

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 N° 2020-002093-27

Description by Genethon

The study includes 3 parts:

- **Part 1:** a dose escalation part where up to three dose levels will be studied in order to find the optimal dose. The participants in this part will receive one dose level and there will be two to three participants per dose level. The completion of this part will allow an independent data monitoring committee to suggest the most efficient dose of the gene therapy with the best and acceptable safety profile, defined as the optimal dose that will be used for the following part 2 of the study.
- **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

Trial Status Recruiting

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

Trial Sponsor
Genethon

Mutation Specific
Mutation specific therapies,
Exclude mutations affecting
exons 1-17 inclusive

Recruitment Target
Approximately 50
participants

Ambulatory
Ambulant

Age
6 to 10 years

Muscle Biopsy
Muscle Biopsy Required

Therapeutic Category
Gene Therapy

MRI
Yes

Phase
Phase I/II/III study

Length Of Participation
5 to 6 years

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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 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: this is 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 evaluate the how long the benefits of the treatment last.

The study protocol has been approved by health authorities and currently opened for Part 1 recruitment in UK and in France (as of December 2023).

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

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: Inclusion - Week 8]

- 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
- 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?

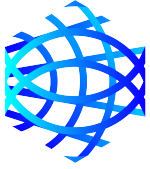
Inclusion Criteria

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 1 through 17
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
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, 6MWT, 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)
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.



Duchenne
UK

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