Amsterdam Molecular Therapeutics Successfully Lowers Cholesterol In Vivo with Enhanced Novel MicroRNA AAV Gene Therapy

Amsterdam October 25, 2010 – Amsterdam Molecular Therapeutics (AMT) Holding N.V. (Euronext: AMT), a leader in the development of gene based therapies, today announced that its gene therapy product incorporating siRNA sequences into microRNA scaffolds to silence Apolipoprotein B100 (AAV-miApoB) was able to significantly lower plasma cholesterol levels in vivo over a period of 18 weeks. These preliminary results suggest that this approach could lead to a treatment for high cholesterol in humans.

"Successful hepatocyte-specific delivery of microRNA (miRNA) and significant demonstration of gene silencing again illustrates the strength of AMT's AAV platform. We announced previously success with our short hairpin RNA targeting ApoB (shApoB) gene product but our newest data suggests our miRNA product is proving to be even better and safer," stated Jörn Aldag, CEO of AMT. "Certainly of the two approaches, the natural characteristics of miRNA, such as prolonged stable long term expression, undetectable toxicity profile, tissue specificity, as well as the significant efficacy, suggest a more favorable route to a viable treatment for high cholesterol. This future application of our technology may circumvent some of the delivery issues with the RNA approach. We intend to seek partners to exploit the full AAV technology potential in the RNA field."

Using its proprietary adeno-associated viral vectors (AAV), a single injection of AAV-miApoB transduced murine hepatocytes almost entirely and resulted in a reduction of total plasma cholesterol of 60-80% for an 18 week period. AAV delivery of miRNA, expressed from a liver-specific promoter, constitutes the second powerful approach by which AMT has demonstrated to lower plasma cholesterol, together with AMT's AAV shApoB gene therapy product tested in the same model of the disease. In our new approach, we went one step further and limited the expression of the inhibitory miApoB molecule only to the hepatocytes, which provides a higher safety profile, a feature very important for future clinical applications. Data were presented at the Hepatocyte User Group and Medicon Valley Hepatocyte User Forum (22-23 October) in Montpellier, France, and at the European Society for Gene and Cell Therapy Annual Conference (22-25 October) in Milan, Italy.

In the new study, mice received intra-venous injections with equal doses of 10^{11} gc per animal AAV-shApoB or AAV-miApoB and were examined for 18 weeks. Expression of the shApoB and miApoB resulted in 90% ApoB protein knock-down, associated with 80% cholesterol decrease in murine plasma for the first 6 weeks. However, after 8 weeks the effect of the shApoB started to wear off, while miApoB remained effective in ApoB and cholesterol reduction for up to 18 weeks. Ongoing research aims to determine the mechanism for the differences seen between long-term AAV-shApoB and AAV-miApoB efficacy in murine livers. We believe that the long-term stability of the miApoB is due to its lower toxicity and off-target properties compared to shApoB because expression of miApoB is specifically limited to hepatocytes.

ApoB100 is the structural protein of Low Density Lipoprotein (LDL) particles that carry cholesterol. Silencing the activity of ApoB100 with miRNA or shRNA lowers plasma LDL-cholesterol by 60-80% and has the potential to be used to treat hypercholesterolemia and associated cardiovascular disease.

About Amsterdam Molecular Therapeutics

AMT is a leader in the development of human gene based therapies. Using adeno-associated viral (AAV) derived vectors as the delivery vehicle of choice for therapeutic genes, the company has been able to design and validate what is probably the first stable and scalable AAV production platform. This proprietary platform can be applied to a large number of rare (orphan) diseases that are caused by one faulty gene. Currently, AMT has a product pipeline with several AAV-based gene therapy products in LPLD, Hemophilia B, Duchenne Muscular Dystrophy, Acute Intermittent Porphyria, and Parkinson's Disease at different stages of research or development. AMT was founded in 1998 and is based in Amsterdam.

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