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**Nonconfidential**

**September 2019**

# Forward Looking Statements

Any statements, other than statements of historical facts, made in this presentation regarding our future financial or business performance, conditions, plans, prospects, trends, or strategies and other financial and business matters; our ability to obtain additional financing; the estimated size of the market for our product candidates, the timing and success of our development and commercialization of our anticipated product candidates; and the availability of alternative therapies for our target market, are, or may be deemed, forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. In some cases, you can identify forward-looking statements by terms such as "may," "will," "could," "should," "would," "anticipate," "believe," "estimate," "continue," "design," "expect," "intend," "plan," "potential," "predict," "seek" or the negative of these words and similar expressions and their variants may identify forward-looking statements.

These forward-looking statements reflect management's current expectations, are based on certain assumptions and involve certain risks and uncertainties, which change over time. Our actual results may differ materially from the results discussed in these forward-looking statements due to various factors. Important factors that may cause actual results to differ materially from the results discussed in these forward-looking statements include, but are not limited to, risks related to securing and maintaining relationships with collaborators; risks relating to our clinical trials; risks relating to the commercialization, if any, of our proposed product candidates (such as marketing, regulatory, product liability, supply, competition, and other risks); dependence on the efforts of third parties; dependence on intellectual property; and risks related to our cash resources and ability to obtain working capital to fund our proposed operations. Further information regarding on the factors that could affect our business, financial conditions and results of operations are contained our filings with the U.S. Securities and Exchange Commission, which are available at www.sec.gov. These forward-looking statements represent management's expectations as of the date hereof only, and we specifically disclaim any duty or obligation to update forward-looking statements as a result of subsequent events or developments, except as required by law.

# Pipeline: Madrigal has Initiated the Phase 3 in NASH Fibrosis

**Madrigal is focused on the development of its pipeline of THR-β agonists for the treatment of NASH and Dyslipidemia**

| Compound | Indication | Pre-Clinical | Phase 1 | Phase 2 | Phase 3 | Upcoming Catalysts |
|---|---|---|---|---|---|---|
| **MGL-3196** Thyroid Hormone Receptor-β (THR-β) Agonist | Nonalcoholic Steatohepatitis (NASH) With Fibrosis Stage 2-3 | | | | → | ■ Phase 3 Initiated |
| | Dyslipidemia | | | → | | ■ Dyslipidemia Phase 3 study in NAFLD/NASH in planning stage |
| **MGL-3745** THR-β Agonist | NASH and Dyslipidemia / FH | → | | | | |



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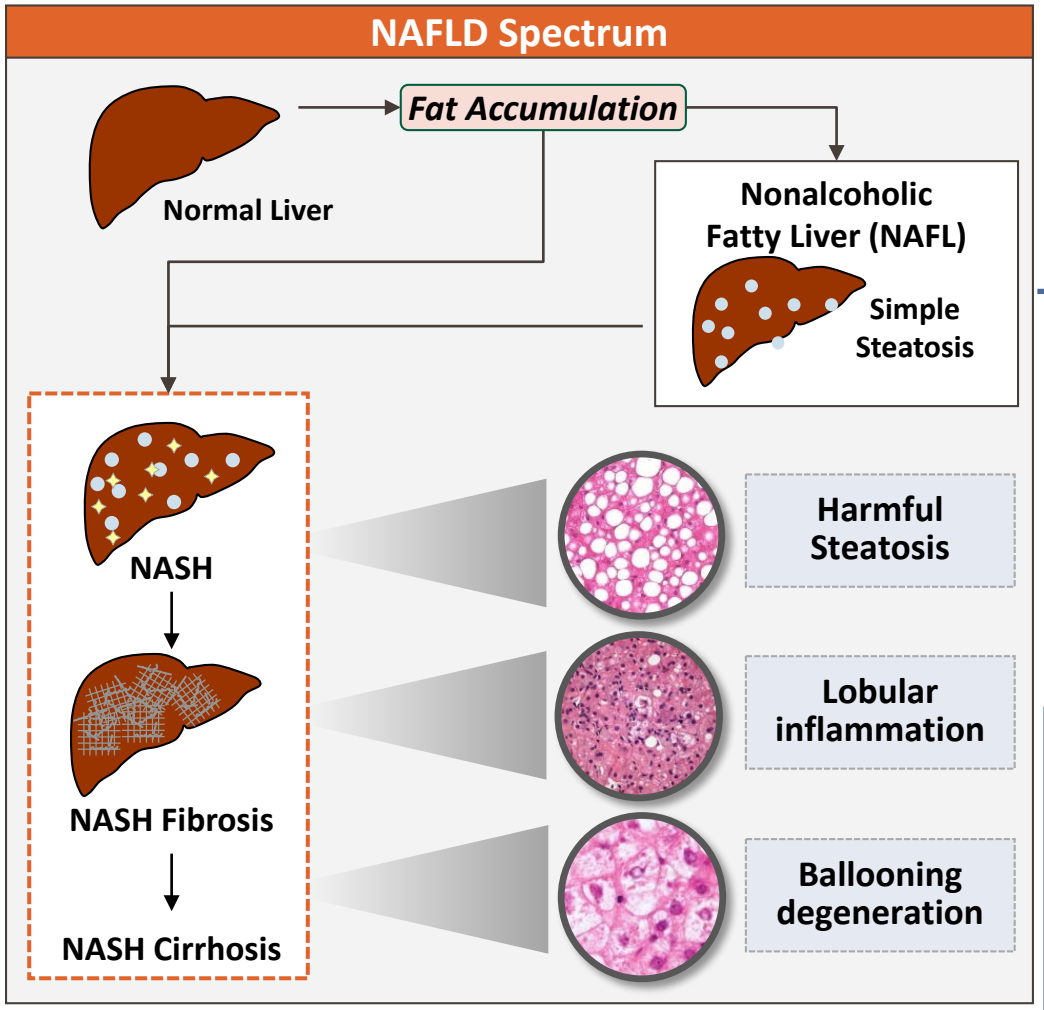
# Non-Alcoholic Fatty Liver Disease (NAFLD) Ranges from Simple Steatosis (NAFL) to NASH, a Progressive Form of Liver Disease




**DISEASE**

- NAFLD results from accumulation of excess fat within the liver (steatosis) unrelated to alcohol use
- Some patients with NAFLD have NASH (nonalcoholic steatohepatitis)

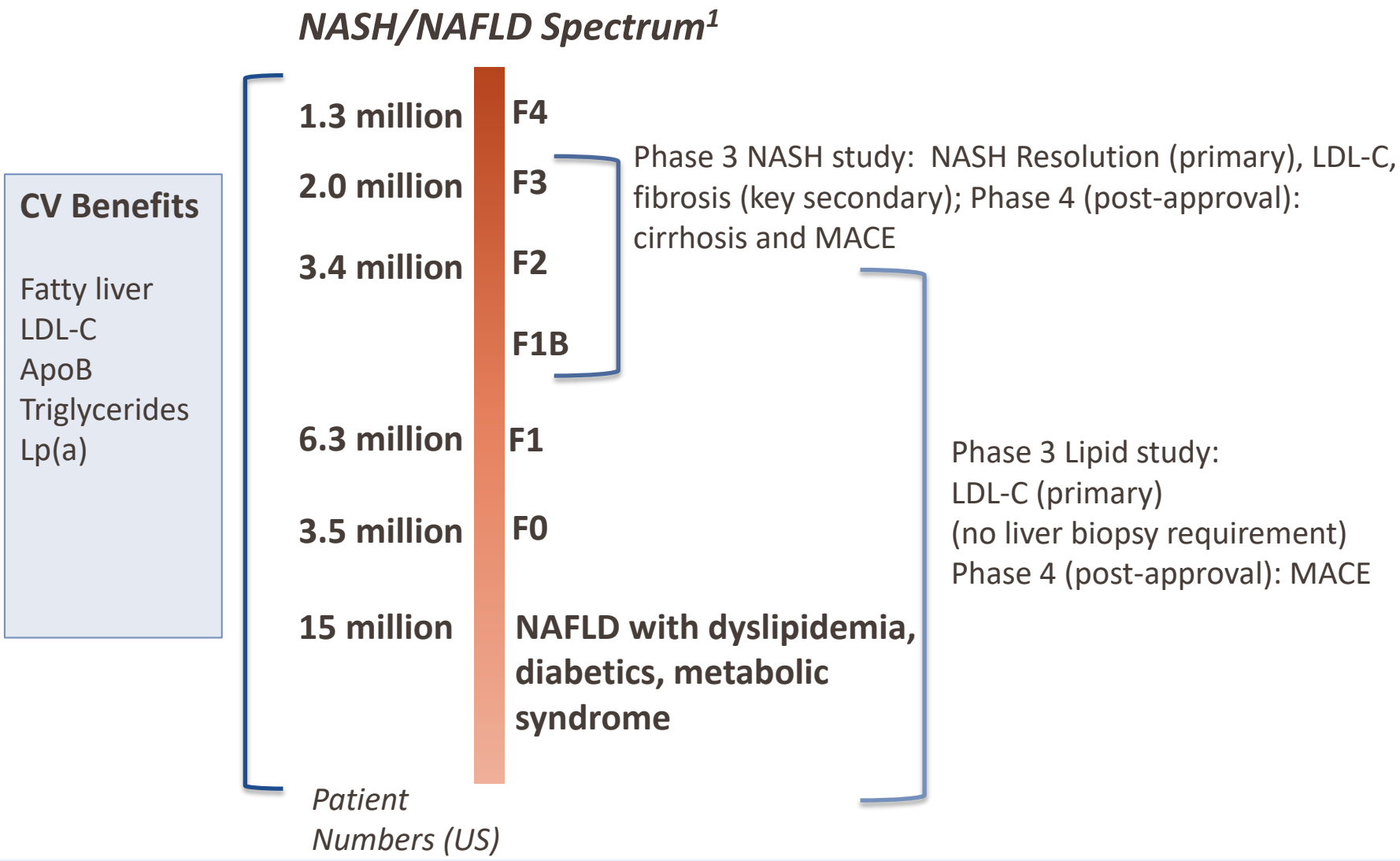
**INCIDENCE**

- 25 – 30% of all adults in Western countries have NAFLD
- NASH afflicts 3 – 12% of the U.S. population. In certain populations such as diabetics fat in the liver is virtually always NASH.

**OUTCOME**

- NAFLD leads to an increased risk of morbidity and mortality from:
  - Cardiovascular disease (leading cause of death for NAFLD patients)
  - Liver-related events
- 11% of advanced NASH patients progress to cirrhosis over a 15 year period

# MGL-3196 Development Path Across the Spectrum of NAFLD/NASH




[1] Estes et al; *Hepatology*, Vol. 67, No. 1, 2018



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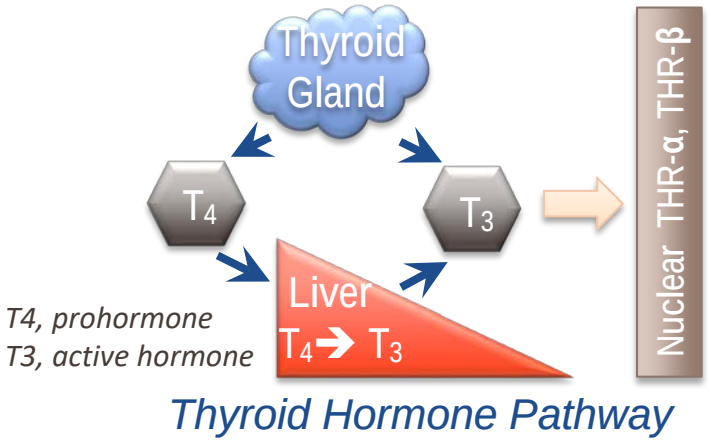
# Resmetirom - High Potential to Resolve NASH, Improve Fibrosis and Provide Cardiovascular Protection

- Once a day oral
- Selective thyroid receptor-β agonist - intrinsically 28 fold $\beta$ selective relative to $\alpha$
- Liver directed - no exposure outside liver, >99% protein bound, does not cross blood brain barrier, requires transport proteins expressed on hepatocytes for cellular penetration
- Well-tolerated - proven safety in over 300 subjects and patients, NO activity at the systemic $\alpha$-receptor, NO change in levels of thyroid stimulating hormone or HPT axis effects

- Improved all major features of NASH in our studies to date:
  - Steatosis
  - Hepatocyte Dysfunction / Death
  - Inflammation
  - Fibrosis

# 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

Sinha and Yen Cell Biosci (2016) 6:46
DOI 10.1186/s13578-016-0113-7; Autophagy, 11:8, 1341-1357, DOI: 10.1080/15548627.2015.1061849



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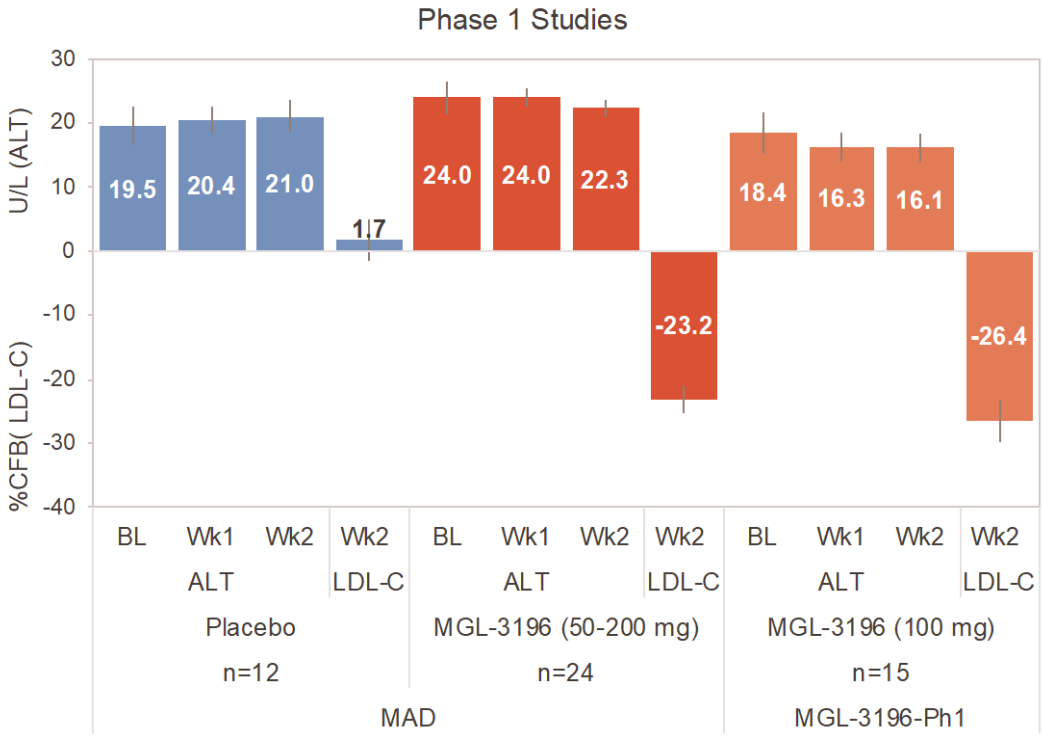
# MGL-3196, First and Best-in-Class Liver-Directed THR-β Agonist

First bona fide THR-β selective molecule with key advantages

- Discovery of MGL-3196 utilized a novel in vitro functional assay, 28 fold THR-β selective with virtually no THR-α activity
  - Other thyromimetic compounds lacked beta selectivity in this assay
- in vivo preclinical and clinical data confirm MGL-3196's high liver uptake and safety
  - Avoids activity at the systemic **THR-α** receptor (no increased heart rate, osteoporosis)
  - Long-term animal studies completed: no cartilage/bone findings in chronic toxicology
  - Multiple Phase 1 studies completed, well-tolerated in clinical dosing, normal thyroid axis and vital signs, no liver enzyme increases (right panel)




J Med Chem. 2014;57(10):3912-3923; Atherosclerosis 230 (2013) 373e380



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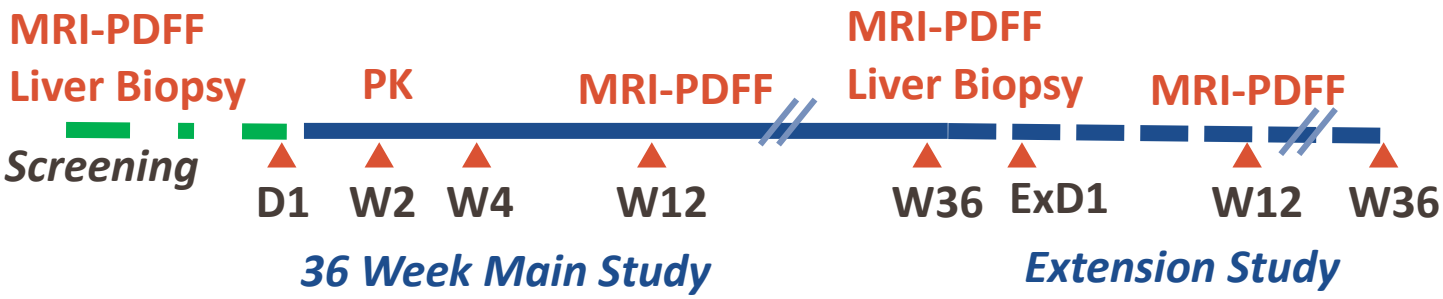
# Phase 2 NASH Study Design: Randomized, Double-Blind, PBO Controlled




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

# 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
- Completed 36 week extension study in 30 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

# Safety

**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, GI Aes not increased in Phase 1 or NASH extension study
- 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

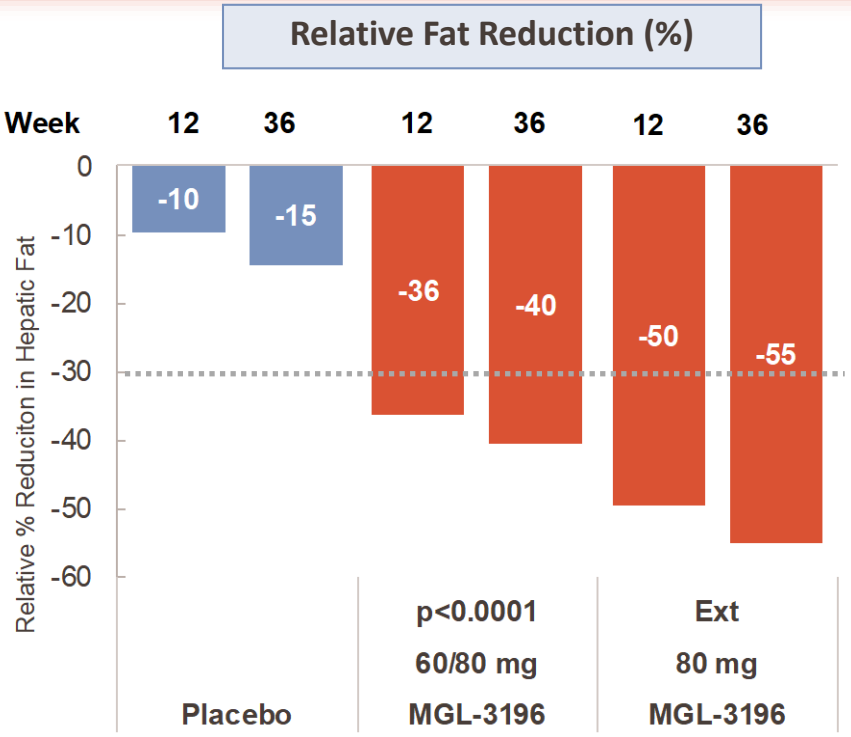
# Resmetirom: Potential Improvements in NASH and Fibrosis

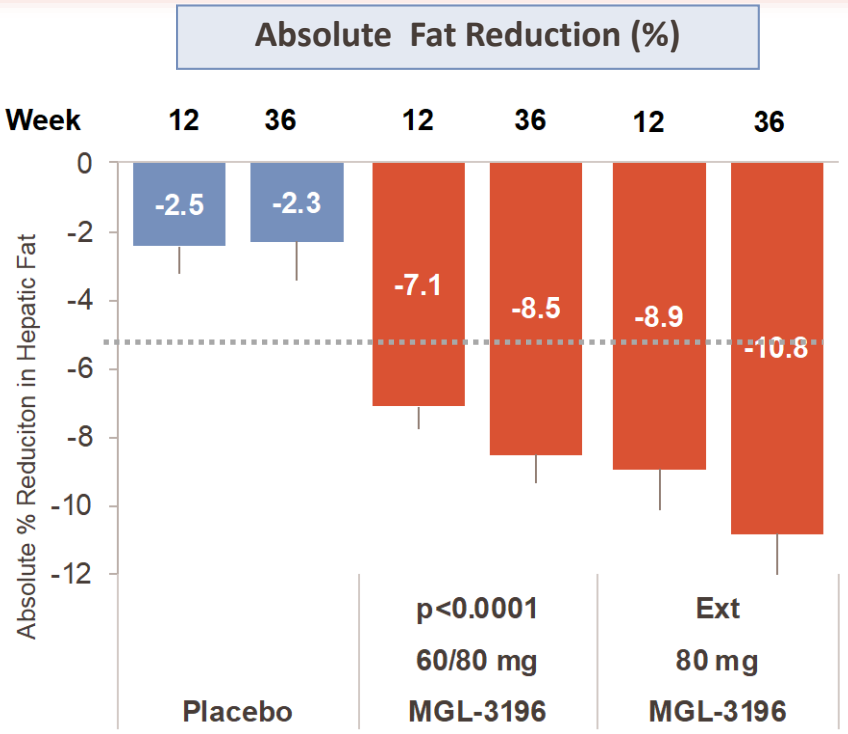
1. **Steatosis:**
    a. Resmetirom, administered at Phase 3 doses (80 or 100 mg/qd) clears more liver fat (MRI-PDFF), than other agents at doses that are adequately tolerated.
    b. Emerging data indicate ≥30% hepatic fat removal predicts higher rates of NASH resolution & decreased fibrosis on biopsy. At Phase 3 doses of resmetirom, ~90% of patients should clear at least this amount of fat (mean clearance ~55%)
2. **Hepatocyte Dysfunction / Death:**
    a. Reduction of GGT, statistically significant compared with placebo
    b. Decrease in ballooned hepatocytes on biopsy
    c. Statistically significantly more resmetirom vs. placebo patients achieving ≥ 2-point NAS improvement and resolution of NASH;
    d. Stimulates mitochondrial biogenesis
3. **Inflammation**
    a. Decrease in inflammation score on biopsy
    b. Continued, sustained decrease in elevated liver enzymes, many reaching normal levels (60% with ALT <30 by 36 weeks);
    c. Statistically significant reduction in reverse T3, a marker of inflammation.

# Resmetirom - High Potential to Resolve NASH, Improve Fibrosis and Provide Cardiovascular Protection (continued)

4. **Fibrosis:**
    a. Trend favoring resmetirom in Phase 2 (the study was not powered for 1-point improvement in fibrosis);
    b. 50% of patients who resolved NASH also resolved fibrosis, 61% of NASH resolvers achieved ≥ 1 point improvement in fibrosis;
    c. Statistically significant reductions in multiple fibrosis markers, most pronounced in patients with advanced fibrosis at baseline (F2 / F3);
    d. Half of F3 patients showed ≥ 1-point improvement in fibrosis, compared to no placebo F3 patients, using Second Harmonic Generation laser quantification;
    e. Phase 3 NASH study is >90% powered to show a 1-point improvement in fibrosis.

# Dose-related 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%

## 36 Week Extension Study

- Thirty patients, 14 former placebo patients were treated with MGL-3196, 80 mg for an additional 36 weeks
- Well tolerated, excellent safety, lipid and liver enzyme responses

P value, placebo compared to MGL-3196; MGL-3196, n=78; placebo, n=38; extension study shown for former pbo patients, 3 took 100 mg, 11/14, 80 mg.



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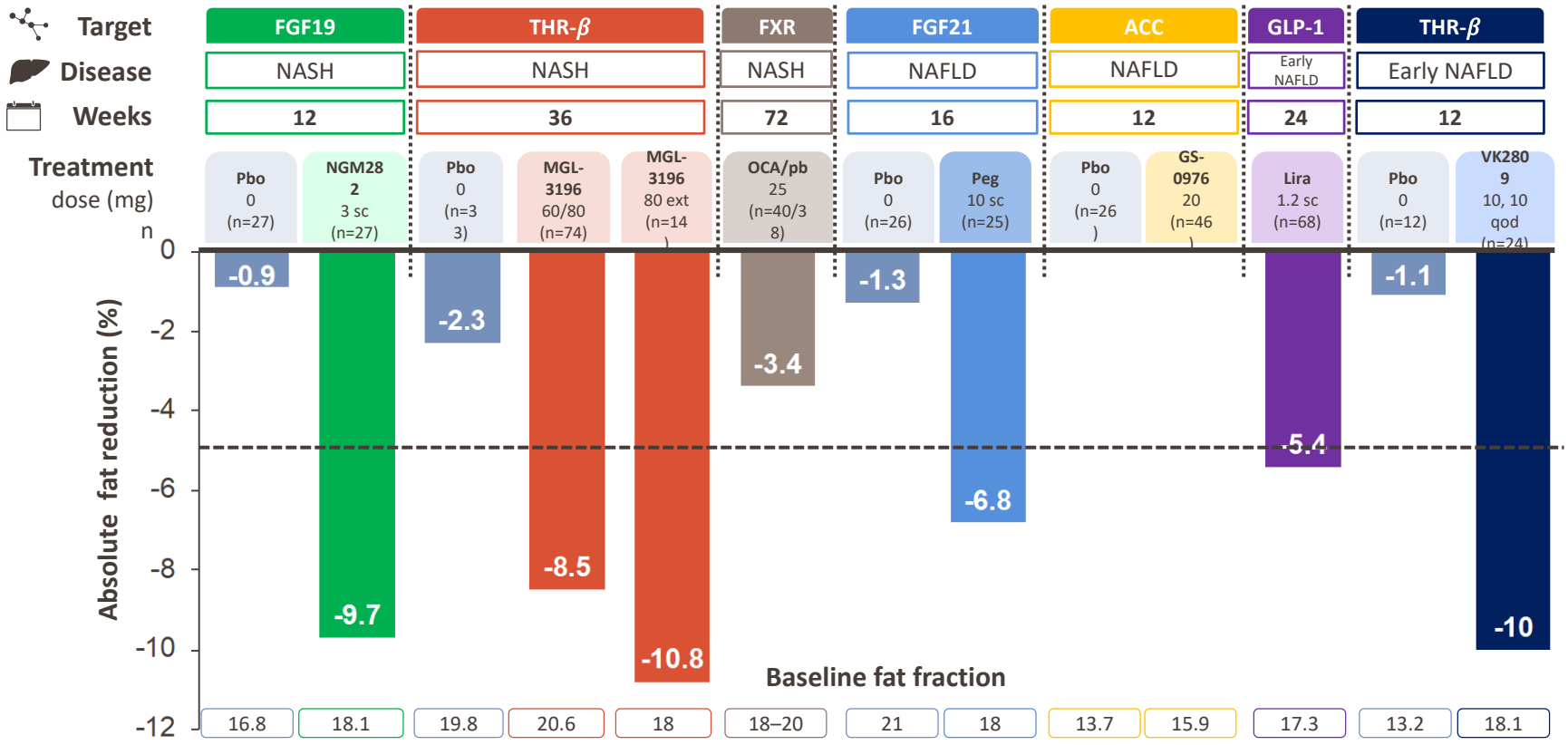
# MRI-PDFF Absolute Fat Reduction (%)




ACC, acetyl-CoA carboxylase; FGF, fibroblast growth factor; FXR, farnesoid X receptor; GLP-1, glucagon-like peptide-1; Lira, liraglutide; MRI-PDFF, magnetic resonance imaging – proton density fat fraction; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; OCA, obeticholic acid; Pbo, placebo; Peg, pegbelfermin; sc, subcutaneous; THR, thyroid hormone receptor. Harrison SA. *Lancet*. 2018;391:1174–85; Harrison AASLD 2018; Loomba AASLD 2017; Sanyal AJ. *Lancet*. 2018;392:2705-717; Loomba R. *Gastroenterology*. 2018;155:1463–1473; Petit JM. *J Clin Endocrinol Metab*. 2017;102:407–15; Loomba AASLD 2018.



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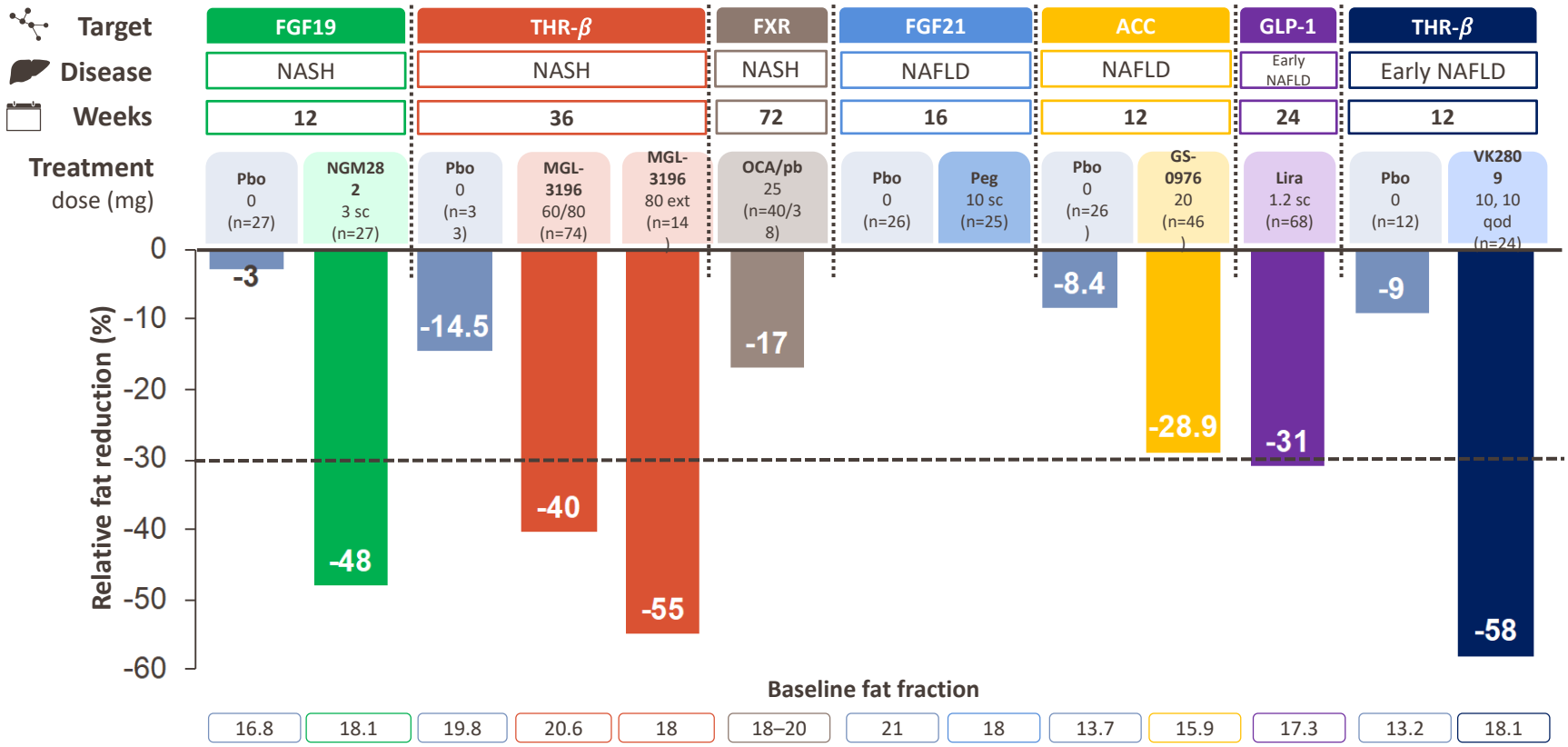
# MRI-PDFF Relative Fat Reduction (%)




ACC, acetyl-CoA carboxylase; FGF, fibroblast growth factor; FXR, farnesoid X receptor; GLP-1, glucagon-like peptide-1; Lira, liraglutide; MRI-PDFF, magnetic resonance imaging – proton density fat fraction; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; OCA, obeticholic acid; Pbo, placebo; Peg, pegbelfermin; sc, subcutaneous; THR, thyroid hormone receptor. Harrison SA. *Lancet*. 2018;391:1174–85; Harrison AASLD 2018; Loomba AASLD 2017; Sanyal AJ. *Lancet*. 2018;392:2705-717; Loomba R. *Gastroenterology*. 2018;155:1463–1473; Petit JM. *J Clin Endocrinol Metab*. 2017;102:407–15; Loomba AASLD 2018.



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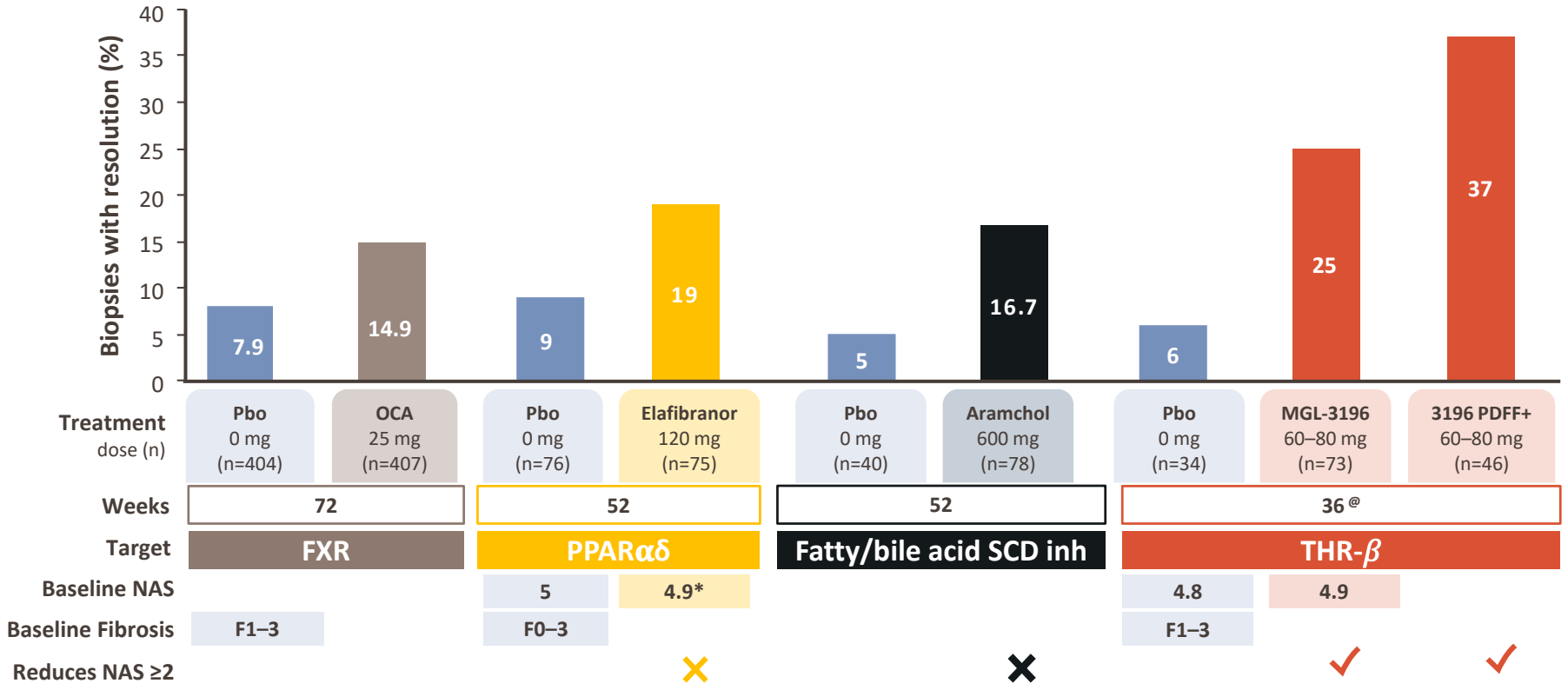
# NASH Resolution: Ballooning = 0; Inflammation = 0,1; No worsening of fibrosis stage




*included NAS=3; @ NASH resolution required at least a 2-pt NAS reduction in addition to ballooning 0; inf 0,1, no fibrosis worsening ; FXR, farnesoid X receptor; NASH, non-alcoholic steatohepatitis; NAS, NAFLD activity score; OCA, obeticholic acid; Pbo, placebo; PDFF, proton density fat fraction; PPAR, peroxisome proliferator-activated receptor; THR, thyroid hormone receptor. Younossi ZM. EASL 2019 (F1-F3 population); Ratziu Gastroenterology 2016;150:1147-1159; Ratziu AASLD 2018; Harrison AASLD 2018. For elafibrinor only enrolled patients with NAS>3 at baseline were evaluated for NASH resolution



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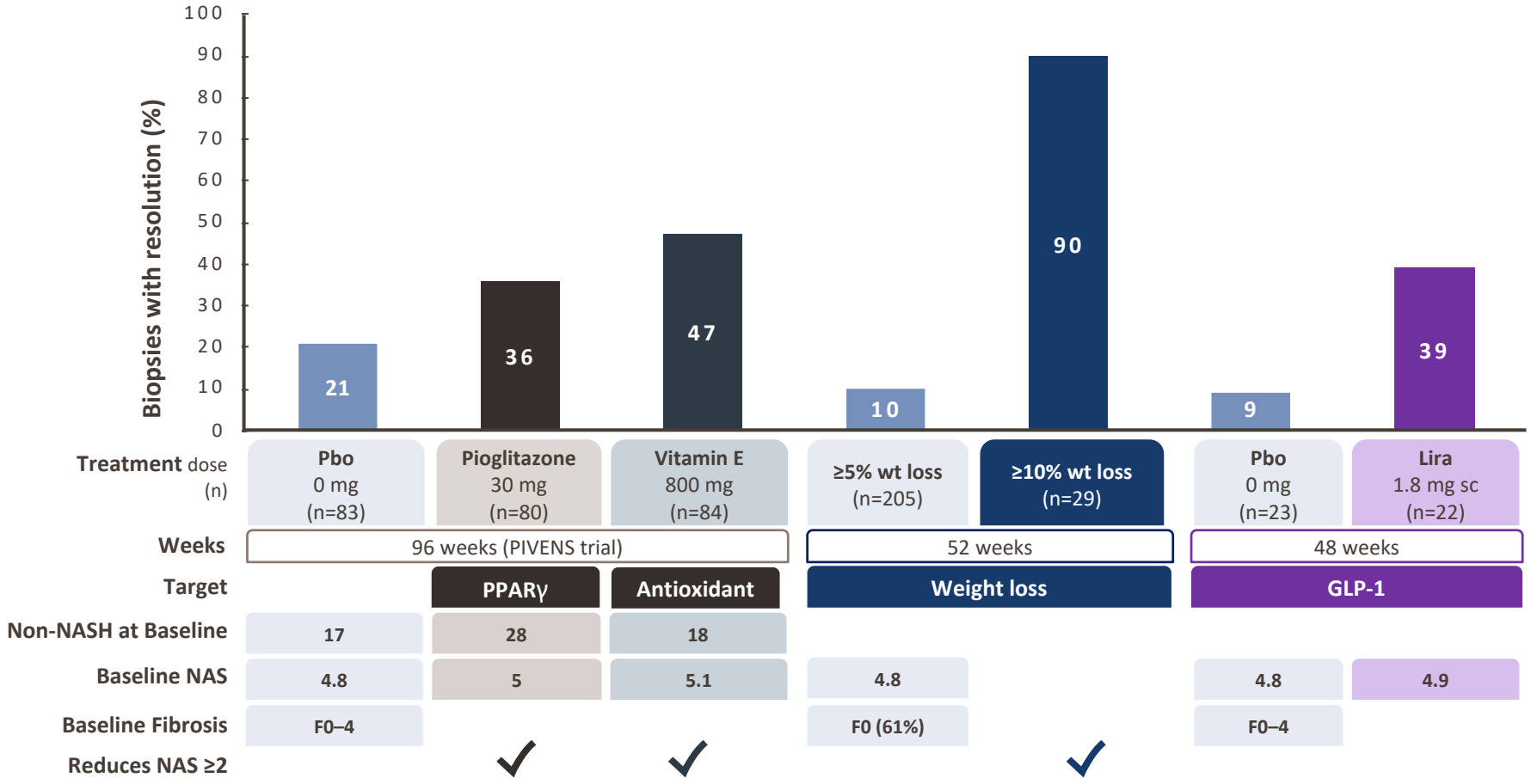
# NASH Resolution: ”Non-NASH” or Ballooning=0; no worsening of fibrosis

*In older studies Inflammation score not considered*




GLP-1, glucagon-like peptide-1; Lira, liraglutide; NAS, NAFLD activity score; NASH, non-alcoholic steatohepatitis; Pbo, placebo; PPAR, peroxisome proliferator-activated receptor. sc, subcutaneous.
Sanyal AJ et al. *N Engl J Med*. 2010;362:1675–85; Vilar-Gomez et al. *Gastroenterology*. 2015;149:367–78; Armstrong MJ et al. *Lancet*. 2016;387:679–90.



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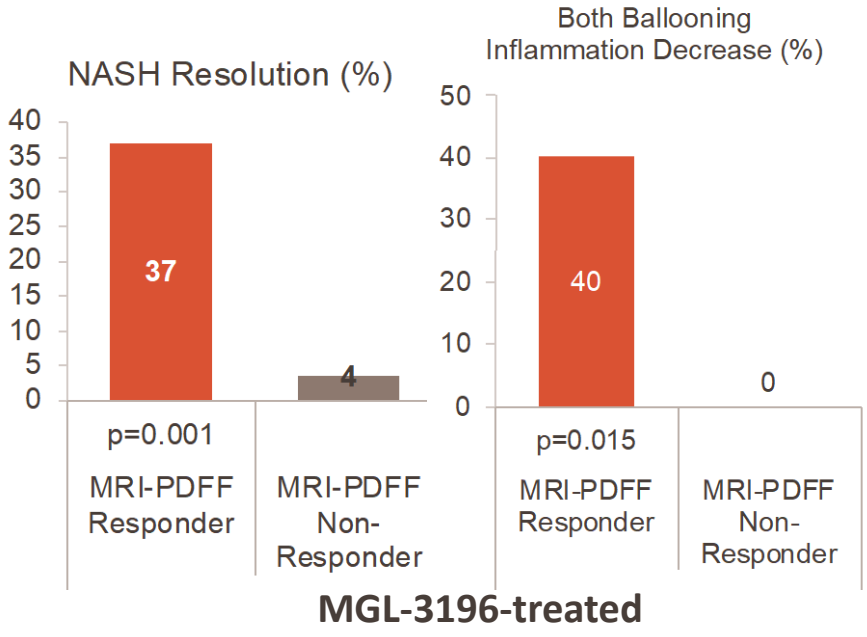
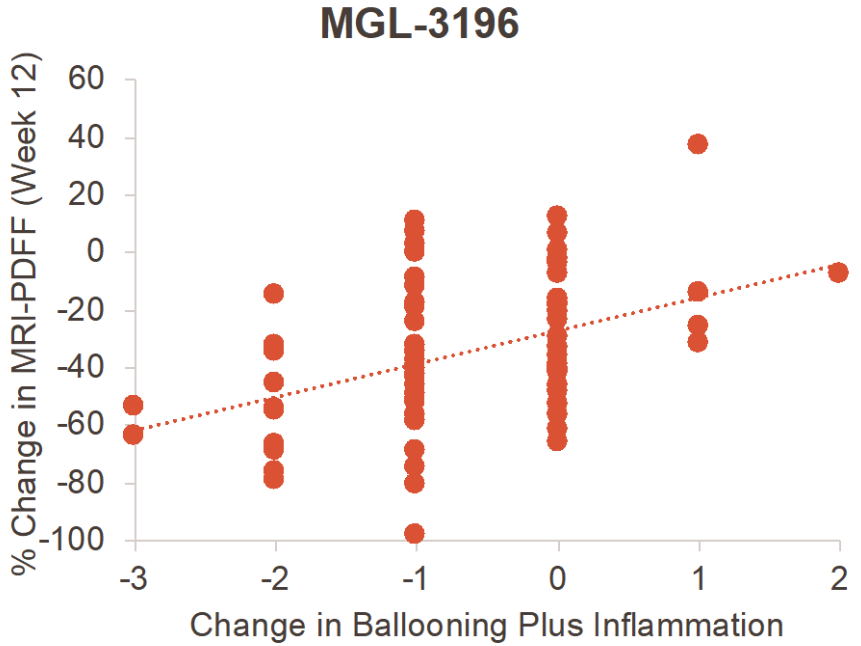
# Correlation of Decrease in Hepatic Fat (MRI-PDFF) with Improvement in Ballooning and Inflammation on Liver Biopsy

**NASH Resolution (%); Biopsies with Both Ballooning and Inflammation Improvement**




**MRI-PDFF Week 12, % Relative Change: Correlation with Change in Ballooning and 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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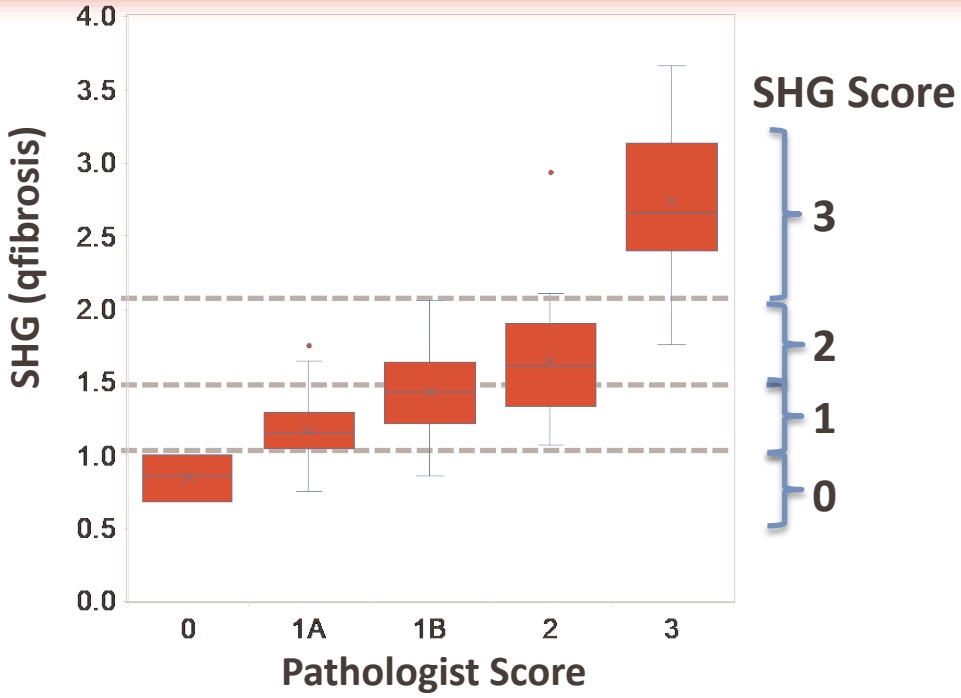
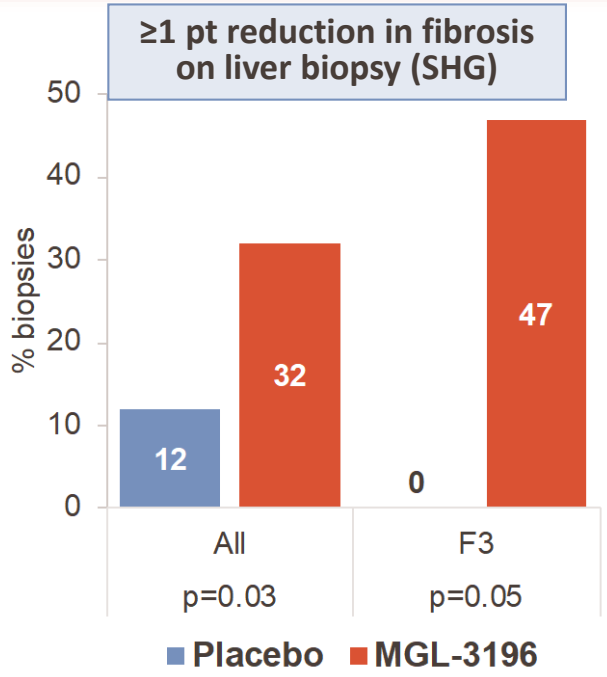
# Week 36: Change in Fibrosis Score on Liver Biopsy




- 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 readers.



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# Phase 3/4: MGL-3196 NASH Trial

| Study Overview | |
|---|---|
| Drug | MGL-3196 (resmetirom) |
| Design | Blinded 1:1:1 |
| Stage | Phase 3/4 |
| Number of Patients | Phase 3: 900<br>Phase 4: up to 2000 |
| Centers | ~150, USA; EU |
| Treatment Duration | 52 Weeks; 4.5 years |

## Study Details

**Inclusion/Exclusion**

- NASH on liver biopsy: NAS≥4, high risk F1, F2/3

**Comparator/Arms**

- MGL-3196 80 or 100 mg or Placebo, once daily

**Primary Endpoint**

- Phase 3: Liver biopsy at 52 weeks - resolution of NASH associated with a ≥2 pt reduction in NAS and no worsening of fibrosis
- Phase 4: reduction in liver related events or progression to cirrhosis

**Key Secondary Endpoints**

- LDL-C lowering
- ≥1 pt reduction in fibrosis with no worsening of NAS

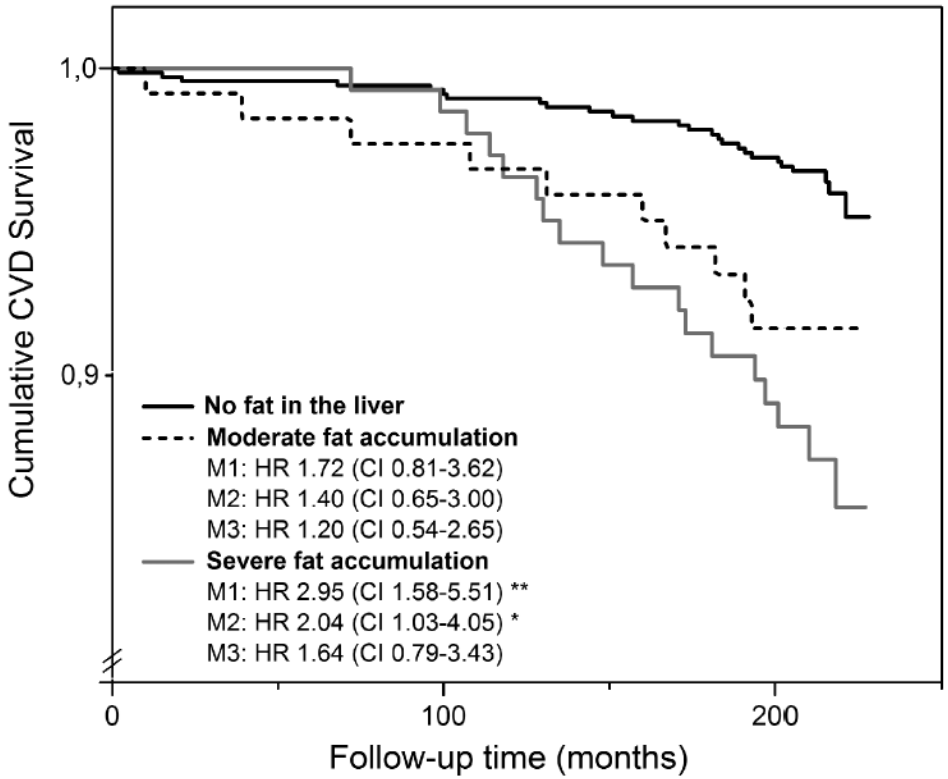
**Other Secondary and Exploratory Endpoints**

- Additional NASH biopsy endpoints
- Imaging MRI-PDFF
- Fibrosis biomarkers

# Phase 3 Largely Replicates the Phase 2 Design at Higher Doses

| Phase 2 NASH | Phase 3 NASH |
|---|---|
| Liver biopsy confirmed NASH; NAS≥4 F1-3 | NAS≥4, F2-F3, primary assessment; F1B |
| MRI-PDFF≥10% fat fraction | MRI-PDFF ≥8% fat fraction |
| Enrollment 125 1:2 placebo: resmetirom | Enrollment 900 1:1:1 placebo: 2 doses |
| Dose: 60, 80 mg once daily | Dose: **80, 100 mg once daily** |
| 36 Weeks | 52 Weeks |
| Centers: USA, 30 | Centers: Global, 150, primary USA |
| Primary endpoint: Relative reduction in liver fat on MRI-PDFF | Primary endpoint: NASH resolution with at least a 2-point reduction in NAS, no worsening of fibrosis *powered >>90% to achieve endpoint* |
| Secondary endpoints: 2-pt reduction in NAS | Key secondary endpoints: |
| LDL-C, other lipids | LDL-C *powered>>90% to achieve endpoint* |
| NASH resolution with at least a 2-point reduction in NAS and no worsening of fibrosis; 1 stage fibrosis reduction with no NAS worsening | At least a 1 stage reduction in fibrosis with no worsening of NAS *powered>90% to achieve endpoint* |
| Multiple exploratory biomarkers for fibrosis, inflammation, imaging assessed in Phase 2 and 3 | Phase 4: Clinical benefit, reduction in cirrhosis, liver related outcomes up to 4.5 years |

# Fatty Liver Associates with Overall CVD Mortality




Pisto P et al. *BMJ Open* 2014;4:e004973. doi:10.1136/bmjopen-2014-004973



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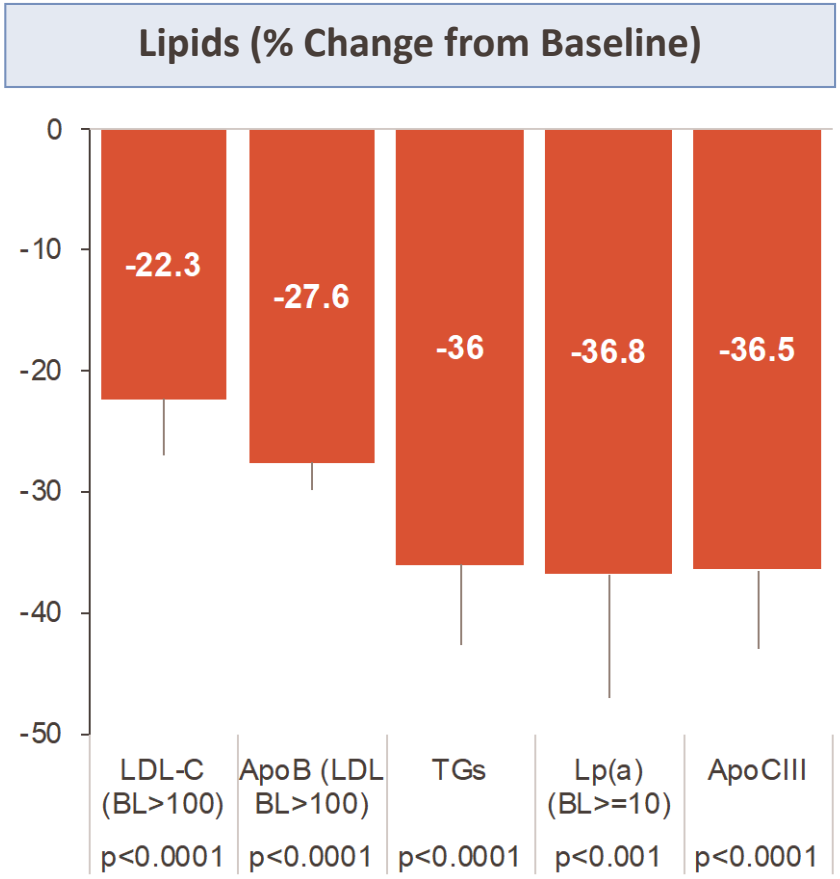
# CV Risk in NASH and NAFLD

- Strong association between NAFLD, particularly NASH fibrosis, and increased risk of CVD events and mortality
  - Death from CVD much more common than death from liver disease (Angulo, 2015)
- Patients with NAFLD have a pro-atherogenic lipid profile:
  - Increased triglycerides
  - Increased apolipoprotein B
  - Higher concentration of small dense LDL
- Fatty liver appears to confer an independent cardiovascular risk, potentially related to increased inflammation in NASH
- Thus, aggressive modification of CVD risk factors is mandatory in all patients with NAFLD

# Week 36: Sustained Robust Lipid Lowering




- MGL-3196 is the only NASH therapeutic able to lower lipids, consistent with regulatory approval for dyslipidemia; an also reduces fatty liver, an independent CV risk factor
- ApoB, not LDL-C is the major risk factor in CV disease
- NASH patients die of CV disease more frequently than liver disease

**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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# Phase 3: MAESTRO-NAFLD-1

| Study Overview | |
|---|---|
| Drug | MGL-3196 |
| Design | 1:1:1:1 |
| Stage | Phase 3 |
| Number of Patients | 700 |
| Centers | 50, USA |
| Treatment Duration | 12 months |

## Study Details

**Inclusion/Exclusion**

- NASH/NAFLD patients not at target on standard care lipid therapy (LDL-C ≥00 or TGs>150; ≥ 70 mg/dL in patients with CV disease, very high risk diabetics)
- Eligibility: fibroscan, ultrasound, NASH on biopsy
- Excludes advanced patients F2/F3 NAS≥4 who qualify for MAESTRO-NASH

**Comparator/Arms**

- MGL-3196 80, 100 mg or Placebo, once daily; open label 100 mg arm in up to 100 patients

**Primary Endpoint**

- LDL cholesterol

**Key Secondary Endpoints**

- ApoB, TGs, Lp(a),
- MRI-PDFF
- Safety

# Catalysts: Our Expectations for Development Timing

**2017** | **2018** | **2019**

**Completed Milestones:**

- ✓ Initiation of 12-week Phase 2 trial of MGL-3196 for HeFH
- ✓ Positive topline data from Phase 2 trial of MGL-3196 for HeFH
- ✓ Completion of 36 Week NASH Extension Study
- ✓ Positive topline 12-week data from Phase 2 trial of MGL-3196 for NASH
- ✓ Positive 36-week topline liver biopsy data from Phase 2 trial of MGL-3196 for NASH
- ✓ Initiation of Phase 3 Study in NASH

- Ongoing NASH Phase 3 milestones
- Potential initiation of Phase 3 MAESTRO-NAFLD in 2H 2019

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**September 2019**