

Press Release
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Gene therapy: Généthon starts a clinical trial to test a gene therapy treatment for a rare liver disease, Crigler-Najjar Syndrome

Généthon, a laboratory created by AFM-Téléthon, starts a European phase I/II clinical trial to test a treatment for Crigler-Najjar Syndrome, a rare liver disease. The trial, sponsored by Généthon, will include 17 patients in four centres in Europe, and will assess safety and therapeutic efficacy of the gene therapy product developed by Généthon.

Crigler-Najjar Syndrome is a rare genetic liver disease (incidence around 1/1 000 000 births) associated with the abnormal accumulation of bilirubin — a yellow pigment produced by the liver — in all the body's tissues, particularly the brain tissues. This hyperbilirubinaemia is caused by a deficiency in UGT1A1, the enzyme that converts bilirubin into an eliminable substance. When this enzyme does not work, bilirubin levels build up, leading to severe chronic icterus (jaundice) and becoming toxic to the brain. If it is not treated quickly, hyperbilirubinaemia can cause significant neurological damage and be deadly.

At present, to maintain bilirubin levels below the toxicity threshold, patients are subjected to 10 to 12 hours of phototherapy every day. The alternative is a liver transplant, a complicated and highly invasive procedure.



A phase I/II trial in 17 patients with Crigler-Najjar Syndrome

This European trial will include 17 patients over 10 years old, (the age when the liver reaches maturity); it aims to assess the tolerance of the product, determine the optimal dose, and assess the therapeutic efficacy of the drug candidate. The trial takes place in four investigation centres in Europe: France (Prof Labrune - Hôpital Bécclère in Clamart), Italy (Prof Brunetti-Pierrri – Hôpital Federico II, Prof d'Antiga - Azienda Ospedaliera Papa Giovanni XXIII in Bergamo) and the Netherlands (Prof Beuers - Academic Medical Center in Amsterdam).

The technology used in the trial was developed by the 'Immunology and Gene Therapy for Liver Disease' team at Généthon, headed by Dr Federico Mingozzi. In partnership with research teams in Italy and the Netherlands, Généthon has developed an Adeno-Associated Viral (AAV) vector that is able to transfer a copy of the UGT1A1 gene (coding for the production of bilirubin-GT) to the liver cells. Tested first of all in the Gunn rat, an animal model of the disease, a single injection of this drug candidate has enabled the long-term correction of the disease in murine models (*Molecular Therapy Methods and Clinical Development* – July 2016).

YposKesi — an industrial platform dedicated to the manufacture of gene and cell therapy products, created by AFM-Téléthon and BPI France in November 2016 in Evry (91) — is producing pharmaceutical-grade vector for the clinical trial.

"We are delighted to be starting a clinical trial of the gene therapy product we have designed to treat Crigler Najjar Syndrome, a very serious liver disease. The trial was made possible by Généthon's pioneering research into gene therapy for rare diseases, over a period of almost 20 years. Today, seven clinical trials are taking place across the world, involving products that Généthon's researchers either developed themselves or participated closely in developing " explains Frédéric Revah, CEO of Généthon.

"In 1990, we created Généthon to better understand the genetic diseases that kill our children, and to find innovative treatments to cure them. For many years, our laboratory has been one of the global leaders in the gene therapy field. As a firm that has met many therapeutic challenges, it is now beginning the first human trial for this rare liver disease. At this very moment, my thoughts go out to the families, who for months have been looking forward eagerly to us getting the go-ahead from the official agencies to begin the trial, in which I realise they place so much hope", says Laurence Tiennot-Herment, President of AFM-Téléthon.

About Genethon - www.genethon.fr

Created and financed by AFM-Téléthon, Généthon aims to provide patients with innovative gene therapy treatments. Having played a pioneering role in deciphering the human genome, Généthon now employs almost 180 researchers, doctors, engineers and regulatory affairs specialists, and is one of the leading international centres for preclinical and clinical research and development in gene therapy treatments for rare diseases.

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About AFM-Téléthon - www.afm-telethon.fr

L'AFM-Téléthon is an association of patients and their relatives, committed to fighting disease. Thanks to donations from the Téléthon, it has become a major player in biomedical research into rare diseases in France and across the world. Today, it supports clinical trials testing treatments for genetic diseases of the eyes, blood, brain, immune system and muscles. It is unlike other associations in that its laboratories have the ability to design, produce and test their own innovative therapies.

Free telephone number for affected families: 0800 35 36 37

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