The THR-Beta Agonist ALG-055009 Has a Favorable Safety and Pharmacokinetic Profile and Dose Proportionally Lowers Lipid Biomarkers in a Phase 1 Study

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2. Biotrial, Rennes, France
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Personal

I am an employee of Aligos Therapeutics

Corporate

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Background

- Thyroid hormone receptor-beta (THR-β) is the primary THR expressed in liver and plays an important role in lipid metabolism.
- Therapeutics targeting THR-β represent a promising approach to treating patients with fatty liver by decreasing hepatic fat content and improving liver histology.
- ALG-055009 is a THR-β agonist that in preclinical models demonstrated:
  - High selectivity for THR-β and nanomolar potency.
  - High efficacy in diet-induced obese rat and mouse models.
  - A favorable PK profile with low plasma clearance, metabolic stability, high oral bioavailability and a long plasma half-life.
- Summarized here are data from a Phase 1 study evaluating the safety, pharmacokinetics (PK), and pharmacodynamics of single/multiple doses of ALG-055009 in healthy volunteers (HVs) and subjects with hyperlipidemia (Study ALG-055009-301, NCT05090111).

Study Design
Typical SAD, MAD Design

Part 1: Single Ascending Dose (SAD)
N = up to 64 Healthy Volunteers
n = 8 per Cohort, n = 6 ALG-055009 and n = 2 Placebo

Part 2: Multiple Ascending Dose (MAD) – Dosing PO QD X 14 days
N = up to 80 Subjects with Hyperlipidemia (LDL-C>110 mg/dL)
n = 10 per Cohort, n = 8 ALG-055009 and n = 2 Placebo
Demographics
Balanced, Typical for HVs, Hyperlipidemia Patients

<table>
<thead>
<tr>
<th>ALG-055009 Dose</th>
<th>SAD</th>
<th>MAD</th>
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<tbody>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>N=10</td>
<td>N=8</td>
</tr>
<tr>
<td>Age (years)</td>
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<td>41.3 (5.5)</td>
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<tr>
<td>Male, N (%)</td>
<td>10 (100%)</td>
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<tr>
<td>Non-Hispanic, N (%)</td>
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<tr>
<td>BMI, kg/m²</td>
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<tr>
<td>Weight, kg</td>
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<tr>
<td>Free T4, ng/dL</td>
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<td>1.1 (0.1)</td>
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<tr>
<td>Free T3, pg/dL</td>
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<td>295.5 (7.8)</td>
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<td>TSH, mIU/L</td>
<td>1.6 (0.1)</td>
<td>1.3 (0.2)</td>
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<tr>
<td>SHBG, nmol/L</td>
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<td>36.6 (3.6)</td>
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<tr>
<td>LDL-C, mg/dL</td>
<td>133.8 (12.4)</td>
<td>147.9 (13.9)</td>
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<tr>
<td>TG, mg/dL</td>
<td>127.7 (11.2)</td>
<td>125.2 (14.8)</td>
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<td>Apo-B, mg/dL</td>
<td>105.7 (9.3)</td>
<td>113.0 (8.4)</td>
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<table>
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<tr>
<th>0.1 mg</th>
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<th>0.9 mg</th>
<th>2.6 mg</th>
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<td>35.2 (5.5)</td>
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<td>49.4 (3.9)</td>
<td>41.4 (4.1)</td>
<td>33.4 (4.8)</td>
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<td>Male, N (%)</td>
<td>6 (100%)</td>
<td>6 (100%)</td>
<td>6 (100%)</td>
<td>6 (100%)</td>
<td>8 (100%)</td>
<td>8 (100%)</td>
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<tr>
<td>Non-Hispanic, N (%)</td>
<td>6 (100%)</td>
<td>6 (100%)</td>
<td>6 (100%)</td>
<td>6 (100%)</td>
<td>8 (100%)</td>
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<td>7 (87.5%)</td>
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<td>BMI, kg/m²</td>
<td>25.4 (1.0)</td>
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<td>28.1 (0.8)</td>
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<td>Weight, kg</td>
<td>80.6 (4.7)</td>
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<td>76.2 (1.6)</td>
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<td>88.4 (4.5)</td>
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<td>Free T4, ng/dL</td>
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<td>1.3 (0.1)</td>
<td>1.3 (0.1)</td>
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<td>Free T3, pg/dL</td>
<td>343.9 (8.0)</td>
<td>350.5 (19.9)</td>
<td>325.5 (14.6)</td>
<td>335.5 (15.0)</td>
<td>318.0 (20.7)</td>
<td>296.7 (7.3)</td>
<td>295.5 (7.3)</td>
<td>300.5 (12.6)</td>
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<tr>
<td>TSH, mIU/L</td>
<td>2.1 (0.3)</td>
<td>2.2 (0.5)</td>
<td>2.3 (0.3)</td>
<td>1.7 (0.3)</td>
<td>2.1 (0.3)</td>
<td>1.6 (0.3)</td>
<td>1.4 (0.2)</td>
<td>1.8 (0.2)</td>
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<tr>
<td>SHBG, nmol/L</td>
<td>40.4 (5.0)</td>
<td>33.7 (5.6)</td>
<td>33.7 (5.6)</td>
<td>36.9 (3.9)</td>
<td>39.1 (6.0)</td>
<td>36.6 (3.6)</td>
<td>37.4 (16.3)</td>
<td>42.2 (6.3)</td>
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<tr>
<td>LDL-C, mg/dL</td>
<td>125.9 (13.5)</td>
<td>125.4 (16.0)</td>
<td>144.9 (14.3)</td>
<td>129.6 (15.7)</td>
<td>141.7 (10.1)</td>
<td>150.5 (10.0)</td>
<td>142.0 (5.9)</td>
<td>125.8 (4.8)</td>
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<tr>
<td>TG, mg/dL</td>
<td>99.1 (27.1)</td>
<td>111.9 (7.2)</td>
<td>82.1 (9.1)</td>
<td>117.8 (21.9)</td>
<td>160.8 (22.1)</td>
<td>173.9 (33.2)</td>
<td>153.6 (27.7)</td>
<td>123.4 (10.1)</td>
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<td>Apo-B, mg/dL</td>
<td>93.5 (10.8)</td>
<td>98.7 (11)</td>
<td>92.3 (9.7)</td>
<td>87.8 (9.8)</td>
<td>97.8 (9.8)</td>
<td>113.0 (8.4)</td>
<td>113.0 (4.6)</td>
<td>117.6 (5.4)</td>
</tr>
</tbody>
</table>

All values summarized as mean (SEM) unless otherwise noted.
Safety
No Safety Findings

- No serious adverse events (SAEs), treatment emergent adverse events (TEAEs) leading to discontinuation, or Grade ≥3 TEAEs
- No clinical evidence of hyper- or hypo-thyroidism
- Most common (≥2 subjects reported) TEAEs

<table>
<thead>
<tr>
<th>TEAE Term</th>
<th>SAD Dose (mg)</th>
<th>MAD Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo 0.1 0.3 ≥0.9</td>
<td>Placebo 0.3 0.5 0.6 1</td>
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<tr>
<td>Headache</td>
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<td>1 1 2</td>
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<td>Rhinopharyngitis</td>
<td>1 1</td>
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<tr>
<td>Insomnia</td>
<td>0 2</td>
<td></td>
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<tr>
<td>Abdominal distension</td>
<td></td>
<td>1 1 2</td>
</tr>
<tr>
<td>Diarrhea</td>
<td></td>
<td>1 1</td>
</tr>
</tbody>
</table>

- No clinically concerning laboratory, ECG, vital sign or physical examination findings
Pharmacokinetics (Solution Formulation)
Linear PK with Low Variability

SAD

MAD

\[ T_{1/2} = 20-24 \text{ hrs (supports QD dosing)} \]
Pharmacokinetics (Solution vs. Gelcap (Ph2) Formulation)
Similar PK with Low Variability: Ph2 Formulation Confirmed

Gelcap relative bioavailability ~85%
Biomarkers - Sex Hormone Binding Globulin
Dose Dependent Increase in SAD, MAD

![Graph showing dose dependent increase in SAD, MAD](image-url)
Biomarkers – Atherogenic Lipids (LDL, Apo-B, Triglycerides)
Dose Dependent Decrease in SAD, MAD

**LDL (MAD)**

**Apo-B (MAD)**
Biomarkers – Thyroid Hormones
Dose Dependent Decrease in SAD, MAD

All mean thyroid hormone levels in normal range for doses ≤0.6 mg
Summary

• Single ALG-055009 doses up to 4 mg and multiple doses up to 1 mg x 14 days were well tolerated in Study ALG-055009-301
  – No concerning TEAEs, labs, EKGs, vital signs, physical exams
  – No evidence of clinical hyper- or hypo-thyroidism

• ALG-055009 showed favorable PK after single, multiple doses
  – Dose-proportional increases in exposure (solution formulation)
  – Similar PK profiles for liquid and gelcap (Ph2) formulations
  – Low variability (both formulations)

• Expected thyromimetic effects observed. Dose proportional
  – Increases in SHBG
  – Decreases in lipids, thyroid hormones

• Favorable risk-benefit profile observed
  – Phase 2 dose finding study (gelcaps) evaluating MRI-PDFF (12 weeks) planned to initiate in Q4 2023
Acknowledgments

• We wish to thank
  – Study subjects for their participation
  – Biotrial (study site) and their staff
  – Additional Aligos team members
    › Genevieve Harrington
    › Chris Burnett
    › Meenakshi Venkatraman
    › Dinah Misner
    › Doug Clark