

Alipogene Tiparvovec (Glybera®) - a Gene Therapy for LPLD

Glybera® (alipogene tiparvovec) has been approved by the European Commission for commercialization in the European Union. It is the first gene therapy to receive approval in the Western world.

Glybera has been developed for the treatment of lipoprotein lipase deficiency (LPLD), a very rare inherited condition that is associated with increased levels of fat in the blood. LPLD is caused by alterations in the gene that codes for an enzyme called lipoprotein lipase (LPL). The LPL enzyme has an important role in dealing with the fats from the food that we eat. When the LPL enzyme does not work properly, or there is not enough of it, fat levels in the blood increase dramatically.

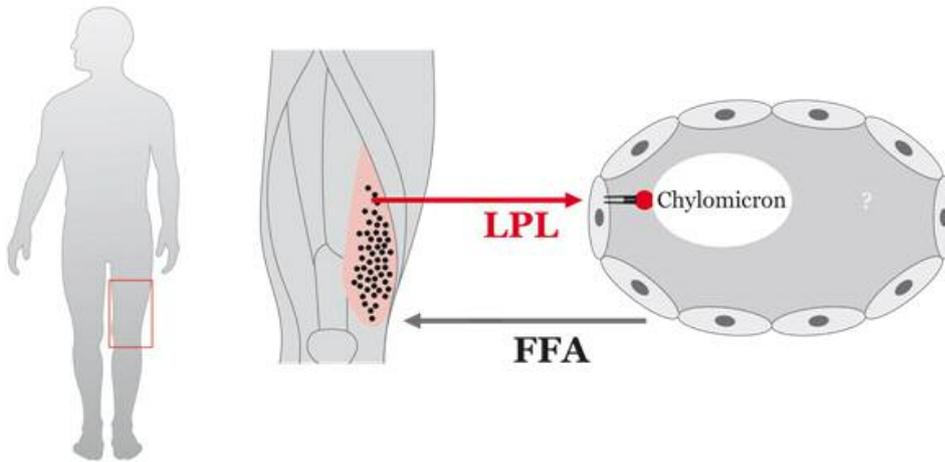
Glybera introduces a normal, healthy LPL gene into the body so that it can make functional LPL enzyme. The LPL gene is packaged in a vector derived from adeno-associated virus (AAV), serotype 1, which has a natural propensity towards muscle cells. As muscle cells are normally the most important tissue contributing to healthy LPL enzyme production, this particular AAV is very suitable for correction of LPLD. Glybera is administered via a one-time series of small intramuscular injections in the legs.

Glybera Clinical Data

Glybera has been tested in three clinical studies conducted in the Netherlands and in Canada, in which a total of 27 LPLD patients participated. One follow-up study is still ongoing. In all three clinical trials, Glybera was well tolerated and no relevant safety signals were detected.

Data from the clinical trials indicates that fat concentrations in blood were reduced after therapy in nearly all patients between 3 and 12 weeks after injection of Glybera. Importantly, a single dose administration of Glybera resulted in a long-term presence and biological activity of the enzyme in the injected muscle. In addition, the data indicated a clinically important reduction in the frequency of acute pancreatitis, the most debilitating complication of LPLD.

Additionally, new clinical data from the last clinical study in Canada provided a basis for explaining the mechanism of action. These data indicate that a single administration of Glybera in LPLD patients results in a remarkable long-term improvement in the ability to break down chylomicrons, a protein-lipid complex in the blood that transports dietary fat. LPLD patients are incapable of clearing chylomicrons. This leads to a build up of these particles in the blood and can cause significant morbidity and mortality. In particular, very high levels of chylomicrons newly-produced after meals are thought to be the eliciting factor in new acute pancreatitis episodes. By clearing these chylomicrons, Glybera helps prevent new episodes of pancreatitis.



Single administration
into leg muscle

About LPLD

LPLD affects only around one to two in every million people worldwide, although in certain geographic areas, such as parts of Canada, the disease is more common. Symptoms include, among others, abdominal pain and, in particular, an increased risk of pancreatitis.

LPLD is caused by alterations in the gene that codes for an enzyme called lipoprotein lipase (LPL). The LPL enzyme has an important role in dealing with the fats from the food that we eat. When the LPL enzyme does not work properly, or there is not enough of it, fat levels in the blood increase dramatically.

As LPLD is an inherited disorder, genetic testing of the person with suspected symptoms is the most reliable method of diagnosis in most cases. There are over 100 different alterations in the LPL gene that can cause LPLD. Detecting these alterations involves isolating DNA from a sample of blood or saliva and examining the entire coding region of the LPL gene for abnormalities. Genetic testing can detect individuals with LPLD (people with two altered LPL genes) and those who are carriers (people with only one altered LPL gene). The parents and the children of people with LPLD are usually 'carriers' of the disease, and do not have symptoms of LPLD. Brothers and sisters of someone with LPLD have a 25% chance of also having the disease, and have a 50% chance of being a carrier. They also have a 25% chance of having completely 'normal' LPL genes. Because genetic testing may have emotional, family, and social implications, counseling is advised.

The standard disease management approach for LPLD is to reduce symptoms and reduce the risk of pancreatitis by reducing chylomicron and blood fat levels. This may be achieved by severely restricting the fat content of the diet. Fat lowering drugs, often used in other conditions involving raised blood fat levels, are generally not effective in LPLD.