ALG-055009, a Potent and Selective THR Beta Agonist for the Treatment of NASH, Demonstrates Significant Cholesterol Reduction in a Diet-Induced Obese (DIO) Mouse Efficacy Model

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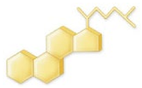
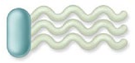
Background: Nonalcoholic steatohepatitis (NASH) is characterized by liver inflammation and damage caused by a buildup of fat in the liver. Although no drugs have been approved for the treatment of NASH, thyroid hormone receptor β (THR-β) agonists have demonstrated potential to reduce liver fat, restore liver functions, and possibly reverse fibrosis. Here we present the effect of ALG-055009, a second-generation THR-β agonist, in a DIO mouse efficacy model.

Beneficial Effects of THR-β Agonists on NAFLD/NASH

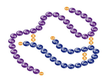


↓ Cholesterol
- ↓ **synthesis** (↓ HMGCoA Reductase)
- ↑ **catabolism** (↑ Chol. 7ª hydrolase = Cyp7A)
- ↑ **liver uptake** (↑ HDL receptor SR-B1 expression, ↑ LDL receptor expression)



↓ Triglycerides (and fatty acids)
- ↓ **synthesis** (↓ Sterol Regulatory Element Binding Transcription Factor-1 = SREBP1c also ↓VLDL assembly)
- ↑ **catabolism** (↑ Mitochondrial O_2 consumption & Thermogenesis via CPT1a, ACC, FAS, spot14, etc.)
- ↑ **liver uptake** (↑ HDL receptor SR-B1 expression, ↑ LDL receptor expression)

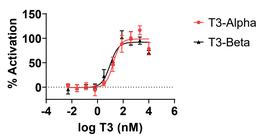
↓ Atherosclerosis plaques
- ↓ LDL and HDL cholesterol
- ↓ ApoA1 lipoprotein
- ↓ Lipoprotein(a) Lp(a)



↓ Insulin resistance
- Effect on glycogenolysis and glycogenesis

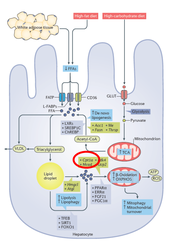
In Vitro Activation of THR-β and –α by ALG-055009 and other Agonists

- **THR-β /THR-α Reporter Cell-based Assay**
  - luciferase THR/RXR assay
  - HEK 293T cells

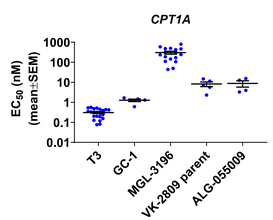


HEK293T Reporter	EC_{50} α (nM)	EC_{50} β (nM)	β selectivity
T_3	14.3	11.5	1.2
GC-1	9.8	4.6	2.1
MGL-3196	**5927**	**2366**	**2.5**
VK-2809 parent	**366**	**269**	**1.4**
ALG-055009	**191**	**50**	**3.8**

- **Huh-7 qPCR Cell-based Assay**
  - CPT1a (Carnitine palmitoyltransferase 1A), key mitochondrial enzyme involved in fatty acid metabolism (beta-oxidation)

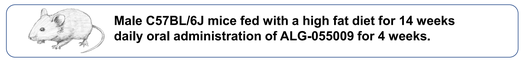


Compound	*CPT1a* EC_{50} (nM)
T3	0.3
GC-1	1.3
MGL-3196	303
VK-2809 parent	8.3
ALG-055009	8.8

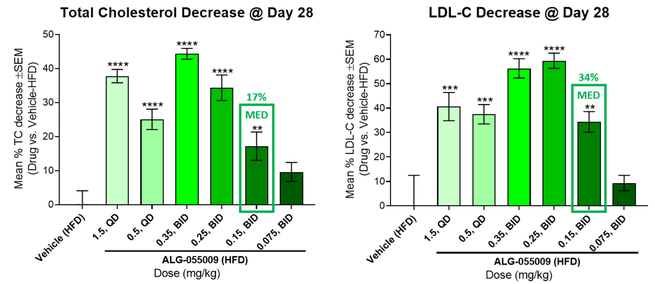


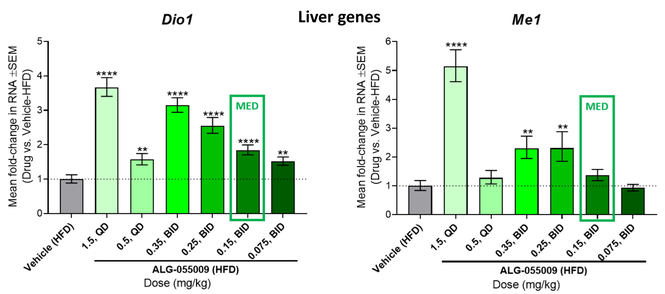
- **Cell-based reporter assay: THR-β EC_{50} of ALG-055009 = 0.050 µM, THR-α/β selectivity = 3.8x**
  - **35x more potent against THR-β than MGL-3196, and 3.8x more selective than VK-2809**
- **ALG-055009 is 34x more potent than MGL-3196 In human hepatic Huh-7 cells**

Cholesterol and Gene Expression Changes in a DIO Mouse Efficacy Model



Male C57BL/6J mice fed with a high fat diet for 14 weeks daily oral administration of ALG-055009 for 4 weeks.

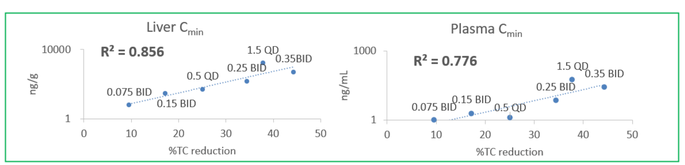




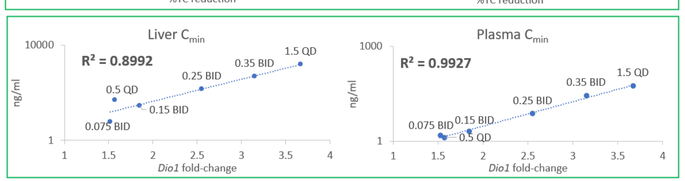
- **The total cholesterol and LDL-C Minimum Effective Dose (MED) of ALG-055009 is 0.15 mg/kg BID**
- ***Dio1* increased starting at 0.075 mg/kg: early biomarker of target engagement in liver**
- ***Me1* is a second biomarker of THR activation in liver**

ALG-055009 PK-PD Correlation in the DIO Mouse Model

Total Cholesterol (TC)

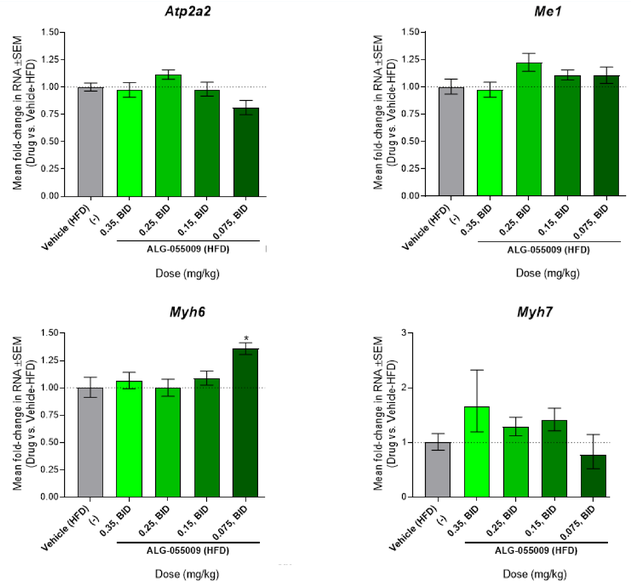


***Dio1* gene**



- **The efficacy of ALG-055009 (TC and *Dio1* gene) correlated well with liver and plasma C_{min}**

Heart Gene Expression after 28-Days in the DIO Mouse Model



- **Typical thyroid hormone heart activation profile (T3):↑ *Atp2a2, ↑ Myh6, ↑ Me1, and ↓ Myh7***
- **ALG-055009: no significant changes in gene expression in the heart**

Results and Conclusions

Following four weeks of administration in DIO mice, ALG-055009 resulted in dose-dependent decrease in serum cholesterol. The minimum efficacious dose of 0.15 mg/kg/dose BID resulted in 17 and 34% reduction in total and LDL cholesterol, respectively. Increases in *Dio1* and *Me1* gene expression provided direct evidence of hepatic THR-β target engagement at all dose groups. None of the doses induced any significant changes in expression of *Atp2a2, Myh6, Me1*, and *Myh7* genes in the heart, indicating a potentially wide safety margin. The pharmacological effects of ALG-055009 on cholesterol reduction and liver gene activation correlated well with liver and plasma C_{min}. Effective induction of liver gene expression with ALG-055009 in mice was consistent with its potent transcriptional activation in Huh-7 cells where ALG-055009 was 34x more potent than MGL-3196.

Conclusion: This study demonstrated that ALG-055009 was highly efficacious in the DIO mouse model, and its pharmacological effect was primarily driven by plasma and liver C_{min}. With its high and selective potency combined with low projected human doses, ALG-055009 has the potential to be a best-in-class THR-β agonist for the treatment of NASH.

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