ALG-020572, a GalNAc-conjugated Antisense Oligonucleotide, Demonstrates In Vivo Efficacy and Favorable Preclinical Profile for the Treatment of Chronic Hepatitis B

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Background

Worldwide, more than 248 million people are affected by chronic hepatitis B (CHB). Current treatment options do not achieve "functional cure," defined as achieving sustained undetectable HBV surface antigen (HBsAg) and HBV DNA levels in serum 6 months after therapy. We are developing ALG-020572, a liver-targeting GalNAc antisense oligonucleotide (ASO) for the reduction of HBV via ribonuclease H induced cleavage of hepatitis B viral RNAs.

Methods

ALG-020579, the active unconjugated ASO of ALG-020572, was tested in HepG2.2.15 cells and HBV-infected primary human hepatocytes (PHH) for in vitro activities. The in vivo efficacy was determined in an adeno-associated virus (AAV-HBV) mouse-model from which a Pharmacokinetic/Pharmacodynamic (PK/PD) correlation was established. The PK properties of ALG-020572 were assessed following a single IV infusion in monkeys and subcutaneous (SC) administration in mice and monkeys. Metabolism of ALG-020572 was studied in vitro using mouse liver homogenates and in vivo.

In vitro activity of ALG-020579, the active unconjugated ASO of ALG-020572

- ALG-020579 demonstrated potent inhibition of HBsAg release in vitro
- No significant cytotoxicity observed at the highest tested concentration

ALG-020572 Reduces Serum HBsAg in AAV-HBV Mice

- Plasma profile following a single SC 3 mg/kg dose in mouse and monkey
- The dose-dependent reduction of HBsAg in ALG-020572-treated groups correlated with ALG-020572 liver concentration
- Antiviral EC50 is projected at the liver concentration of 72.4 µg/g ALG-020579
- Lower efficacy observed with ALG-020579 dosing despite high liver concentrations (data not shown), confirming hepatocyte targeting with ALG-020572

Pharmacokinetic/pharmacodynamic correlation

- Liver and kidney concentrations of ALG-020579 increased with dose albeit less than dose proportionally
- Greater than dose-proportional increase, no accumulation and no sex difference in plasma exposures of ALG-020572
- Rapid uptake in liver with efficient conversion to ALG-020579; ALG-020572 was not detected in tissues

Tissue distribution and half-life following repeated SC doses

- Liver and kidney concentrations of ALG-020579 increased with dose albeit less than dose proportionality
- Half-life of ALG-020579 in liver was 8 days in mouse and 19 days in monkey
- ALG-020572 (GalNAc conjugate) was BQL at all timepoints

Conclusions

The in vitro and in vivo efficacy, hepatocyte targeting, a favorable PK profile of ALG-020572 and long half-life of ALG-020579 in liver following SC administration warrant its advancement into clinical development as a potential treatment for chronic hepatitis B. This compound is currently being evaluated in Phase 1 studies (NCT05001022).

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