PRECLINICAL EVALUATION OF A MODIFIED MRNA FOR THE TREATMENT OF OTC DEFICIENCY

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Ornithine transcarbamylase (OTC) deficiency is a rare X-linked genetic disorder characterized by complete or partial lack of the OTC enzyme. OTC plays a key role in the urea cycle; its absence leads to inability to metabolize ammonia and is associated with permanent brain damage and death. Genevant and BioNTech are collaborating to co-develop an mRNA therapy enabled by Genevant’s industry-leading nucleic acid delivery capabilities to treat OTC deficiency.

Codon-optimized, nucleoside-modified human OTC mRNA was encapsulated in lipid nanoparticles before being delivered to both wild-type (WT) and OTC-deficient mice (OTCspf-ash). OTCspf-ash mice are a widely accepted model for the study of OTC deficiency with residual OTC expression levels of ∼5% compared to WT, and a low tolerance to a high protein diet. Here, we have used the challenge of a high protein diet in OTCspf-ash mice to demonstrate the efficacy of our OTC mRNA-LNP in a diseased state. We subsequently tested the lead mRNA-LNP in a multi-dose NHP study leading to robust OTC protein expression and no changes in liver parameters at low dose levels.