Genethon- Microdystrophin Gene Therapy (GNT-016-MYDF)

GNT-016-MYDF: A phase I/II/III study with a dose determination part followed by an efficacy and safety evaluation of selected dose part and then by a long-term follow-up part in ambulant boys aged 6 to 10 years with DMD

Hub Summary

GNT0004 is a recombinant adenovirus-associated viral (AAV) vector gene therapy, composed of an AAV8 serotype capsid containing a sequence-optimised gene for a human microdystrophin.

Duchenne muscular dystrophy (DMD) is a neuromuscular disorder caused by dystrophin gene mutations leading to absence (almost absence) of functional dystrophin, a key protein that prevents muscle cell damage during physiological contractions. Conceptually, adding a functional copy of the gene to muscle cells would, in principle, treat the underlying cause of the disease. However, there are two main obstacles to overcome to achieve this. First, a vehicle (vector) is needed to transport the functioning gene to target muscle cells. AAV capsids are frequently used as the vehicle to transport genes in other gene therapy products. The specific type of AAV capsid in GNT0004 is called AAV8. The second obstacle to overcome is the size of the dystrophin gene. It is one of the largest genes in our bodies and because it is so large it cannot fit inside the AAV capsid. To address this obstacle, the Genethon research group has developed a miniaturized but functional version of dystrophin (Microdystrophin).

The principle of GNT0004 is to deliver an optimized microdystrophin protein to target tissues (heart and skeletal muscles) in DMD subjects. It is expected to significantly delay or slow down the progression of the disease in humans in a similar manner to how it has shown to be able to do this in animal models with the disease.

In order to help GNT0004 reach muscles throughout the body, GNT0004 will be given as a one-time intravenous (IV) infusion.

Study Number: EUDRACT NÂ° 2023-505187-11-00

Description by Genethon

The study includes 3 parts: Part 1: a dose escalation part where two dose levels were studied. Five DMD boys participated this part (2 received the lower dose and 3 the higher dose). 12 weeks data of these 5 participants have been reviewed by an independent data monitoring committee. The higher dose (3X1013 vg/kg) has been considered as the most efficient dose of the gene therapy GNT0004 with the best and acceptable safety profile, therefore defined as the optimal dose that will be used for the following part 2 of the study. This first part was completed.

Part 2: a confirmatory part to evaluate the efficacy and side effects of GNT0004. Participants will be randomly assigned to one of two groups, half of them will receive GNT0004 and the other half will receive placebo (dummy treatment with indistinguishable appearance as GNT0004 but no active drug). This part is blinded, which means neither the study doctor/study site staff, participant/family, or study monitors will not know which group a particular participant is in. This part lasts one year for each participant. At the end of one year, participants in the placebo group will receive GNT0004 and those that received GNT0004 will get placebo, so that everyone in the study is able to eventually receive gene therapy in the study.

Part 3: a long-term follow-up part in which all participants who received GNT0004 in both Part 1 and 2 will be followed for a total of 5 years from dosing to monitor any potential late onset side effect and also to to assess the duration of the beneficial effects of the treatment. The above mentioned 5 participants of dose escalation Part 1 of the study are currently being followed in this Part 3.

A new version of the study protocol has been approved by health authorities in UK and in France and the recruitment of this part 2 is opening cross participating sites in these two countries (as of September 2025). Additional countries will be opened in the coming months.

Primary Outcome Measures

For Part 1:

- Safety measurements
- Microdystrophin protein expression and Microdystrophin positive myofibers level from muscle biopsy at week 8

For Part 2:

- NSAA scale (age-appropriate modified North Star Ambulatory Assessment) change from baseline at week 52

Trial Status
Recruiting

UK Locations
London - GOSH, Recruiting, Newcastle, Not yet recruiting

Trial Sponsor
Genethon

Phase
Phase I/II/III study

Length Of Participation
5 to 6 years

Recruitment Target
Approximately 69 participants : Part I: 5 participants (completed) - Part II: 64 participants (recruiting)

Ambulatory
Ambulant

Therapeutic Category
Gene Therapy

Age
6 to 10 years

Mutation Specific
Mutation specific therapies, Exclude mutations affecting exons 8 and/or 9

Muscle Biopsy
Muscle Biopsy Required

MRI
Yes

For Part 3:

- Safety measurements (item as described above)
- Main outcome measures and timeframes:

- Safety measurements including: Physical examination/ ECG, Echocardiography, cardiac MRI/ laboratory tests (blood, urine, stool)/ inflammatory biomarkers/ Side effect detection [Time Frame: Screening - 5 years post GNT0004]

- Microdystrophin protein expression and Microdystrophin positive myofibers level from muscle biopsy [Time Frame: Week 8 post GNT0004]

- NSAA scale (age-appropriate modified North Star Ambulatory Assessment) [Time Frame: Screening - 5 years post-GNT0004]

    - Motor Function Measurement: a 17-item measurement that doctors used to evaluate the ability of motor functions such as stand, walk, run, jump etc.

- Timed rise from floor (RFF) test [Time Frame: Screening - 5 years post GNT0004] Time function Test

- 10 Meter Walk/ Run test (10MW/RT) [Time Frame: Screening - 5 years post GNT0004] Time function Test

- 6 Minute Walk Test (6 MWT) [Time Frame: Screening – 2 years post GNT0004] Motor Function Measurement (not applicable for Part 2 participants)

- Myoset: Myo-grip, -pinch [Time Frame: Screening - 5 years post GNT0004] Upper limb strength Measurement

- ACTIMYO or equivalent device [Time Frame: Inclusion - 5 years post GNT0004] Remote Motor Function Measurement

- Muscle Nuclear Magnetic Resonance Imaging (NMRI) [Time Frame: Inclusion- 5 years post GNT0004] Muscle Imaging to evaluate the changes inside muscles, a non-invasive measurement

- Pulmonary Function Test (PFT) [Time Frame: Inclusion- 5 years post GNT0004] Respiratory Function Assessment

- ECG – Echocardiography- Cardiac Nuclear Magnetic Resonance Imaging (cMRI) [Time Frame: Inclusion - 5 years post GNT0004] Cardiac Function Assessment

- ACTIVLIM [Time Frame: Inclusion 5 years post GNT0004] Patient Reported Outcome

- EQ-5D [Time Frame: Inclusion 5 years post GNT0004] Questionnaire of Life

Can I take part?

Inclusion Criteria

1. Male, ambulant

2. 6 to 10 years old inclusive

3. Enrolled in the GNT-014-MDYF study (a natural history study preceding the present gene therapy study)

4. Diagnosis of DMD based upon Gene testing positive with detailed genotyping except subjects with any mutations affecting exons 8 and/or 9

5. Able to achieve a score in the NSAA (North Star Ambulatory Assessment) scale 18 and Time to Rise From Floor (RFF) 7 sec at screening visit

6. Ongoing corticosteroid therapy with prednisolone (or prednisone) according to standard of care (participants receiving deflazacort or vamorolone daily dose can switch to prednisolone (or prednisone) 4 weeks before screening)

7. Up to date vaccination record including hepatitis A and B, PCV

Exclusion Criteria

1. Presence of antibodies against AAV8

2. Cardiomyopathy based on physical/cardiological examination and echocardiography

3. Any respiratory assistance needed as defined in protocol

4. Any co-morbidity(ies) and/or previous or planned surgical event(s), which may interfere with DMD evolution / or evaluation of Investigational Medicinal Product (IMP)'s tolerability, or which could preclude patients' safety

5. Clinically significant laboratory abnormality values that is either not expected or is of a greater intensity than what is expected in DMD patients

6. Inability to cooperate with or contraindications to planned outcome assessment (e.g.: NSAA, Myoset, Actimyo and equivalent device, respiratory functions test, MRI etc.)

7. Unwilling and/or unable to comply with all the study protocol requirements and/or procedures

8. Concomitant medications within timeframe specified in the protocol that may interfere with Investigational Medicinal Product (IMP) or planned non-Investigational Medicinal Product (NIMP) of the study and that could preclude patients' safety

9. Contraindication to non-Investigational Medicinal Product (NIMP) of the study

10. Previously or currently treated with any drug(s) that may interfere with either natural disease course and/or IMP evaluation (except for corticosteroid therapy) without respecting a sufficient wash-out period as required in the protocol

11. Previous inclusion to another clinical trial with an Investigational Medicinal Product (IMP), within the protocol defined washout period or concomitant participation to any other clinical trial

For contact details and to find out more, please refer to dmdhub.org.

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Duchenne UK

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