HERALD

ALG-055009, a Novel Thyroid Hormone Receptor Beta (THR-β) Agonist, was Well-tolerated with Significant Reductions in Liver Fat at Week 12 in Non-cirrhotic MASH Patients in the Randomized, Double-Blind, Placebo-controlled Phase 2a HERALD Study

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AASLD The Liver Meeting® Nov. 15-19, 2024

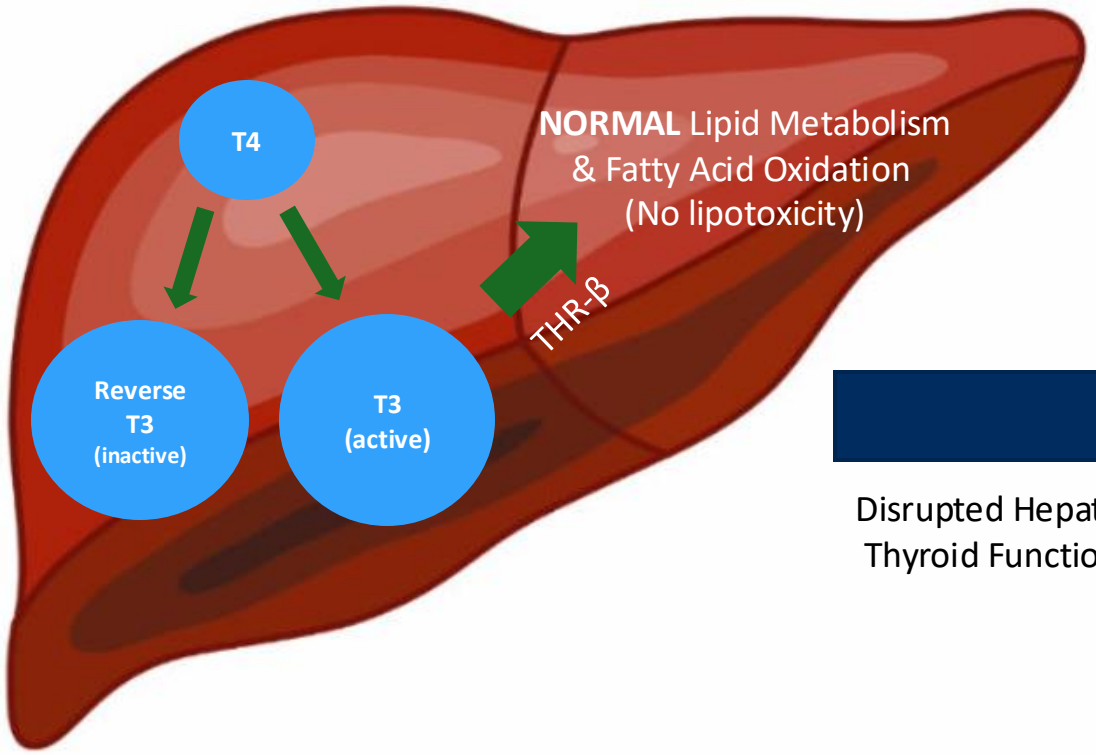
Disclosures

I disclose the following financial relationship(s) with a commercial interest:

- Scientific advisor or consultant for: Eli Lilly & Co., 89bio, Aardvark, Aligos, Altimmune, Alnlyam/Regeneron, Amgen, Arrowhead, AstraZeneca, Bristol Myers Squibb, CohBar, Galmed, Gilead, Glympse Bio, Hightide, Inipharma, Intercept, Inventiva, Ionis, Janssen, Inc., Madrigal Pharmaceuticals, Merck, Metacrine, Inc., NGM Biopharmaceuticals, Novartis, Pfizer, Sagimet Biosciences, Terns Pharmaceuticals, Theratechnologies, Viking Therapeutics
- Share options: 89bio, Sagimet Biosciences
- Grant/Research Support: Arrowhead, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, Galectin Therapeutics, Galmed, Gilead, Hanmi, Intercept, Inventiva, Ionis, Janssen Inc., Madrigal Pharmaceuticals, Merck, NGM Biopharmaceuticals, Novo Nordisk, Pfizer, Sonic Incytes, Terns Pharmaceuticals
- Co-founder: LipoNexus, Inc.

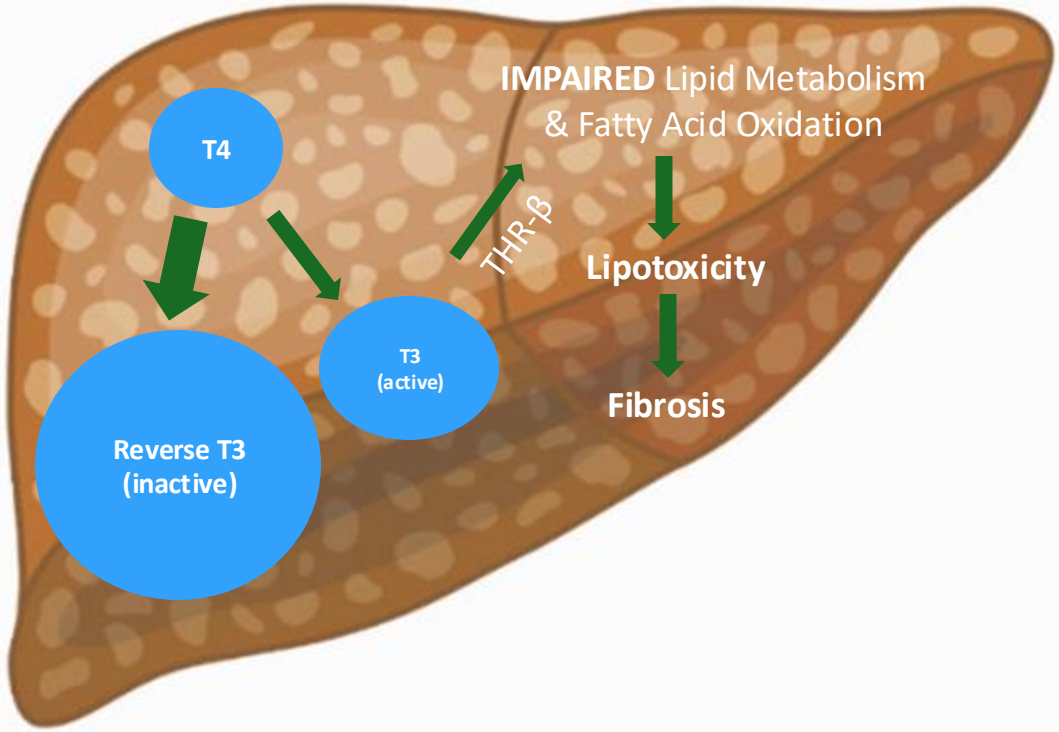
Role of Hepatic Thyroid Dysfunction in MASLD/MASH Pathogenesis

Healthy Liver



Disrupted Hepatic Thyroid Function

MASH Liver



Hatziagelaki et al. Trends in Endocrinology & Metabolism. 2022; 33(11).
Liver figures adapted from https://www.gblhospital.com/centre-for-excellence/gi-liver-surgeries/advance-liver-institute/fatty-liver/.
T3=triiodothyronine; T4=thyroxine; THR-β=thyroid hormone receptor beta.

Reduced active T3 production in MASLD/MASH allows increased production of pro-inflammatory lipotoxic fat that causes hepatocellular injury/death, fibrosis, and cancer

ALG-055009 is a Highly Potent and Selective THR-β Agonist

- Thyroid hormone receptor-beta (THR-β) is the primary THR expressed in the liver and plays an important role in lipid metabolism.[1,2]
- THR-β agonists reduce atherogenic lipids, decrease hepatic fat, and improve liver histology in MASH.[3]
- ALG-055009 is a novel next generation THR-β agonist with β-selectivity, in vitro potency exceeding that of first generation THR-β drugs with no expected CYP450 or liver transporter-based drug-drug interaction potential.[4,5]

Relative THR-α and THR-β Activity in Cell-Based Assays

	EC_{50} α (nM)	EC_{50} β (nM)	Relative THR-β Selectivity (α/β)
ALG-055009	**191**	**50**	**3.8**
Resmetirom	5927	2366	2.5
VK-2809 Parent	297	269	1.1

1. Sinha RA et al. Nat Rev Endocrinol. 2018; 14 (5): 259-269.
2. Pramfalk C. et al. Biochim & Biophys Acta 2011; 1812: 929-937.
3. Harrison S. et al. EASL 2023. Abstract #GS-001.
4. Luong XG et al. PLoS One. 2020; 15(12).
5. Vandyck K et al. Journal of Medicinal Chemistry. 2024; 67(17): 14840.

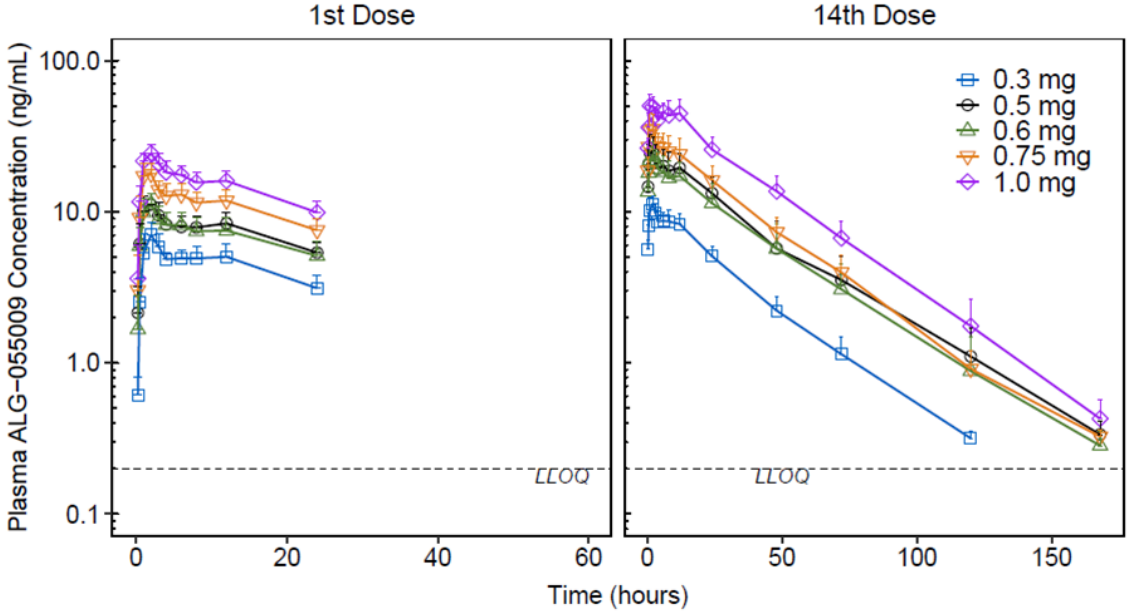
ALG-055009 is ~5-50 fold more potent *in vitro* and more β selective than other THRβ agonists

ALG-055009 was Well Tolerated in Phase 1, with Favorable Pharmacokinetics and Pharmacodynamics

- In Phase 1, single (up to 4.0 mg) and multiple (up to 1.0 mg QD for 14 days) doses of ALG-055009[1]:
  - Were well-tolerated
  - Had dose proportional PK and low variability
  - Demonstrated expected thyromimetic effects, including dose-dependent increases in sex hormone binding globulin (SHBG) and reductions in lipid/lipoproteins

1. Charfi H. et al. AASLD 2023 Abstract #41459.

ALG-055009 Multiple Dose PK



Data presented as mean ± SD

Phase 2a HERALD

Aim of this Phase 2a study was to examine the safety, tolerability, pharmacokinetics, and pharmacodynamics of oral daily doses of ALG-055009 vs placebo over 12 weeks of treatment in adult patients with presumed MASH and F1-F3 fibrosis.

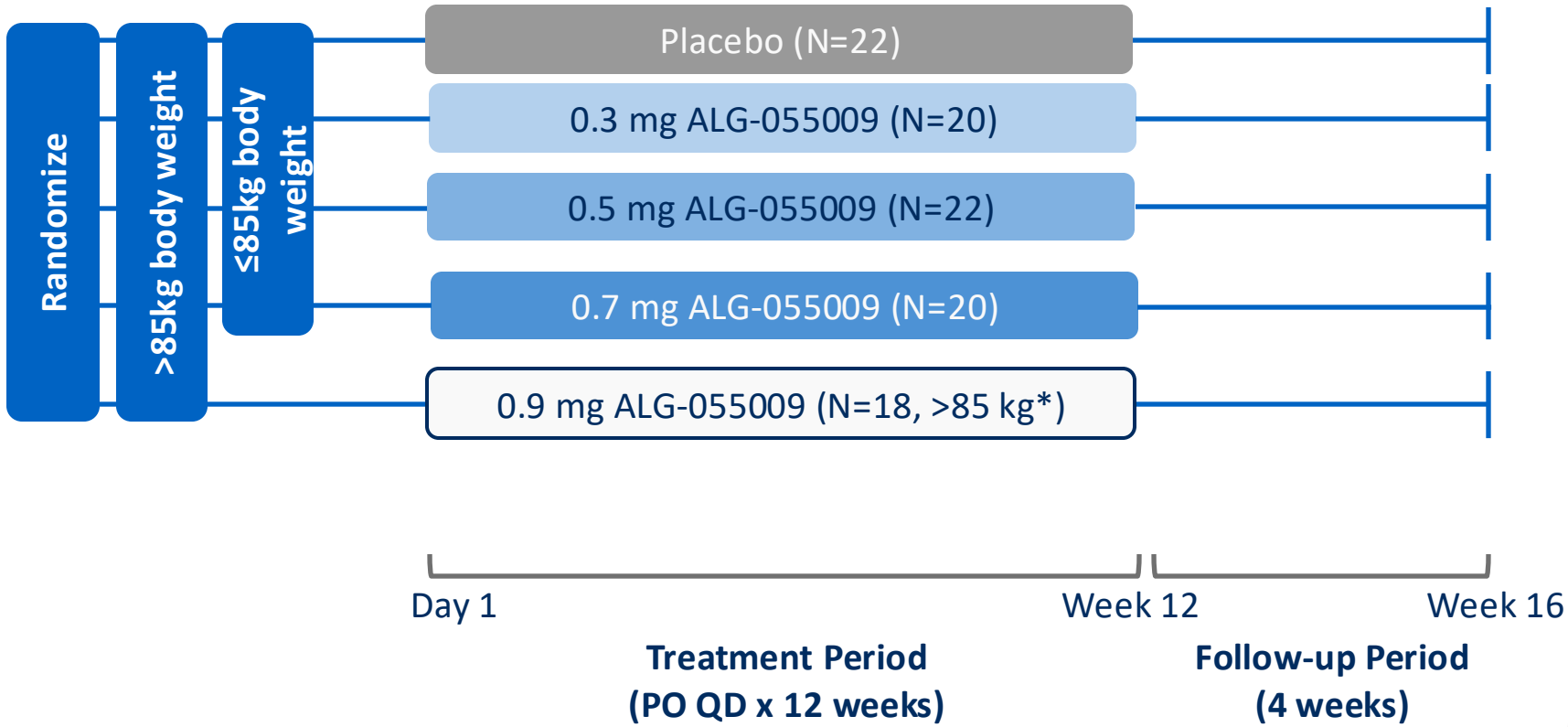
ALG-055009

Phase 2a HERALD Study Design: Randomized, Double-Blind, Placebo-Controlled

Key Entry Criteria:
- 18-75 years old
- BMI ≥25 kg/m^2
- Presumed MASH
- Non-cirrhotic (F1-F3)
- MRI-PDFF ≥10%
- GLP-1 agonist use must be stable (≥12 wks before dosing)

Primary endpoint: Percent relative change in liver fat content by MRI-PDFF at Week 12

Key secondary endpoints: Safety/tolerability, lipid and lipoproteins, SHBG



NCT06342947.

*Only subjects weighing >85 kg were enrolled in the 0.9 mg dose group, no body weight restrictions were implemented in other dose groups

HERALD: Baseline Characteristics Generally Balanced Across Arms

Consistent with Today's At-Risk MASH Population

	Placebo (N=22)	ALG-055009			
		0.3 mg (N=20)	0.5 mg (N=22)	0.7 mg (N=20)	0.9 mg* (N=18, >85 kg)
Age, mean (years)	48.5	53.3	49.5	51.4	48.1
Female, n (%)	21 (95.5)	12 (60.0)	8 (36.4)	14 (70.0)	8 (44.4)
Hispanic, n (%)	13 (59.1)	9 (45.0)	8 (36.4)	8 (40.0)	9 (50.0)
BMI, mean (kg/m^2)	42.1	37.8	39.0	37.4	40.2
Weight, mean (kg)	109.1	107.0	115.2	106.4	116.5*
MRI-PDFF, mean (%)	18.6	18.2	17.9	19.4	19.0
Type 2 Diabetes, n (%)	11 (50.0)	9 (45.0)	10 (45.5)	10 (50.0)	7 (38.9)
GLP-1 Agonists, n (%)^	4 (18.2)	3 (15.0)	5 (22.7)	5 (25.0)	1 (5.6)
Statins, n (%)	4 (18.2)	11 (55.0)	7 (31.8)	8 (40.0)	6 (33.3)
ALT, mean (U/L)	39.5	39.9	51.3	38.3	38.5

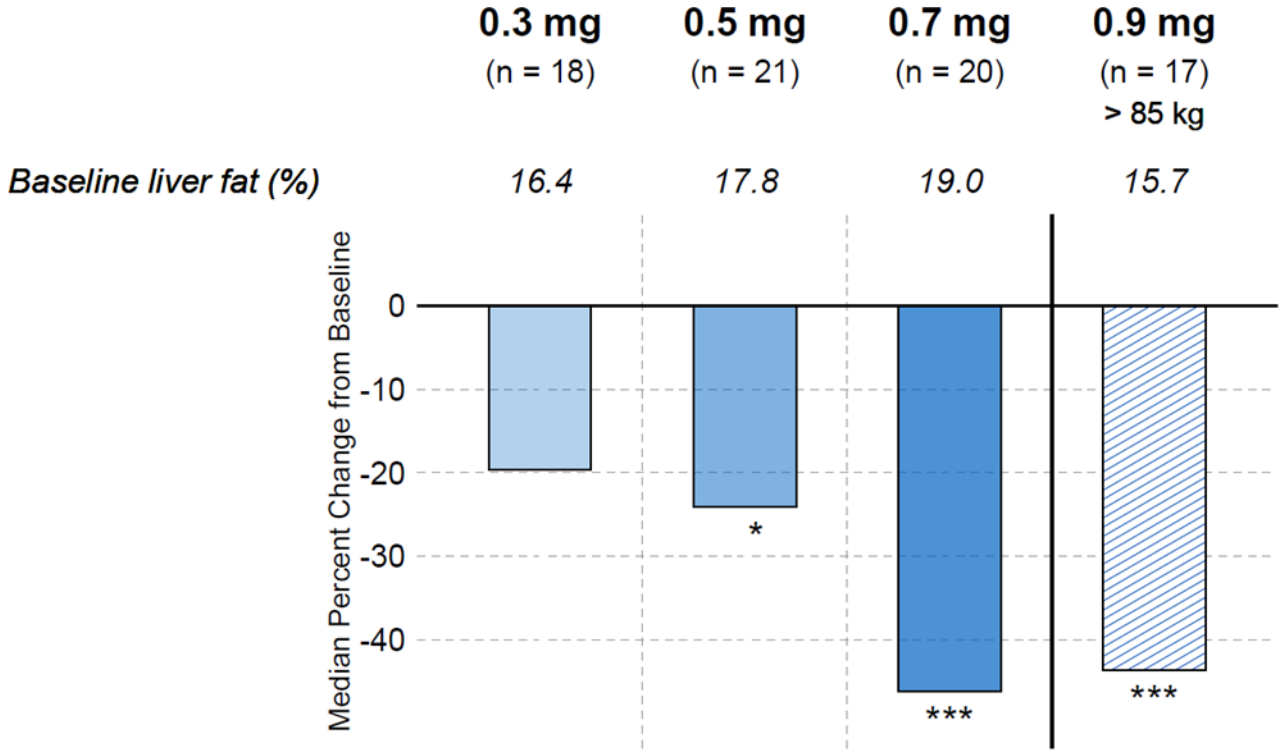
BMI = body mass index; ALT = alanine aminotransferase; GLP-1 = glucagon-like peptide-1; BW = body weight.

^stable use (67% subjects for >1 year)

*Only subjects weighing >85 kg were enrolled in the 0.9 mg dose group, no body weight restrictions were implemented in other dose groups

HERALD: Primary Endpoint Achieved

Placebo-Adjusted Median Relative Change in Liver Fat at Week 12

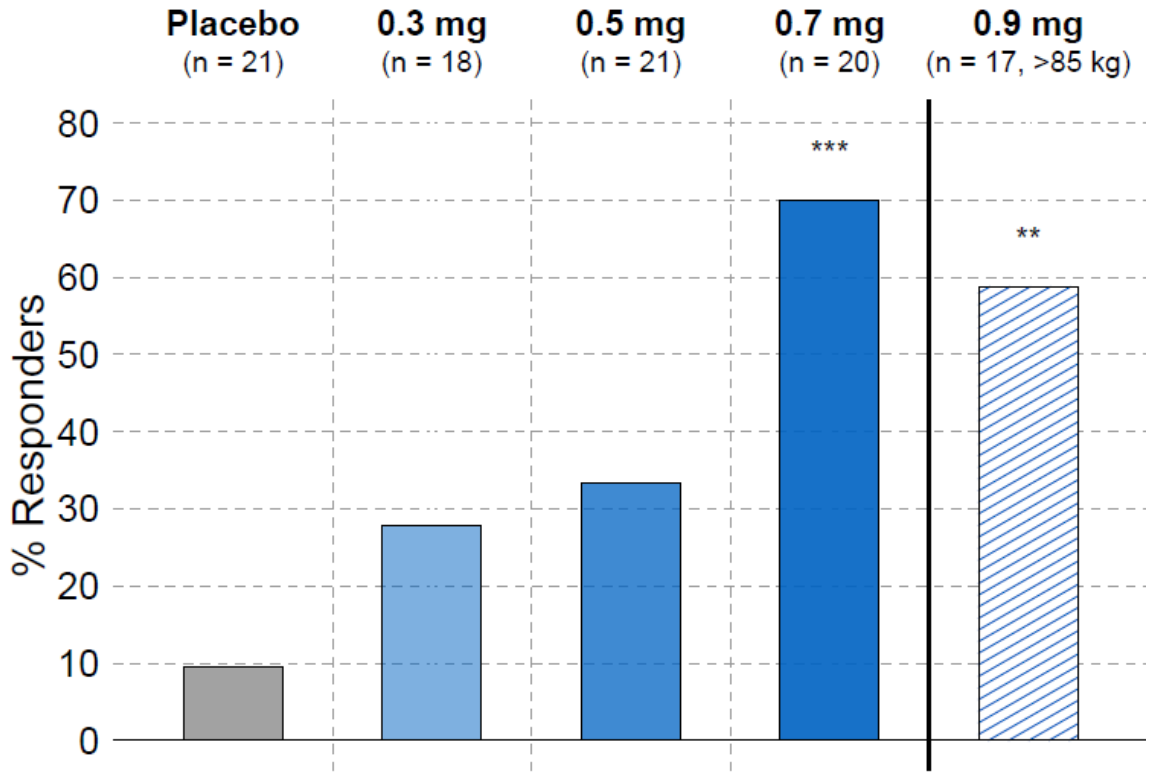


Note: Data from MRI-PDFF analysis dataset, defined as all randomized subjects who have MRI-PDFF measurements available at both baseline and Week 12; median % change in placebo was +7.2%; *p<0.05 ***p<0.001.

Significant decreases in liver fat, with up to 46% placebo-adjusted median reductions from baseline

HERALD: Significant MRI-PDFF Response Rates at Week 12

Up to 70% of Patients Achieved ≥30% Relative Reduction in Liver Fat



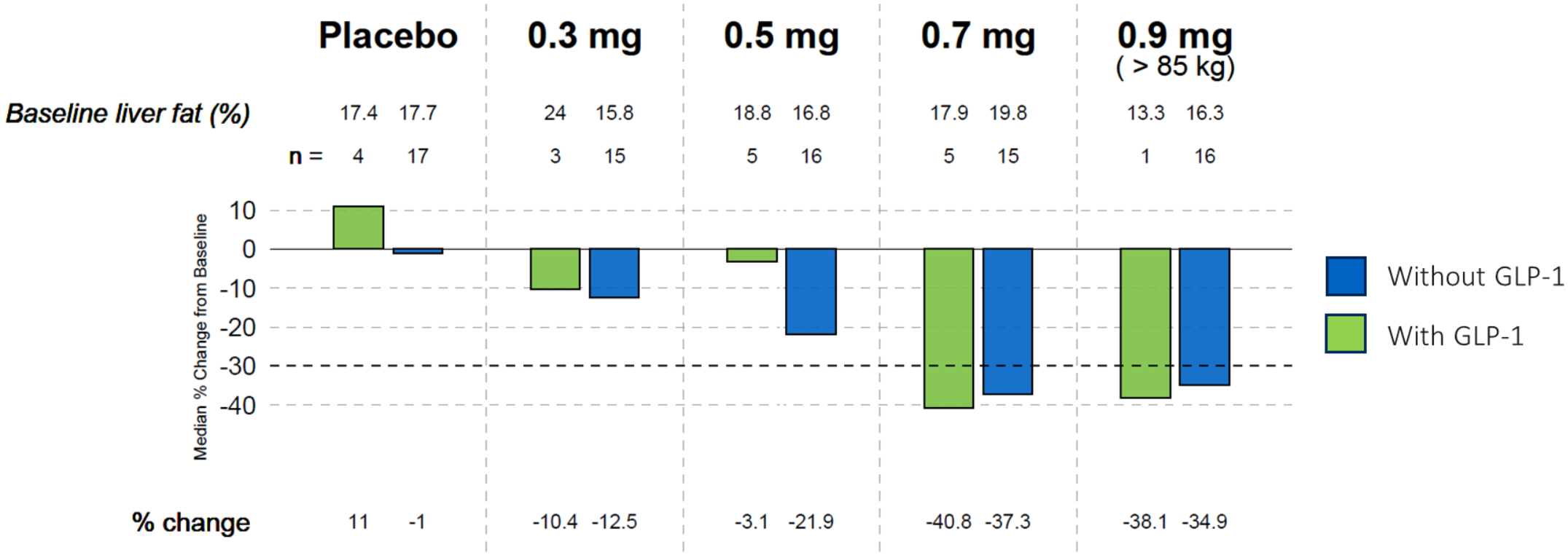
	Placebo (n = 21)	0.3 mg (n = 18)	0.5 mg (n = 21)	0.7 mg (n = 20)	0.9 mg (n = 17, >85 kg)
Responders (%)	9.5%	27.8%	33.3%	70.0%	58.8%
p-value vs. Placebo		0.1603	0.0842	0.0004	0.0073

1. Loomba et al. Hepatology (2021). **p<0.01 ***p<0.001.

MRI-PDFF response of ≥30% relative reduction in liver fat is predictive of histologic improvements[1]

Additional Fat Reduction in Subjects with Stable Use of GLP-1 Agonists

Median Relative Percent Change in Liver Fat at Week 12

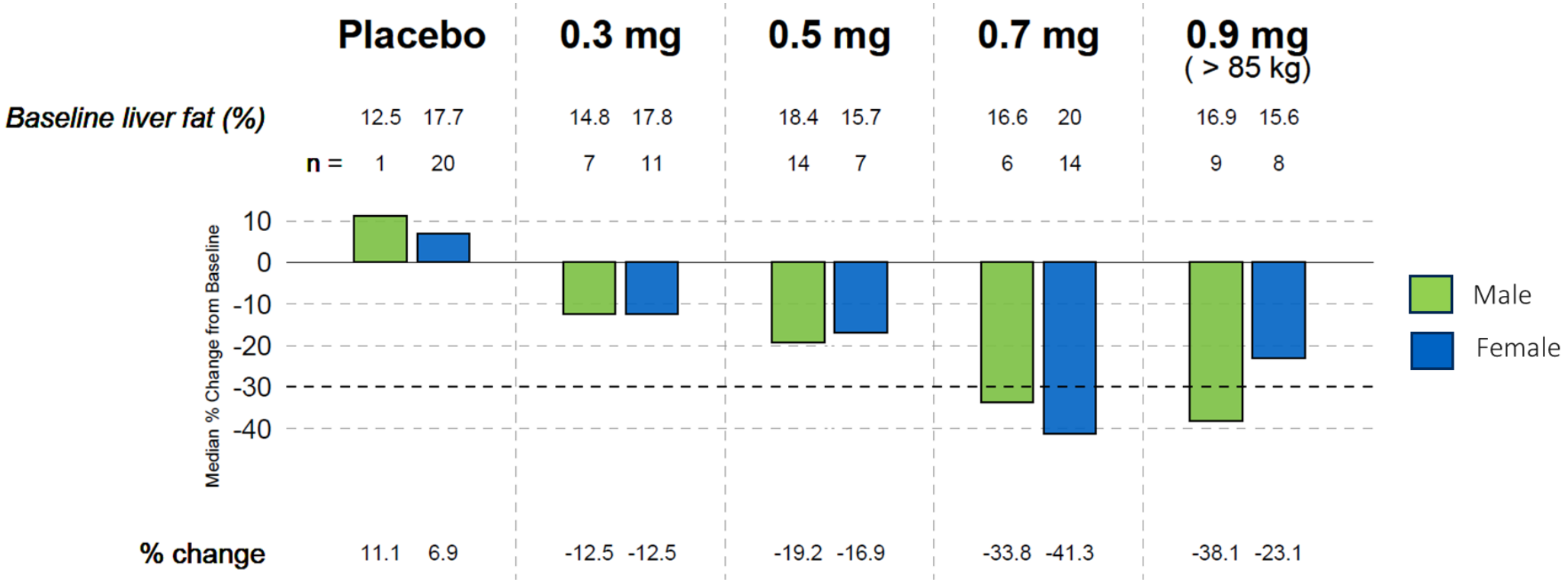


Note: Subjects on GLP-1 agonists (semaglutide (n=12), liraglutide (n=4) or dulaglutide(n=2)) at baseline were required to have stable use for ≥12 weeks prior to randomization; for derivation of duration of use, if a month and/or day for the start of GLP-1 agonist use was unknown, it was imputed as January and/or the 1st of the month, respectively. Bolded dashed line indicates 30% relative reduction in liver fat.

11/14 subjects on stable GLP-1 treated with ALG-055009 had liver fat decreases, whereas 4/4 subjects on stable GLP-1 treated with placebo had liver fat increases

No Apparent Impact of Gender on Liver Fat Reduction with ALG-055009

Median Relative Percent Change in Liver Fat at Week 12

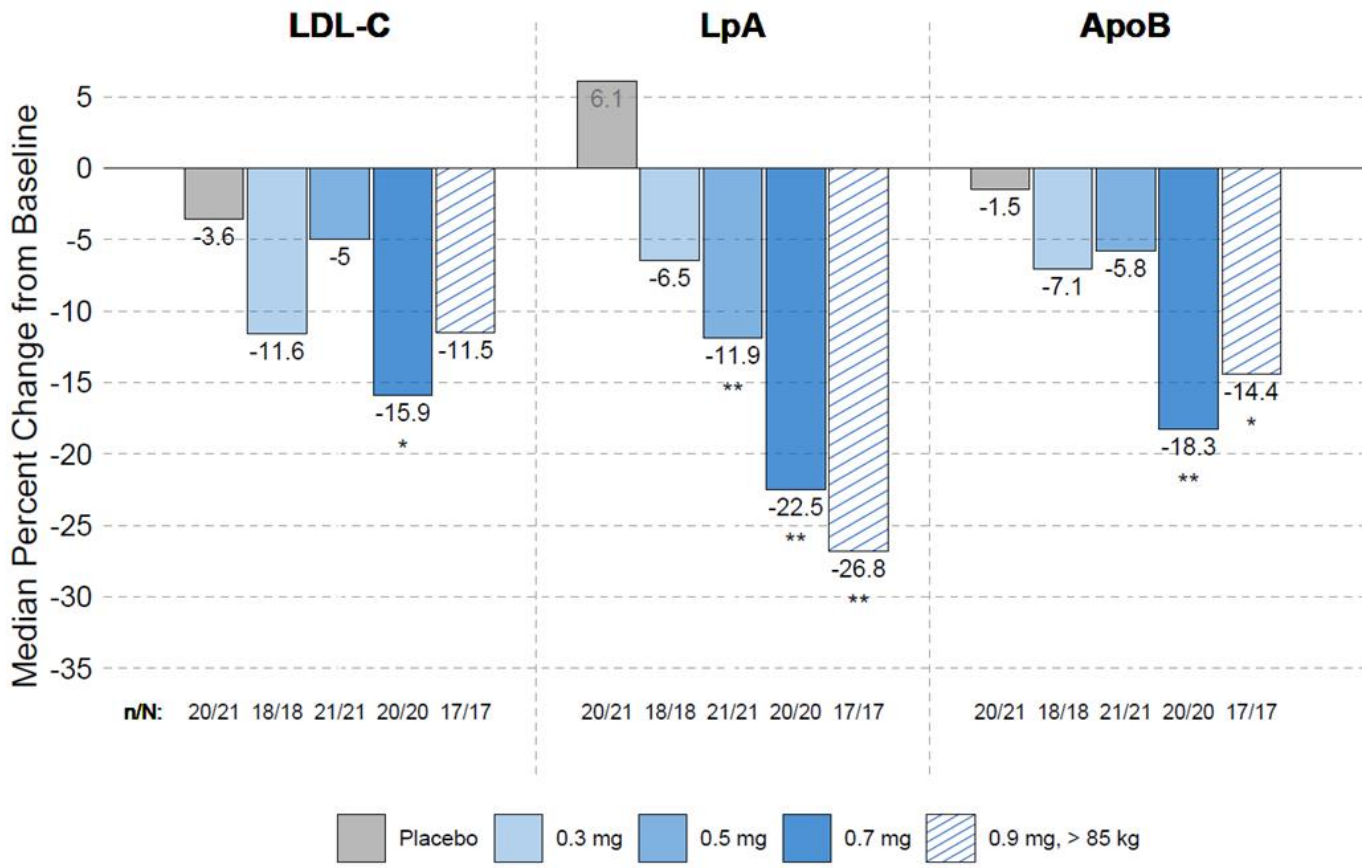


Note: Bolded dashed line indicates 30% relative reduction in liver fat.

Substantial, dose-dependent liver fat reductions observed among both males and females

ALG-055009 Demonstrated Improvements in Lipid/Lipoproteins

Median Percent Change from Baseline at Week 12

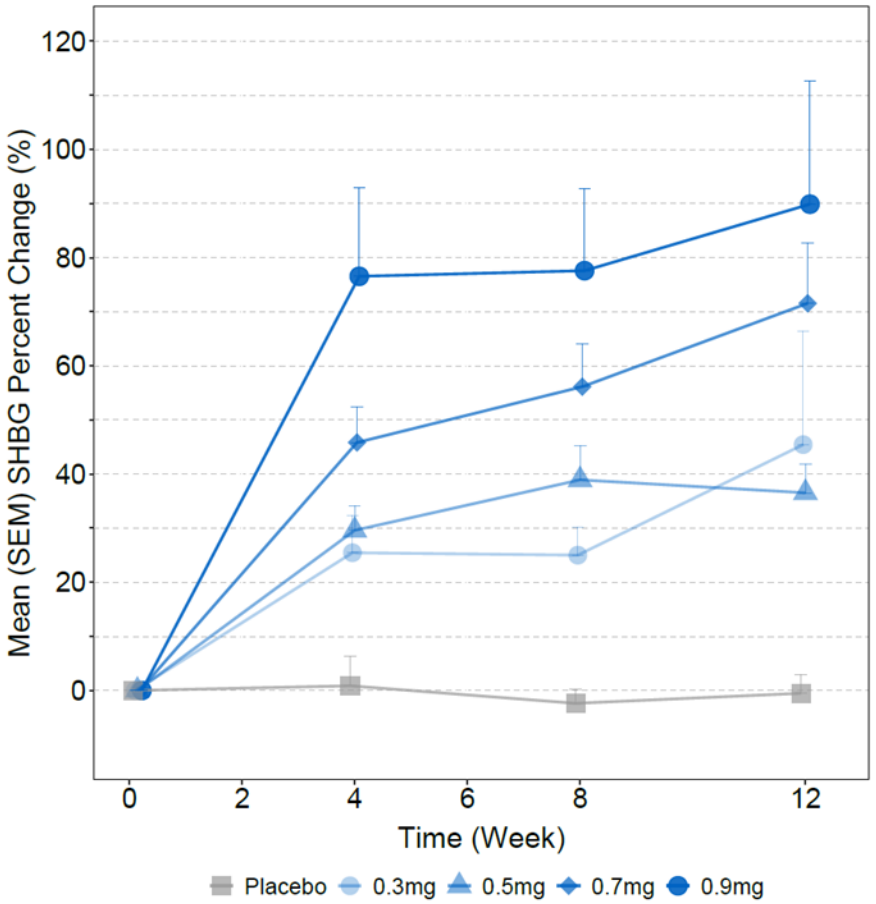


LDL-C = low density lipoprotein cholesterol; LpA = lipoprotein (a); ApoB = apolipoprotein B; n: number of subjects with available data at week 12; N: number of subjects in MRI-PDFF analysis set; *p<0.05 **p<0.01.

Significant reductions in LDL-C, lipoprotein (a), and apolipoprotein B

HERALD: Dose-dependent Increases in Sex Hormone Binding Globulin

Up to ~90% Increase from Baseline in Sex Hormone Binding Globulin (SHBG)



SHBG is a marker of THR-β target engagement in the liver
Significant ($p<0.0001$) increases compared to placebo observed

HERALD: Favorable Safety and Tolerability Profile

Rates of GI-related TEAEs Similar to Placebo

- No SAEs in subjects receiving ALG-055009
  - One unrelated SAE (hemangioma of bone) in a subject receiving placebo
- One discontinuation due to a treatment emergent adverse event (TEAE) of worsening insomnia in a subject with pre-existing insomnia
- Majority of TEAEs (97%) mild or moderate with no clinical hypo/hyperthyroidism
- Similar rates of diarrhea noted for active dose groups compared to placebo, with no dose-response
- No clinically concerning laboratory, ECG, physical exam or vital sign trends/findings

HERALD: Favorable Safety and Tolerability Profile

Rates of GI-related TEAEs Similar to Placebo

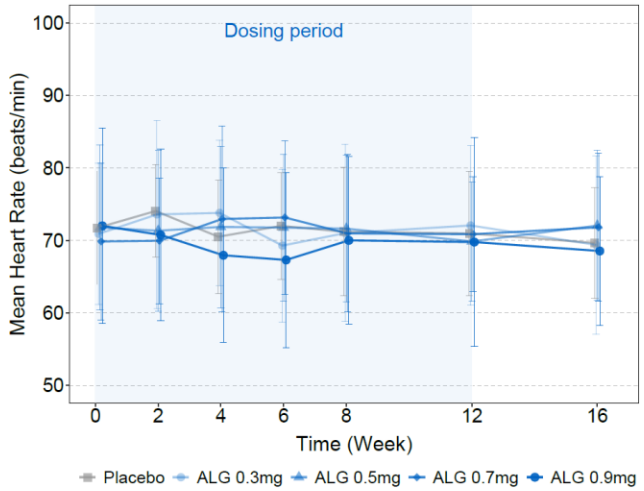
n, (%)	Placebo (N=22)	ALG-055009			
		0.3mg (N=20)	0.5mg (N=22)	0.7mg (N=20)	0.9mg (N=18)
Any TEAE	17 (77.3)	14 (70.0)	11 (50.0)	14 (70.0)	11 (61.1)
TEAE Leading to Study Drug Discontinuation	0	0	1[a] (4.5)	0	0
Serious AE	1[b] (4.5)	0	0	0	0
Grade 3 or higher TEAE	1[b] (4.5)	1[c] (5.0)	0	0	0
Gastrointestinal TEAEs	5 (22.7)	4 (20.0)	2 (9.1)	7 (35.0)	5 (27.8)
Diarrhea	5 (22.7)	1 (5.0)	0 (0.0)	2 (10.0)	2 (11.1)
Constipation	0 (0.0)	2 (10.0)	0 (0.0)	3 (15.0)	0 (0.0)
Nausea	1 (4.5)	2 (10.0)	0 (0.0)	0 (0.0)	1 (5.6)
Vomiting	1 (4.5)	1 (5.0)	1 (4.5)	0 (0.0)	0 (0.0)

TEAE = treatment emergent adverse event

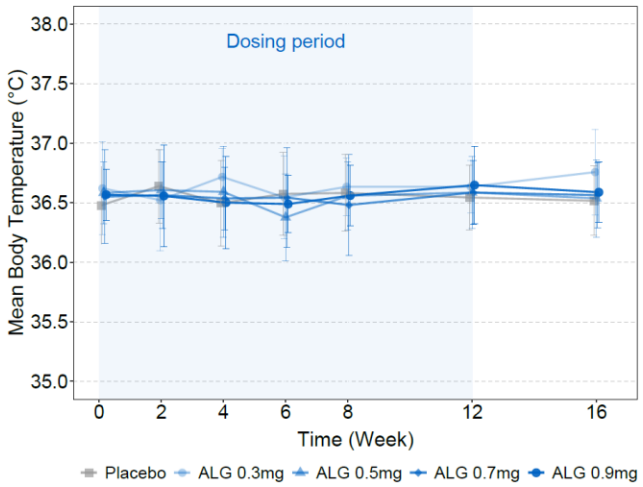
a. Grade 2 worsening insomnia in a subject with pre-existing insomnia; b. Grade 3 hemangioma of bone; c. Grade 3 anemia assessed by the Investigator as not related to study drug in a subject with heavy menstrual bleeding and a history of polycystic ovary syndrome and heavy menstrual periods.

HERALD: No Treatment Emergent Changes in Vital Signs Observed

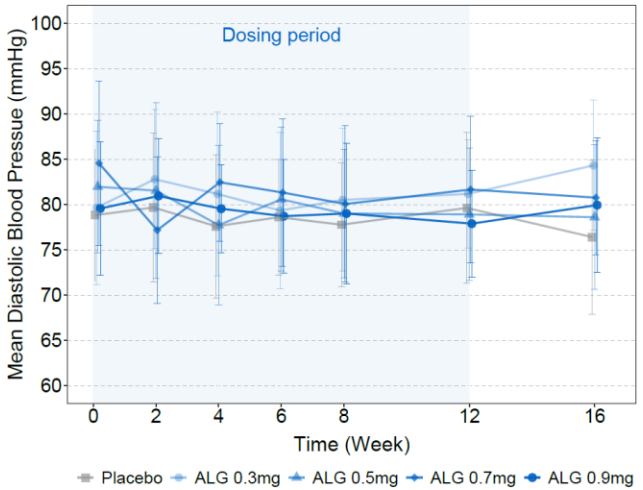
Heart Rate



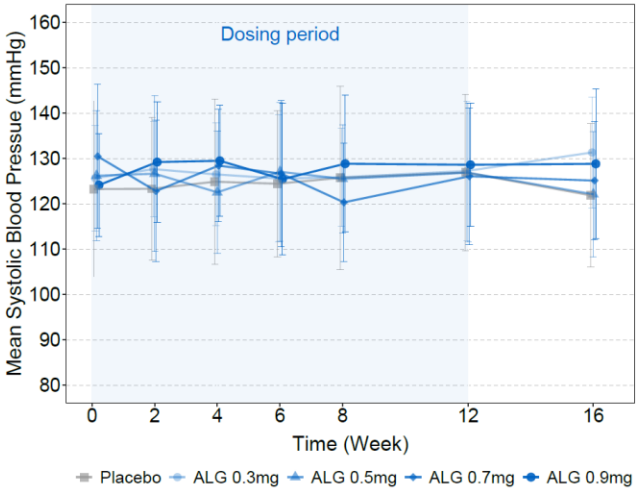
Body Temperature



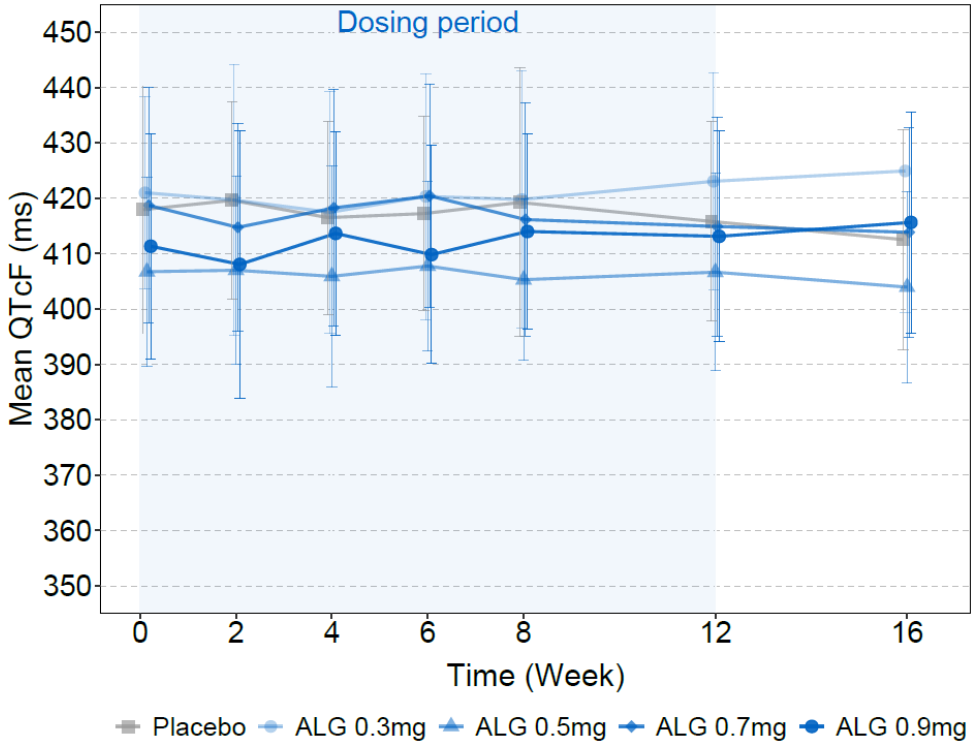
Diastolic Blood Pressure

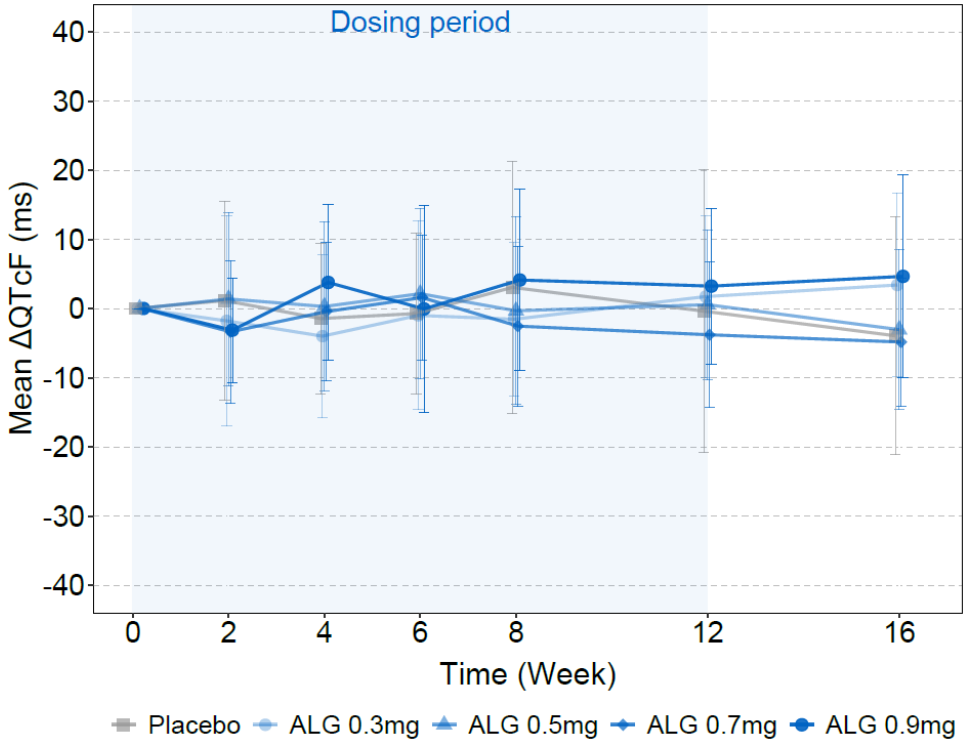


Systolic Blood Pressure



HERALD: ALG-055009 has no Apparent Effect on QTcF Intervals





No trends for QTcF prolongation across dose levels
No subject receiving ALG-055009 experienced a QTcF >500 ms and/or change from baseline in QTcF of >60 ms

HERALD Phase 2a Study

Conclusions

- **Primary endpoint achieved, with robust reductions in liver fat content at Week 12**
  - Up to 46% placebo-adjusted median relative reductions
  - Up to 70% of patients with ≥30% decrease in liver fat
  - 11/14 subjects on stable GLP-1 treated with ALG-055009 had liver fat decreases, whereas 4/4 subjects on stable GLP-1 treated with placebo had liver fat increases
- **Significant reductions in atherogenic lipids, including LDL-C, lipoprotein (a) and apolipoprotein B**
- **Dose-dependent increases in SHBG (marker of THR-β activation)**
- **Well-tolerated, with rates of GI-related AEs similar to placebo**
  - No SAEs in subjects who received ALG-055009 and 1 study drug discontinuation (1/102 or 1% of patients)
  - Majority of TEAEs (97%) mild or moderate
  - No increased rates of diarrhea noted for active dose groups compared to placebo, with no dose response
- **This data supports evaluation of longer durations of ALG-055009 (e.g., 48-52 weeks) and its effect on liver histology in Phase 2b**

ALG-055009 has demonstrated robust reductions in liver fat with a favorable tolerability and PK profile, and convenient once daily oral dosing

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Acknowledgements

We wish to thank the patients, and the investigators and their support staff who participated in this study.

We would like to give a special thanks to Dr. Stephen Harrison who played a pivotal role in the design of the HERALD study