Use of non-invasive tests to diagnose and follow NASH with liver fibrosis patients treated with resmetirom

As presented at AASLD 2024

Naim Alkhouri[1], Sam Moussa[2], Arun J. Sanyal[3], Rebecca Taub[4], Dominic Labriola[4], Mazen Noureddin[5]

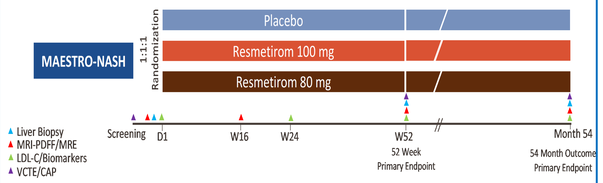
Poster 3190

1. Arizona Liver Health, Phoenix, AZ, USA; 2. University of Arizona, Tucson, AZ, USA; 3. Virginia Commonwealth University, Richmond, VA, USA; 4. Madrigal Pharmaceuticals, Inc., West Conshohocken, PA, USA; 5. Houston Methodist Hospital, Houston, TX, USA

Background

- Resmetirom, an oral, liver-directed THR-β–selective agonist, was approved in March 2024 for the treatment of adult patients with noncirrhotic NASH and liver fibrosis consistent with F2 to F3 stages
- Approval was based on efficacy demonstrated in MAESTRO-NASH (NCT03900429), an ongoing 54-month, randomized, double-blind, placebo-controlled Phase 3 trial in adult patients with biopsy-confirmed NASH and fibrosis
  - In MAESTRO-NASH, 966 patients with biopsy-confirmed NASH were randomly assigned in a 1:1:1 ratio to receive resmetirom 80 mg, resmetirom 100 mg, or placebo once daily (**Figure 1**)

Figure 1. MAESTRO-NASH trial design



- In MAESTRO-NASH, both resmetirom doses achieved either NASH resolution with no worsening of fibrosis or ≥1-stage improvement in fibrosis with no worsening of NASH at Week 52
- Biopsy is less commonly used in real-world clinical practice due to its invasive nature, procedure-related limitations, and potential for serious complications.
- As such, the diagnosis of suspected MASH in most patients is based upon clinical, laboratory, and imaging data that are collectively referred to as results of noninvasive tests (NITs) with appropriate exclusion of other liver conditions.
- This analysis of data from MAESTRO-NASH aimed to assess the accuracy of NASH/fibrosis diagnosis and follow-up of resmetirom-treated patients long-term using real-world, readily available non-invasive testing

Methods

- Machine learning models were used to evaluate the relative importance of intrinsic characteristics and screening/baseline biomarkers of patients with fibrosis stages F0 (no fibrosis) to F4 (cirrhosis) on liver biopsy
  - The random forest model was selected for its predictive performance
- Long-term effects of resmetirom treatment on results of non-invasive tests and biomarkers were evaluated at baseline and at Months 12, 24, and 36 post randomization
  - 23 baseline clinical characteristics were used
  - Only readily available tests (FibroScan [VCTE], ELF, standard blood chemistries) were used to determine the accuracy in diagnosing patients with NASH consistent with F2 to F3

Results

Subjects

- Data from 1247 patients with F0 to F4 on liver biopsy were analyzed
- The F2 to F3 population from MAESTRO-NASH was analyzed

Analysis

- In the F2 to F3 population (n=888), FibroScan VCTE was 12 (10, 15) median kPa and ELF was 9.7 (9.2, 10.4)
- Using 23 baseline clinical characteristics, standard labs, FibroScan, and ELF, the random forest model determined that the most important markers distinguishing F2 to F3 from either F0/1 or F4 were FibroScan VCTE, platelets, FIB-4, FAST, and ELF
- The AUC (SD) for separation from F0/F1 or F4 were 0.76 (0.03) and 0.90, respectively
- Among patients with F2 to F3:
  - 58% were correctly predicted to be F2/F3
  - 26% were incorrectly predicted to be F0/F1
  - 16% were incorrectly predicted to be F4
- Among patients with F4:
  - 72% were correctly predicted to be F4
  - 19% were incorrectly predicted to be F2/3
- The addition of MRE/MRI-PDFF increased diagnostic accuracy for F2/F3 to 68% and F4 to 81%
- FIB-4 (**Figure 2**) poorly predicts non-cirrhotic NASH fibrosis stage
- Including a lower cutoff of VCTE (8.5-10) is important to capture many F2 and F3 patients (**Figure 2**)
  - Help to gain confidence in fibrosis staging
  - A low ELF with a high VCTE suggests repeating the VCTE

Week 52 Response to Resmetirom

- Resmetirom showed improvement relative to placebo on multiple responses at Week 52, including MRI-PDFF (the most predictive of a biopsy response), liver enzymes, lipids, and FibroScan CAP and VCTE
- ALT response at Week 48 (**Figure 3**) was equivalent at both doses
- PDFF reduction in resmetirom treated patients (**Figure 4**) 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 80 mg and 100 mg responders for NASH resolution and fibrosis improvement, respectively
- The % reduction in PDFF rather than resmetirom dose impacted the response on biopsy
- The response on biopsy at 80 mg and 100 mg was equally correlated with the magnitude of PDFF response. Doses were combined in this predictive model
- Resmetirom responses FibroScan CAP/VCTE (**Figures 5 and 6**) were durable/increased at Months 24 and 36 relative to placebo

Figure 3. ALT Response at Week 48 in all randomized patients

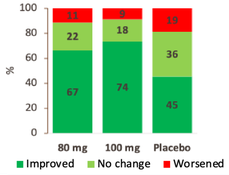


Figure 4. MRI-PDFF in Resmetirom Treated Patients

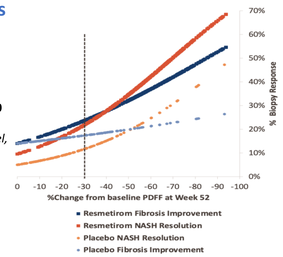


Figure 5. CAP from BL to Month 36 (mean)

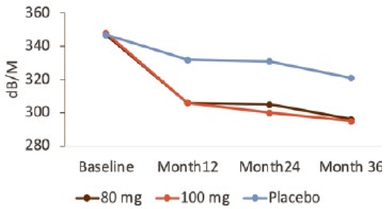


Figure 6. VCTE from BL to Month 36 (mean)

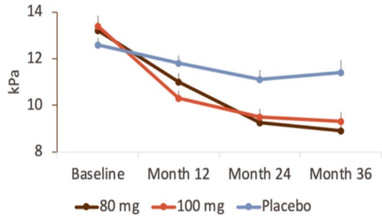
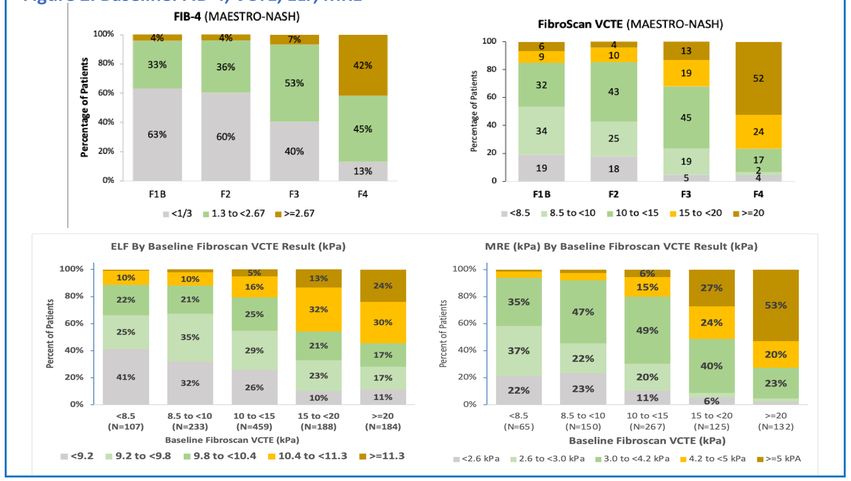


Figure 2. Baseline: FIB-4, VCTE, ELF, MRE



Conclusions

- **Identification of patients with NASH F2 to F3 was achieved with FibroScan VCTE, ELF, and readily available blood tests. F1B are F2 equivalent (F1B is moderate fibrosis on biopsy)**
- **In addition to FibroScan VCTE, practitioners may consider expanded noninvasive criteria (ELF, MRE) to help refine fibrosis staging**
- **Patients with fibrosis stage F4 were effectively ruled out**
- **Long-term follow-up of resmetirom-treated patients with non-invasive tests showed durability of treatment response relative to placebo**

Disclosures

- **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**
- **Moussa and Sanyal report Madrigal Pharmaceuticals, Inc.**
- **Taub and Labriola are employees of Madrigal**
- **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.**