Primary Results From MAESTRO-NASH: A Pivotal Phase 3 52-week Serial Liver Biopsy Study in 966 Patients With NASH & Fibrosis

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Disclosures

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

- Scientific advisor or consultant for Akero, Aligos, Altimmune, Arrowhead, Bluejay Therapeutics, Boxer Capital, Chronwell, Echosens, Enyo, Foresite Labs, Galectin, Galecto, Gilead, GSK, Hepagene, Hepion, Hepta Bio, HistoIndex, Humana, Intercept, Ionis, Madrigal, Medpace, NeuroBo Pharmaceuticals, Northsea, Novo Nordisk, Perspectum, Pfizer, Sonic Incytes, Sagimet, Terns, Viking.
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Resmetirom

- Resmetirom is an oral, liver-targeted **THR-β selective agonist** in development for NASH[1]
- In patients with NASH, selectivity for THR-β may provide metabolic benefits of thyroid hormone that are mediated by the liver (**reduction of excess hepatic fat & atherogenic lipids/lipoproteins**), while avoiding negative systemic effects of excess thyroid hormone in heart & bone
- In the randomized, double-blind, placebo-controlled Phase 2 serial liver biopsy trial in adults with biopsy-confirmed NASH (NCT02912260), resmetirom treatment resolved NASH in a significantly greater percentage of patients & reduced liver enzymes, inflammatory biomarkers, & fibrosis compared with placebo[2]
- MAESTRO-NASH is a randomized, double-blind, placebo-controlled Phase 3 serial liver biopsy trial evaluating the efficacy & safety of resmetirom in adults with biopsy-confirmed NASH (NCT03900429)

Here we report Week 52 data in 966 patients with NASH & F1B, F2, or F3 fibrosis from the MAESTRO-NASH trial

1. Kelly MJ, et al. *J Med Chem.* 2014;57(10):3912-3923. 2. Harrison SA, et al. *Lancet*. 2019;394(10213):2012-2024

NASH, nonalcoholic steatohepatitis; THR, thyroid hormone receptor.

MAESTRO-NASH Trial Design

KEY ELIGIBILITY CRITERIA

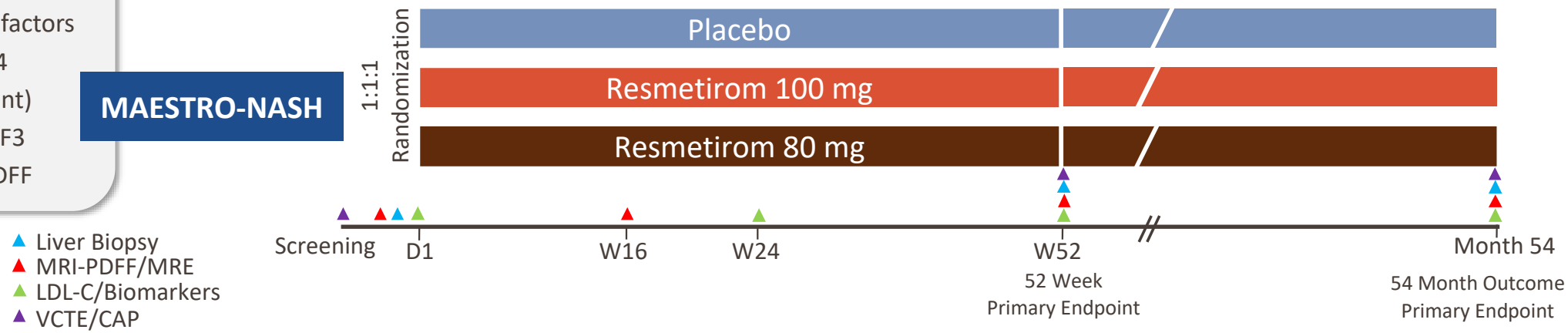
Presence of ≥3 metabolic risk factors

NASH on biopsy: NAS ≥4
(with ≥1 in each component)

Fibrosis stage F1B, F2, or F3

≥8% hepatic fat by MRI-PDFF

MAESTRO-NASH



DUAL PRIMARY ENDPOINT AT WEEK 52

NASH resolution (ballooning score=0, inflammation score=0/1, & ≥2-point reduction in NAS) with no worsening of fibrosis

≥1-stage improvement in fibrosis with no worsening of NAS

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LDL-C, low-density lipoprotein cholesterol; MRI-PDFF, magnetic resonance imaging-proton density fat fraction; NAS, nonalcoholic fatty liver disease activity score; NASH, nonalcoholic steatohepatitis.

Demographic & Baseline Characteristics (Primary Analysis Population n=966)

	Resmetirom 80mg (n=322)	Resmetirom 100mg (n=323)	Placebo (n=321)
Age, years	55.9 (11.5)	57.0 (10.8)	57.1 (10.5)
Sex, male	140 (43.5)	141 (43.7)	143 (44.5)
Race, White	291 (90.4%)	291 (90.1%)	281 (87.5%)
Ethnicity, Hispanic or Latino	71 (22.0%)	81 (25.1%)	52 (16.2%)
Body mass index	35.5 (6.4)	36.2 (7.4)	35.3 (6.5)
Type 2 diabetes	224 (69.6)	213 (65.9)	210 (65.4)
Hypertension	243 (75.5)	254 (78.6)	257 (80.1)
Dyslipidemia	230 (71.4)	236 (73.1)	224 (69.8)
Hypothyroidism*	39 (12.1)	46 (14.2)	45 (14.0)
FibroScan VCTE/LSM, kPa	13.3 (6.8)	13.6 (7.1)	12.9 (5.5)
FibroScan CAP, dB/m	346.1 (37.2)	349.4 (38.7)	347.2 (37.0)
MRI-PDFF, % fat fraction	18.2 (6.8)	17.2 (6.6)	17.8 (6.8)
MRE, kPa	3.5 (0.9)	3.7 (1.1)	3.5 (1.0)
Baseline medications			
GLP-1 RA	54 (16.8)	41 (12.7)	42 (13.1)
Statin	149 (46.3)	166 (51.4)	157 (48.9)
Baseline liver biopsy			
NAS ≥5	266 (82.6)	288 (89.2)	253 (78.8)
Fibrosis 1B	16 (5.0)	15 (4.6)	18 (5.6)
Fibrosis 2	107 (33.2)	100 (31.0)	112 (34.9)
Fibrosis 3	194 (60.2)	203 (62.8)	186 (57.9)

Data are mean (SD) or n (%)

*Patients on thyroxine replacement therapy at screening.

CAP, controlled attenuation parameter; GLP-1 RA, glucagon-like peptide-1 receptor agonist; LSM, liver stiffness measurement; mITT, modified intent-to-treat; MRE, magnetic resonance elastography; MRI-PDFF, magnetic resonance imaging-proton density fat fraction; NAS, nonalcoholic fatty liver disease activity score; SD, standard deviation; VCTE, vibration-controlled transient elastography.

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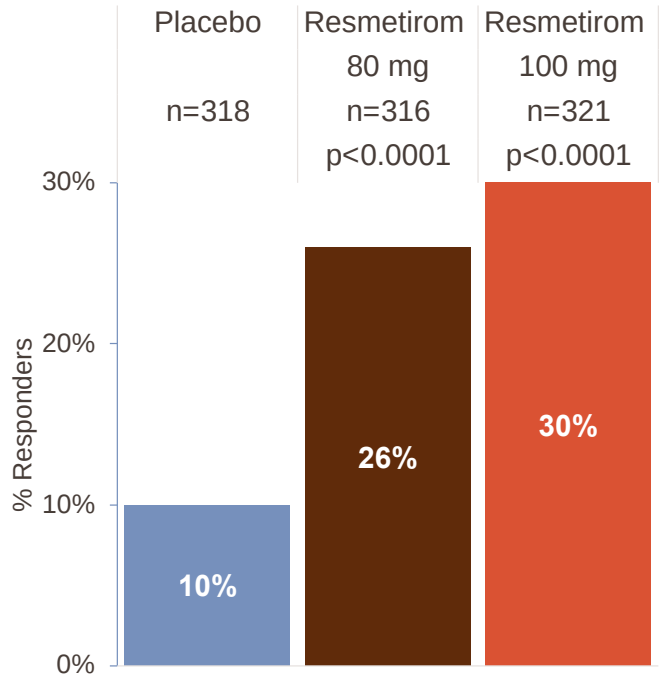
Analysis of Primary Endpoints

- Reread of all baseline biopsies by 2 central pathologists
- ITT includes all patients with at least a baseline biopsy with appropriate fibrosis stage
- Biopsies were included if conducted before Week 60; patients with biopsies after Week 60 were considered non-responders as were all patients who had only a baseline biopsy
  - 11 patients who had their biopsy conducted after Week 60 (e.g., due to COVID-19 site closures) were not included in the primary (ITT) analysis c/w FDA guidance
- All baseline & Week 52 biopsies were read independently by 2 central pathologists (glass slides) for the primary analysis
  - Each pathologist's scores showed a similar statistically significant magnitude of response at both doses for both primary liver biopsy endpoints
  - Results were combined statistically using CMH to generate a single treatment effect
- Baseline biopsies rescored as F1A, C were considered exploratory & will be evaluated separately

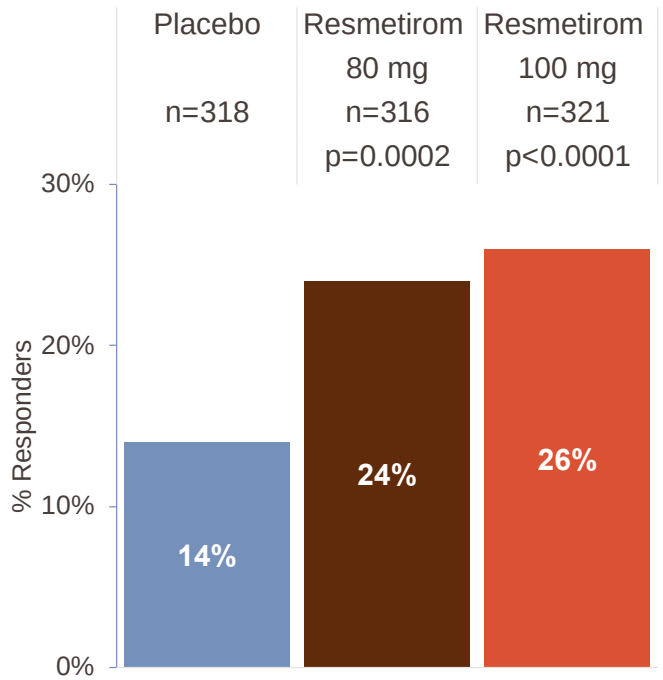
CMH, Cochran-Mantel-Haenszel.

Dual Primary Endpoints (Week 52): Primary Analysis

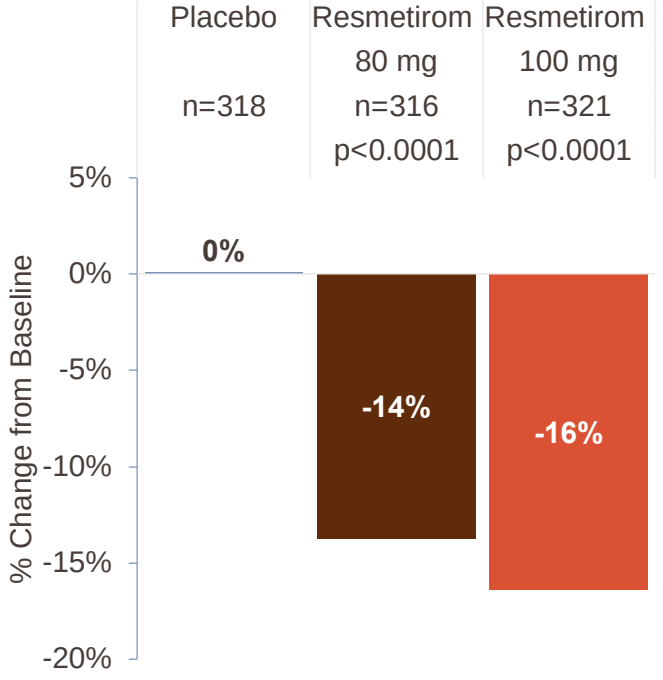
NASH Resolution*



≥1 Stage Fibrosis Improvement*



LDL Cholesterol



Both primary liver biopsy endpoints and the key secondary endpoint of LDL cholesterol lowering were met

*NASH Resolution with no worsening of fibrosis; ≥1 Stage Fibrosis Improvement with no worsening of NAS

NASH, nonalcoholic steatohepatitis.

Dual Primary Endpoints (Week 52): Consensus Assessment

Primary Endpoint	Resmetirom 80 mg (n=316)	p-value	Resmetirom 100 mg (n=321)	p-value	Placebo (n=318)
NASH resolution (ballooning 0, inflammation 0,1) with ≥2-point reduction in NAS and no worsening of fibrosis	24%	<0.0001	28%	<0.0001	8%
≥1-stage improvement in fibrosis with no worsening of NAS	24%	<0.0001	26%	<0.0001	12%

- As a sensitivity analysis, a consensus read of digitized images was conducted when the pathologists' scores disagreed regarding whether there was a response for either primary endpoint
- Multiple other prespecified sensitivity and supportive analyses were conducted that demonstrated the same effects as the primary analysis including additional statistical models, multiple imputation and tipping point
- Multiple confirmatory subgroups and additional analyses (ITT, paired biopsy, baseline fibrosis stage, digitized image secondary read)

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NAS, nonalcoholic fatty liver disease activity score; NASH, nonalcoholic steatohepatitis.

Additional Secondary Biopsy Endpoints (Week 52)

	Resmetirom 80mg (n=316)	Resmetirom 100mg (n=321)	Placebo (n=318)
≥2-point reduction in NAS (with ≥1-point reduction in ballooning or inflammation) with no worsening of fibrosis			
Response rate, %	**41.3**	**44.9**	**21.2**
Difference from placebo (95% CI)	20.2 (13.8, 26.5)	23.8 (17.4, 30.2)	
p-value	<0.0001	<0.0001	
2-stage fibrosis improvement (F2-F3 patients with ≥2-point reduction in fibrosis) with no worsening of NAS			
Response rate, %	**8.3**	**10.1**	**2.8**
Difference from placebo (95% CI)	5.6 (2.5, 8.7)	7.4 (3.9, 10.8)	
p-value	0.0001	<0.0001	
NASH resolution & ≥1-stage improvement in fibrosis			
Response rate, %	**14.2**	**16.0**	**4.9**
Difference from placebo (95% CI)	9.5 (5.4, 13.6)	11.6 (7.5, 15.8)	
p-value	<0.0001	<0.0001	
NASH resolution (with ≥2 pt reduction in NAS and no worsening of fibrosis), Observed Data (both baseline and week 52 biopsy pair)			
Response rate, %	**31.8**	**38.7**	**11.2**
Difference from placebo (95% CI)	20.9 (14.6,27.1)	28.5 (22.1,34.9)	
p-value	<0.0001	<0.0001	
≥1-stage Fibrosis Improvement with no Worsening of NAS, Observed Data (both baseline and week 52 biopsy pair)			
Response rate, %	**29.7**	**33.5**	**16.3**
Difference from placebo (95% CI)	13.6 (7.3,19.9)	17.2 (10.8,23.6)	
p-value	<0.0001	<0.0001	
NASH Resolution OR Fibrosis Improvement	**42%**	**50%**	**19%**

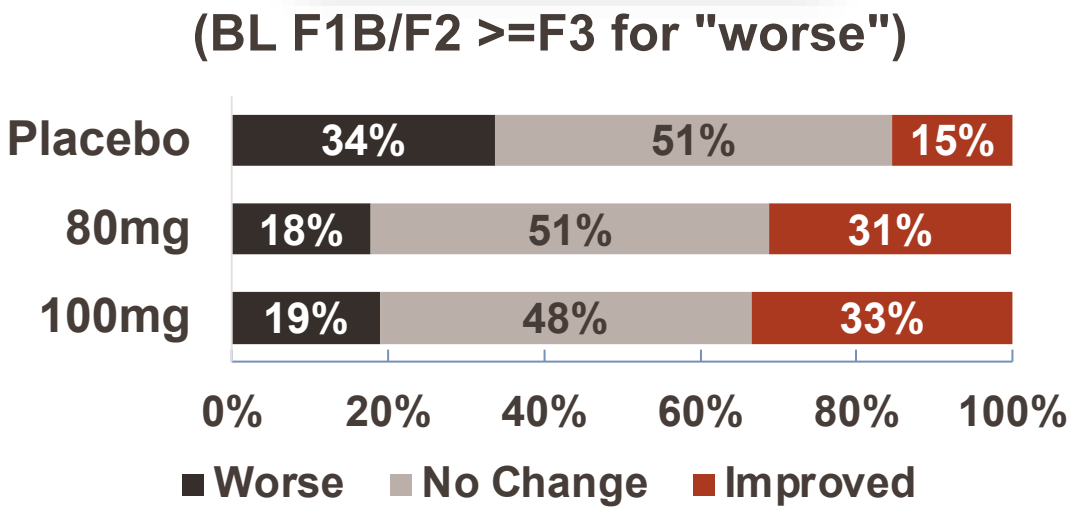
CI, confidence interval; NAS, nonalcoholic fatty liver disease activity score; SD, standard deviation.

NASH Biopsy Component Responses

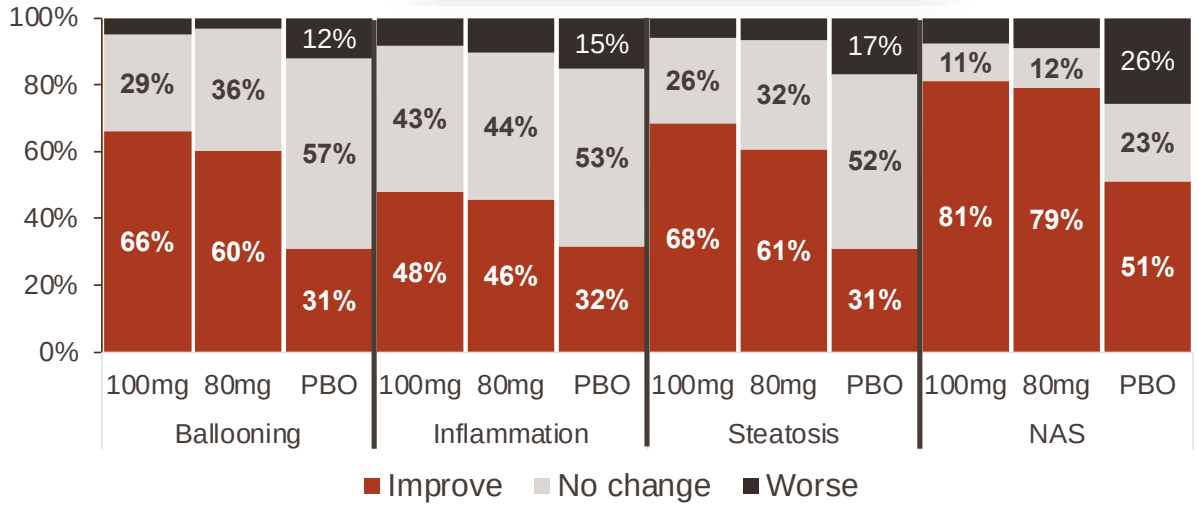
- For public data release, FDA restricted data on worsening of fibrosis to baseline F1B and F2 biopsies because conversion of F3 to F4 is an outcome in the blinded ongoing 54-month primary endpoint of MAESTRO-NASH

- Resmetirom-treated showed improvement in NAS components and fibrosis and less worsening compared with placebo

Fibrosis Change



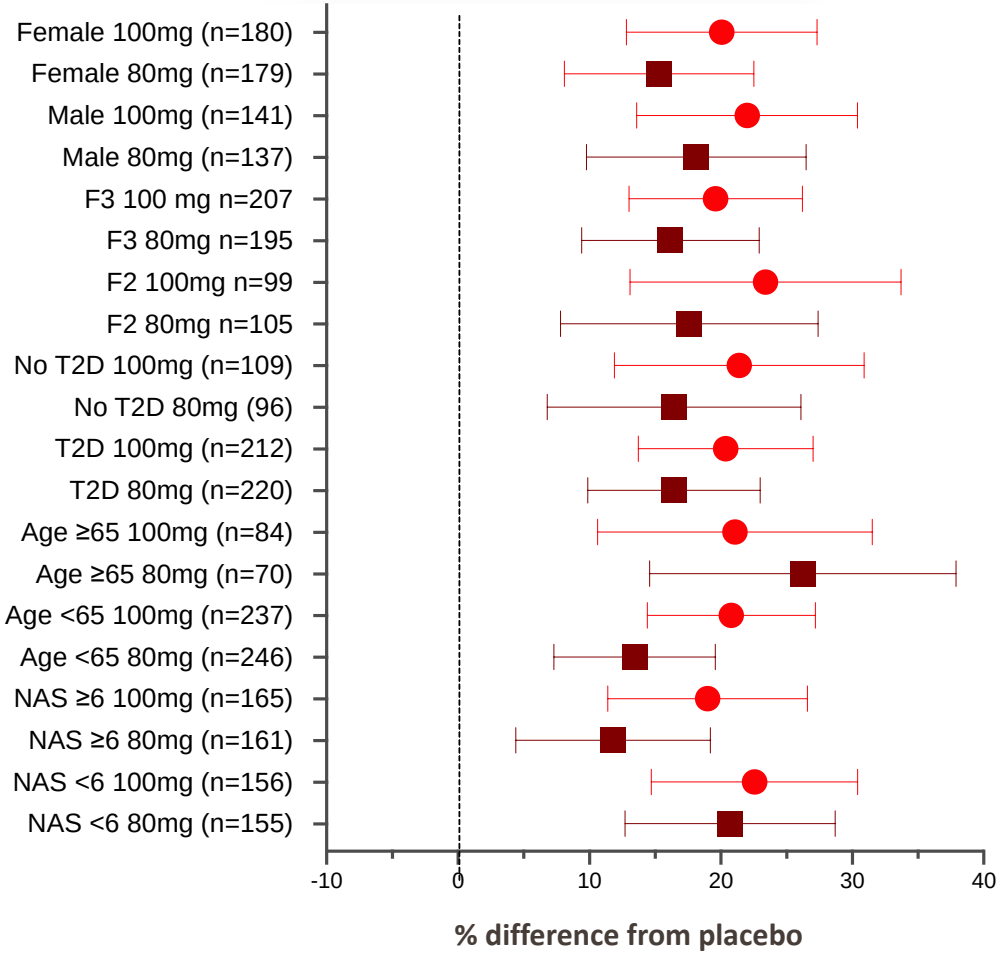
NAS Components



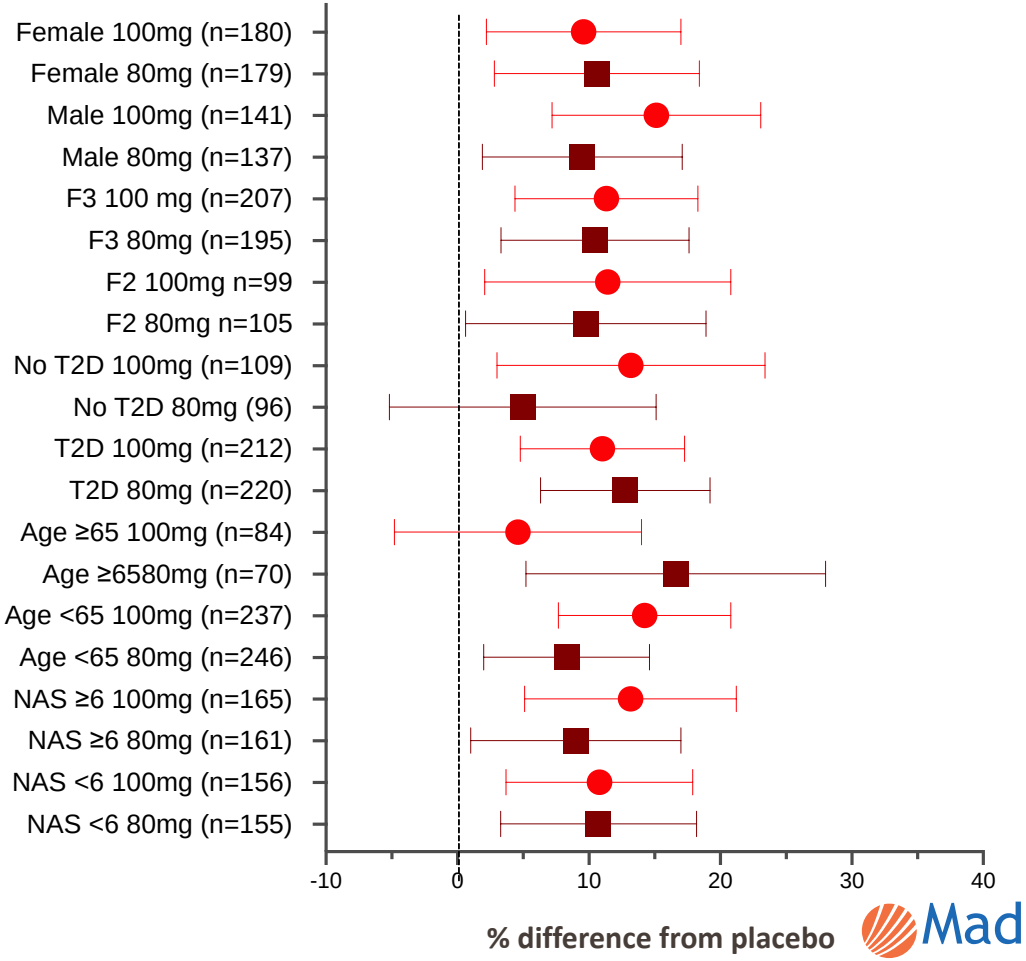
Note that in biopsies with a baseline inflammation score of 1 there was less decrease in inflammation; inflammation is infrequently scored as 0

Key Subgroups: Primary Endpoints

NASH Resolution



Fibrosis Improvement



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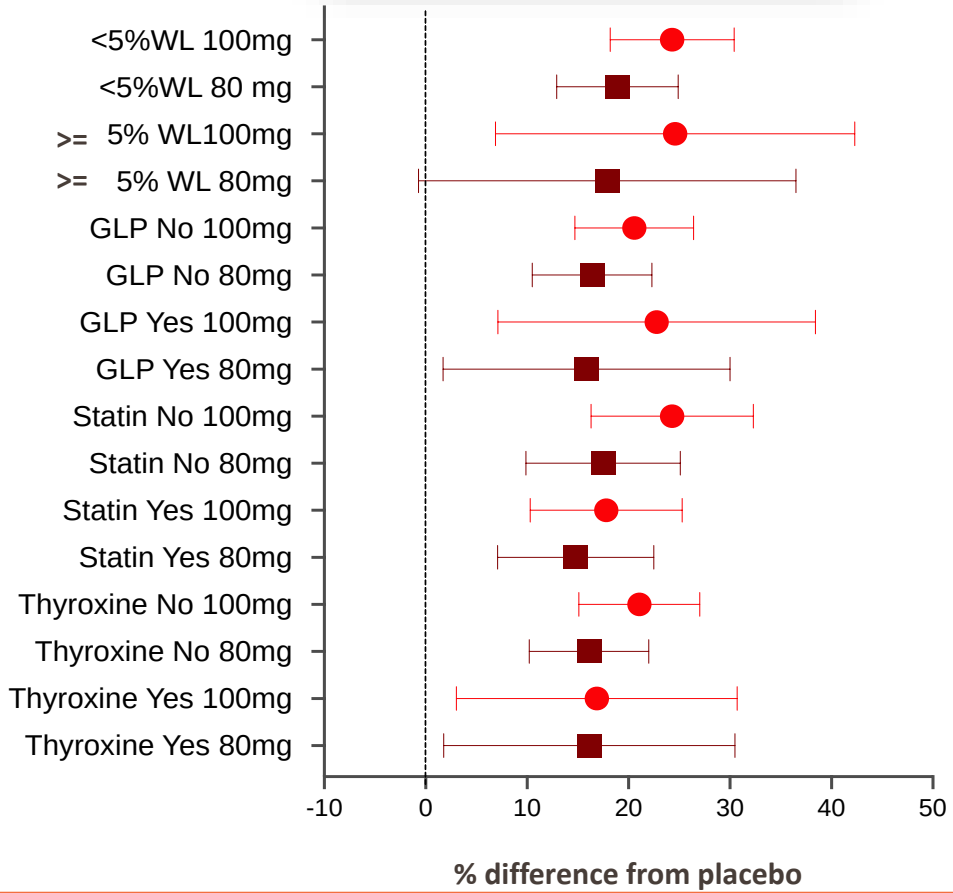
T2D, Type 2 Diabetes; NAS, NAFLD Activity Score

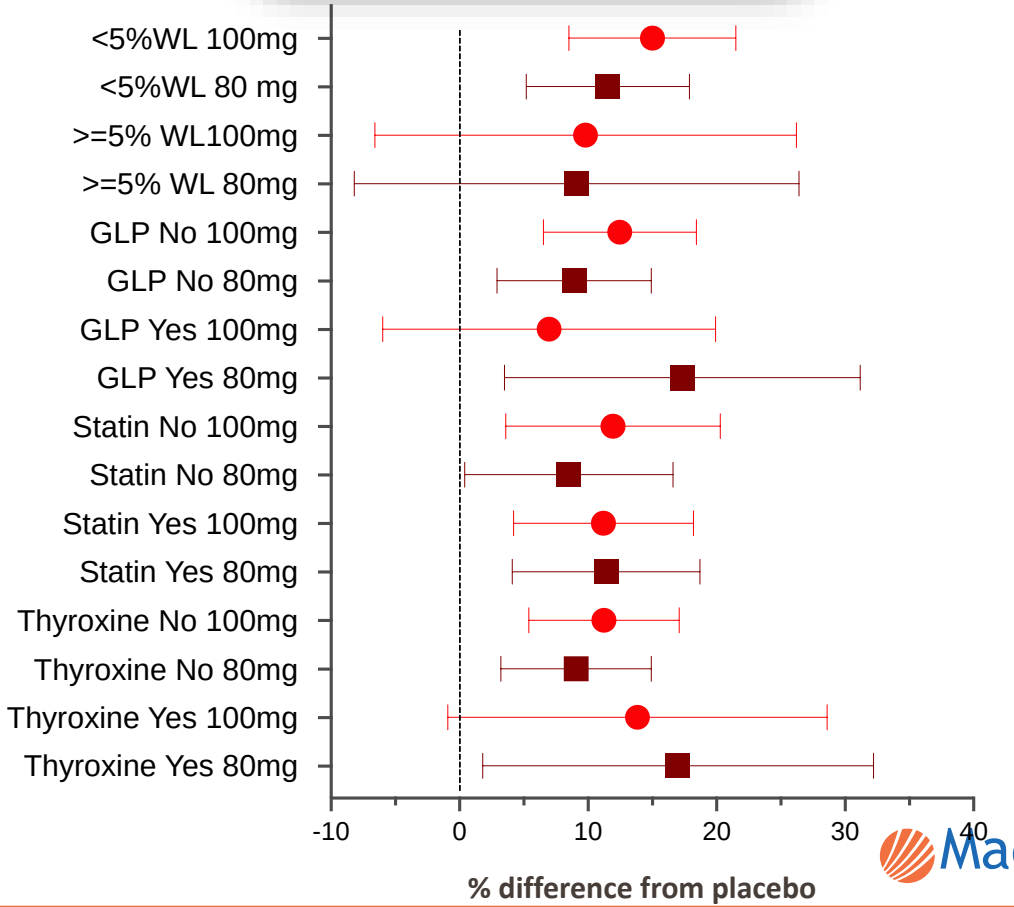
Weight Loss or Concomitant Drug Therapies

- GLP therapy, 14%; thyroxine, 13%; and statins, ~50% of patients in each arm; small differences relate to the small size of subgroups (>=5% weight loss n=47, 80 mg; n=57, 100mg; n=36, placebo)

NASH Resolution

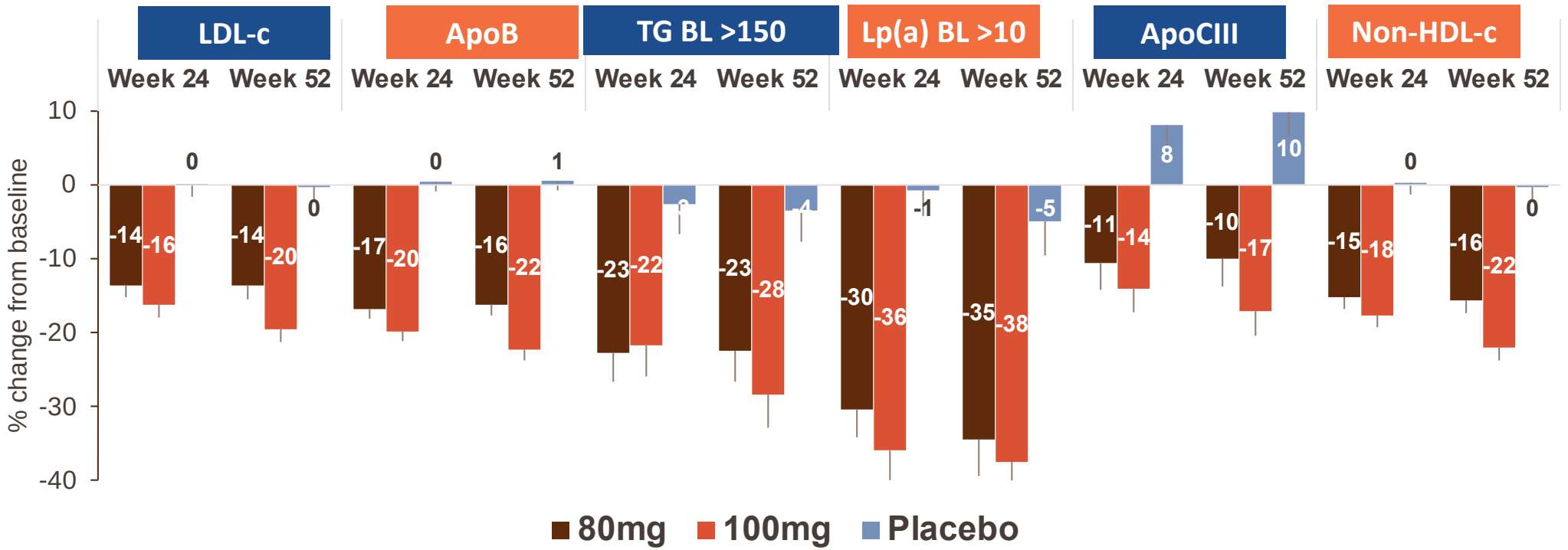


Fibrosis Improvement



WL, weight loss; GLP, Glucagon-like peptide-1 receptor agonist

Percent Change from Baseline in Lipids/Lipoproteins (Weeks 24 & 52)



Key secondary endpoint met (LDL-C lowering)

Significant effect of resmetirom 80 & 100 mg on multiple atherogenic lipids/lipoproteins at Week 24 and 52

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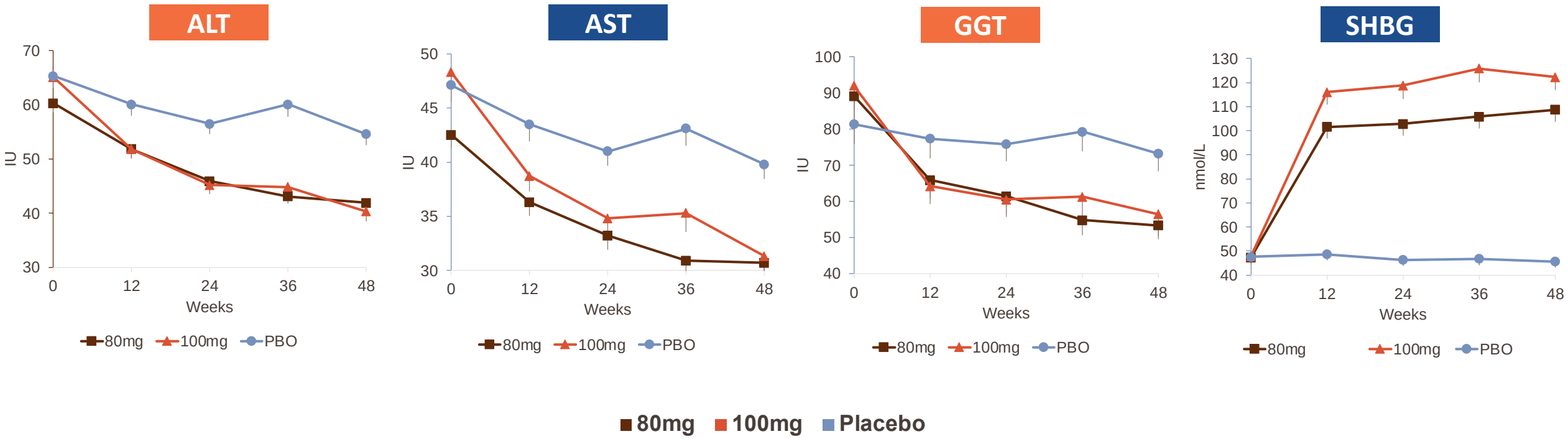
ApoB, apolipoprotein B; TG, triglycerides; ApoCIII, apolipoprotein CIII; BL, baseline; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein (a); non-HDL-C, non-high-density lipoprotein cholesterol; PBO, placebo

Change from Baseline in Liver Enzymes* & SHBG

- Significant reduction of liver enzymes relative to placebo, both percentage change and absolute reduction
- Associated with the neutral biomarker SHBG that increases in proportion to resmetirom target engagement (exposure)

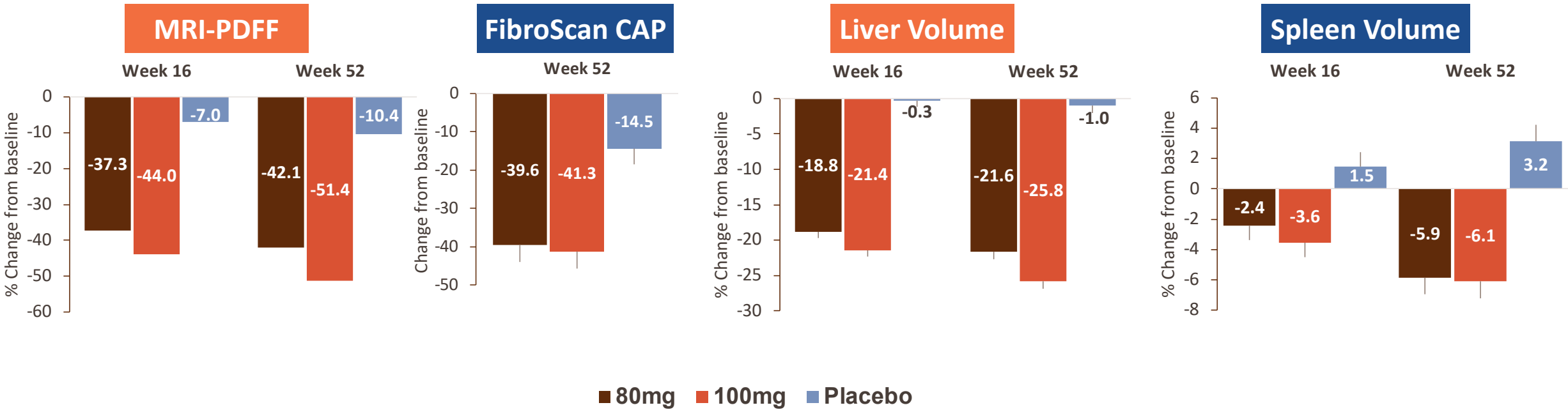


*Evaluated in patients with baseline ALT ≥30 IU.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; PBO, placebo; SHBG, sex hormone binding globulin.

Change from Baseline in MRI-PDFF & FibroScan CAP

- Significant effect of resmetirom 80 & 100 mg on both MRI-PDFF & FibroScan CAP
- Significant effect of resmetirom to reduce liver and spleen volume as assessed on serial MRI-PDFF
  - Liver volume corrected MRI-PDFF reduction is a mean of 60% at the 100 mg dose



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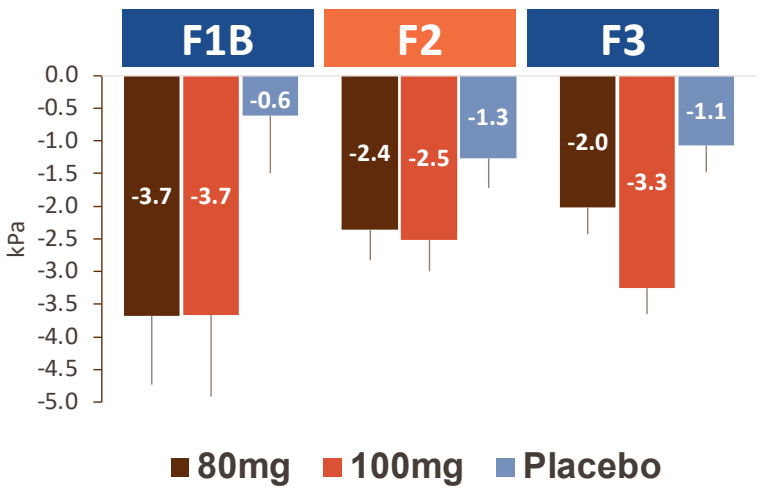
CAP, controlled attenuation parameter; CFB, change from baseline; MRI-PDFF, magnetic resonance imaging-proton density fat fraction; NASH, nonalcoholic steatohepatitis; PBO, placebo.

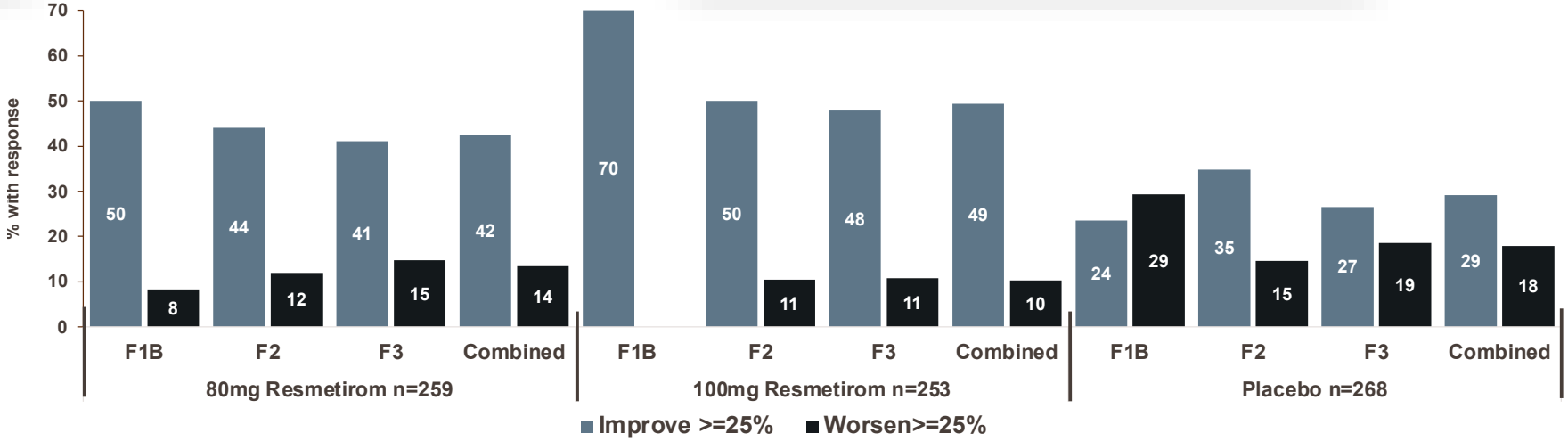
Change from Baseline in FibroScan VCTE/LSM (Week 52)

Significant effect of resmetirom 80 & 100mg on liver stiffness measured by FibroScan VCTE, mean change from baseline (A) & responder analysis (B)
Other fibrosis endpoints achieved: Reduction in MRE, ELF

A - FibroScan VCTE Mean Change



B - FibroScan VCTE Responder Analysis



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LSM, liver stiffness measurement; PBO, placebo; VCTE, vibration-controlled transient elastography.

Safety Overview

n (%)	Resmetirom 80mg (n=322)	Resmetirom 100mg (n=323)	Placebo (n=321)
≥1 TEAEs	**296 (91.9)**	**296 (91.6)**	**269 (92.2)**
Grade 1 (mild)	71 (22.0)	65 (20.1)	77 (24.0)
Grade 2 (moderate)	180 (55.9)	183 (56.7)	167 (52.0)
≥ Grade 3 (severe)	45 (14.0)	48 (14.9)	52 (16.2)
≥1 drug-related TEAEs	122 (37.9)	134 (41.5)	86 (26.8)
≥1 serious TEAEs	**38 (11.8)**	**41 (12.7)**	**39 (12.1)**
≥1 drug-related serious TEAEs	2 (0.6)	0	1 (0.3)
TEAEs leading to study discontinuation (in 52 Weeks)	**6 (1.9)**	**22 (6.8)**	**8 (2.5)**
Fatal TEAE	**1 (0.3)**	**1 (0.3)**	**1 (0.3)**
3-pt MACE* (adjudicated)	**1 (0.3)**	**1 (0.3)**	**1 (0.3)**
Other cardiovascular events (adjudicated)	**0**	**1 (0.3)**	**3 (0.9)**

Study discontinuations in the 100 mg arm were increased relative to placebo only during the first 12 weeks and were similar in all treatment groups for the remaining period of the first 52 weeks; after 52 weeks, placebo discontinuations were higher than drug treatment arms

Most AE discontinuations in the 100 mg arm were **GI-related**

No DILI events (adjudicated)

*Nonfatal stroke, nonfatal myocardial infarction, & cardiovascular death.

MACE, major adverse cardiovascular event; TEAE, treatment-emergent adverse event.

TEAEs Reported in >5% of Patients Overall

n (%)	Resmetirom 80mg (n=322)	Resmetirom 100mg (n=323)	Placebo (n=321)
Diarrhea	89 (27.6)	109 (33.7)	50 (15.6)
COVID-19	78 (24.2)	56 (17.3)	68 (21.2)
Nausea	70 (21.7)	62 (19.2)	40 (12.5)
Arthralgia	46 (14.3)	34 (10.5)	40 (12.5)
Back pain	36 (11.2)	27 (8.4)	38 (11.8)
Urinary tract infection	33 (10.2)	26 (8.0)	29 (9.0)
Fatigue	32 (9.9)	26 (8.0)	27 (8.4)
Pruritus	26 (8.1)	37 (11.5)	22 (6.9)
Abdominal pain upper	25 (7.8)	27 (8.4)	29 (9.0)
Headache	30 (9.3)	24 (7.4)	27 (8.4)
Vomiting	28 (8.7)	35 (10.8)	17 (5.3)
Type 2 diabetes	25 (7.8)	27 (8.4)	25 (7.8)
Abdominal pain	27 (8.4)	30 (9.3)	18 (5.6)
Constipation	21 (6.5)	27 (8.4)	18 (5.6)
Muscle spasms	14 (4.3)	22 (6.8)	21 (6.5)
Hypertension	16 (5.0)	13 (4.0)	25 (7.8)
Dizziness	21 (6.5)	19 (5.9)	11 (3.4)

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Conclusions

- Resmetirom is the **first treatment to achieve meaningful effects on both primary liver biopsy endpoints** that are reasonably likely to predict clinical benefit in a **Phase 3** trial in patients with NASH
- Both 80 and 100 mg doses were effective offering optionality for patients
- **Multiple supportive analyses and additional data** using non-invasive measures increase the confidence in the liver biopsy data.
- The safety profile of resmetirom in MAESTRO-NASH was consistent with previous Phase 2/3 trials in which the most common AEs were diarrhea & nausea at treatment initiation
- A limitation of these data are:
  - Lack of clinical outcomes data to correlate with the biopsy data; however, the MAESTRO-NASH trial will continue for 54 months to accrue & evaluate clinical outcomes
- These data from the MAESTRO-NASH trial **support the potential for resmetirom to provide benefit to patients with NASH**

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AE, adverse event; FDA, Food & Drug Administration; NASH, nonalcoholic steatohepatitis.

Acknowledgements

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