Liver enzymes reductions from baseline over time in resmetirom treated patients in a Phase 3 study, MAESTRO-NASH

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Poster 3220

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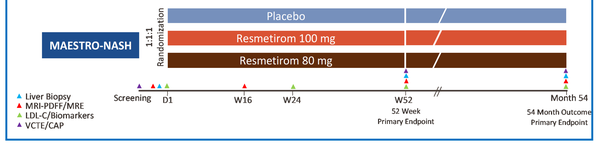
Background

- Resmetirom is an orally administered THR-b agonist indicated for the treatment of adults with NASH with moderate to advanced liver fibrosis (consistent with stages F2 to F3)
- Approved by the US FDA in March 2024
- Pivotal trial: MAESTRO-NASH (NCT03900429), an ongoing 54-month, randomized, double-blind, placebo-controlled Phase 3 trial in adult patients with biopsy-confirmed NASH and fibrosis (**Figure 1**)

Figure 1. MAESTRO-NASH trial design



- As patients receiving resmetirom may also be receiving treatment with statins, it is important to determine the effects of resmetirom and statin coadministration on liver function
- The objective of this analysis was to evaluate the effects of resmetirom and statins, alone and in combination, on levels of the liver enzymes ALT, AST, and GGT over time

Methods

- Patients in MAESTRO-NASH study were monitored for changes from baseline in ALT, AST, and GGT
  - Enzyme levels were measured at baseline and at 4, 12, 24, 36, 48 weeks post-randomization
  - Changes in liver enzymes were assessed according to statin treatment at baseline in each of the study arms
- Eligible patients have biopsy-confirmed NASH and fibrosis and an NAFLD activity score of >4 on a scale of 0 to 8 (higher scores=more severe disease)
- Prescreening criteria require AST >17 IU (women) and AST >20 IU (men)
- Patients were excluded if serum ALT was >250 U/L

Results

Statin Use at Baseline	Total Population (N=966)
Any Statin, n (%)	473 (49)
Atorvastatin	223 (23.1)
Lovastatin	7 (0.7)
Pitavastatin	3 (0.3)
Pravastatin	63 (6.5)
Rosuvastatin	114 (11.8)
Simvastatin	64 (6.6)
High-intensity statin therapy*, %	13
Moderate to low-intensity statin therapy, %	36

*Rosuvastatin 20 mg; atorvastatin 40 mg.

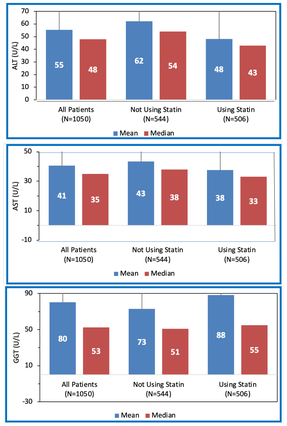
ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; THR, thyroid hormone receptor; US FDA, United States Food & Drug Administration.

Results

Effects of Statin Use on Liver Enzyme Levels

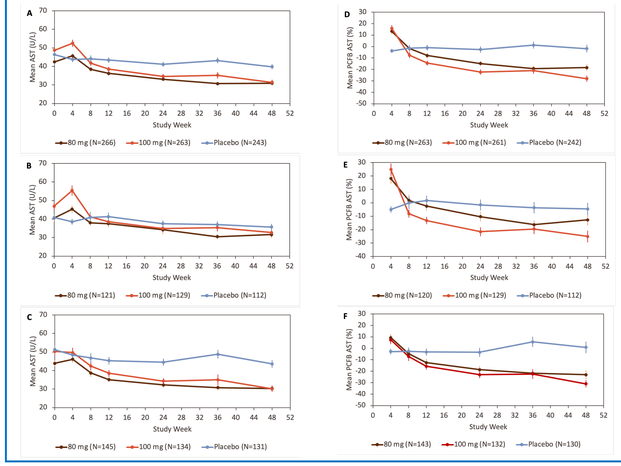
- Among patients receiving statins at baseline, a total of 149 patients received resmetirom 80 mg, 166 received resmetirom 100 mg, and 158 received placebo
- At baseline, patients receiving statins had lower ALT and AST levels than those not receiving statins (**Figure 2**)
- A mild, transient increase in AST and ALT levels (<1.5-fold baseline) was observed at Week 4 in patients receiving statins compared with patients not receiving statins (**Figures 3-4**)
  - This increase did not exceed the level of ALT or AST at Week 4 in patients not receiving statins
  - Elevations resolved by Week 8, and liver enzyme levels declined thereafter
- GGT levels declined from the time resmetirom treatment was initiated (**Figure 5**)

Figure 2. Baseline Liver Enzymes: Statin/No Statin



Baseline liver enzymes in patients on statins are lower for ALT and AST and higher for GGT in patients with NASH

Figure 4. AST Levels at Baseline and Post Randomization. A= all patients with baseline levels ≥30 I/U. B= patients on statin. C= patients not on a statin. D, E, F: PCFB= percentage change from baseline



Week 48 Results

- In patients with ALT levels ≥30 IU at baseline,
  - ALT declined from baseline by 20% and 24% in the resmetirom 80 and 100 mg arms, respectively, in patients receiving statins (P<0.001 vs placebo)
  - ALT declined from baseline by 37% and 43% in the resmetirom 80 and 100 mg arms, respectively, in patients not receiving statins (P<0.001 vs placebo)

Figure 3. ALT Levels at Baseline and Post Randomization. A= all patients with baseline levels ≥30 I/U. B= patients on statin. C= patients not on a statin. (D, E, F: PCFB= percentage change from baseline)

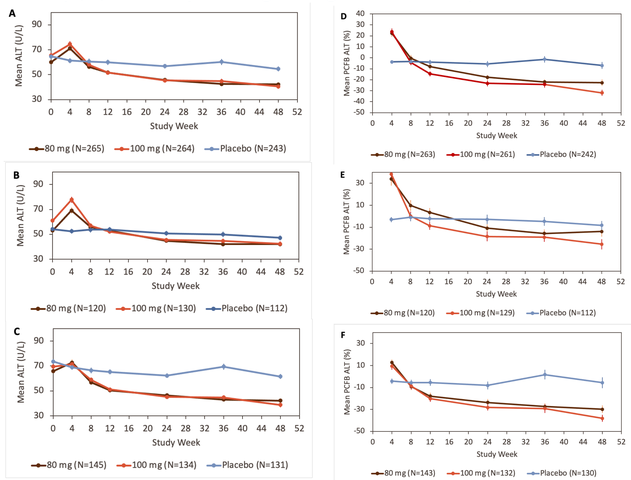
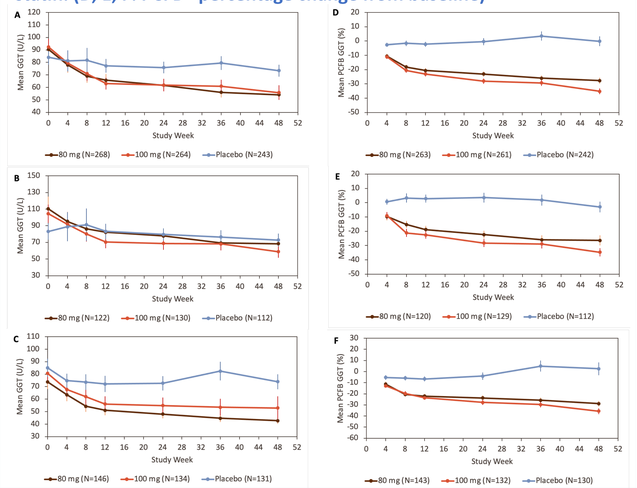


Figure 5. GGT Levels at Baseline and Post Randomization. A= all patients with baseline levels ≥30 I/U. B= patients on statin. C= patients non on a statin. (D, E, F: PCFB= percentage change from baseline)



Conclusions

- **Liver enzyme levels declined significantly in resmetirom treated patients relative to placebo beginning at Week 12**
- **Transient increases in ALT and AST of <1.3-fold over baseline occurred at Week 4 in patients co-dosed with resmetirom and statins; resmetirom patients not on statins showed <10% increase in liver enzymes at Week 4. Liver enzymes declined below baseline in all patients irrespective of statin after Week 4.**
- **Patients receiving statins had lower baseline ALT and AST levels, and elevations at Week 4 were generally not higher than levels in patients not on statins.**
- **Lipid lowering, NASH resolution and Fibrosis improvement rates were similar in patients on statins versus not on statins indicating that early liver enzyme excursions do not impact either safety or efficacy**
- **GGT levels declined from the time resmetirom treatment was initiated in all patients**

Disclosures

- **Baum reports: Altimmune, Amgen, Axcella, Beren Therapeutics, Boehringer Ingelheim, Eli Lilly, Esperion, Ionis Pharmaceuticals, Madrigal Pharmaceuticals, Merck, Novartis, Regeneron**
- **Taub and Labriola are employees of Madrigal Pharmaceuticals**
- **Alkhouri reports: 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**
- **Noureddin reports: 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.**