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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

ALIGOS THERAPEUTICS

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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.

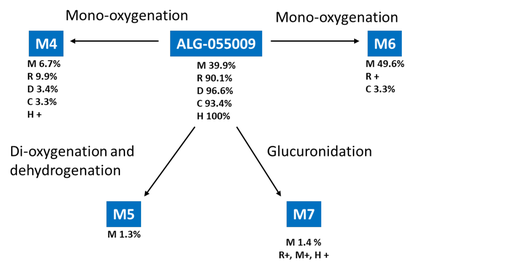
Methods

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 (V_d) for ALG-055009 were predicted.

ALG-055009 displays favorable in vitro ADME/Tox profile

- **Moderate Caco-2 permeability (2.2 x 10^{-6} cm/s)[1]**
- **No liability to inhibit CYP450s (IC_{50} range 12 to >50 µM), gut, hepatic or renal transporters (IC_{50} >100 µM, except 3.7 µM for OAT3), and UGT enzyme (37 µM)**
- **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 (≤50% binding at 10 µM)**
  - **No cytotoxicity in primary 3D InSight™ rat and dog liver microtissues (IC_{50} > 10 µM)**
  - **In vitro hERG potassium channel >100 µM; hNav1.5 and hCav1.2 IC_{50} >10 µM, the highest tested concentration**

High metabolic stability in liver microsomes and hepatocytes across species



Abundance as percent of total UV peak urea
+ = trace level; M=mouse, R =rat, D = dog, C = cynomolgus monkey, H = human cryopreserved hepatocytes

- **Metabolic pathways in the preclinical species are shown above**
- **No human specific metabolite observed**

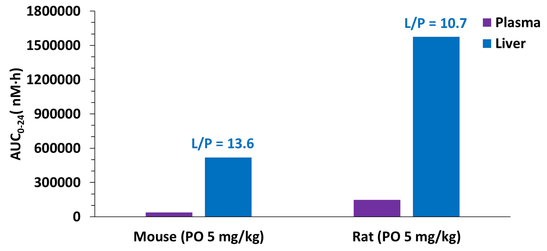
ALG-055009 has desirable preclinical pharmacokinetic properties

PK Parameters*	Mouse	Rat	Dog	Monkey
CL (mL/min/kg)	3.52	1.40	0.895	1.59
Vd (L/Kg)	0.69	0.63	0.69	0.60
$t_{1/2}$ (h)	2.27	7.22	10.6	7.72
F%	75.8	101	55.7	83.3

*IV (intravenous) dose at 5 mg/kg (mouse) and 1 mg/kg (other species); PO (oral) dose at 5 mg/kg
CL=clearance, Vd =volume of distribution, $t_{1/2}$ =half-life, F=bioavailability

Favorable PK properties: low clearance, low volume of distribution, long plasma half-life and good oral bioavailability as solution

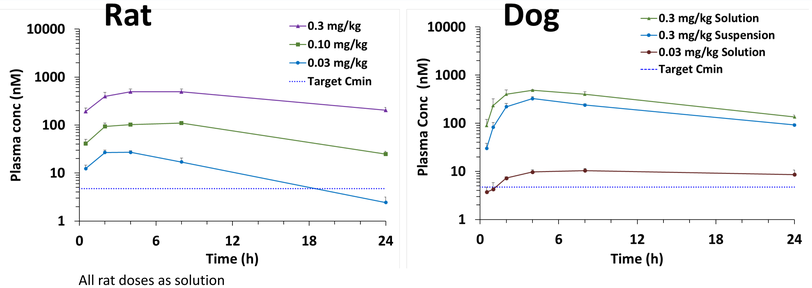
Preferential distribution to liver, the target tissue for efficacy



L/P = liver to plasma AUC ratio
Liver collection at 0.5, 2 (M), 4 (R), 6 (M), 12 and 24 hours postdose; M = mouse, R = rat

- **ALG-055009 shows preferential NTCP-mediated uptake in liver, the target organ for efficacy; low to negligible exposures in heart, blood cells and brain**

Plasma profile of ALG-055009 Following low PO doses in Rat and Dog

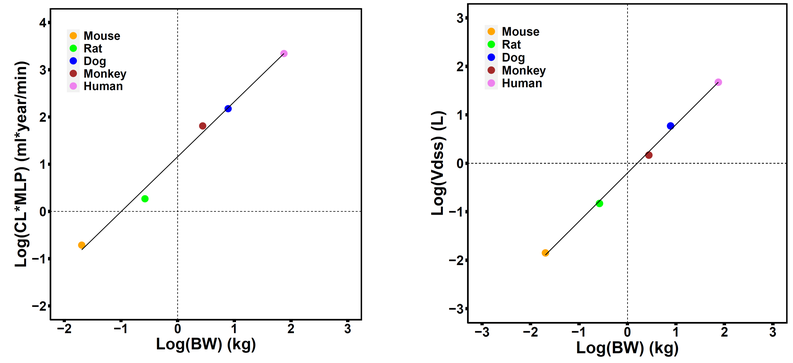


All rat doses as solution

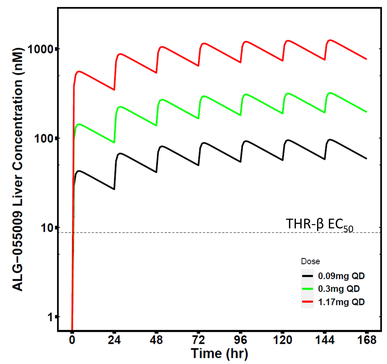
- **Plasma concentrations were quantifiable at all timepoints in rat and dog**
- **Plasma C_{min} at the lowest evaluated dose was at or above the plasma C_{min} (4.7 nM) at minimal efficacious dose in the DIO mouse model, plasma and liver C_{min} correlated with efficacy[2]**
- **Greater than dose proportional increase in exposure**
- **The exposures at 0.3 mg/kg as suspension was 62% of the dose as solution in dog**

Human PK Projection of ALG-055009

Allometric scaling of CL and V_d for human PK prediction



Parameter	Predicted Value
CL (mL/min/kg)	**0.26**
Vd (L/kg)	0.63
Oral Bioavailability (%)	82
Liver:plasma ratio	12:1



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 once-daily oral efficacious doses for the treatment of NASH with low risk of drug-drug interactions. Progression of the compound into clinical studies is therefore warranted.

References

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

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