

Europe gives gene therapy the green light

Europe officially approved its first gene therapy earlier this month for a rare metabolic disorder. Could this mark a turning point for a technique that has struggled to take off? Karl Gruber reports.

On Nov 2, the European Commission announced the official approval of Glybera, a gene therapy for treating lipoprotein lipase deficiency (LPLD), devised by the Dutch company uniQure. The approval is the first of its kind in the Western world and may herald the beginning of a new era for gene therapy, a field plagued by unfulfilled promises and weary investors, all of which has until now overshadowed its progress.

LPLD is an extremely rare and incurable disorder that affects 1–2 people per million, where a defective lipoprotein lipase (LPL) gene leads to a non-functional LPL enzyme. The LPL enzyme is a key player in fat metabolism and people with LPLD are unable to process fats. They suffer from severe abdominal pain during childhood and several other conditions during adulthood, including recurrent acute pancreatitis.

Glybera (alipogene tiparvovec) is a recombinant, non-integrating, non-replicating adeno-associated viral vector expressing Ser447X, a naturally occurring functional variant of the LPL gene associated with lower rates of cardiovascular disease and increased efficiency in fat metabolism. The basic principle of Glybera is to compensate for the defective LPL gene by introducing functional copies of this gene into muscle cells lacking active LPL. Patients receive a single treatment that, according to clinical data, results in long-term improvement of the conditions associated with LPLD, including a reduction in pancreatitis incidence up to 2 years after treatment.

The road to Glybera's approval was not simple, being hurdled by three rejections before success. The first two rejections, back when uniQure was Amsterdam Molecular

Therapeutics, were due to the low number of patients studied. The third rejection happened by a very tight vote (16 to 15) and one absentee that tipped the balance against them. However, the safety of the treatment was never in question, the European Medicine Agency acknowledged that Glybera met all safety standards.

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A spokesperson for uniQure tells *The Lancet* that the big problem was to answer the question: is it effective? “We said yes, but the Agency was not certain.” Part of the difficulty was establishing statistically significant efficacy with the low number of patients studied. “With 1000s of patients that are treated in clinical trials for large indications that is much more straightforward; but with 27, it becomes a very different equation. And regulators need to come to terms with that when faced with orphan drugs.” It seems “good will” came after the fourth application, with a request that uniQure keeps a record following up the wellbeing of their patients.

The approval of Glybera in Europe will likely have important repercussions in the development of gene therapy. As Thierry VandenDriessche, former president of the European Society for Cell and Gene Therapy and current Head of the Division of Gene Therapy and Regenerative Medicine at the Free University of Brussels, Belgium, explains, “It sets a precedent for future gene therapy development and I hope it will foster collaboration between academia and industry and help to

catalyse industry-driven product development.” This collaboration is an important aspect, as a key hurdle that prospective gene therapies will face is in the translation process. Most laboratories that develop the first stages of a gene therapy (eg, genomic studies, vector design) are not equipped to take their experimental therapies through to clinical testing. However, a successful collaboration with industry could just do the trick.

Interestingly, many of these so-called orphan diseases that have no available treatment, such as LPLD, may be profitable to address, despite the sometimes small patient numbers. As the uniQure spokesperson explains, “There are incentives, of course. If you have an orphan designation, it grants market exclusivity in the US for 7 years and 10 years in Europe, if you are the first to reach the market. So, there is a match between high unmet medical needs and economic incentive.”

However, Fulvio Mavilio, Scientific Director at Genethon, a French non-profit research and development organisation for biotherapies, sees problems. He says that Glybera's journey is an example of how difficult the regulatory process is, and unless that changes, few therapies will reach the market in the next few years. “What may change the course of gene therapy is an economic model that will make these forms of treatment attractive to the industry, and a regulatory framework less punishing than the existing one, at least in Europe.”

Meanwhile, he adds: “The success of Glybera, in commercial terms, will depend on how it will be priced and how clinicians will perceive its efficacy and usefulness for their patients.”

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