A Phase I/II, open-label, dose escalating with 48-week treatment study to assess the safety and tolerability, pharmacokinetics, pharmacodynamics and efficacy of BMN 053 (previously knoen as PRO053) in subjects with Duchenne muscular dystrophy

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Primary objective: To assess the efficacy of BMN 053 at recommended dosing regimen after 48 weeks treatment in ambulant subjects with Duchenne muscular dystrophy.Secondary objectives: - To assess the safety and tolerability of BMN 053 after single...

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

Summary

ID

NL-OMON43770

Source
ToetsingOnline

Brief title
PRO053-CLIN-01

Condition

- Muscle disorders
- Neuromuscular disorders

Synonym

Duchenne muscular dystrophy, Duchenne's disease

Research involving
Human

Sponsors and support

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

Intervention

Keyword: BMN053, Duchenne Muscular Dystrophy, Open label, Phase I/II

Outcome measures

Primary outcome

Change from baseline in 6MWD after 48 weeks of treatment phase for primary

evaluation at recommended regimen

Secondary outcome

Efficacy (at all available study visits):

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

• Muscle strength (handheld myometry)

• Pulmonary function (spirometry)

• 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 and KIM 1)

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

• Complement C3 and 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

• DEXA

• Standard renal ultrasound

Pharmacokinetic parameters

• t * (if reliable)

• AUC: 0-24h, 0-72h, 0-7d, 0- (where applicable)

• Cmax, Ctrough, 7d

• tmax

• Vd (for IV) or Vd/F (for SC)

• CL (for IV) or CL/F (for SC)

• BMN 053 concentrations in urine

• BMN 053 concentrations 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 53 mRNA (in muscle biopsy)

• Exploratory PD endpoints:

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

• Exploratory biomarkers(e.g. 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 glucocort/costeroids 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 53 applies to a subset of patients (~8%). Non-clinical studies on BMN053 have shown its skipping efficiency, safety and favourable PK profile, and proof-of-concept for therapeutic exon 53 skipping therapy; inducing novel dystrophin production in cultured muscle cells from a DMD patient with a relevant mutation.

The aim of BioMarin's 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 053 at recommended dosing regimen after 48 weeks treatment in ambulant subjects with Duchenne muscular dystrophy.

Secondary objectives:
- To assess the safety and tolerability of BMN 053 after single intravenous (IV) and subcutaneous (SC) dose in subjects with Duchenne muscular dystrophy.
- To investigate the pharmacokinetics BMN 053 at different dosing regimens in subjects with Duchenne muscular dystrophy.
- To assess the safety and tolerability at different dosing regimens in subjects with Duchenne muscular dystrophy.
- To assess the pharmacodynamics of BMN 053 at different dosing regimens in subjects with Duchenne muscular dystrophy.
- To assess efficacy trends and safety of BMN 053 in subjects with Duchenne Muscular Dystrophy not included in the primary analysis after 48 weeks of dosing and/or dosing extension.

Study design

A Phase I/II, open-label study. The study consists of four phases; a dose-escalation phase, a regimen selection phase, a treatment phase and a dose extension phase.

Intervention

Doses with the IP, BMN 053, will be administered intravenously weeklyto study subjects in the regimen selection phase of the study.

The proposed starting doses in each regimen selecition group are as follows:
Group 1: 6 mg/kg/week sc voor 48 weken. Dit gedeelte is afgerond
Group 2: 3 mg/kg via IV infuus voor 48 weken.
Group 3: Potentieel varierend van 4-6 mg/kg/week IV infuus

Treatment phase:
BMN 053 will be given to 30 treatment naïve subjects at the recommended regimen for 48 weeks based upon data from the dose escalation and regimen selection phases of the study.

Dose extension phase:
Subjects who have completed the dose escalation and regimen selection phases of the study, and subjects who have completed the treatment phase will continue BMN 053 treatment in this extension phase.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:
Regimen selection phase: 48 weeks
Treatment phase: 48 weeks
Dose Extension phase: 48 weeks
Follow-up period: 24 week

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 053.

This is the first time that BMN 053 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 strenght 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

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

Inclusion criteria

1. Duchenne muscular dystrophy resulting from a mutation correctable by treatment with BMN053 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 300 metres in the 6 minute walking distance (6MWD) test at the first screening visit and also at the baseline visit. In addition, results of 2 of any of the 3 pre-treatment 6MWD tests (assessed screen
1, screen 2, baseline) must be within ±30 metres of each other prior to first BMN053 administration. Subjects must also be able to rise from the floor in <= 7 seconds at the first screening visit and also at the baseline visit.
3. Adequate quality for biopsy (confirmed with MRI) of the lateral head of the gastrocnemius muscle. Only under exceptional circumstances will an alternative muscle (preferably brachii) be considered for biopsy and only following discussion between the Principal Investigator and the BioMarin Medical Monitor.
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 BMN053 administration. Subjects must have been receiving glucocorticosteroids for at least 6 months prior to the first BMN053 administration.
6. Willing and able to adhere to the study visit schedule and other protocol requirements.
7. Written informed consent signed (by parent(s)/legal guardian and/or the subject, according to the local regulations).
8. In France, a subject will be eligible for inclusion in this study only if either affiliated to, or a beneficiary of, a social security category.
9. Anticipated adequate vein access for intravenous (IV) infusion.

Exclusion criteria

1. Current or history of liver disease or impairment.
2. Current or history of renal disease or impairment.
3. Screening aPTT above upper limit of normal (ULN)
4. Screening platelet count below the lower limit of normal (LLN).
5. Acute illness within 4 weeks prior to first dose of BMN053 which may interferewith the study assessments.
6. Severe mental retardation and/or behavioural problems which, in the opinion of the Investigator, prohibit participation in this study.

7. 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.
8. Expected need for daytime mechanical ventilation within the next year.
9. Use of anticoagulants, antithrombotics or antiplatelet agents.
10. Use of idebenone or other forms of coenzyme Q10 within 1 month prior to the start of the screening for the study.
11. Use of nutritional or herbal supplements which, in the opinion of the Investigator, may influence muscle performance within 1 month prior to first dose of BMN053.
12. 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):	28-08-2013
Enrollment:	5
Type:	Actual

Ethics review

Approved WMO

Date:	14-03-2013
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO

Date:	13-06-2013
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	10-04-2014
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	21-05-2014
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	01-07-2014
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	15-07-2014
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	15-01-2015
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	10-07-2015
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Not approved Date:	01-09-2015
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den

	Haag)
Approved WMO Date:	12-01-2016
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	05-02-2016
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	09-02-2016
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	21-04-2016
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	21-07-2016
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	EUCTR2011-005042-35-NL
CCMO	NL43736.000.13