Early and Week 52 biomarker (MRI-PDFF, ALT, MRE and PRO-C3) responses to resmetirom predict improvements in MASH and liver fibrosis

Rohit Loomba,[1] Rebecca Taub,[2] Krishna Padmanabhan,[2] Dominic Labriola,[2] Mazen Noureddin,[3] Naim Alkhouri[4]

[1]UC San Diego School of Medicine, San Diego, CA, USA; [2]Madrigal Pharmaceuticals, Inc., West Conshohocken, PA, USA; [3]Pinnacle Clinical Research, San Antonio, TX, USA; [4]Summit Clinical Research, San Antonio, TX, USA

POSTER
FRI-179

MASLD: Therapy

INTRODUCTION

- Metabolic dysfunction–associated steatohepatitis (MASH) is a progressive liver disease that can lead to liver cirrhosis and adverse clinical outcomes[1]
- Resmetirom is an oral, liver-directed thyroid hormone receptor β agonist indicated in conjunction with diet and exercise for the treatment of adults with noncirrhotic MASH with moderate to advanced fibrosis (consistent with fibrosis stages F2 to F3)[2,3]
- In the ongoing phase 3 MAESTRO-NASH (NCT03900429) trial, resmetirom 80 mg and 100 mg demonstrated improvements in histologic endpoints at Week 52 after treatment initiation in patients with MASH and F2 to F3 fibrosis[4]
- Noninvasive biomarkers of liver fat, inflammation, and fibrosis, such as alanine aminotransferase (ALT), magnetic resonance elastography (MRE), magnetic resonance imaging proton density fat fraction (MRI-PDFF), and N-terminal propeptide of type III collagen (PRO-C3), are increasingly used to assess disease activity and may enable early prediction of treatment response and histologic outcomes in MASH[1,5]

AIM

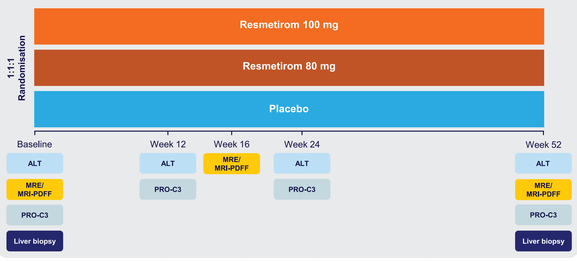
- To evaluate the association between early and Week 52 biomarker changes and Week 52 biopsy-confirmed MASH resolution and fibrosis improvement, and the effect of resmetirom on biomarker response and histologic outcomes

METHODS

Study design

- MAESTRO-NASH (NCT03900429) is an ongoing phase 3, randomised, double-blind, placebo-controlled trial in which patients with MASH were randomly assigned 1:1:1 to receive once-daily resmetirom 80 mg, resmetirom 100 mg, or placebo.[4] This analysis includes data through Week 52 (**Figure 1**)

FIGURE 1. Study design and outcome measures of the first 52 weeks of the MAESTRO-NASH trial



Patients in both resmetirom arms were pooled for the analyses described in this poster. All comparative results are reports for resmetirom versus placebo.
ALT and PRO-C3 assessments occurred at additional time points during the MAESTRO-NASH trial; the time points shown here were selected for longitudinal biomarker analyses.
ALT, alanine aminotransferase; MRE, magnetic resonance elastography; MRI-PDFF, magnetic resonance imaging proton density fat fraction; PRO-C3, N-terminal propeptide of type III collagen.

Population

- The trial included patients aged ≥18 years with biopsy-confirmed MASH and fibrosis stages F1B to F3 at baseline[4]
- Baseline demographic, clinical, imaging, and lipid parameters are summarised by treatment group

Outcomes

- The primary outcomes of MAESTRO-NASH are MASH resolution and fibrosis improvement at Week 52 and clinical outcomes at Month 54.[4] These analyses are based on Week 52 data
- Outcomes assessed in this exploratory analysis include liver biochemistry (ALT), imaging-based measures of liver stiffness (MRE) and liver fat (MRI-PDFF), as well as the serum fibrosis marker PRO-C3
- Biomarker responses were assessed at multiple time points (Weeks 12, 16, 24, and 52, where available) using predefined clinically relevant thresholds (≥20% reduction in ALT, ≥15% reduction in liver stiffness as measured by MRE, and ≥30% reduction in liver fat as measured by MRI-PDFF). Change and percentage change in PRO-C3 was evaluated as an exploratory fibrosis-related biomarker in patients with F3 fibrosis at Weeks 12, 24, and 52. Although ALT and PRO-C3 were assessed more frequently during the trial, selected time points were used for longitudinal biomarker analyses for brevity and consistency (**Figure 1**)
- Exploratory analyses evaluated the association between biomarker responses and Week 52 histologic outcomes (MASH resolution and fibrosis improvement)

Statistical analyses

- Associations between early and Week 52 biomarker responses (ALT, MRE, MRI-PDFF and PRO-C3) and Week 52 histologic outcomes were evaluated using 2×2 contingency tables. Odds ratios (ORs) were estimated using a Fisher exact test with chi-square testing for significance
- Treatment effects were assessed by comparing the odds of achieving biomarker response with resmetirom versus placebo using logistic regression models
- Descriptive analyses of percentage change in PRO-C3 were also performed in patients with baseline F3 fibrosis to compare biomarker reductions between patients with fibrosis improvement versus those without

RESULTS

Patient characteristics

- The Week 52 paired liver biopsy population was used for this analysis, including all patients who received at least 1 dose of the study drug, had a baseline liver biopsy, and completed the Week 52 visit with an acceptable liver biopsy
- A total of 782 patients were included in the analysis, of whom 506 received resmetirom and 276 received placebo
- Baseline demographic and disease characteristics were well balanced between treatment groups, with comparable age, sex distribution, liver disease severity, and fibrosis stage (**Table 1**)

TABLE 1. Baseline characteristics

Characteristic	Resmetirom (n = 506)	Placebo (n = 276)
Age, mean ± SD, years	56.2 (11.0)	57.0 (10.0)
Sex, male, n (%)	223 (44.1)	120 (43.5)
Race, n (%)		
Asian	12 (2.4)	8 (2.9)
Black	7 (1.4)	9 (3.3)
White	460 (90.9)	238 (86.2)
Other	27 (5.3)	21 (7.6)
Ethnicity, Hispanic or Latino, n (%)	121 (23.9)	47 (17.0)
CAP by VCTE, median (Q1, Q3), dB/m	350.0 (320.0, 380.0)	348.5 (321.5, 377.0)
LSM by VCTE, median (Q1, Q3), kPa	11.5 (9.4, 15.2)	11.7 (9.4, 14.5)
LSM by MRE, median (Q1, Q3), kPa	3.4 (2.9, 4.0)	3.4 (2.8, 4.0)
% liver fat by MRI-PDFF, median (Q1, Q3)	16.7 (12.8, 22.0)	16.9 (12.5, 22.4)
ALT, median (Q1, Q3), U/L	48.0 (34.0, 66.0)	46.0 (31.0, 70.0)
Fibrosis stage, n (%)		
F1B	24 (4.7)	18 (6.5)
F2	156 (30.8)	92 (33.3)
F3	319 (63.0)	162 (58.7)

ALT, alanine aminotransferase; CAP, controlled attenuation parameter; dB, decibel; F, fibrosis stage (F1B: mild fibrosis [substage B], F2: moderate fibrosis, F3: advanced fibrosis); kPa, kilopascal; LSM, liver stiffness measurement; MRE, magnetic resonance elastography; MRI-PDFF, magnetic resonance imaging proton density fat fraction; Q, quartile; VCTE, vibration-controlled transient elastography.

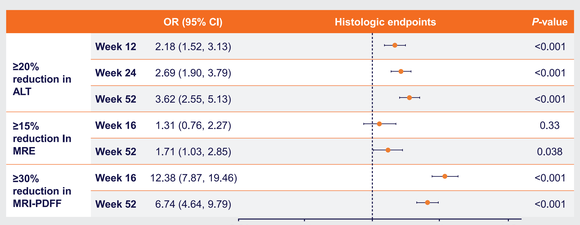
Association between biomarker response and Week 52 histologic outcomes

- A ≥20% reduction in ALT at Weeks 12, 24, and 52, a ≥15% reduction in liver stiffness as measured by MRE at Weeks 16 and 52, and a ≥30% reduction in liver fat as measured by MRI-PDFF at Weeks 16 and 52, respectively, were each associated with a higher OR of fibrosis improvement and MASH resolution at Week 52
- In data combining resmetirom and placebo arms, ORs for association of these biomarker response thresholds with Week 52 fibrosis improvement or MASH resolution ranged from 2.04 to 8.83, with every *p*-value <0.001
- This establishes statistically significant associations for these biomarker response thresholds with histologic improvements assessed at Week 52 of the trial

Resmetirom vs placebo treatment effect on biomarker response

- Resmetirom significantly increased the likelihood of achieving a ≥20% reduction versus placebo in ALT at Weeks 12, 24, and 52 (ORs, 2.18, 2.69, and 3.62, respectively; $P < 0.001$ for all; **Figure 2**)
- Resmetirom was associated with higher odds of achieving a ≥15% reduction versus placebo in liver stiffness as measured by MRE at Week 52 (OR, 1.71, $P = 0.038$), but not at Week 16 (OR, 1.31, $P = 0.33$; **Figure 2**)
- Resmetirom significantly increased the likelihood of achieving a ≥30% reduction versus placebo in liver fat as measured by MRI-PDFF at Weeks 16 and 52 (ORs, 12.38 and 6.74, respectively; both $P < 0.001$; **Figure 2**)

FIGURE 2. Treatment effect of resmetirom versus placebo on biomarker response

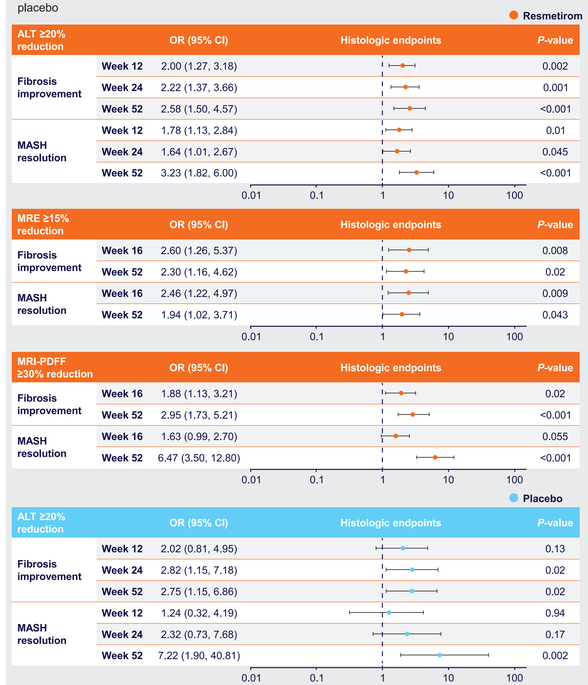


ALT, alanine aminotransferase; MRE, magnetic resonance elastography; MRI-PDFF, magnetic resonance imaging proton density fat fraction.

Association between biomarker response and histologic outcomes within treatment groups

- Amongst patients treated with resmetirom, a ≥20% reduction in ALT at Weeks 12, 24, and 52 was associated with significantly higher odds of Week 52 fibrosis improvement compared with placebo (ORs, 2.00, 2.22, and 2.58, respectively; all $P \leq 0.002$); similar trends were observed for MASH resolution (**Figure 3**)
- A ≥15% reduction in liver stiffness as measured by MRE was associated with significantly higher odds of Week 52 fibrosis improvement in the resmetirom group (ORs, 2.60 and 2.30 at Weeks 16 and 52, respectively; $P \leq 0.02$ for both), with weaker associations in placebo; similar trends were observed for MASH resolution (**Figure 3**)
- A ≥30% reduction in liver fat as measured by MRI-PDFF in the resmetirom group was associated with significantly increased odds of Week 52 fibrosis improvement (ORs, 1.88 and 2.95 at Weeks 16 and 52, respectively; $P \leq 0.02$ for both) and MASH resolution (ORs, 6.47 at Week 52) (**Figure 3**)

FIGURE 3. Association between biomarker response and Week 52 histologic outcomes for resmetirom and placebo

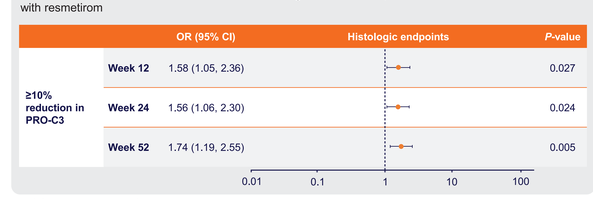


ALT, alanine aminotransferase; MASH, metabolic dysfunction–associated steatohepatitis; MRE, magnetic resonance elastography; MRI-PDFF, magnetic resonance imaging proton density fat fraction.

Association between PRO-C3 change and fibrosis improvement (F3 population only)

- PRO-C3, a marker of type III collagen formation and fibroblast activity directly related to fibrogenesis,[7] was evaluated as an exploratory biomarker of fibrotic activity in patients with F3 fibrosis
- In patients with F3 fibrosis, achieving a ≥10% reduction in PRO-C3 at Weeks 12 and 52, but not Week 24, was associated with fibrosis improvement at Week 52
- Percentage change in PRO-C3 at Weeks 24 and 52 demonstrated a relationship with fibrosis improvement across all treatment groups, with greater Week 52 reductions observed in patients with fibrosis improvement versus those without; (resmetirom 80 mg: −23% vs −7%; 100 mg: −20% vs −14%; placebo: −20% vs 0%). This relationship was supported by regression analyses (resmetirom, $P = 0.0017$; placebo, $P = 0.04$)
- Resmetirom significantly increased the likelihood of achieving a ≥10% reduction in PRO-C3 at Weeks 12, 24, and 52 (ORs, 1.58, 1.56, and 1.74; all $P < 0.05$; **Figure 4**)

FIGURE 4. Association between PRO-C3 and histologic outcomes for patients with advanced fibrosis treated with resmetirom



PRO-C3, N-terminal propeptide of type III collagen.

CONCLUSION

- Early and Week 52 biomarker responses, defined by prespecified reduction thresholds in ALT, MRE, MRI-PDFF, and PRO-C3 (F3), were associated with Week 52 histologic outcomes in placebo and resmetirom arms, supporting their utility as indicators of treatment response in MASH
- Resmetirom significantly increased the likelihood of achieving early and sustained (at Week 52) biomarker responses compared to placebo in ALT and MRI-PDFF, showing strong relationships with fibrosis improvement and MASH resolution on the Week 52 liver biopsy
- Resmetirom also significantly increased the likelihood of achieving a ≥10% reduction in PRO-C3 at Weeks 12, 24, and 52 compared with placebo in patients with F3 fibrosis
- Early changes in noninvasive biomarkers may enable timely identification of resmetirom treatment response, support prediction of longer-term histologic outcomes, and provide practical tools for monitoring disease progression and therapeutic efficacy without repeat biopsy

DISCLOSURES

RL is a shareholder of 89bio and Sagimet Biosciences; a cofounder of LipoNexus, Inc.; and reports grant/research support from Madrigal Pharmaceuticals, Inc., 89bio, Aardvark Therapeutics, Altimmune, Alnylam/Regeneron, Amgen, Arrowhead Pharmaceuticals, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, CohBar, Galectin Therapeutics, Galmed Pharmaceuticals, Gilead, Glympse Bio, Hanmi, Hightide, Inipharma, Intercept, Inventiva, Ionis, Janssen, Inc., Lilly, Merck, Metacrine, Inc., NGM Biopharmaceuticals, Novartis, Novo Nordisk, Pfizer, Sagimet Biosciences, Sonic Incytes, Terns Pharmaceuticals, Theratechnologies, and Viking Therapeutics. **RT**, **KP**, and **DL** are employees and shareholders of Madrigal Pharmaceuticals, Inc. **MN** is a shareholder of ChronWell, CytoDyn, Inc., and Rivus Pharmaceuticals and reports advisory/consulting, speaker fees, and/or other relationships with Madrigal Pharmaceuticals, Inc., Akero Therapeutics, Inc., Aligos Therapeutics, Allergan Pharmaceuticals, Altimmune, AstraZeneca, Boehringer Ingelheim, Boston Pharmaceuticals, Bristol Myers Squibb, Conatus Pharma, Corcept Therapeutics, Inc., CytoDyn, Inc., Enanta Pharmaceuticals, Inc., Galectin Therapeutics, Gilead Sciences, Genfit, GSK, Lilly, Merck, Novartis, Novo Nordisk, Takeda Pharmaceutical Company Ltd., Terns Pharmaceuticals, Inc., Viking Therapeutics, and Zydus Pharmaceuticals, Inc. **NA** reports consulting and/or grant/research support from Madrigal Pharmaceuticals, Inc., 89bio, Akero, Arbutus Biopharma, AstraZeneca, BioAge, Boehringer Ingelheim, Bristol Myers Squibb, Corcept Therapeutics, CymaBay Therapeutics, DSM, Echosens, Fibronostics, Galectin Therapeutics, Genentech, Genfit, Gilead Sciences, Healio, Hepagene Therapeutics, Intercept Pharmaceuticals, Inventiva Pharma, Ionis Pharmaceuticals, Ipsen, Lilly, LiverRight, Merck, NGM Biopharmaceuticals, Noom, NorthSea Therapeutics, Novo Nordisk, Perspectum, Pfizer, PharmaIN, Poxel, Regeneron, Viking Therapeutics, and Zydus Pharmaceuticals.

ACKNOWLEDGEMENTS

Medical writing assistance was provided by ApotheCom (San Francisco, CA, USA) and funded by Madrigal Pharmaceuticals, Inc., West Conshohocken, PA, USA. Funding for this research was provided by Madrigal Pharmaceuticals, Inc., West Conshohocken, PA, USA.

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