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

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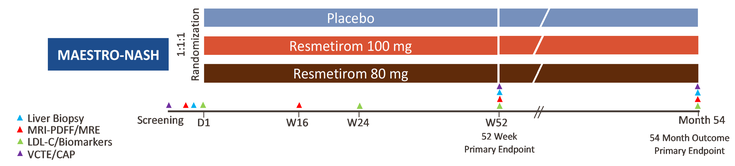
Background

- Resmetirom, an oral, liver-directed THR-β–selective agonist, was approved in March 2024 for the treatment of adult patients with noncirrhotic NASH (MASH) and liver fibrosis consistent with F2 to F3 stages
- Application for European Union approval was filed based on efficacy demonstrated in MAESTRO-NASH, 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 NASH 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
  - EASL recommends stratifying patients using FIB-4, and most guidelines recommend using VCTE cutoffs lower than 10 to <15 kPa for treatment
- 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
- Results from NITs (FIB-4, VTCE) were assessed against biopsy results to determine how well they diagnosed noncirrhotic NASH patients (F2-F3 at baseline)
- The utility of a lower VCTE cutoff (8.5 to <10 kPa) in capturing F2 and F3 patients that would have been missed was evaluated
- The addition of MRE/MRI-PDFF or ELF to VTCE to improve diagnostic utility was evaluated

Results

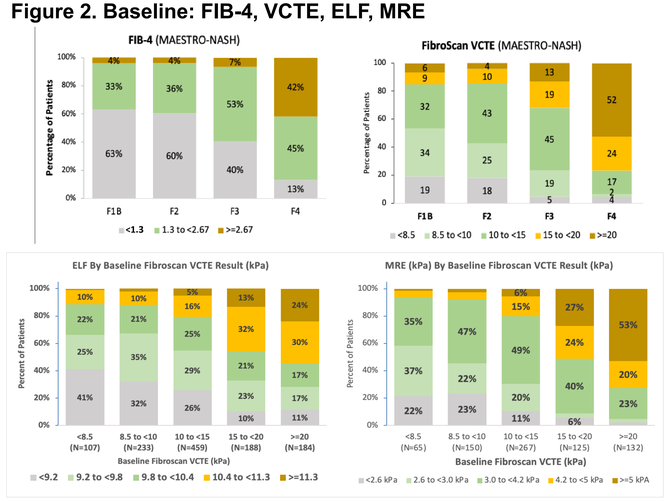
Subjects

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

Analysis

- FIB-4 (**Figure 2**) poorly predicts non-cirrhotic NASH fibrosis stage
- Including a lower cutoff of VCTE (8.5–10) is important for capturing 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
- 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/F3
- The addition of MRE/MRI-PDFF increased diagnostic accuracy for F2/F3 to 68% and F4 to 81%

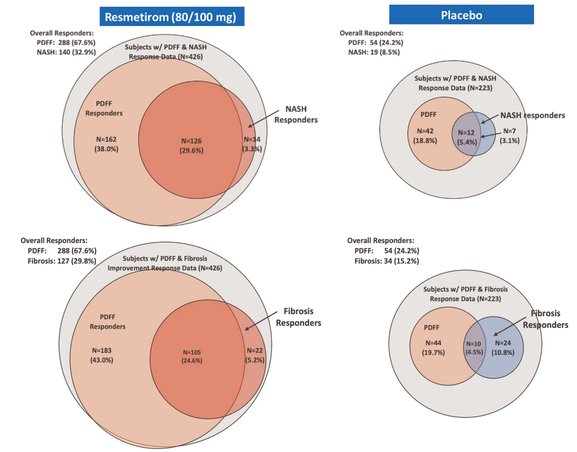
Figure 2. Baseline: FIB-4, VCTE, ELF, MRE



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
- In resmetirom-treated patients, 90% of Week 52 biopsy NASH resolution responders and 81% of Week 52 biopsy fibrosis responders also had ≥30% PDFF reduction (**Figure 3**)
- In patients receiving placebo, there was no association between PDFF-response and NASH resolution or fibrosis response on biopsy
- 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 percent 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

Figure 3. MRI-PDFF Response Predicts Biopsy Response in Resmetirom-Treated Patients



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)
- Patients with fibrosis stage F4 were effectively ruled out
- In addition to FibroScan VCTE, practitioners may consider expanded noninvasive criteria (ELF, MRE) to help refine fibrosis staging