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
Kusum Gupta1, Xuan Luong1, Sucheta Mukherjee1, Sarah Stevens1, Andreas Jekle1, Tse-I Lin2, Dinah Misner1, Sushmita Chanda1, Jyanwei Liu1, Caroline Williams1, Antitsa Stoycheva1, Lawrence M. Blatt1, Leonid Beigelman1, Julian A. Symons1, Pierre Raboissonn2, Koen Vandyck2, Dave McGowan2, and Jerome Deval1

1Aligos Therapeutics, Inc., South San Francisco, CA; 2Aligos Belgium BV, Leuven, Belgium; *Corresponding author: jdeval@aligos.com

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.

**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 a 17 and 34% reduction in total and LDL cholesterol, respectively. Increases in Diet1 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 Dio1 and Me1 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 Cmin. 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.

**Conclusions:** 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 Cmin. 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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