any dose limiting toxicities in any given dose group, subjects who discontinue for any non-safety related reason prior to completing 5 weeks of dosing, will be replaced.

Intervention

Doses with the IP, BMN 045, will be administered by subcutaneous (SC) injection once per week.
Five groups of three subjects are planned in the dose-escalation phase. The proposed starting doses in each group are as follows:
Group 1: 0.15 mg/kg BMN 045
Group 2: 1 mg/kg BMN 045
Group 3: 3 mg/kg BMN 045
Group 4: 6 mg/kg BMN 045
Group 5: 9 mg/kg BMN 045

Dose groups will be started sequentially, and all three subjects in each group will ideally start dosing within the space of one week (the subjects within a group will each be separated by a minimum of two days for safety reasons). The safety data from at least the first 3 doses of BMN 045 for each subject in Group 1 will be reviewed by a Data Safety and Monitoring Board (DSMB) and assuming there are no safety concerns, Group 2 will be started at the dose recommended by the DSMB (i.e. at a higher dose). This procedure will continue for all groups.

Prior to moving to the treatment phase (30 patients and 15 patients from dose-escalation phase), the dose will be determined by examining a number of parameters from the dose-escalation phase, including:
- Safety and tolerability
- Dystrophin expression
- PK
- Tissue concentration levels
- Additional cellular biomarkers (exploratory)
- MRS (exploratory)

As DMD subjects lose function month on month during the normal course of their disease, a gap of up to 12 months whilst the next study is initiated is not felt to be appropriate. Many subjects would no longer be eligible to enter the treatment phase on the optimal dose and this would impact the available subject numbers for the treatment phase. All Subjects from the dose-escalation phase will continue into the treatment phase for safety and secondary efficacy analysis.

The expected duration of the study is in total:
Screening period: 2 weeks
Dose-escalation phase: Group1 39 weeks up to 1 year
Treatment phase: 48 weeks
Follow-up period: 21 weeks

Study burden and risks

DMD is a lethal disease for which at present no effective treatment is available. In view of the observed toxicity profile in non-clinical studies and the experience obtained with compounds with similar chemistry in clinical studies, as well as the proposed safety management in the study, it is considered acceptable to initiate the clinical development of BMN 045.

This is the first time that BMN 045 is studied in humans. The most common side effects reported with similar oligonucleotides are: injection site reactions, changes in hepatic and renal protein levels and decrease of platelets in the blood. Furthermore pro-inflammatory effects have been observed. Other risks are as follows: a small bleeding at the place of injection or at the place where the blood is drawn, pain at the place where the biopsies are taken, the site of the biopsy may feel numb or become infected, a scar at the place of biopsy and it is possible that the strength of the muscle may be slightly reduced in the short term, and a reaction to the general anaesthesia.

Patients will receive standard treatment, in addition patients will receive an injection every week with the study drug.
There are risks involved in joining this study and also the burden is increased, as patients need an injection every week and blood is drawn regularly. However, if this treatment is a succes in these patients, there will be a change in the severity of their disease and it is expected that this will lead to an improved outcome.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Children (2-11 years)

Inclusion criteria

1. Duchenne muscular dystrophy resulting from a mutation correctable by treatment with BMN 045 confirmed by a state-of-the-art DNA diagnostic technique covering all DMD gene exons, including but not limited to MLPA (Multiplex Ligation-dependent Probe Amplification), CGH (Comparative Genomic Hybridisation), SCAIP (Single Condition Amplification/Internal Primer) or HRMCA (High-Resolution Melting Curve Analysis)
2. Ambulant boys aged at least 5 years on the day of first dosing able to walk for at least 230 meters in the 6 minute walking distance (6MWD) at the first screening visit and also at the baseline visit. In addition, 2 of the 3 pre-treatment 6MWD tests (screen 1, screen 2, baseline) must be within ± 30 meters of each other prior to first BMN 045 administration
3. Adequate quality for biopsy (confirmed with MRI) of the lateral head of the gastrocnemius muscle.
4. Life expectancy of at least 3 years after inclusion in the study.
5. Glucocorticosteroid use which is stable for at least 3 months prior to first BMN 045 administration. Subjects must have been receiving glucocorticosteroids for at least 6 months prior to the first BMN 045 administration.

Exclusion criteria

1. Known presence of dystrophin in >=5% of fibres in a pre-study diagnostic muscle biopsy (i.e. historic muscle biopsy taken prior to written informed consent for this study).
2. Current or history of liver disease or impairment
3. Current, or history of, renal disease or impairment.
4. at least two aPTT above ULN within the last month
5. Screening platelet count below the lower limit of normal (LLN).
6. Acute illness within 4 weeks prior to first dose of BMN 045 which may interfere with the study assessments.
7. Severe mental retardation or behavioural problems which, in the opinion of the investigator, prohibit participation in this study
8.Severe cardiomyopathy which in the opinion of the investigator prohibits participation in this study. If a subject has a left ventricular ejection fraction <45% at screening, the investigator should discuss inclusion of the subject with the Medical Monitor.

9. Expected need for daytime mechanical ventilation within the next year.
10. Use of anticoagulants, antithrombotics or antiplatelet agents.
11. Use of idebenone or other forms of coenzyme Q10 within 1 month prior to the start of the screening for the study.
12. Use of nutritional or herbal supplements which, in the opinion of the investigator, may influence muscle performance, within 1 month of the study
13. Use of any other investigational product or participation in another trial with an investigational product, within 6 months prior to the start of the screening for the study.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	30-08-2013
Enrollment:	5
Type:	Actual

Ethics review

Approved WMO Date:	01-11-2012
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	04-06-2013

Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	01-07-2013
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	27-08-2013
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	10-10-2013
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	11-10-2013
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	26-03-2014
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	11-06-2014
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	19-01-2015
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO Date:	15-07-2015
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	10-11-2015
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	02-02-2016
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	31-03-2016
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

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	EUCTR2011-005040-10-NL
CCMO	NL42348.000.12