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

Dinah Misner[1], Kusum Gupta[1], Xuan Luong[1], Jerome Deval[1], Kha Le[1], Doug Clark[1], Dave McGowan[2], Matthew McClure[1], David B. Smith[1], Tse-I Lin[2], Julian A. Symons[1], Lawrence M. Blatt[1], Leonid N. Beigelman[1], and Sushmita Chanda[1]

[1]Aligos Therapeutics, Inc., South San Francisco, CA; [2]Aligos Belgium BV, Leuven, Belgium

Email: dmisner@aligos.com

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Background and Aims

MASH (formerly known as NASH) is characterized by hepatic inflammation/damage as a reaction to build-up of fat in the liver. Although no drugs are approved to treat NASH, thyroid hormone receptor β (THRβ) agonists have 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.

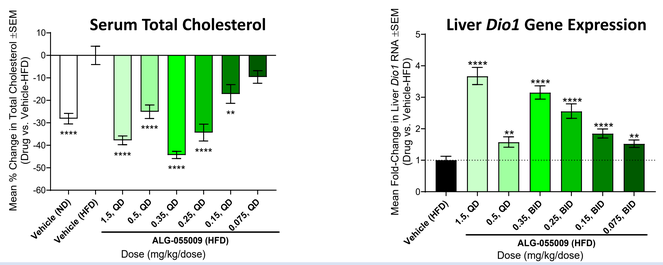
Methods

ALG-055009 was profiled for in vitro efficacy, ADME, and toxicology assays, and in vivo pharmacokinetic studies across species. The in vitro efficacy was evaluated using three different methods: a cell-free LanthaScreen™ time-resolved fluorescence energy transfer (TR-FRET) assay, a luciferase reporter assay in HEK293 cells, and a differential gene expression assay using Huh-7 cells. The in vivo activity of ALG-055009 was evaluated in a diet induced obesity (DIO) mouse model where male C57BL/6J mice were fed with a high fat diet for 14 weeks, followed by once daily (QD) or twice daily (BID) oral administration of ALG-055009 for 28 days. Pharmacodynamic endpoints included total/LDL cholesterol, liver enzymes, and thyroid hormones. Liver and heart gene expression was determined by qPCR. Repeat-dose toxicology studies were conducted in rats and dogs, up to 13-weeks in duration, and clinical pathology endpoints including thyroid hormones were assessed at 2-, 6-, and 13-weeks, as well as following 2- to 4-weeks of recovery.

ALG-055009 is a potent and selective THRβ agonist in vitro

Compound	EC_{50} (nM) THRα	EC_{50} (nM) THRβ	THRβ Selectivity (THRα EC_{50}/THRβ EC_{50})
	THR Coactivator Biochemical Assay		
ALG-055009	360.4 ± 108.2	62.7 ± 42.5	5.7
VK2809A (active, parent)	25. 5± 7.0	10.1 ± 2.7	2.5
Resmetirom	933.8 ± 175.2	73.1 ± 9.3	12.8
	Luciferase Reporter Assay in HEK293T		
ALG-055009	191.1 ± 100.0	50.0 ± 12.6	3.8
VK2809A (active, parent)	297.4 ± 41.4	269.0 ± 30.9	1.1
Resmetirom	5927.4 ± 1117.6	2365.8 ± 689.5	2.5
	CPT1a Gene Expression Assay in Huh-7		
ALG-055009	8.8 ± 6.1		NA
VK2809A (active, parent)	8.3 ± 2.2		NA
Resmetirom	303.1 ± 50.9		NA

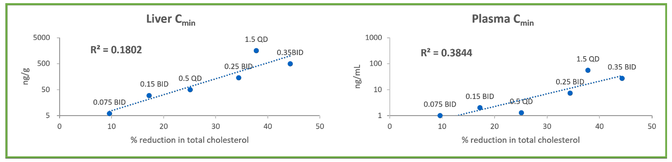
ALG-055009 is a potent and selective THRβ agonist in vitro



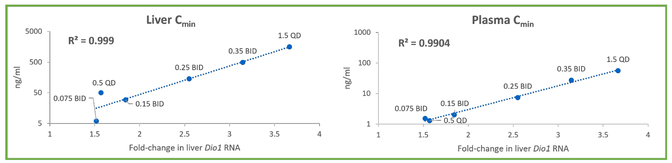
ALG-055009 demonstrated efficacy by lowering serum lipid content, while simultaneously increasing *Dio1* liver expression. No modulation of key THR-regulated genes in the heart (data not shown) was observed, overall indicating target engagement and suggesting target specificity.

PK/PD relationship of ALG-055009 in diet-induced obesity mouse model demonstrates C_{min} shows best correlation

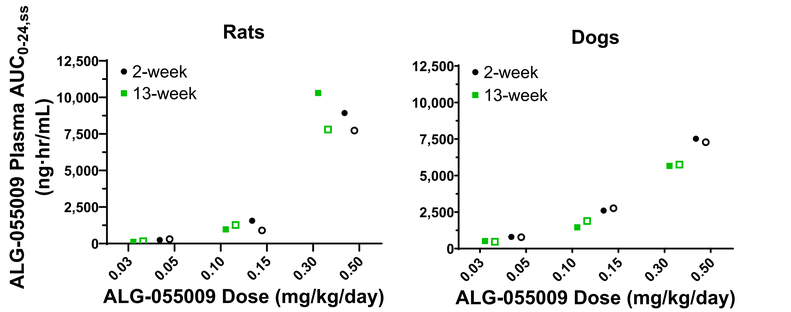
Total cholesterol in serum



Dio1 RNA in liver

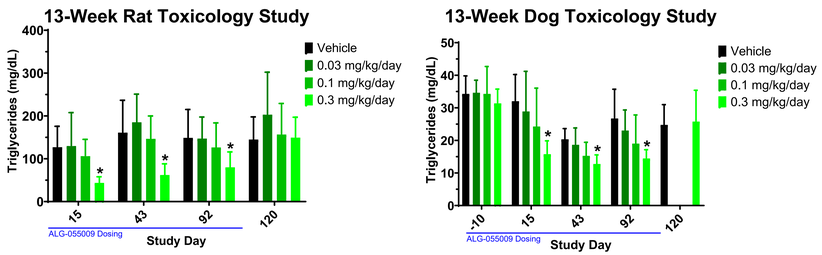


Dose proportional increases in plasma ALG-055009 AUC_{0-24} exposures in dogs but greater than dose proportional increases ALG-055009 AUC_{0-24} exposures in rats observed in repeat-dose toxicology studies



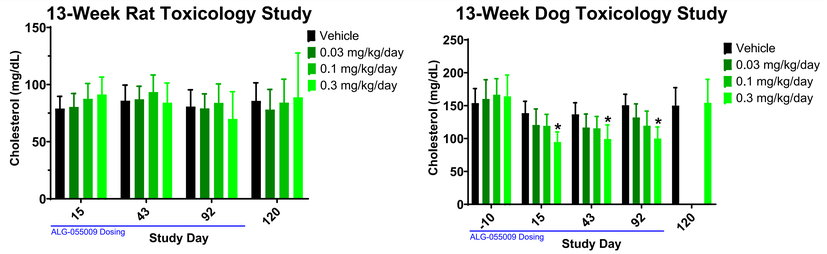
Males represented in solid symbols and females in open symbols for both species

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



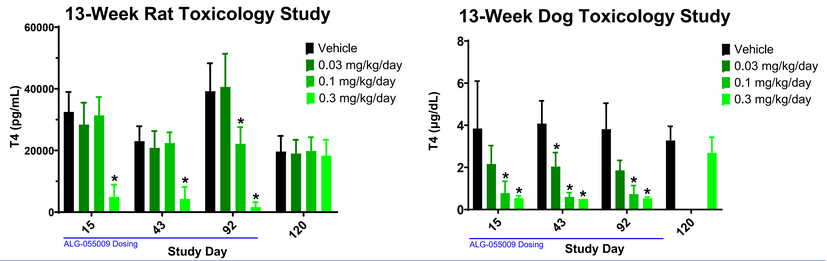
ALG-055009 significantly decreases triglycerides in young healthy rats and dogs maintained on a normal diet in 2-week toxicology studies at doses ≥0.05 mg/kg/day in dogs (up to 52%) and in 13-week toxicology studies at 0.3 mg/kg/day (up to 67% in rats and 63% in dogs).

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

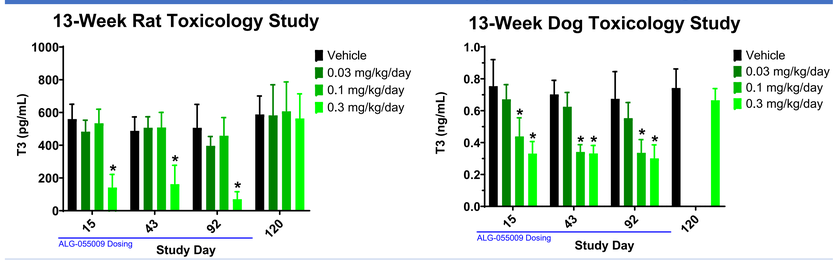


ALG-055009 significantly decreases serum total cholesterol in young healthy dogs maintained on a normal diet in the 2-week study at ≥0 .05 mg/kg/day (up to 44%) and 13-week study at 0.3 mg/kg/day (up to 45%). No decreases were observed in rats in either 2- or 13-week toxicology studies.

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



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



ALG-055009 significantly decreases serum total T3 and T4 in both the 2- and 13-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 to 13 weeks.

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. Multiple oral doses of ALG-055009 (0.3 – 1.0 mg solution) x 14 days demonstrated a favorable safety, PK and PD profile in subjects with hyperlipidemia, supporting evaluation of this dose range in a longer duration Phase 2 study of MASH patients (2900-A, AASLD 2023). This profile indicates ALG-055009 has the potential to be a best-in-class THR-β agonist for the treatment of MASH.

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