Press release
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Genethon Presents Positive Initial Results from a Phase 1/2/3 Trial of its Gene Therapy (GNT0004) for Duchenne Muscular Dystrophy at ASGCT Breakthroughs in Muscular Dystrophy in Chicago

- *Based on positive safety and efficacy data in the Phase 1/2 dose escalation phase of the all-in-one study, Genethon expects to launch pivotal trial in Europe in 2025 and in the US.*
- *The results showed that one to two years after treatment at the higher of two doses of GNT0004, patients experienced stabilization in the North Star Ambulatory Assessment measuring motor functions compared with a decline in untreated patients in the parallel disease natural history study. See the video of one patient's remarkable improvement (https://youtu.be/LSeJzj-vUKk)*

PARIS, FRANCE (November 19, 2024) – Genethon, a pioneering gene therapy research organization created by AFM-Telethon, today presented positive results from the Phase 1/2 dose escalation part of an international multicenter all-in-one Phase 1/2/3 trial evaluating its gene therapy, GNT-0004, for Duchenne muscular dystrophy (DMD) at the ASGCT Breakthroughs in Muscular Dystrophy conference, Nov. 19 – 20, 2024, in Chicago, IL. Based on these results, Genethon expects to launch pivotal trial in Europe in Q2/2025 and in the US.

Frederic Revah, Genethon's Chief Executive Officer, observed, "The results of treatment with our GNT0004 gene therapy are very positive in patients treated at the higher of two doses, both in terms of micro-dystrophin expression and clinical outcomes. In addition, the strength of our product lies in this selected dose, which is lower than those used in other gene therapy trials for DMD. GNT0004 has the potential to be the best-in-class curative gene therapy for DMD."

Dr. Revah emphasized, "These clinical results demonstrate that gene therapy can provide solutions to one of the most complex genetic diseases. Our aim is to start the confirmatory (pivotal) phase in more than 60 children in Europe in the second quarter of 2025, followed by the US."

The presentation, titled "GNT0004, Genethon's AAV8 Vector-delivered Microdystrophin Gene Therapy for Duchenne Muscular Dystrophy: First Data from Phase 1/2 Part of GNT-016-MDYF All-in-one Clinical Trial in Ambulant Boys," was made by Serge Braun, PhD, Genethon's Director of Neuromuscular Strategy.

The Phase1/2 part of the all-in-one study, designed to assess tolerance and initial evidence of efficacy, was completed at the end of October and determined the therapeutic dose of GNT0004 to be used in the pivotal study. Five patients, between ages 6 and 10, were treated at one of two doses; two at the first level and three at a higher level.

The safety and pharmacodynamic data showed good tolerance of GNT0004 combined with transient immunological prophylaxis, as well as efficacy data, both in terms of micro-dystrophin expression and functional improvement. The findings in patients receiving the second dose level ($3x10^{13}$ vg/kg) showed:

- Eight weeks after injection, up to 85% of muscle fibers expressed micro-dystrophin (mean 54%; 15%-85%) as measured by immunohistochemistry, and reconstitution of the dystrophin-associated protein complex. This expression coincides with a significant number of vector genome copies/muscle fiber nuclei, up to 2.4 (mean 1.2; 0.4-2.4).
- A fall in creatine phosphokinase (CPK) levels (a biomarker of muscular suffering) of between 50% and 87% (mean: 74%) 12 weeks after treatment, and persistent (up to 18 months of follow-up for the first two patients treated at this dose).

For all patients treated at the effective dose, the results also demonstrated, one to two years after treatment**,** stabilization of motor functions measured by a 34-point clinical evaluation scale. For one patient, an improvement was observed, reaching the maximum score of 34 at 12 months, and confirmed at 18 months post-treatment. See the video of the patient's improvement: https://youtu.be/LSeJzj-vUKk

This development was remarkable compared with that of untreated patients in Genethon's parallel natural history study, for whom mean motor function declined rapidly over the same period. After review and advice from the independent monitoring committee, these conclusive results enable Genethon to launch the confirmatory part of the trial (pivotal phase) with the inclusion of the first patients in mid-2025.

About GNT0004 and the trial
The GNT0004 gene therapy is composed of an AAV8 (adeno-associated virus) vector and the optimized hMD1 transgene, a shortened but functional version of the gene encoding dystrophin, the protein deficient in people with DMD. This vector is designed to be expressed in muscle tissue and also in the heart, thanks to a tissue-specific Spc5-12 promoter sequence. GNT0004 is administered by a single intravenous injection. It was developed by Genethon, in partnership with the teams of Prof. Dickson (University of London, Royal Holloway) and the Institut de Myologie (Paris). The trial, sponsored by Genethon, combines Phases 1/2/3, a dose-escalation phase followed by a pivotal phase at the dose finally chosen. The trial is being carried out in France and the UK, and includes boys aged 6 to 10 with DMD who have retained their ability to walk.

About Duchenne muscular dystrophy
DMD is a rare, progressive genetic disease affecting all the body's muscles, and mainly boys (1 in 5000). It is due to abnormalities in the gene responsible for producing dystrophin, a structural protein essential for the stability of muscle fiber membranes and their metabolism. The absence of dystrophin leads to progressive degeneration of skeletal and cardiac muscles, loss of walking and respiratory capacity, cardiomyopathy and death between the ages of 20 and 40.

About Genethon
A pioneer in the discovery and development of gene therapies for rare diseases, Généthon is a non-profit organization created by the AFM-Téléthon. The first gene therapy to treat spinal muscular atrophy, incorporating technologies developed at Genethon, is marketed worldwide. With over 200 scientists and professionals, Genethon pursues its goal of developing innovative therapies that change the lives of patients suffering from rare genetic diseases. Thirteen products from Genethon's R&D or collaborations are in clinical trials for diseases of the liver, blood, immune system, muscles and eyes. A further seven products could enter clinical trials in the next five years. To find out more www.genethon.com

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