Development of NTLA-2001, a CRISPR/Cas9 Genome Editing Therapeutic for the Treatment of ATTR

Kristy Wood1, Melissa Pink1, Jessica Seitzer1, Noah Gardner2, Seth Alexander2, Tracy DiMesso2, Adam Amaral3, Samantha Soukamneuth1, Arti Kanjolia1, Rubina Parmar1, Ellen Roche1, Reynald Lescaubeau1, Cindy Shaw1, Tanner Distine1, Cami Boiselle1, Kathryn Walsh1, Bo Han1, Maria Saraiva4,5, Eva Essig1, John Leonard1, Michael McCaman1, Yong Chang1

1Intellia Therapeutics, Cambridge, MA, USA; 2Instituto de Investigacao e Inovacao em Saude, Universidade do Porto, Porto, Portugal; 3IBMC – Instituto de Molcular and Cell Biology, Porto, Portugal; 4IBMC – Institute for Molecular and Cell Biology, Porto, Portugal

INTRODUCTION

Translucrin amyloidosis (ATTR) is a progressive disease caused by accumulation of amyloid deposits of misfolded transthyretin (TTR) protein in multiple tissues including the heart, nerves and gastrointestinal tract. Reduction of TTR monomer via stabilization of circulating tetramer and silencing of TTR gene expression in hepatocytes of ATTR patients have emerged as successful therapeutic strategies for chronically- administered medicines. As such, specific disruption (or knockdown) of the TTR gene in hepatocytes using the CRISPR/Cas9 gene editing system is a potentially attractive next-generation treatment for ATTR, which may durably reduce the expression of TTR without the need for chronic therapy.

Objective: To develop NTLA-2001, a lipid nanoparticle (LNP) formulated CRISPR/Cas9 system enabling therapeutic targeting the human TTR gene for the treatment of ATTR. NTLA-2001 is advancing toward the clinic with an IND submission planned for mid-2020.

RESULTS

Achieved Persistent Serum TTR Protein Reduction for 12 Months in Mouse After a Single Administration of TTR LNPs with No Histological Findings

Liver editing was determined by NGS from a core needle liver biopsy and circulating serum TTR concentration was determined by an LC/MS assay specific for the TTR protein.

TTR LNPs and Cargo Exhibit 17–24 Hour T1/2 and Are Cleared from Circulation and Liver Within 5 days in NHP

Ionizable lipid concentration was determined by an LC/MS assay. gRNA and Cas9 mRNA were measured by qRT-PCR assay with primers and probes specific for the analyze.

CONCLUSIONS

• NTLA-2001 is advancing toward the clinic in collaboration with Regeneron Pharmaceuticals, Inc with an IND submission planned for mid-2020
• TTR LNPs enable significant knockdown of the TTR protein by editing of the TTR gene across multiple species, including mouse and NHP
• In NHP, achieved a therapeutically meaningful level of TTR protein reduction that correlated with robust and significant editing in the liver
• Cas9 mRNA, gRNA and ionizable lipid are quickly cleared from circulation, with the lipid having plasma and liver half-lives of 20 hours and 17 hours, respectively, in NHP
• Following a single dose of LNP-delivered CRISPR/Cas9 in mice:
  - Editing levels achieved that resulted in >97% reduction in circulating serum TTR protein
  - Reduction of circulating levels of TTR sustained for at least 12 months
• No significant histopathology findings noted
• Humanized mouse model of hATTR that expresses the V30M mutant form of the human TTR protein demonstrated rescue of TTR deposition in multiple tissues after a single dose of LNPs containing the CRISPR/Cas9 components
• Demonstrated the potential of LNP delivered in vivo CRISPR/Cas9 gene editing: suggests that future therapies based on this platform may enable next-generation, curative treatment paradigms for chronic genetic diseases such as ATTR