Preclinical Pharmacokinetic Profiling of ALG-055009, a Potent and Selective Thyroid Hormone Receptor Beta Agonist for the Treatment of Nonalcoholic Steatohepatitis, and Prediction of its Human Pharmacokinetics

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Background

Nonalcoholic steatohepatitis (NASH) is becoming a major public health issue, with no approved treatment. Thyroid hormone receptor β (THR-β) agonists have demonstrated the potential to reduce liver fat, restore liver function, and possibly reverse fibrosis in NASH patients. ALG-055009 is being developed as a highly potent and selective THR-β agonist. Previously, we have shown that ALG-055009 is efficacious in a diet-induced obesity (DIO) mouse model at low doses. Here we describe the preclinical pharmacokinetic (PK) characteristics of ALG-055009 across species and human efficacious-dose projections.

Methods

PK properties of ALG-055009 were evaluated in mouse, rat, dog and monkey following intravenous and oral gavage administration at 1-5 mg/kg. Additionally, rats and dogs were dosed orally at sub-mg/kg dose levels as solutions or suspension. Plasma and tissue samples were analyzed by LC/MS-MS. Cross-species comparison of in vitro metabolic stability inhibition of cytochrome-P450 (CYP) enzymes and selected transporters were conducted. Human clearance (CL) and volume of distribution (Vd) for ALG-055009 were predicted.

High metabolic stability in liver microsomes and hepatocytes across species

- Moderate Caco-2 permeability (2.2 x 10⁻⁶ cm/s)
- No liability to inhibit CYP450s (IC₅₀ range 12 to >50 µM), gut, hepatic or renal transporters
- Substrate for hepatic uptake transporter NTCP and efflux transporter P-gp
- Not a substrate of OATP1B1 and OATP1B3 or BCRP
- Favorable in vitro toxicity profile
  - No significant activity in the CEREP Safety Screen 44 panel and the CEREP kinase panel (IC₅₀ >100 µM, except 3.7 µM for OAT3), and UGT enzyme (37 µM)
  - Moderate Caco-2 permeability (2.2 x 10⁻⁶ cm/s)¹
  - No cytotoxicity in primary 3D InSight (≤50% binding at 10 µM)
  - No significant activity in the CEREP Safety Screen 44 panel and the CEREP kinase panel (IC₅₀ >100 µM, except 3.7 µM for OAT3), and UGT enzyme (37 µM)

Favorable human PK: predicted low clearance and low volume of distribution; Sub- to low milligram QD dose projected to achieve efficacious exposure in target tissue (liver).

Conclusions

ALG-055009 is a potent and selective THR-β agonist with a promising PK profile in rodents and non-rodents; it is projected to result in sub- to low milligram QD dose projected to achieve efficacious exposure in target tissue (liver).

References

1. Deval et al AASLD 2019, Poster # 2149
2. Gupta et al AASLD 2020 Poster # 1656

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