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Nonclinical Toxicology Profile of ALG-055009, a Novel and Potent Thyroid Hormone Receptor β Agonist, for the Treatment of Metabolic Dysfunction-Associated Steatohepatitis (MASH)

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Background and Aims

MASH is characterized by hepatic inflammation/damage as a reaction to build-up of fat in the liver. Recently, Rezdiffra™ (resmetirom) was approved to treat MASH, demonstrating the utility of thyroid hormone receptor β (THRβ) agonists in MASH. Additional THR-β agonists have demonstrated reduced liver fat, restored liver function and reversed inflammation/fibrosis in clinical trials. Here we present the preclinical development of ALG-055009, a second-generation THRβ agonist with improved potency and favorable selectivity.

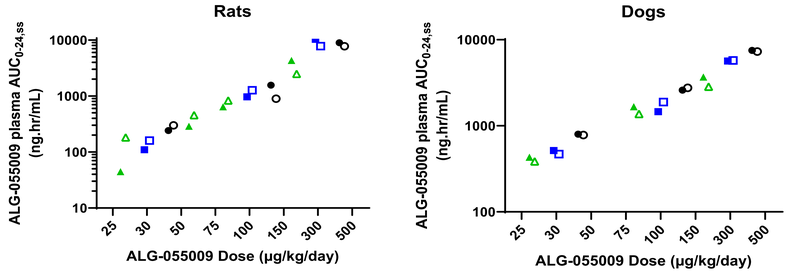
Methods

ALG-055009 was profiled in in vivo pharmacokinetic and toxicology studies across species. In vivo pharmacokinetic studies were conducted in mice, rats, rabbits, dogs, and non-human primates. Repeat-dose toxicology studies were conducted in rats and dogs using once daily (QD) oral gavage administration, up to 26 weeks in rats and 39 weeks in dogs. Clinical pathology endpoints including thyroid hormones were assessed at 6-, 13-, 26-, and 39-weeks (dogs only), as well as following 4 weeks of recovery. Pharmacodynamic endpoints included total/LDL cholesterol, liver enzymes, and thyroid hormones.

ALG-055009 demonstrated good oral bioavailability in all nonclinical species following single doses

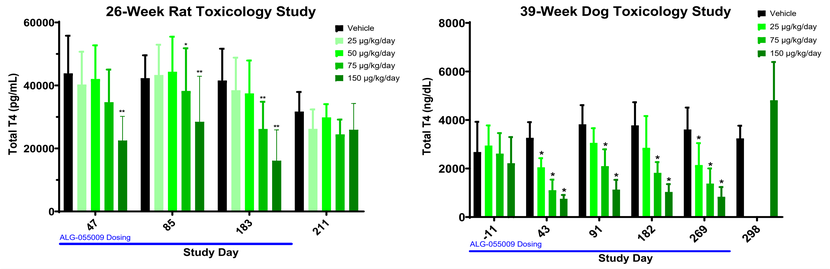
Parameter	Mouse	Rat	Rabbit	Dog	Monkey
Dose (mg/kg)	5	5	15	5	5
C_{max} (ng/mL)	3547	7560	844	4673	8107
$AUC_{0\text{-}inf}$ (ng•hr/mL)	17,977	60,124	4486	51,873	45,735
$t_{1/2}$ (h)	2.97	7.59	5.13	9.26	8.03
%F	75.8	101	N.D.	55.7	83.3

Dose-dependent increases in plasma ALG-055009 $AUC_{0\text{-}24}$ exposures were observed in repeat-dose toxicology studies in rats and dogs

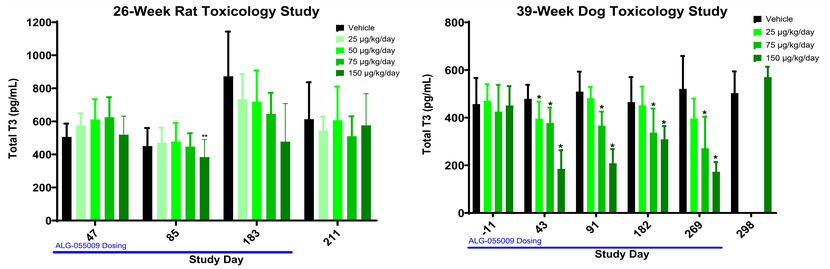


Males represented in solid symbols and females in open symbols for both species.

ALG-055009 reversibly decreased T4 in repeat-dose toxicology studies

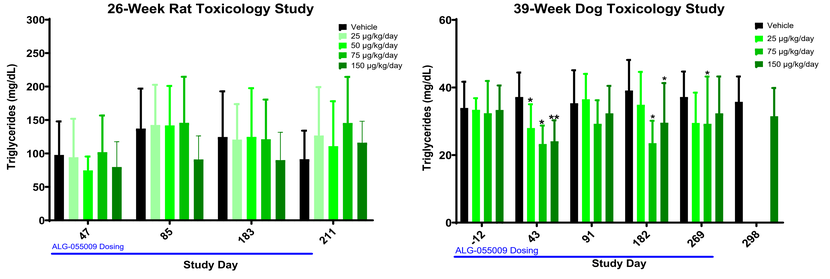


ALG-055009 reversibly decreased T3 in repeat-dose toxicology studies



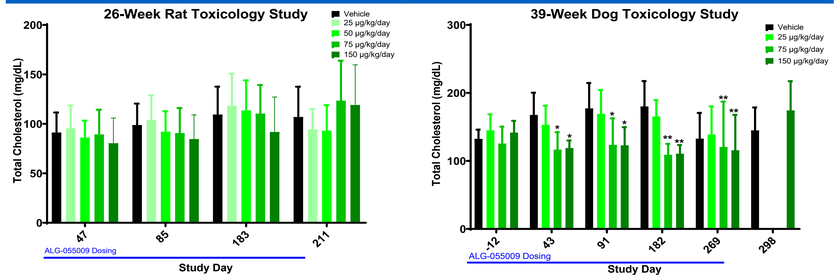
ALG-055009 significantly decreased serum total T3 and T4 in the 2-, 13-, and 26/39-week repeat-dose toxicology studies at similar exposures in rats and dogs. The total T3 and T4 decreases did not progress in magnitude with a longer duration of dosing from 2 weeks of treatment through 26 (rats) or 39 (dogs) weeks of dosing.

ALG-055009 decreased serum triglycerides in repeat-dose toxicology studies



ALG-055009 significantly decreased triglycerides in young healthy rats and dogs maintained on a normal diet in 2-week toxicology studies at doses ≥50 µg/kg/day in dogs (up to 52%), 13-week toxicology studies at 30 µg/kg/day (up to 67% in rats and 63% in dogs), and in 39-week toxicology studies in dogs only at ≥75 µg/kg/day (up to 37%). A trend for decreased triglycerides was noted in the 26-week toxicology study in rats but was not statistically significant at any timepoint.

ALG-055009 decreased serum total cholesterol in repeat-dose toxicology studies in dogs but not in rats



ALG-055009 significantly decreased serum total cholesterol in young healthy dogs maintained on a normal diet in the 2-week study at ≥50 µg/kg/day (up to 44%), 13-week study at 300 µg/kg/day (up to 45%), and at ≥75 µg/kg/day (up to 32%). No decreases were observed in rats in toxicology studies up to 26 weeks in duration.

ALG-055009 demonstrated a favorable toxicology profile

Species	x	ALG-055009 Doses (µg/kg/day)	NOAEL $AUC_{0\text{-}24,\ SS}$ (ng·hr/mL)
Rat	2-week	0 (vehicle), 50, 150, 500	1230
	13-week	0 (vehicle), 30, 100, 300	9050
	26-week	0 (vehicle), 25, 50, 75, 150	3395
Dog	2-week	0 (vehicle), 50, 150, 500	7400
	13-week	0 (vehicle), 30, 100, 300	1680
	39-week	0 (vehicle), 25, 75, 150	3270

No adverse histopathological findings were noted in either rat or dog chronic toxicology studies up to the highest doses tested. All non-adverse clinical pathology or histopathology effects were reversible following 4 weeks recovery.

ALG-055009 had no effects on rat and rabbit embryofetal development

Species	ALG-055009 Doses (µg/kg/day)	NOAEL $AUC_{0\text{-}24,\ SS}$ (ng·hr/mL)
Rat	0 (vehicle), 50, 150, 500	7810
Rabbit	0 (vehicle), 1000, 5000, 15,000	10,900

Conclusions

ALG-055009 is a potent and selective THR-β agonist with favorable in vitro safety and ADME properties and repeat-dose toxicity profile in rats and dogs. ALG-055009 also dose-dependently reduced levels of atherogenic lipids. Combined, this profile indicates ALG-055009 has the potential to be a best-in-class THR-β agonist for the treatment of MASH. Recently, the HERALD Phase 2a study was completed, and the topline data indicated that the primary endpoint was met, demonstrating statistically significant placebo-adjusted median relative reductions in liver fat up to 46.2%.

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