

# 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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# Disclosures

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## Personal

I am an employee of Aligos Therapeutics

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# Background

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- Thyroid hormone receptor-beta (THR- $\beta$ ) is the primary THR expressed in liver and plays an important role in lipid metabolism<sup>1,2</sup>
- Therapeutics targeting THR- $\beta$  represent a promising approach to treating patients with fatty liver by decreasing hepatic fat content and improving liver histology<sup>3</sup>
- ALG-055009 is a THR- $\beta$  agonist that in preclinical models demonstrated:
  - High selectivity for THR- $\beta$  and nanomolar potency<sup>4</sup>
  - High efficacy in diet-induced obese rat and mouse models<sup>4,5</sup>
  - A favorable PK profile with low plasma clearance, metabolic stability, high oral bioavailability and a long plasma half-life<sup>5,6</sup>
- 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)

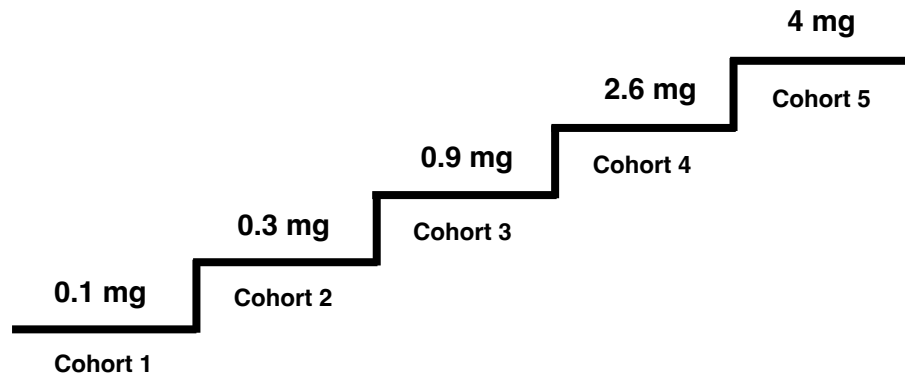
# Study Design

## Typical SAD, MAD Design

### Part 1: Single Ascending Dose (SAD)

N = up to 64 Healthy Volunteers

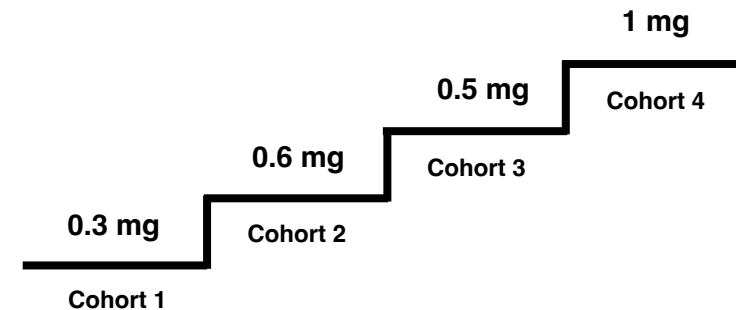
n = 8 per Cohort, n = 6 ALG-055009 and n = 2 Placebo



### 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

|                        | SAD          |              |              |              |              |              | MAD          |              |              |              |              |
|------------------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|
| ALG-055009 Dose        | Placebo      | 0.1 mg       | 0.3 mg       | 0.9 mg       | 2.6 mg       | 4 mg         | Placebo      | 0.3 mg       | 0.5 mg       | 0.6 mg       | 1 mg         |
| N                      | N=10         | N=6          | N=6          | N=6          | N=6          | N=6          | N=8          | N=8          | N=8          | N=8          | N=8          |
| Age (years)            | 42.2 (3.3)   | 41.7 (2.7)   | 35.7 (4.7)   | 30.7 (4.5)   | 35.2 (5.5)   | 38.8 (4.9)   | 41.3 (5.5)   | 39.1 (4.1)   | 49.4 (3.9)   | 41.4 (4.1)   | 33.4 (4.8)   |
| Male, N (%)            | 10 (100%)    | 6 (100%)     | 6 (100%)     | 6 (100%)     | 6 (100%)     | 6 (100%)     | 8 (100%)     | 7 (87.5%)    | 6 (75%)      | 8 (100%)     | 8 (100%)     |
| Non-Hispanic, N (%)    | 10 (100%)    | 6 (100%)     | 6 (100%)     | 6 (100%)     | 6 (100%)     | 6 (100%)     | 8 (100%)     | 8 (100%)     | 8 (100%)     | 8 (100%)     | 7 (87.5%)    |
| BMI, kg/m <sup>2</sup> | 25.7 (0.9)   | 25.4 (1.0)   | 25.7 (1.9)   | 23.0 (1.3)   | 25.0 (1.1)   | 24.7 (1.0)   | 25.6 (1.3)   | 28.1 (0.8)   | 28.4 (1.3)   | 27.1 (1.1)   | 24.7 (1.4)   |
| Weight, kg             | 82.2 (3.1)   | 80.6 (4.7)   | 83.3 (6.5)   | 69.3 (7.1)   | 83.2 (5.2)   | 76.2 (1.6)   | 80.7 (5.6)   | 85.8 (2.5)   | 84.5 (4.8)   | 88.4 (4.5)   | 78.4 (5.4)   |
| Free T4, ng/dL         | 1.3 (0.1)    | 1.2 (0.1)    | 1.3 (0.1)    | 1.3 (0.1)    | 1.3 (0.1)    | 1.3 (0.03)   | 1.1 (0.1)    | 1.2 (0.03)   | 1.1 (0.03)   | 1.2 (0.1)    | 1.1 (0.02)   |
| Free T3, pg/dL         | 328.5 (7.9)  | 343.9 (8.0)  | 322.2 (10.2) | 350.5 (19.9) | 325.5 (14.6) | 335.5 (15.0) | 295.5 (7.8)  | 318.0 (20.7) | 296.7 (7.3)  | 295.5 (8.0)  | 300.5 (12.6) |
| TSH, mIU/L             | 1.6 (0.1)    | 2.1 (0.3)    | 1.5 (0.2)    | 2.2 (0.5)    | 2.3 (0.3)    | 1.7 (0.3)    | 1.3 (0.2)    | 2.1 (0.3)    | 1.6 (0.3)    | 1.4 (0.2)    | 1.8 (0.2)    |
| SHBG, nmol/L           | 36.4 (4.1)   | 40.4 (5.0)   | 33.7 (5.6)   | 33.7 (5.6)   | 36.9 (3.9)   | 39.1 (6.0)   | 36.6 (3.6)   | 37.4 (16.3)  | 42.2 (6.3)   | 36.3 (3.9)   | 31.1 (4.2)   |
| LDL-C, mg/dL           | 133.8 (12.4) | 123.0 (12.3) | 125.9 (13.5) | 125.4 (16.0) | 144.9 (14.3) | 129.6 (15.7) | 147.9 (13.9) | 141.7 (10.1) | 150.5 (10.0) | 142.0 (5.9)  | 125.8 (4.8)  |
| TG, mg/dL              | 127.7 (11.2) | 99.1 (27.1)  | 116.0 (22.1) | 111.9 (7.2)  | 82.1 (9.1)   | 117.8 (21.9) | 125.2 (14.8) | 160.8 (22.1) | 173.9 (33.2) | 153.6 (27.7) | 123.4 (10.1) |
| Apo-B, mg/dL           | 105.7 (9.3)  | 93.5 (10.8)  | 98.7 (11)    | 92.3 (9.7)   | 87.8 (9.8)   | 97.8 (9.8)   | 113.0 (8.4)  | 113.0 (4.6)  | 117.6 (5.4)  | 112.6 (5.2)  | 96.6 (3.7)   |

# Safety

## No Safety Findings

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

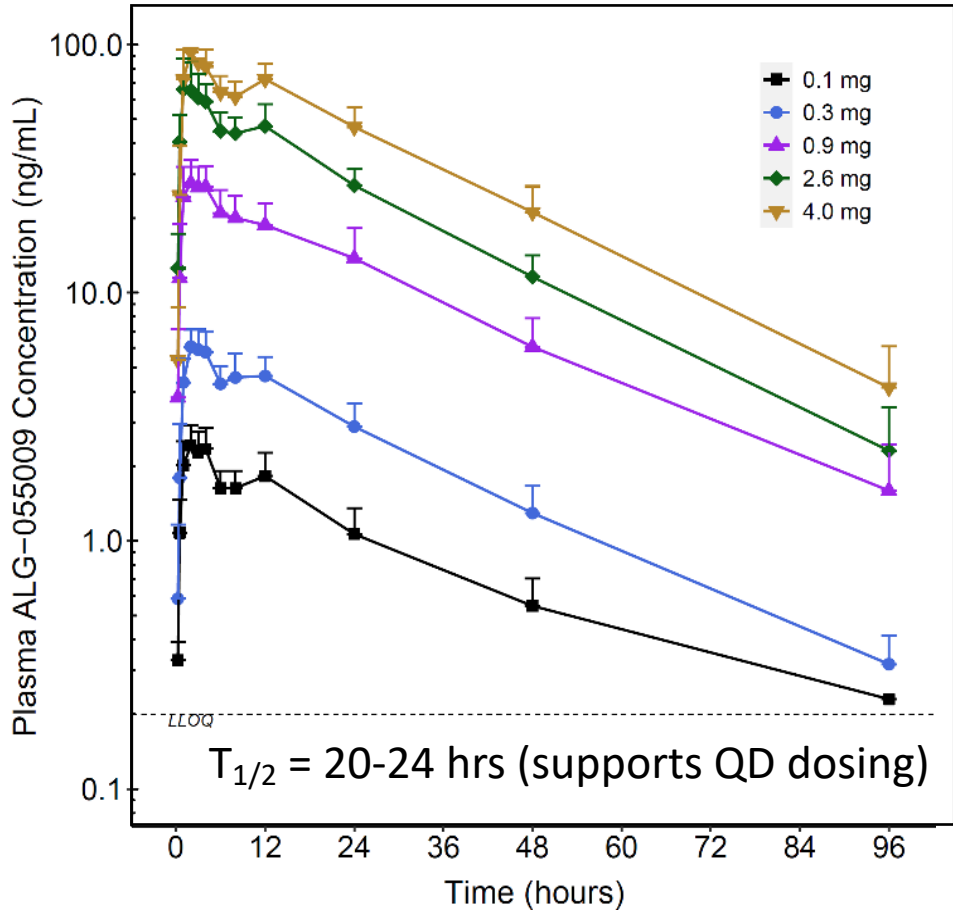
| TEAE Term            | SAD Dose (mg) |     |     |            | MAD Dose (mg) |     |     |     |   |
|----------------------|---------------|-----|-----|------------|---------------|-----|-----|-----|---|
|                      | Placebo       | 0.1 | 0.3 | $\geq 0.9$ | Placebo       | 0.3 | 0.5 | 0.6 | 1 |
| Headache             | 1             |     | 1   |            | 1             |     | 1   | 2   |   |
| Rhinopharyngitis     | 1             | 1   |     |            |               |     |     |     |   |
| Insomnia             |               |     |     |            | 0             | 2   |     |     |   |
| Abdominal distension |               |     |     |            | 1             |     | 1   | 2   |   |
| Diarrhea             |               |     |     |            |               |     |     | 1   | 1 |

- No clinically concerning laboratory, ECG, vital sign or physical examination findings

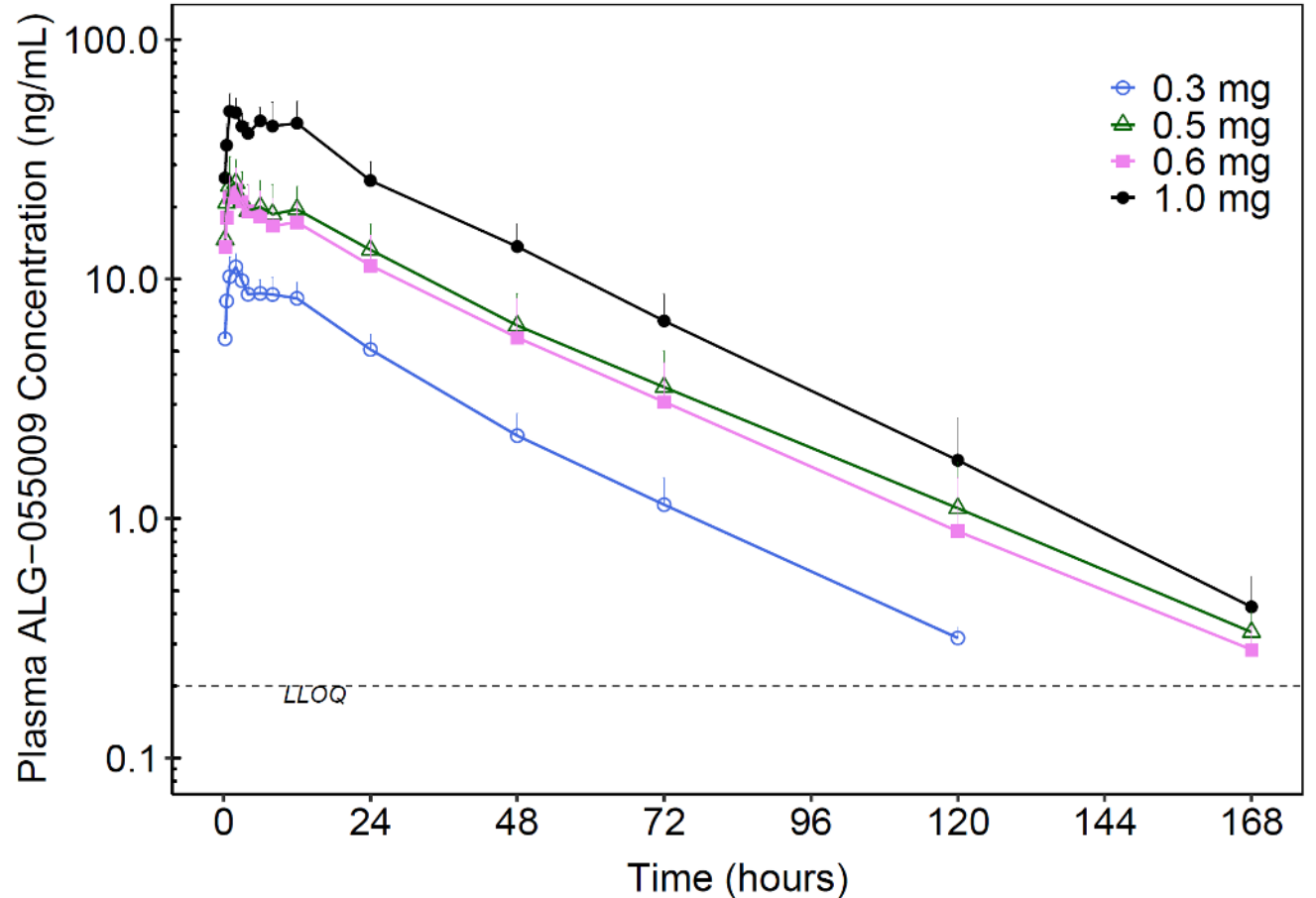
# Pharmacokinetics (Solution Formulation)

## Linear PK with Low Variability

SAD

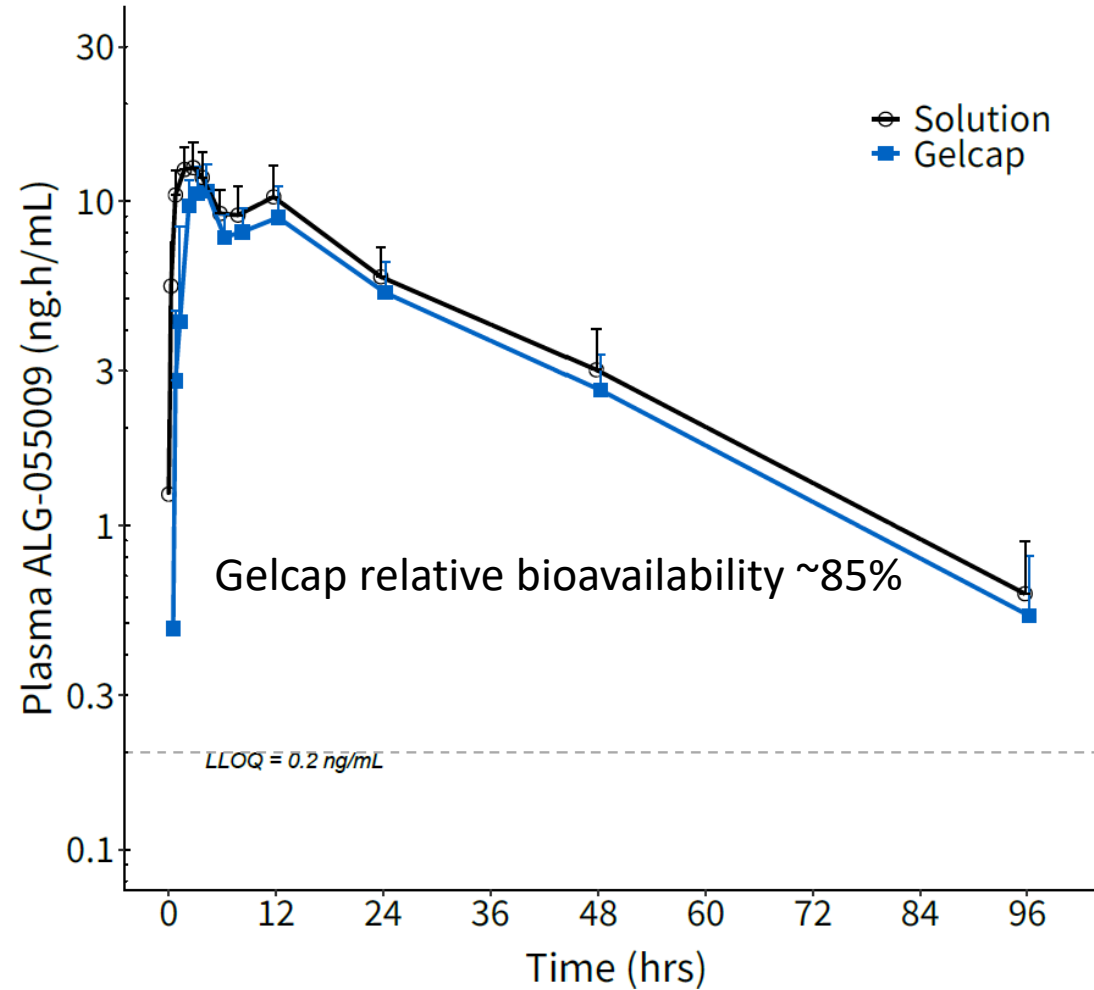


MAD



# Pharmacokinetics (Solution vs. Gelcap (Ph2) Formulation)

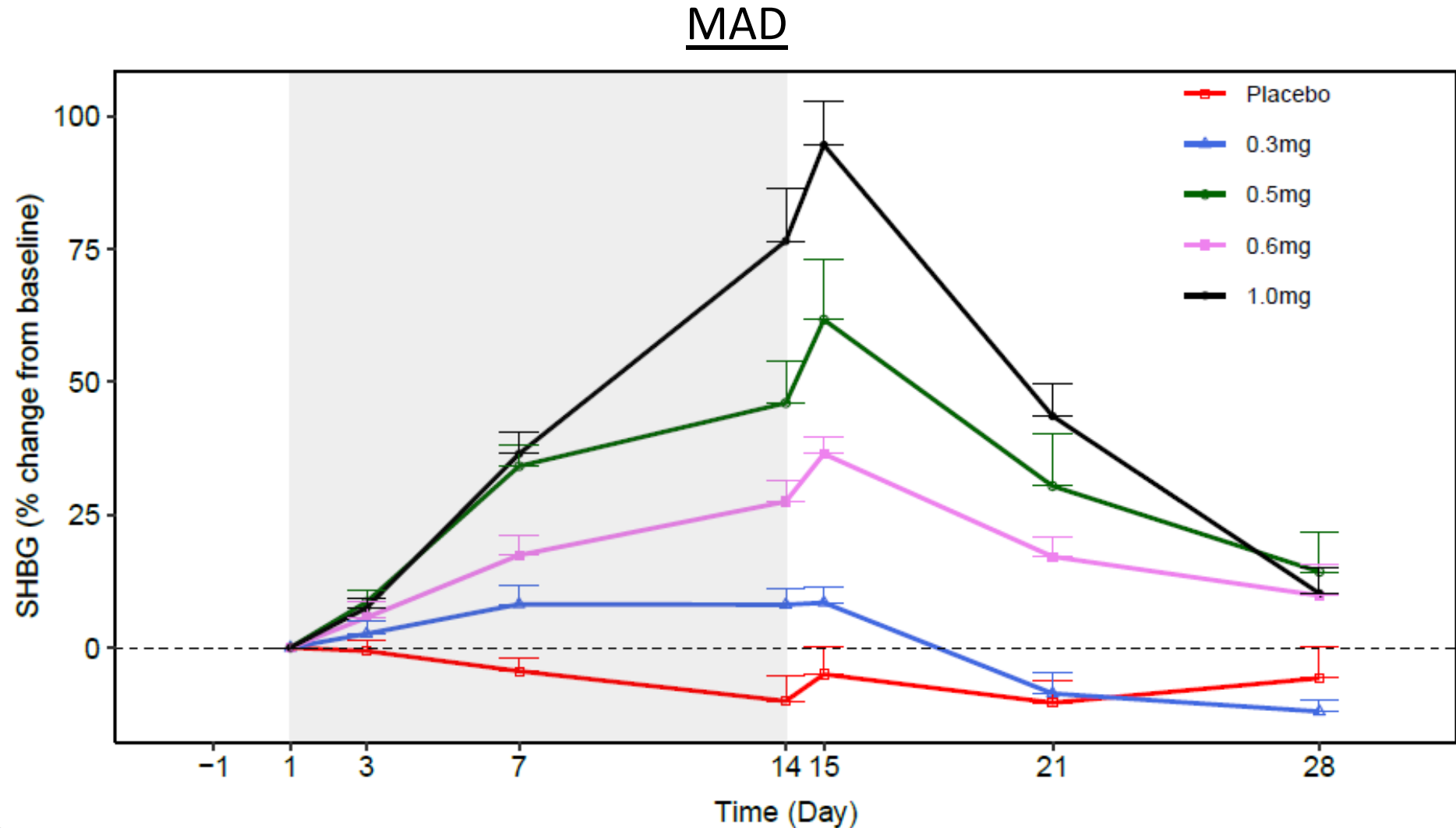
## Similar PK with Low Variability: Ph2 Formulation Confirmed





# Biomarkers - Sex Hormone Binding Globulin

## Dose Dependent Increase in SAD, MAD

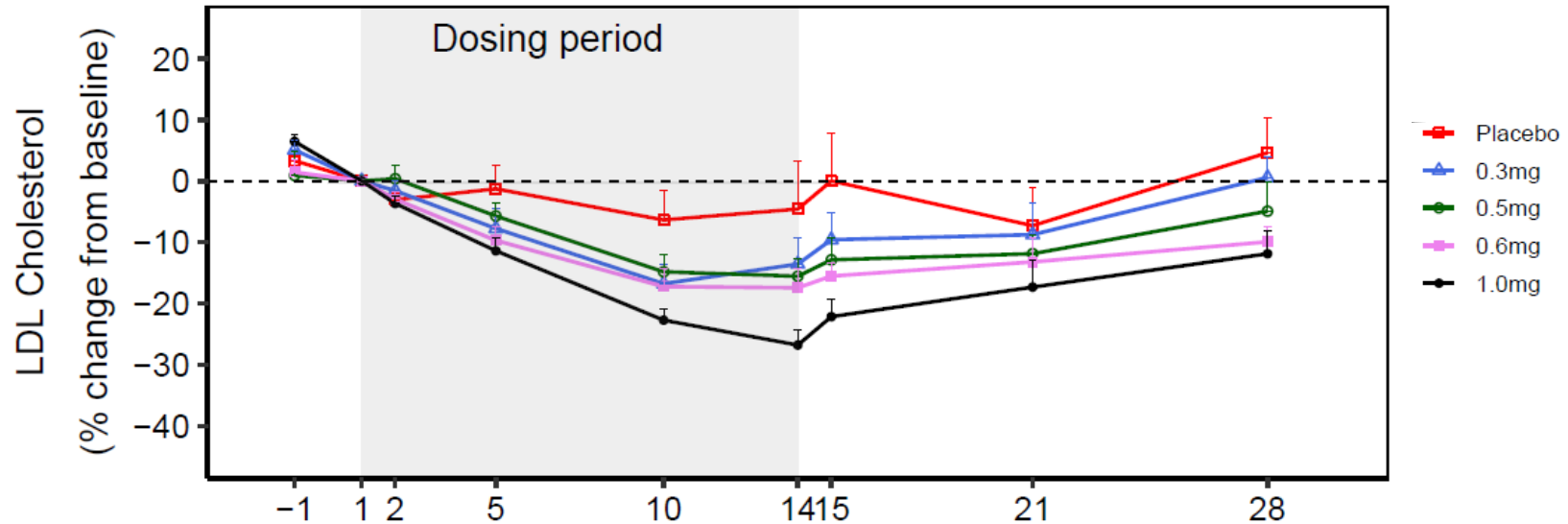


Mean  $\pm$  SEM

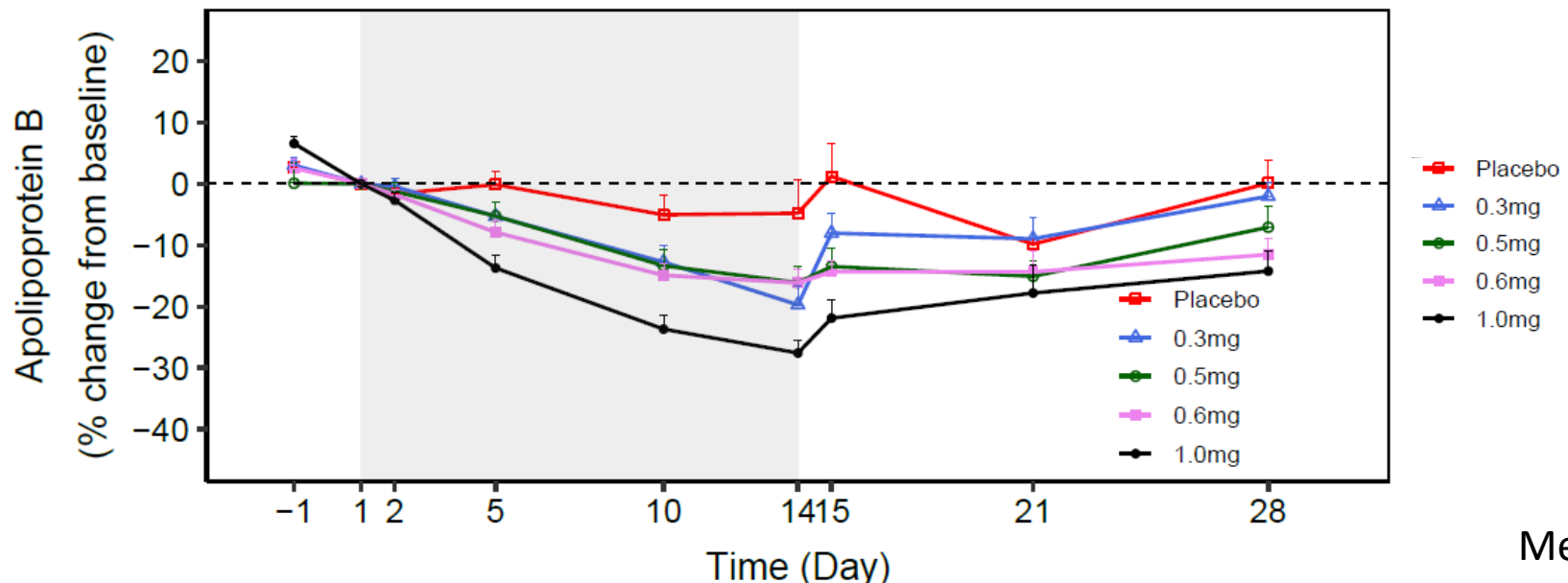
# Biomarkers – Atherogenic Lipids (LDL, Apo-B, Triglycerides)

## Dose Dependent Decrease in SAD, MAD

LDL (MAD)

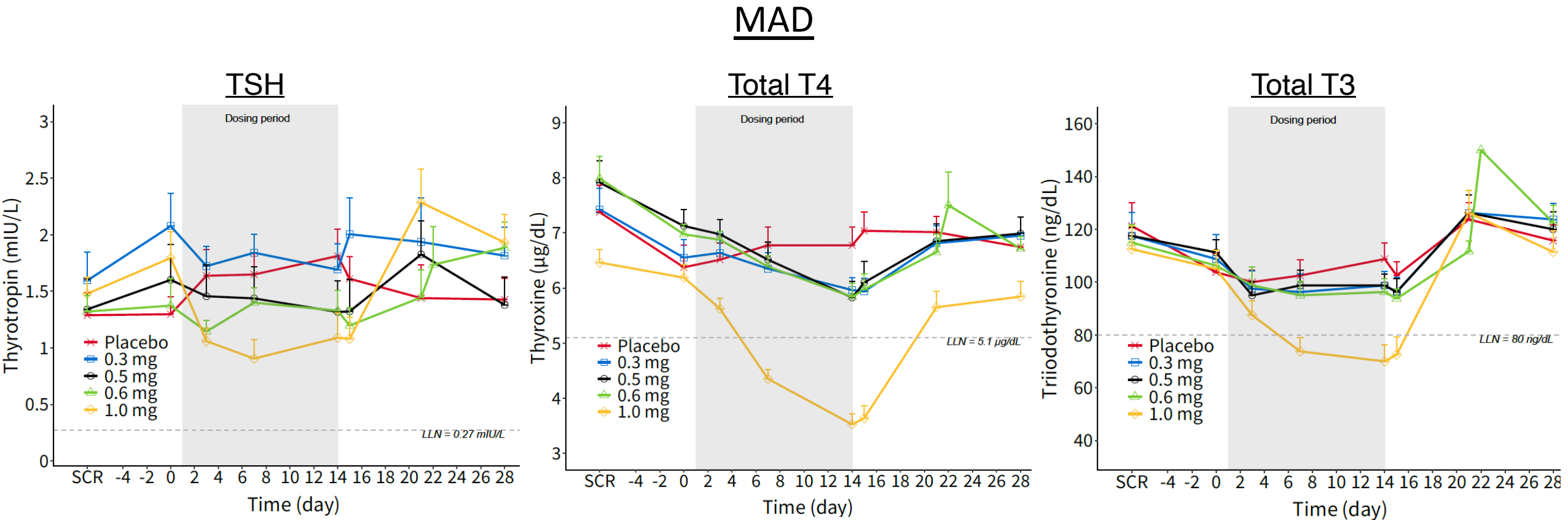


Apo-B (MAD)



# Biomarkers – Thyroid Hormones

## Dose Dependent Decrease in SAD, MAD



All mean thyroid hormone levels in normal range for doses  $\leq 0.6$  mg

# Summary

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- 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-PDFP (12 weeks) planned to initiate in Q4 2023

# Acknowledgments

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- We wish to thank
  - Study subjects for their participation
  - Biotrial (study site) and their staff
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    - › Meenakshi Venkatraman
    - › Dinah Misner
    - › Doug Clark