ALG-00184, a prodrug of capsid assembly modulator ALG-001075, demonstrates best-in-class preclinical characteristics for the treatment of chronic hepatitis B

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Background
Capsid assembly modulators (CAMs) represent a clinically validated strategy for inhibiting hepatitis B virus (HBV) RNA encapsidation, leading to reductions in circulating HBV DNA and RNA in infected patients. We recently reported on ALG-001075, a novel class-II (normal, empty capsid formed) CAM with excellent antiviral activity and in vivo efficacy in a mouse adeno-associated virus-HBV model (Debing et al., AASLD, 2019, poster 699). We now advance ALG-000184, a prodrug of ALG-001075, which demonstrates superior pharmacokinetic properties relative to ALG-001075.

Methods
Antiviral activity on HBV DNA was determined in HepG2.117 and HepG2.2.15 cells using quantitative PCR, with and without 40% human serum. Activity was also assessed in primary human hepatocytes (PHH) infected with HBV. Solubility, stability and permeability of ALG-001075 and ALG-00184 were evaluated in vitro. Pharmacokinetic properties of ALG-001075 were evaluated across species following oral dosing of ALG-001075 or ALG-00184 administered as aqueous formulations.

ALG-001075 is a potent inhibitor of RNA encapsidation and cccDNA establishment in HBV-infected primary human hepatocytes

When ALG-001075 was added to an established HBV infection in primary human hepatocytes (5 days post infection), HBV DNA synthesis was potently inhibited. In addition, ALG-001075, when added at the time of infection, strongly inhibited cccDNA formation, as shown by reductions in extracellular HBsAg and intracellular HBV RNA.

ALG-000184 was developed to achieve high exposure of ALG-001075.

ALG-000184 conversion to ALG-001075 was efficient across species when dosed in aqueous vehicle, achieving linear PK in rats and dogs. Following oral administration of ALG-000184 in aqueous solution, high exposures to ALG-001075 were obtained in preclinical species. The conversion to the parent compound was efficient with ALG-00184 exposure typically <0.2% of ALG-001075 exposure. In rats and dogs, systemic exposures to ALG-001075 increased linearly with dose.

ALG-001075 is among the most potent class-II CAMs reported to date

ALG-001075 time concentration blood profiles after ALG-000184 PO administration. ALG-001075 PK profiles after PO administration of ALG-000184

Conclusions

- ALG-001075 is among the most potent class-II CAMs reported to date
- ALG-001075 efficiently blocks both HBV genome encapsidation and de novo cccDNA formation
- Solubility of ALG-001075 was greatly improved by prodrug ALG-000184
- ALG-000184 is a highly soluble prodrug that rapidly and efficiently delivers ALG-001075 following oral dosing
- ALG-000184 is on-track to enter clinical development in Q4 2020

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