In a Placebo Controlled 36 Week Phase 2 Trial, Treatment with MGL-3196 Compared to Placebo Results in Significant Reductions in Hepatic Fat (MRI-PDFF), Liver Enzymes, Fibrosis Biomarkers, Atherogenic Lipids, and Improvement in NASH on Serial Liver Biopsy

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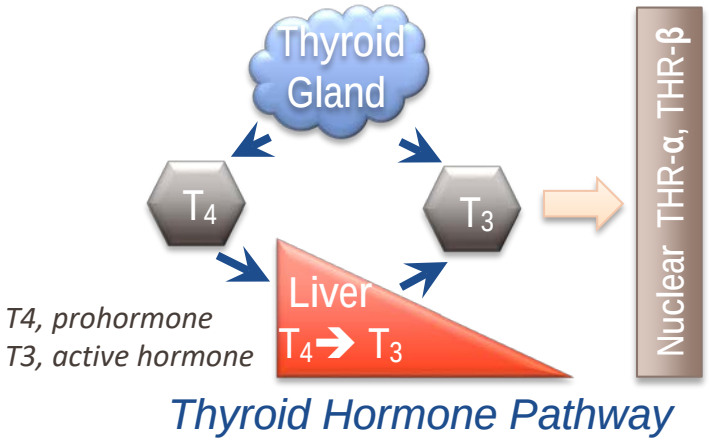
Mechanism of Action: The Importance of Liver THR-β in NASH



Thyroid Hormone Pathway

In humans, thyroid hormone receptor-β (THR-β) agonism:

- ↓ Lowers LDL-cholesterol
- ↓ Lowers triglycerides
- ↓ Lowers liver fat, potentially reducing lipotoxicity, NASH

No thyrotoxicosis (THR-α effect)

MGL-3196

- THR-β selective molecule with proven safety and efficacy in more than 300 subjects and patients treated
  - — No exposure outside the liver or activity at the systemic THR-α receptor
- Pleiotropic effects with potential for addressing the underlying metabolic syndrome and hallmark features of NASH: steatosis/lipotoxicity, inflammation, ballooning, fibrosis (both directly and indirectly)
  - — Reduction of liver fat through breakdown of fatty acids, normalization of liver function

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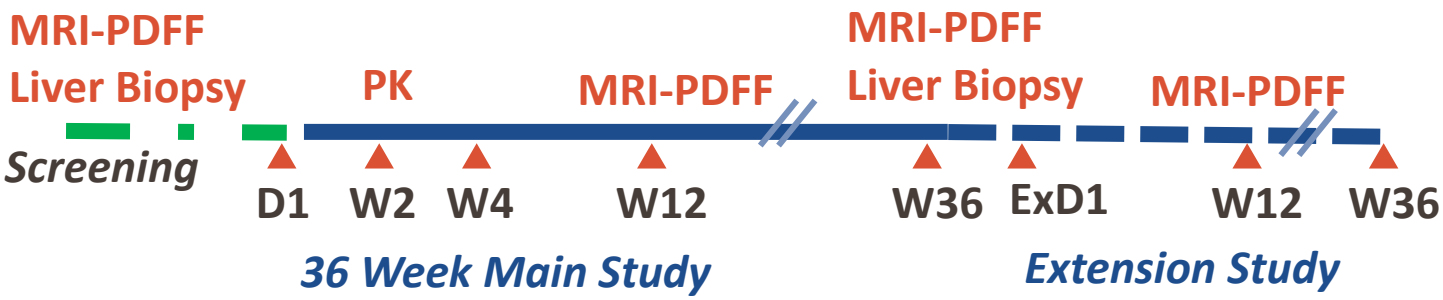
Study Design: Randomized, Double-Blind, PBO Controlled Trial



Comparator/Arms

- 2:1 MGL-3196 to placebo
- 125 patients enrolled in USA, 18 sites
- MGL-3196 or placebo, oral, once daily; dose 80 mg (+/-20 mg dose adjustment possible at Week 4)

Inclusion/Exclusion

- NASH on liver biopsy: NAS≥4 with fibrosis stage 1-3
- ≥10% liver fat on MRI-PDFF
- Includes diabetics, statin therapy, representative NASH population

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Study Endpoints

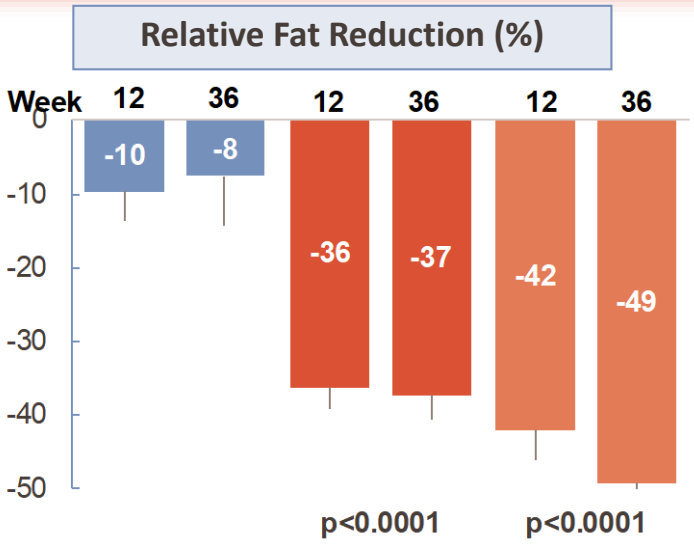
- Primary endpoint
  - Relative reduction of liver fat (MRI-PDFF) at 12 weeks (at 36 weeks, secondary)
- Key secondary endpoints at 12, 36 weeks
  - Reduction (2-point on NAS) or resolution of NASH without worsening of fibrosis with at least a 2-pt reduction in NAS in MGL-3196-treated compared to placebo patients
  - One point reduction in fibrosis on liver biopsy
  - Numbers achieving ≥ 30% liver fat reduction at 12, 36 weeks; absolute liver fat reduction
  - Liver enzymes, fibrosis biomarkers and lipids at 12, 36 weeks
- Ongoing exploratory endpoint extension study in a subset of patients who completed the main 36 week study

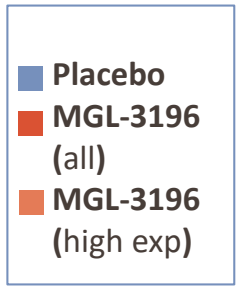
Baseline Characteristics

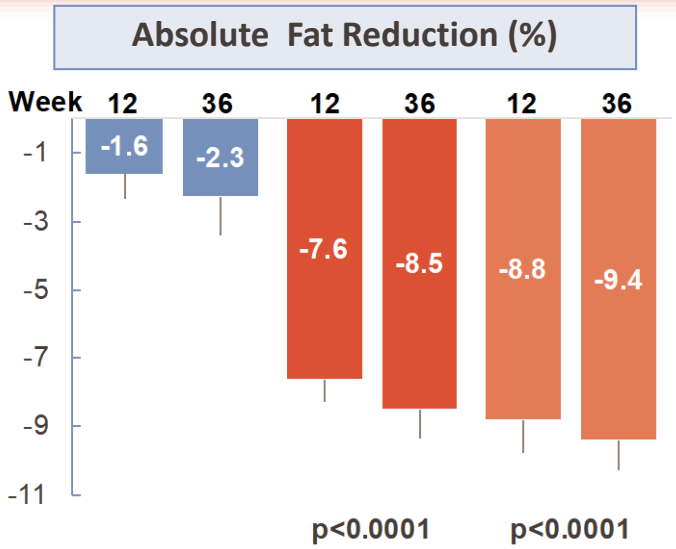
	Placebo (41)	MGL-3196 (84)
Mean age, years (SD)	47.3 (11.7)	51.8 (10.4)
Male, n (%)	24 (58.5)	38 (45.2)
White	37 (90.2)	79 (94.0)
Hispanic/Latino	22 (53.7)	37 (44.0)
Diabetic, n (%)	13 (31.7)	35 (41.7)
Mean BMI (SD)	33.6 (5.8)	35.8 (6.2)
Mean ALT	60.1 (32.8)	50.0 (29.2)
PRO-C3	16.2 (8.3)	17.8 (10.3)
ELF	9.2 (1.0)	9.2 (0.88)
Mean LDL-C	116.9 (30.0)	111.3 (30.4)
Mean Triglycerides (TG)	161.1 (75.2)	178.5 (82.4)
Mean MRI-PDFF*	19.8 (6.7)	20.7 (7.0)
Mean NAS	4.8 (1.1)	4.9 (1.0)
Fibrosis stage** 1, n (%)	19 (46.3)	47 (55.9)
2-3, n (%)	20 (48.8)	36 (42.8)

* Patients with both baseline and week 12 assessments; **F0 placebo=2 (4.9); MGL-3196=1 (1.2) were included in all analyses

Week 36: Sustained Reduction in Liver Fat on MRI-PDFF

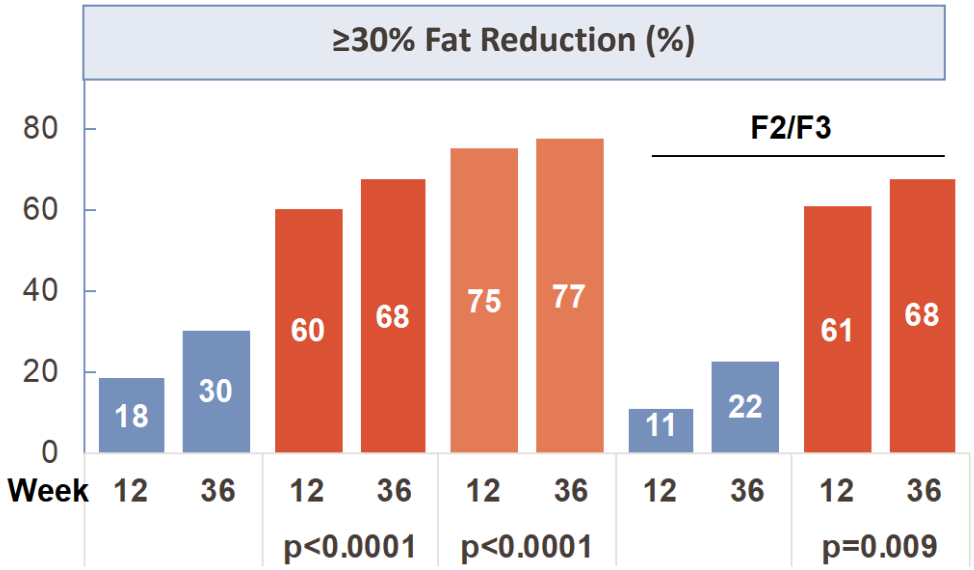






Main, 36 Week Study

- Sustained statistically significant reduction in hepatic fat Week 12 to Week 36
- Placebo response generally related to weight loss ≥5%



P value, placebo compared to MGL-3196; MGL-3196, n=78; placebo, n=38; prespecified high exposure (High Exp) n=44; F2/F3, placebo, n=19; MGL-3196, n=33

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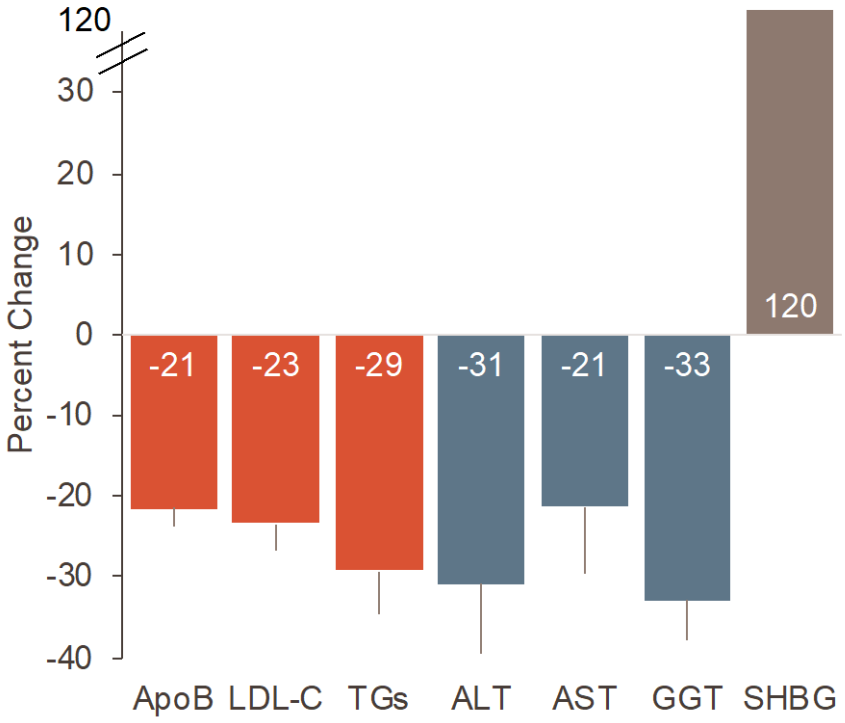
Extension Study of 36 Week Phase 2 Trial

Extension Study

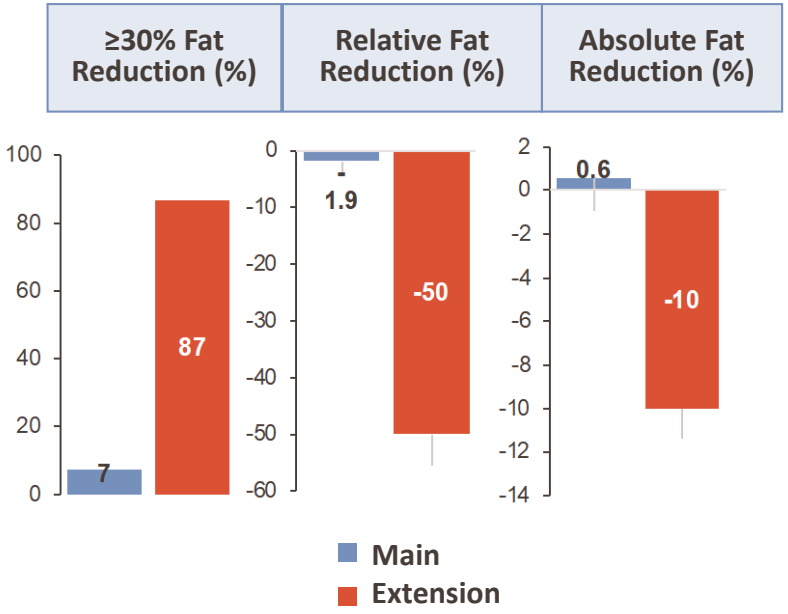
- The Extension study includes 14 former placebo patients with persistently mildly to markedly elevated liver enzymes from the Main 36 Week study, ~ two thirds F2/F3
- 16 former MGL-3196 patients (dose increased to 80 or 100 mg)
- Noninvasive end points, only
- To optimize exposure, all patients in the Extension study received 80 or 100 mg per day of MGL-3196, a higher average dose than in the 36 Week study to move all patients into the “high exposure” category
- Highly significant reduction in lipids including LDL-C, ApoB and triglycerides
- Well tolerated, few AEs, improvement in liver enzymes from baseline
- No increase in GI AEs observed in the 30 patients in the Extension study

Former Placebo Patients

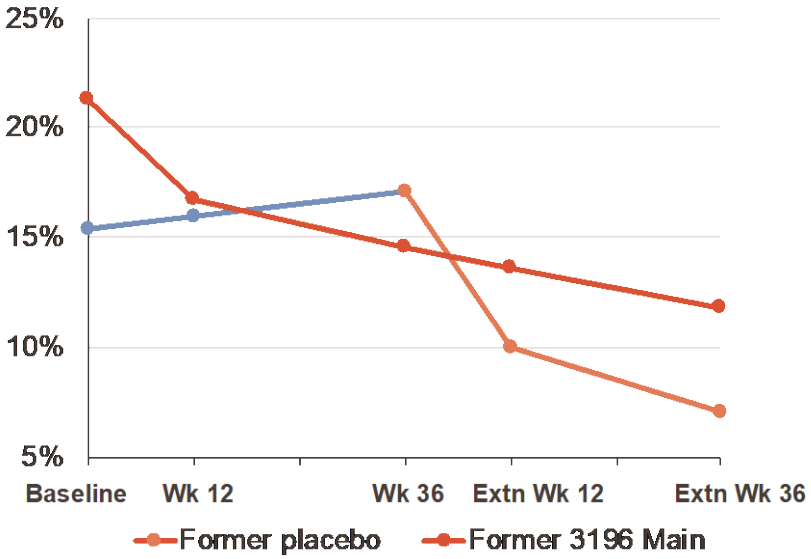


Extension Study: Reduction in Liver Fat on MRI-PDFF

Former Placebo Patients



All Extension Patients



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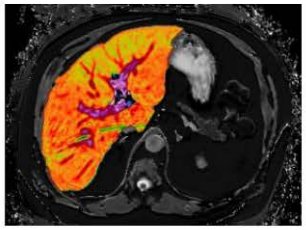
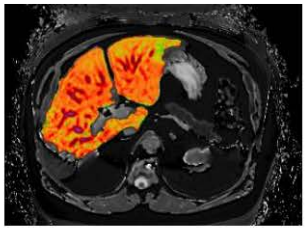
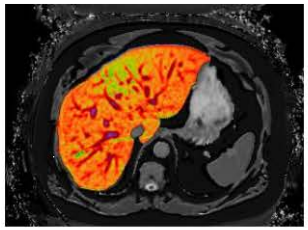
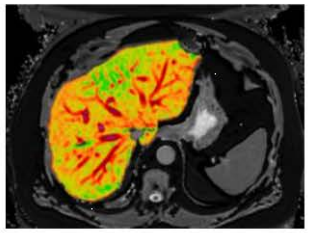
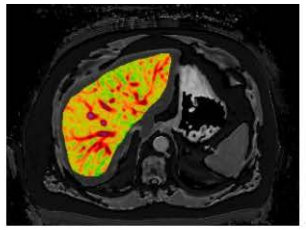
NASH Extension Study

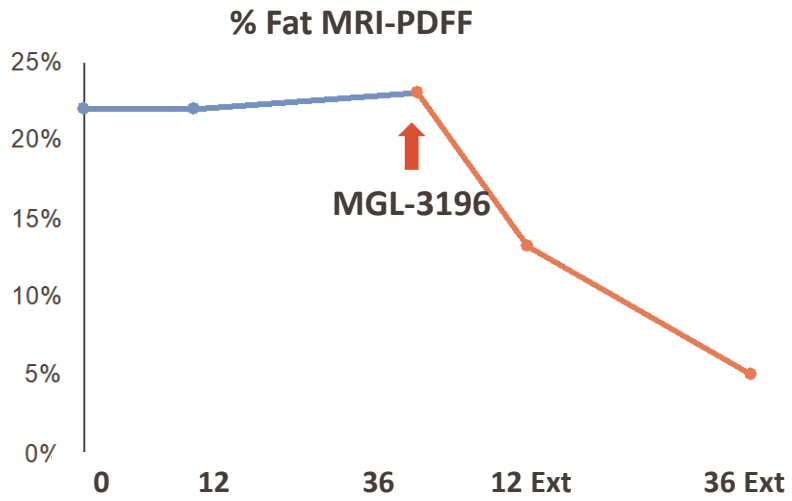






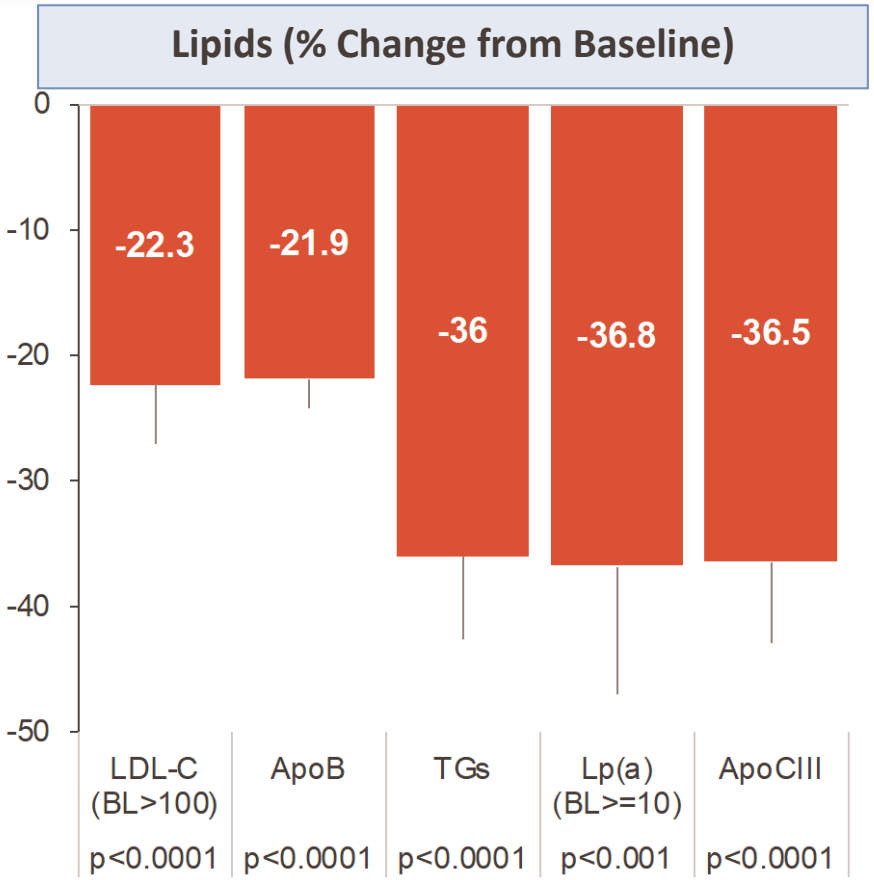






- Former placebo patient, diabetic on multiple medications whose ALT was ~200 IU/L during the Main study
- Following initiation of MGL-3196 at Week 36, rapid decrease in liver fat, improvement in liver imaging (Perspectum) normalized corrected T1 (measure of liver inflammation), 85% decrease in liver enzymes

Week 36: Sustained Robust Lipid Lowering



Significant sustained lowering effect in multiple atherogenic lipids

MGL-3196 compared with placebo; all analyses and cutoffs were prespecified; based on prespecified mITT; placebo n=39; MGL-3196 n=79 (LOCF)

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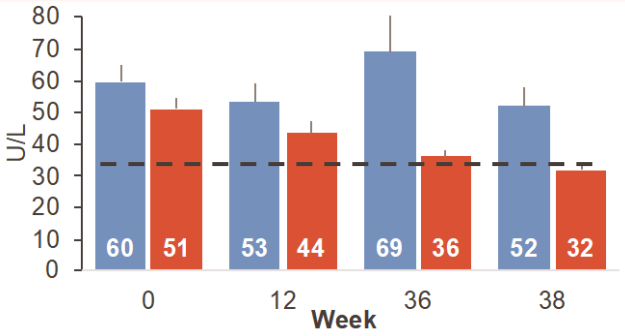
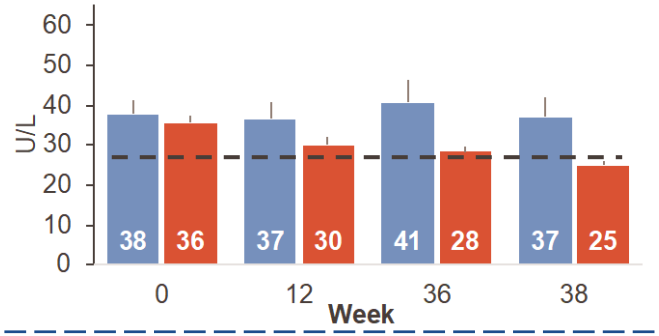
Week 36: Liver Enzymes

ALT



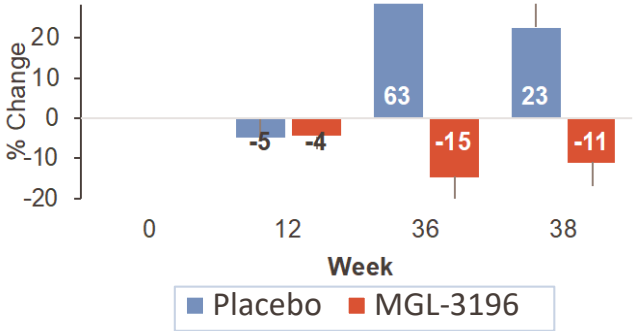
- Week 36, 40% reduction in ALT in MGL-3196 with elevated baseline (p=0.01), and all MGL-3196 relative to placebo patients (p=0.002)
- At Week 36, 60% of MGL-3196 patients with ALT <30 vs 37% of placebo (p=0.03)

AST



- Week 36, statistically significant AST reduction in MGL-3196 vs placebo (% change and absolute change) p=0.002

GGT



- Week 36, statistically significant GGT reduction MGL-3196 vs placebo (% change and absolute change) p=0.002

Statistically significant reductions in ALT, AST and GGT versus placebo; no change in bilirubin or alkaline phosphatase

All analyses were prespecified. Baseline elevated ALT =45 male, 30 female. GGT shown as % change from baseline, females and males have different normal GGT ranges, placebo n=39; MGL-3196, n=79, LOCF

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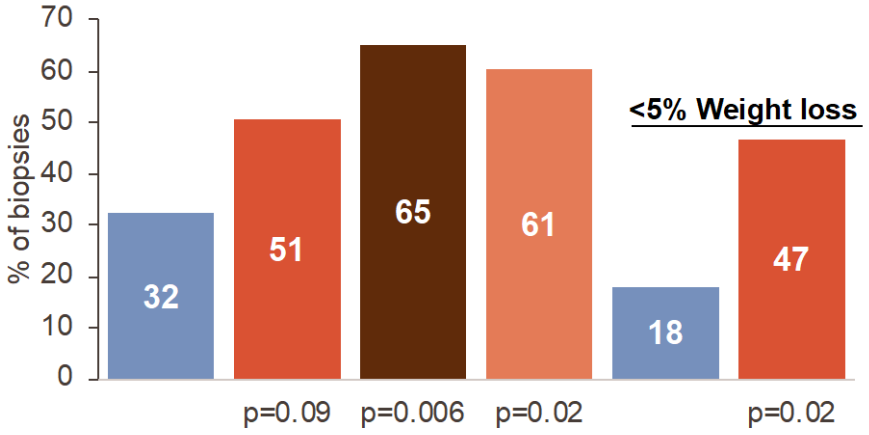
Week 36: NASH Liver Biopsy Endpoints

2-Point NAS Reduction

with at least a 1-pt reduction in ballooning or inflammation

(% of liver biopsies)

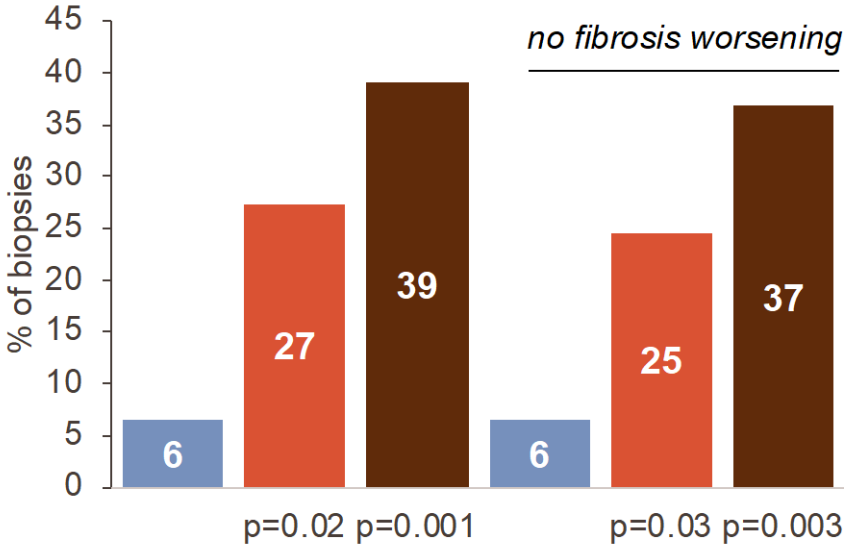


2-pt reduction in NAS in placebo patients was correlated with body weight loss

NASH Resolution

ballooning=0, inflammation =0, 1 with at least 2-point reduction in NAS

(% of liver biopsies)



- **Placebo**
- **MGL-3196** (all)
- **MGL-3196** (high exp)
- **MGL-3196, MRI responder**

In MGL-3196 treated patients with NASH resolution, 50% had fibrosis resolution (F=0)

MRI Responder; ≥ 30% fat reduction on Week 12 MRI-PDFF High Exp,, n=44; 2-pt NAS reduction; MGL-3196, n=73, placebo n=34; NASH Resolution, prespecified endpoint: at least 2-pt reduction in NAS; ballooning=0, inflammation=0, 1; Prespecified: Excluded patients with >9.5% weight loss from NR

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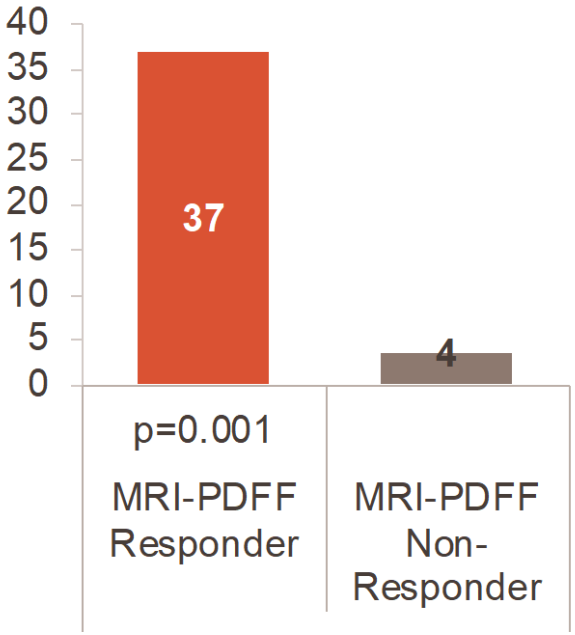
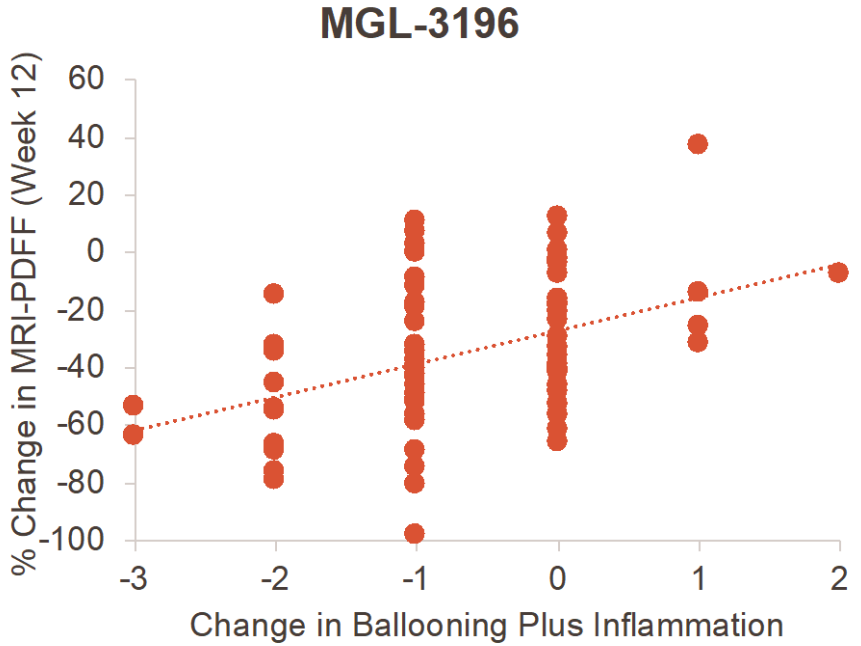
Correlation of Decrease in Hepatic Fat (MRI-PDFF) with Improvement in Ballooning and Inflammation on Liver Biopsy

NASH Resolution (%)
MGL-3196-treated



MRI-PDFF Week 12, % Relative Change: Correlation with Change in Ballooning Plus Inflammation Scores



- Patients who were not MRI-PDFF Responders (≥30% fat reduction) had a low rate of NASH resolution (*left panel*)
- In both MGL-3196 (correlation coefficient 0.42) (*right panel*) and placebo (correlation coefficient 0.58) % relative change in MRI-PDFF was correlated with reduction in ballooning plus inflammation scores on liver biopsy (steatosis score removed)

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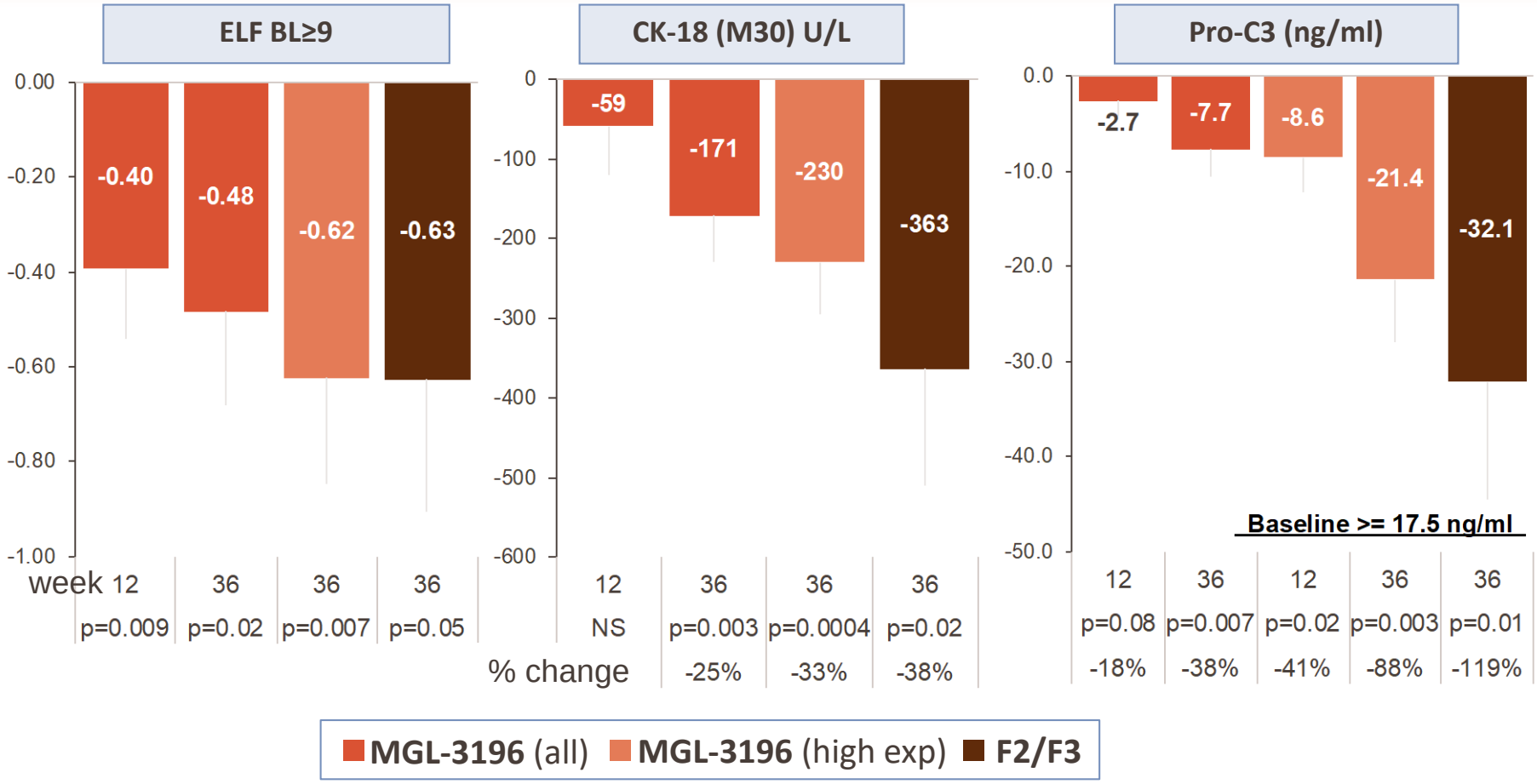
Week 36: Reduction of Fibrosis, Biomarkers



ELF, CK-18 and Pro-C3 scores, biomarkers correlated with liver fibrosis stage, were statistically significantly reduced in MGL-3196 treated, especially in patients with advanced fibrosis at baseline

BL, baseline; compared with placebo; all, placebo n=38; MGL-3196 n=78; ELF≥9 placebo n=21; MGL-3196 n=40; Pro-C3 BL≥17.5, placebo n=12; MGL-3196 n=29; cutoffs (ELF, PRO-C3) were prespecified based on lab normal values; Pro-C3>10 baseline, was also stat sig

*Liver Int. 2015 Feb;35(2):429-37; Journal of Hepatology 2013 vol. 59 j 236–242;

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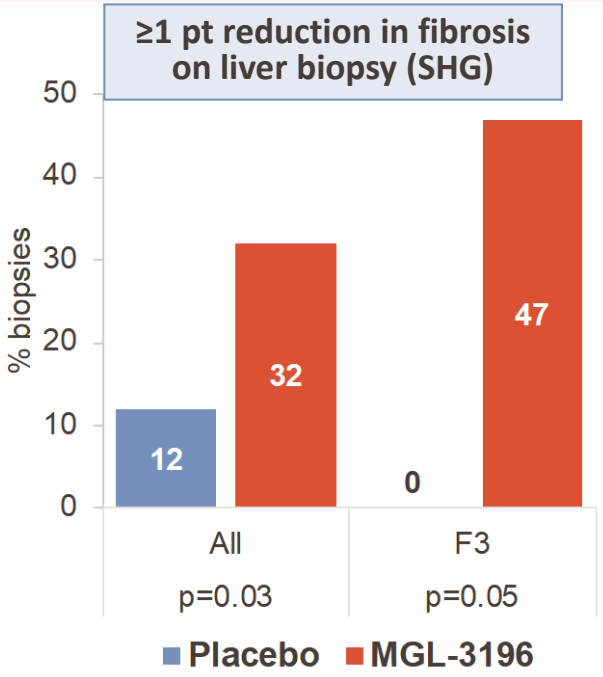
Week 36: Change in Fibrosis Score on Liver Biopsy



- Second Harmonic Generation (SHG) microscopy provides automated fully quantitative assessment of fibrosis on liver biopsy slides based on unique architectural features of collagen
- SHG score was generated and aligned with the pathologist baseline score (baseline, r=0.76), (*left panel*), blinded to treatment code
- Using SHG, MGL-3196 treated compared with placebo showed a statistically significant ≥1-pt reduction in fibrosis score at Week 36. Based on pathology score, fibrosis was reduced by ≥ 1 point in 29% of MGL-3196 treated patients vs. 23% in placebo

https://doi.org/10.1371/journal.pone.0199166

Week 36 pathology scores and treatment code were not provided to SHG

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Safety and Additional Biomarkers

AEs

- AEs, mostly mild, a few moderate, balance between groups. Increase in MGL-3196 treated relative to placebo in loose stools, typically a single episode, only at the beginning of therapy
- No lab abnormalities or other AEs were increased in MGL-3196 compared with placebo patients
- 7 SAEs, distributed between placebo and drug-treated, all single occurrences, none related

Safety Biomarkers

- No effects on TSH, bone mineral density, heart rate, QTc, other CV biomarkers or diabetes biomarkers
- Small (<3%, not statistically significant) reduction in diastolic BP at Week 36 in MGL-3196 patients, consistent with reduced liver fat

Inflammation Biomarker

- Sustained statistically significant reduction in reverse T3
  - Reverse T3 is a marker of inflammation. Elevations in reverse T3 may be indicative of high hepatic thyroid hormone degradation, in NASH, potentially caused by activated stellate cells

Conclusions

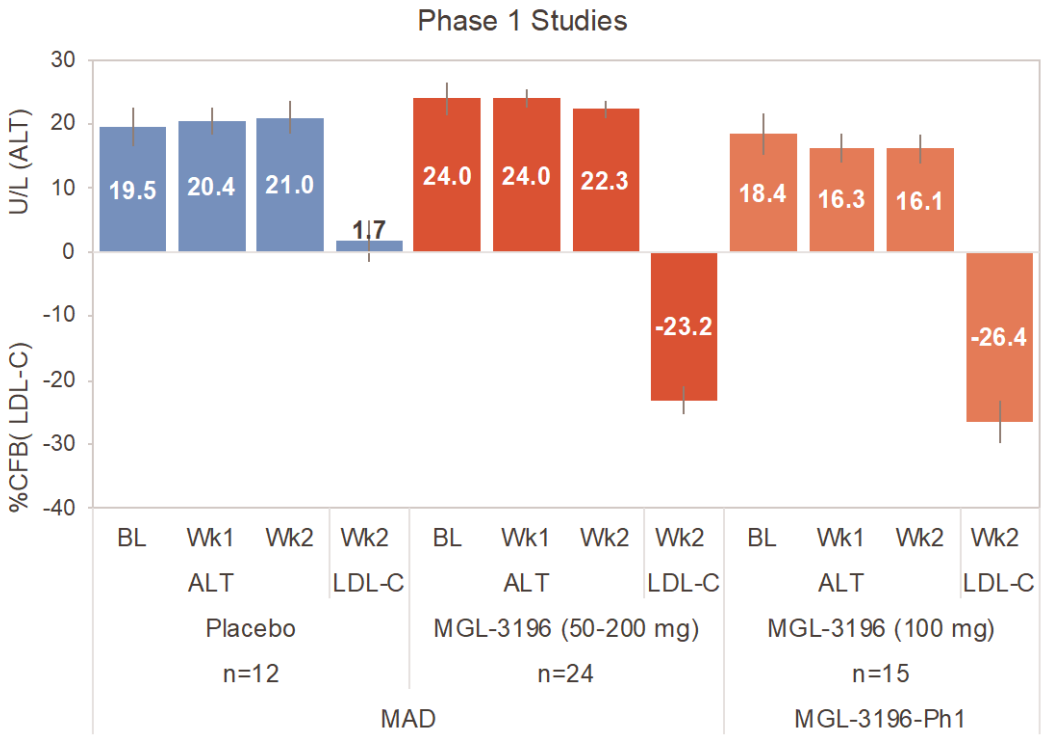
In a Phase 2 36 week serial liver biopsy study in patients with NASH fibrosis stage 1-3, patients treated with MGL-3196 as compared with placebo showed

- Sustained statistically significant reduction in liver fat on MRI-PDFF in MGL-3196 treated as compared with placebo patients
- Sustained statistically significant lowering of multiple atherogenic lipids including LDL-C, ApoB, triglycerides, ApoCIII and Lp(a)
- Statistically significant lowering and normalization of liver enzymes; overall safety
- Statistically significant resolution of NASH that is correlated with reduction in liver fat on MRI-PDFF and provides evidence for efficacy at a registrational endpoint for Phase 3 development in NASH

Acknowledgements

We are grateful to the patients and staff who made this study possible.

Liver Enzymes Phase 1



- Unlike statins or some thyromimetic compounds, MGL-3196 does not elevate liver enzymes
  - Other companies' thyromimetics increased liver enzymes in healthy volunteers, often after a single dose, and liver enzymes were still increasing after 2 weeks of treatment
  - Thyroid hormone given at 5X replacement dose does not elevate liver enzymes
  - No increase in ALT in two weeks of treatment with doses of 50-200 mg of MGL-3196 in healthy volunteers, despite significant LDL cholesterol lowering

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