Assessment of resmetirom efficacy (80 mg vs 100 mg) stratified by baseline body mass index and weight in patients from the MAESTRO-NASH trial

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Poster 3212

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

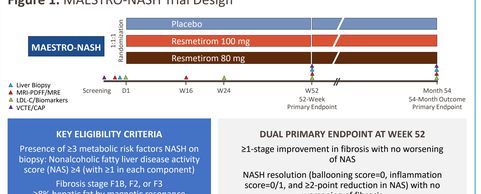
1. Houston Methodist Hospital, Houston, TX, USA; 2. Arizona Liver Health, Phoenix, AZ, USA; 3. Madrigal Pharmaceuticals, Inc., West Conshohocken, PA, USA; 4. University of California San Diego, San Diego, CA, USA

Background

- Resmetirom, an oral, liver-directed thyroid hormone receptor beta (THR-β) selective agonist, was approved in March 2024 in the United States for the treatment of adults with noncirrhotic nonalcoholic steatohepatitis (NASH) with moderate to advanced liver fibrosis (consistent with stages F2 to F3 fibrosis)
- MAESTRO-NASH is an ongoing 54-month, randomized, double-blind, placebo-controlled, Phase 3 serial liver biopsy trial evaluating the efficacy and safety of oral, daily 80 mg or 100 mg resmetirom in adults with biopsy-confirmed NASH (NCT03900429)
- At week 52, both primary endpoints were met at both clinical doses
- The recommended dosage of resmetirom is based on actual body weight. For patients weighing:
  - <100 kg, the recommended dosage is 80 mg **orally** once daily
  - ≥100 kg, the recommended dosage is 100 mg **orally** once daily

MAESTRO-NASH Study Design/Methods

Figure 1. MAESTRO-NASH Trial Design



KEY ELIGIBILITY CRITERIA

Presence of ≥3 metabolic risk factors NASH on biopsy: Nonalcoholic fatty liver disease activity score (NAS) ≥4 (with ≥1 in each component)

Fibrosis stage F1B, F2, or F3

≥8% hepatic fat by magnetic resonance imaging proton density fat fraction (MRI-PDFF)

DUAL PRIMARY ENDPOINT AT WEEK 52

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

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

- In the MAESTRO-NASH study, randomization to 80 mg and 100 mg doses was equal across all body weights (**Figure 1**)
- Analyses were conducted to provide additional evidence of a relationship between **resmetirom dose**, **baseline body weight**, and **body mass index (BMI)** and safety/efficacy readouts (**Table 1**)

Table 1. MAESTRO-NASH Baseline Characteristics

	Resmetirom 80 mg (N=322)	Resmetirom 100 mg (N=323)	Placebo (N=321)
Age, years, mean (SD)	55.9 (11.5)	57.0 (10.8)	57.1 (10.5)
Sex, male, %	44	44	45
Race, White, n (%)	291 (90.4)	291 (90.1)	281 (87.5)
Body mass index, kg/m^2 , mean (SD)	35.5 (6.4)	36.2 (7.4)	35.3 (6.5)
Body weight, kg, mean (SD)	100.1 (22.3)	101.9 (22.9)	100.2 (23.1)
Type 2 diabetes, n (%)	224 (69.6)	213 (65.9)	210 (65.4)
Hypertension, n (%)	243 (75.5)	254 (78.6)	257 (80.1)
Dyslipidemia, n (%)	230 (71.4)	236 (73.1)	224 (69.8)
Hypothyroidism, n (%)	39 (12.1)	46 (14.2)	45 (14.0)
Baseline liver biopsy, n (%)			
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	199 (61.8)	208 (64.4)	191 (59.5)
FibroScan VCTE/LSM, kPa, mean (SD)	13.3 (6.8)	13.6 (7.1)	12.9 (5.5)
FibroScan CAP, dB/m, mean (SD)	346.1 (37.2)	349.4 (38.7)	347.2 (37.0)
MRE, kPa, mean (SD)	3.5 (0.9)	3.7 (1.1)	3.5 (1.0)
MRI-PDFF, % fat fraction, mean (SD)	18.2 (6.8)	17.2 (6.6)	17.8 (6.8)

Results

- Diarrhea adverse events (AEs) and AE discontinuations were higher in the 100 mg resmetirom group; overall discontinuations at 100 mg were higher in the lower body weight groups (<100 kg) (**Figure 2**)
- Discontinuations at 80 mg resmetirom were similar to placebo (**Table 2**)

Figure 2. Discontinuation Rates Through Week 52 in Resmetirom 80 mg vs 100 mg Cohorts

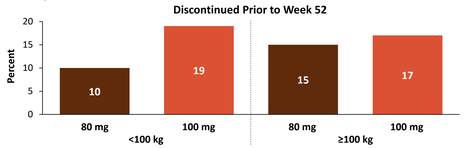
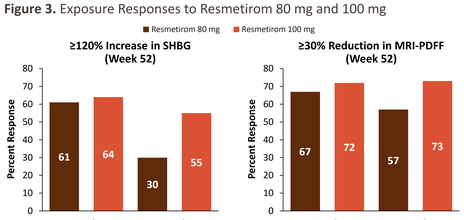


Table 2. Discontinuations Due to Adverse Events Through Week 52

Safety Summary (Primary Population) Event	Resmetirom 80 mg (N=322)	Resmetirom 100 mg (N=323)	Placebo (N=321)
Adverse event leading to trial discontinuation before Week 52, n (%)	6 (1.9)	22 (6.8)	**7 (2.2)**
Adverse events affecting >10% of patients in any group, n (%)			
Diarrhea	87 (27.0)	108 (33.4)	**50 (15.6)**
Covid-19	69 (21.4)	54 (16.7)	**66 (20.6)**
Nausea	71 (22.0)	61 (18.9)	**40 (12.5)**
Arthralgia	48 (14.9)	35 (10.8)	**40 (12.5)**
Back pain	35 (10.9)	27 (8.4)	**38 (11.8)**
Urinary tract infection	33 (10.2)	27 (8.4)	**27 (8.4)**
Fatigue	33 (10.2)	26 (8.0)	**28 (8.7)**
Pruritus	26 (8.1)	37 (11.5)	**22 (6.9)**

Discontinuations related to the COVID pandemic (lost to follow-up/patient decision) resulted in higher-than-expected discontinuation at week 52 in all treatment arms (placebo 11% discontinuation at week 52)

Figure 3. Exposure Responses to Resmetirom 80 mg and 100 mg



- Pharmacokinetic modeling concluded that higher exposure to resmetirom was associated with higher hepatic target engagement as reflected by higher sex hormone-binding globulin (SHBG) responses and higher magnetic resonance imaging proton density fat fraction (MRI-PDFF) reduction (**Figure 3**)
- The only variable that determined exposure to resmetirom in the NASH population was body weight
- More patients treated with 100 mg when compared with 80 mg achieved targets for SHBG and PDFF; differences between doses occurred primarily in patients ≥100kg
- Exposure modeling indicated that higher NASH and fibrosis responses on biopsy were associated with higher exposure to resmetirom (**Figure 4**)
- Study median body weight was 100 kg (220 pounds)
- In the population with both a baseline and week 52 liver biopsy, equivalent biopsy responses were achieved in patients who were <100 kg at 80 mg and 100 mg (**Figure 5**)
- Lower responses were achieved at 80 mg in the ≥100 kg patients

Figure 4. Liver Biopsy Responses to Resmetirom Dose: Body Weight

Paired Biopsy Population (both baseline and week 52 not placebo corrected)

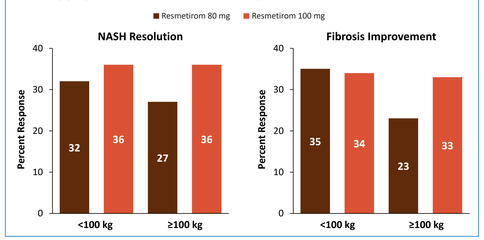
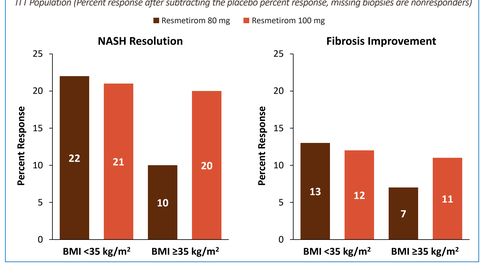


Figure 5. Liver Biopsy Responses to Resmetirom Dose: Effect of BMI (Placebo Adjusted, ITT)

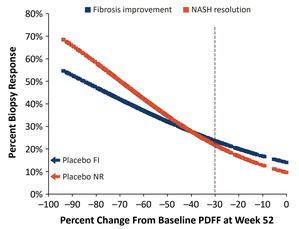
ITT Population (Percent response after subtracting the placebo percent response, missing biopsies are nonresponders)



All resmetirom-treated patients (80 mg and 100 mg combined)

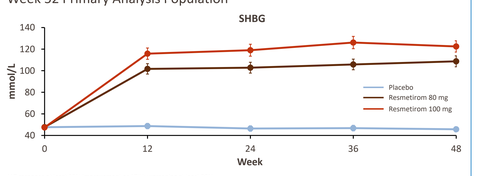
- Logistic regression model, predicting response on biopsy as a function of percent change from baseline in MRI-PDFF (**Figure 6**)
- The graphs show that the greater the week 52 PDFF reduction, the greater likelihood for fibrosis and NASH responses with resmetirom treatment
- PDFF reduction in resmetirom-treated patients was highly associated with both NASH resolution and fibrosis improvement
- Placebo patients with more PDFF reduction had more NASH reduction but not fibrosis improvement
- At least a 30% PDFF response was observed in 96% and 88% of resmetirom 100 mg responders for NASH resolution and fibrosis improvement, respectively
  - The percent reduction in PDFF rather than resmetirom dose impacted the response on biopsy
- The response on biopsy at 80/100 mg was equally correlated with the magnitude of PDFF response. Doses were combined in this predictive model

Figure 6. MRI-PDFF Reduction Strongly Predictive of Resmetirom Biopsy Responses on Fibrosis and NASH



- Sensitive biomarkers SHBG, PDFF, and low-density lipoprotein/ apolipoprotein B showed a persistent dose response over time with a difference between 80 mg and 100 mg (**Figure 7**)
- Other tests like alanine aminotransferase (ALT) showed an equally high response at both doses, regardless of baseline body weight (**Figures 9, 10**)

Figure 7. Change Over Time From Baseline in ALT and SHBG MAESTRO NASH Week 52 Primary Analysis Population



ALT response at least 20% improvement or 171U; worsening at least 20%.

Figure 8. ALT Response Week 48 (All Randomized Patients)

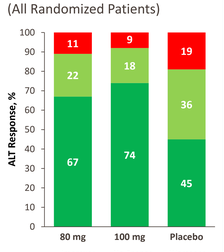
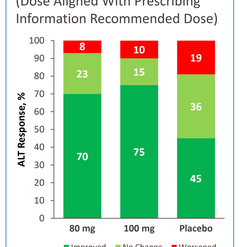


Figure 9. ALT Response Week 48 (Dose Aligned With Prescribing Information Recommended Dose)



- Vibration-controlled transient elastography (VCTE) improved over time (1–3 years) relative to placebo in resmetirom-treated patients, with both doses showing a similar durable response (**Figure 10**)
  - New data have indicated that less than 10 kPa correlated with fewer liver-related events[1]
- Controlled attenuation parameter (CAP) was stable over time, with both doses showing a similar durable response
- VCTE responder analyses at 1–3 years in the MAESTRO-NASH population reflect improvement relative to placebo, and <10% resmetirom-treated patients had worsening of VCTE (**Figure 11**)

Figure 10. CAP/VCTE Over Time (Patients With 3-Year Data)

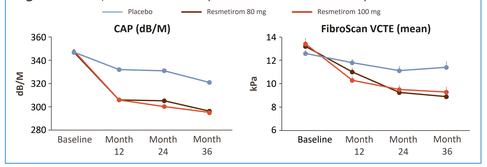
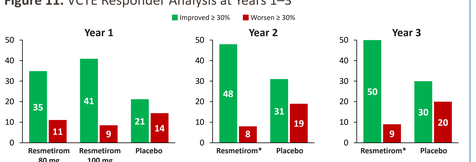


Figure 11. VCTE Responder Analysis at Years 1–3



*All resmetirom-treated patients (80 mg and 100 mg combined).

Conclusions

- **Pharmacokinetic modeling concluded that higher exposure to resmetirom was associated with higher hepatic target engagement, as reflected by higher SHBG responses and higher MRI-PDFF reduction**
- **The only variable that influenced exposure to resmetirom in the NASH population was body weight**
- **Resmetirom was well tolerated at both doses, with a few more discontinuations in the 100-mg treatment group due to gastrointestinal AEs. Discontinuations at 100 mg appeared to be slightly higher than at 80 mg in patients with baseline body weight <100 kg**
- **Slightly lower rates of fibrosis improvement and NASH resolution on biopsy were observed in patients who were ≥100 kg or had BMI ≥35 in the 80-mg treatment group versus the 100-mg treatment group**
- **Other biomarkers, such as ALT, FibroScan, CAP, and VCTE, showed similar improvements relative to placebo at 80 mg and 100 mg. Responses on FibroScan in resmetirom-treated patients were durable out to 3 years of treatment and showed improvement and less worsening than placebo**

Reference

1. Gawrieh S, Vilar-Gomez E, Wilson LA, et al. Increases and decreases in liver stiffness measurements are independently associated with the risk of liver-related events in NAFLD. *J Hepatol.* Published online May 16, 2024. doi:10.1016/j.jhep.2024.05.008

Disclosures

MN: Altimmune, Aligos Therapeutics, AstraZeneca, Boehringer Ingelheim, Boston Pharmaceuticals, CytoDyn Inc., GSK plc., Lilly, Madrigal Pharmaceuticals, Merck & Co., Inc., Novo Nordisk, Takeda Pharmaceutical Company Limited, Terns Pharmaceuticals, Inc., ChronWell, Rivus Pharmaceuticals, Allergan Pharmaceuticals, Akero Therapeutics, Inc., Bristol Myers Squibb, Conatus Pharma, Corcept Therapeutics, Inc., Enanta Pharmaceuticals, Inc., Gilead Sciences, Inc., Galectin Therapeutics, Genfit, Novartis, Viking Therapeutics, Zydus Pharmaceuticals, Inc. **NA:** Echosens, Fibronostics, Gilead Sciences, Inc., 89Bio, Inc., Boehringer Ingelheim, Intercept Pharmaceuticals, Inc., Ionis Pharmaceuticals, Inc., Madrigal Pharmaceuticals, Novo Nordisk, Viking Therapeutics, Zydus Pharmaceuticals, Inc., Novo Nordisk. **RT, DL:** Madrigal Pharmaceuticals. RL: Aardvark Therapeutics, Altimmune, Anylam/Regeneron, Amgen, Arrowhead Pharmaceuticals, AstraZeneca, Bristol-Myer Squibb, CohBar, Eli Lilly, Galmed, Gilead, Glympse bio, Hightide, Inipharma, Intercept, Inventiva, Ionis, Janssen Inc., Madrigal, Metacrine, Inc., NGM Biopharmaceuticals, Novartis, Novo Nordisk, Merck, Pfizer, Sagimet, Theratechnologies, 89 bio, Terns Pharmaceuticals and Viking Therapeutics. Boehringer-Ingelheim, Galectin Therapeutics, Hanmi, Merck, Sonic Incytes, Terns Pharmaceuticals, LipoNexus