Baseline characteristics in patients with well-compensated MASH cirrhosis diagnosed with or without a liver biopsy in MAESTRO-NASH-OUTCOMES, a clinical outcome phase 3 study assessing the effect of resmetirom in well-compensated NASH cirrhosis

Jörn M. Schattenberg[1], Meena Bansal[2], Rebecca Taub[3], Dominic Labriola[3], David Schneider[3], Michael Charlton[3], Vlad Ratziu[4], Mazen Noureddin[5]

1. Metabolic Liver Research Program, I. Department of Medicine, University Medical Center of Johannes Gutenburg University Mainz, Mainz, the Department of Internal Medicine II, Saarland University Medical Center, Homburg, GERMANY,
2. Ichan School of Medicine at Mount Sinai, New York, NY, USA, 3. Madrigal Pharmaceuticals, West Conshohocken, PA, USA,
4. Sorbonne Université, ICAN Institute for Cardiometabolism and Nutrition, Assistance Publique–Hôpitaux de Paris (APHP), INSERM, UMRS 1138, Centre de Recherche des Cordeliers, Paris, FRANCE, 5. Houston Methodist Hospital, Houston,TX, USA

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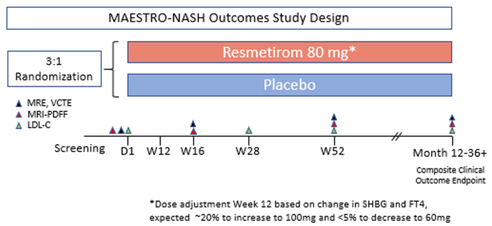
Background

- Resmetirom is a thyroid hormone receptor-beta (THR-β) agonist indicated in conjunction with diet and exercise 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-OUTCOMES (NCT05500222) is an ongoing, multi-national, multicenter, double-blind, randomized, placebo-controlled study evaluating resmetirom treatment in patients with well-compensated MASH/NASH cirrhosis (**Figure 1**)
  - Patients are randomly assigned in a blinded manner in a 3:1 ratio to receive resmetirom 80 mg or matching placebo orally once daily in the morning
  - Treatment is administered until the required number of Composite Clinical Outcome events are achieved
  - Composite Clinical Outcome events are defined as any of the following: mortality, liver transplant, and significant hepatic events, including potential hepatic decompensation events (ascites, hepatic encephalopathy, or gastroesophageal variceal hemorrhage) and confirmed increase of MELD score from <12 to ≥15
- The study comprises an up to 60-day screening period and an approximately 3-year treatment period
- The objective of this analysis of data from MAESTRO-NASH-OUTCOMES was to compare baseline factors between patients diagnosed with NASH cirrhosis with and without liver biopsy

Figure 1. MAESTRO-NASH OUTCOMES Study Design



Methods

- Eligibility criteria
  - NASH cirrhosis with biopsy-confirmed F4 fibrosis with ≥3 metabolic risk factors, meeting other non-invasive testing and eligibility requirements
  - NASH cirrhosis diagnosed non-invasively requiring ≥2 non-invasive tests for screening (FibroScan VCTE ≥15 kPa and/or if FibroScan VCTE <15 kPa, ≥2 other non-invasive tests (MRE ≥4.2, platelets <140 K, ELF ≥10.25, FIB-4 ≥3)
  - Other screening tests include blood tests, MRE, MRI-PDFF, and assessments for HCC and ascites, with MELD <12 (except for Gilbert)
- Patients were divided into 2 groups:
  - NASH cirrhosis diagnosed with liver biopsy
  - NASH cirrhosis diagnosed without liver biopsy
- Baseline factors were compared between groups
- Descriptive statistical outputs were generated

Results

Disposition

- 845 patients were enrolled in MAESTRO-NASH-OUTCOMES at the time of the analysis
  - NASH cirrhosis with biopsy-confirmed F4 fibrosis, n=388
  - NASH cirrhosis diagnosed non-invasively, n=457

Comparison of Baseline Factors Between Groups

- Baseline factors were generally similar between patients diagnosed as NASH cirrhosis with and without liver biopsy (**Table 1**)
- Mean VTCE values and distributions were similar in patients at screening and baseline visits (**Figure 2**). The averaged VCTE of the two visits is considered as the baseline value.
- Approximately one-third of patients had more advanced (but well-compensated) disease, based on MRE ≥6, ELF ≥11.3, MRI-PDFF <5%
- A slightly higher percentage of NASH cirrhosis patients diagnosed without a liver biopsy had baseline characteristics suggestive of more advanced portal hypertension (platelets <140 K, higher MRE, ELF, and FibroScan VCTE) (**Figures 3 and 4, and Table 2**)

Figure 2. FibroScan VTCE at Screening and at Baseline

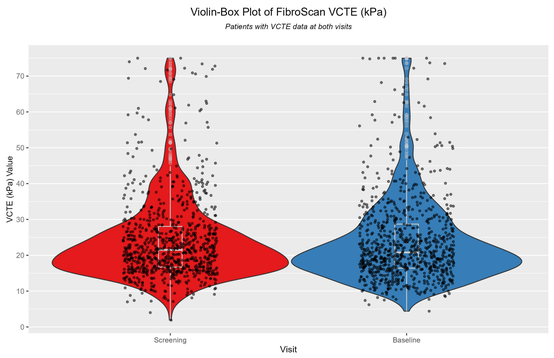


Figure 3. Baseline Characteristics by Liver Biopsy Status

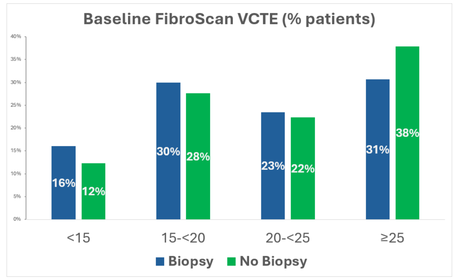


Figure 4. Baseline Characteristics by Liver Biopsy Status

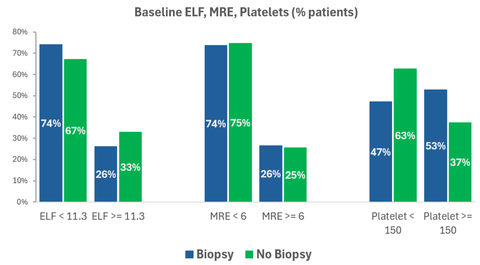


Table 2. Clinically Significant Portal Hypertension (CSPH)

Variable	Parameter	Biopsy (N=388)	No Biopsy (N=457)
BAVENO[1], n (%)	No or Low Risk of CSPH	214 (55.2)	188 (41.1)
	Probably CSPH	55 (14.2)	96 (21.0)
	CSPH	119 (30.7)	173 (37.9)
Mod CSPH[2], n (%)	No or Low Risk of CSPH	200 (51.5)	168 (36.8)
	Probably CSPH	96 (24.7)	141 (30.9)
	CSPH	92 (23.7)	148 (32.4)

[1] BAVENO criteria: CSPH if VCTE ≥ 25; Probably CSPH if (20 ≤ VCTE < 25 and PLAT < 150) or (15 ≤ VCTE < 20 and PLAT < 110)
[2] Modified CSPH criteria: CSPH if VCTE ≥ 25 and (PLAT < 140 or MRE ≥ 5 or ELF ≥ 11.3); Probably CSPH if (15 ≤ VCTE < 25 and PLAT < 140) or (VCTE ≥ 25 but not meeting CSPH)

Table 1. Demographics and Baseline Characteristics by Liver Biopsy Status

Parameter	Patients With Biopsy (N=388)	Patients Without Biopsy (N=457)
Age, years, mean (SD)	62.4 (9.1)	63.5 (9.0)
Sex, male, n (%)	127 (32.7)	186 (40.7)
Ethnicity, Hispanic/Latino, n (%)	68 (17.6)	121 (26.7)
Body weight, kg, mean (SD)	94.2 (22.2)	94.4 (20.6)
Body mass index, kg/m², mean (SD)	34.0 (6.8)	34.0 (6.7)
Hypertension, n (%)	324 (83.5)	381 (83.4)
Hypothyroid, n (%)	98 (25)	113 (25)
Type 2 diabetes, n (%)	314 (80.9)	357 (78.1)
Documented ASCVD, n (%)	20 (5.2)	25 (5.5)
ELF test, mean (SD)	10.7 (0.9)	10.9 (0.9)
ELF test, n	388	456
≥11.3, n (%)	101 (26.0)	150 (32.9)
<11.3, n (%)	287 (74.0)	306 (67.1)
MELD, n	388	456
≥12, n (%)	15 (3.9)	27 (5.9)
9–11, n (%)	83 (21.4)	157 (34.4)
<9, n (%)	290 (74.7)	272 (59.6)
MRI-PDFF, % fat fraction, mean (SD)	8.0 (5.8)	8.4 (5.5)
MRI-PDFF, n	356	407
<5, n (%)	126 (35.4)	135 (33.2)
≥5, n (%)	230 (64.6)	272 (66.8)
MRE, kPa, mean (SD)	5.3 (1.7)	5.2 (1.9)
MRE, kPa, n	322	385
≥6	85 (26.4)	98 (25.5)
<6	237 (73.6)	287 (74.5)
FibroScan VCTE, kPa, mean (SD)	23.1 (10.5)	25.3 (12.0)
FibroScan VCTE, kPa, median (Q1, Q3)	20.5 (16.5, 26.9)	22.0 (17.5, 29.8)
FibroScan TE <15 n (%)	62 (16.0)	56 (12.3)
FibroScan TE 15–20 n (%)	116 (29.9)	126 (27.6)
FibroScan TE 20–25 n (%)	91 (23.5)	102 (22.3)
FibroScan TE ≥25 n (%)	119 (30.7)	173 (37.9)
FibroScan CAP, dB/m, mean (SD)	301.4 (57.9)	295.9 (57.3)
Statin use, n (%)	224 (57.7)	254 (55.6)
Thyroxine any, n (%)	104 (26.8)	116 (25.4)
GLP-1 use, n (%)	127 (32.7)	117 (25.6)
SGLT2 use, n (%)	99 (25.5)	100 (21.9)
Other laboratory parameters, mean (SD)		
FIB-4	2.8 (1.5)	3.3 (1.6)
Total bilirubin, mg/dL	0.8 (0.3)	0.9 (0.4)
Direct bilirubin, mg/dL	0.2 (0.1)	0.2 (0.1)
Platelet count, K	162.3 (60.1)	143.5 (56.9)
Albumin, g/dL	4.3 (0.3)	4.2 (0.3)
INR	1.1 (0.2)	1.2 (0.1)
ALT, IU/L	41.6 (25.1)	39.7 (23.1)
AST, IU/L	40.3 (19.2)	40.6 (19.9)
GGT, IU/L	97.0 (103.3)	116.6 (122.8)

Conclusions

- Baseline data from the Phase 3 MAESTRO-NASH-OUTCOMES study demonstrate that non-invasive tests perform similarly to liver biopsy in identifying patients with well-compensated NASH cirrhosis
- Patients with NASH Child-Pugh A have a high prevalence of metabolic risk factors, including diabetes, obesity, hypertension, and use of statins for dyslipidemia control
- MRI-PDFF <5% was present in approximately 34% of patients with cirrhosis, confirming lower PDFF as a potential indicator of progression to cirrhosis. In NASH cirrhosis patients, while steatosis persists, the concentration of liver fat as measured by PDFF declines due to replacement of liver tissue by fibrosis
- Approximately one-third of patients have baseline Fibroscan VCTE and/or other markers including ELF, MRE and platelets that are consistent with clinically significant portal hypertension

Disclosures **Bansal** declares Histoindex, Siemens, The Kinetix Group, Madrigal, Pfizer, Fibronostics, Novo Nordisk, GSK, Boston Pharma, Merck, Boehringer-Ingelheim, and CurveBio. **Schattenberg** declares AstraZeneca, Apollo Endosurgery, Bayer, Boehringer Ingelheim, BMS, Gilead Sciences, GSK, Intercept Pharmaceuticals, Ipsen, Inventiva Pharma, Madrigal, MSD, NorthSea Therapeutics, Novartis, Novo Nordisk, Pfizer, Roche, Sanofi, Siemens Healthineers, Siemens Healthcare GmbH, AGED Diagnostics, Hepta Bio, Echosens, MedPublico GmbH, Histoindex, and MedPublico **GmbH. Taub, Labriola,** and **Schneider** are employees of Madrigal Pharmaceuticals. **Noureddin** declares 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, and Zydus Pharmaceuticals, Inc. **Loomba** declares Aardvark Therapeutics, Altimmune, Alnylam/Regeneron, Amgen, Arrowhead Pharmaceuticals, AstraZeneca, Bristol Myers 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, Viking Therapeutics, Boehringer-Ingelheim, Galectin Therapeutics, Hanmi, Merck, Sonic Incytes, Terns Pharmaceuticals, and LipoNexus