Press release
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Gene Therapy
Preliminary results of clinical trial for rare liver disease Crigler-Najjar syndrome presented at EASL congress

Preliminary results from the European gene therapy trial for Crigler-Najjar syndrome, conducted by Généthon in collaboration with European network CureCN, were presented at the EASL (European Association for the Study of the Liver) annual International Liver Congress on June 26. Based on initial observations, the drug candidate is well tolerated and the first therapeutic effects have been demonstrated, to be confirmed as the trial continues.

Crigler-Najjar syndrome is a rare genetic liver disease characterized by abnormally high levels of bilirubin in the blood (hyperbilirubinemia). This accumulation of bilirubin is caused by a deficiency of the UGT1A1 enzyme, responsible for transforming bilirubin into a substance that can be eliminated by the body, and can result in significant neurological damage and death if not treated quickly. At present, patients must undergo phototherapy for up to 12 hours a day to keep their bilirubin levels below the toxicity threshold.

Dr. Lorenzo D'Antiga (Azienda Ospedaliera Papa Giovanni XXIII, Bergamo, Italy), one of the investigators working on the gene therapy trial being conducted into Crigler-Najjar syndrome by Généthon, presented the results from the first treated patients at this year's EASL (European Association for the Study of the Liver) congress. **The treatment involves providing the liver cells with a copy of the UGT1A1 gene that encodes an enzyme designed to facilitate bilirubin elimination. Based on initial observations, the results are encouraging.**

Specifically, the first two cohorts reveal that:

- **The product is safe and well tolerated in the four patients undergoing treatment**

- **There appears to be a dose-response relationship (to be confirmed):**
    - In cohort 1, treated at the lowest dose, the clinicians observed a temporary therapeutic effect but that was insufficient to allow prolonged stopping the phototherapy at the sixteenth week post-injection (the product efficacy endpoint)

    - In cohort 2, treated at a higher dose, **a major reduction in bilirubin levels was demonstrated in the first patient, enabling her to stop phototherapy a few weeks ago.** The second patient has also seen a major decrease in her bilirubin levels. Her treatment is too recent to demonstrate a stable decrease, but if this decrease is confirmed she will also be able to discontinue phototherapy in a few weeks' time.

"*We are very excited with the results achieved so far in this trial of AAV-mediated gene therapy for Crigler Najjar syndrome. The treatment, at appropriate doses, has shown to be safe and able to correct the disease to an extent that allowed the first patient to stop daily phototherapy, eliminating the risk of neurological injury. The degree of improvement of the second patient suggests that soon she might be able to stop phototherapy too. Our work on the immunomodulation protocol is now focused on maintaining a durable effect in the long term. This innovative strategy may replace liver transplantation in patients with a genetic liver disease*". Dr. Lorenzo D'Antiga, who treated the last two patients and presented their results at the EASL congress.

The trial uses a technology developed by Généthon's Immunology and Liver Gene Therapy team, headed up by Dr. Giuseppe Ronzitti: *"The team has worked incredibly hard on this project, from designing and developing the approach right through to the trial. We designed the drug candidate, undertook the preclinical efficacy testing, then designed the product for the clinical trial. We are continuing our work to develop new approaches for other liver diseases".*

"These initial observations presented at this year's EASL congress indicate that gene therapy could become an alternative treatment for this severe liver disease. We need to remain cautious, as the trial is ongoing and will allow us to evaluate these initial encouraging results in other patients and over a longer period." Frédéric Revah, CEO of Généthon.

About the trial

This European trial aims to assess the product's safety, identify the optimal dose, and evaluate the therapeutic efficacy of the drug candidate. The clinical trial is being conducted at four European study sites: in France (Prof. Labrune – Hôpital Béclère, Clamart), Italy (Prof. Brunetti-Pierri – Hôpital Federico II; Prof. d'Antiga – Azienda Ospedaliera Papa Giovanni XXIII, Bergamo) and the Netherlands (Prof. Beuers – Academic Medical Center, Amsterdam). The project is supported by European consortium CureCN, which brings together 11 European partners, and has received funding from the European Union's Horizon 2020 research and innovation program.

About Crigler-Najjar syndrome

Crigler-Najjar syndrome is a rare genetic liver disease (1 case in 1,000,000 births) characterized by the abnormal accumulation of bilirubin—a yellow substance produced by the liver—in all the tissues of the body. This hyperbilirubinemia is caused by a deficiency of the enzyme (UGT1A1) responsible for transforming bilirubin into a substance that can be eliminated by the body. When this enzyme does not work, bilirubin builds up, causing severe, chronic jaundice and brain toxicity. If it is not treated quickly, this accumulation of bilirubin can result in significant neurological damage and death. At present, affected patients must undergo phototherapy for up to 12 hours a day to keep their bilirubin levels below the toxicity threshold. The only treatment is liver transplantation — a major, complicated procedure.

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