TREATMENT OF CIRRHOTICS WITH RESMETIROM IN PHASE 3 MAESTRO-NAFLD-1 NASH STUDY OPEN LABEL ARM: EFFECTS ON BIOMARKERS AND IMAGING

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INTRODUCTION

MAESTRO-NAFLD-1 is a 52-week 1200 patient Phase 3 randomized double blind placebo controlled NASH clinical trial to study safety and biomarker effects of resmetirom, a selective thyroid hormone receptor beta agonist, in NASH patients with F1-F4 fibrosis identified using non-invasive biomarkers and imaging (NCT04197479). A goal of this "real life" NASH study is to identify non-invasive markers that correlate with individual patient response to resmetirom treatment. The 36-week Phase 2 resmetirom NASH study provided preliminary evidence of an association between MRI-PDFF (magnetic resonance imaging-proton density fat fraction) reduction and NASH resolution and fibrosis reduction on serial liver biopsy. This study includes an open label active treatment arm in NASH cirrhotic patients.

METHODS

Eligible patients have well compensated NASH cirrhosis with no history of decompensation Child Pugh-A (5-6) as diagnosed by liver biopsy (stage F4 either historic or recent biopsy) or a historic biopsy with NASH F2-F3 fibrosis with subsequent progression to NASH cirrhosis as diagnosed by an expert hepatologist/ gastroenterologist.

All enrolled NASH cirrhotic patients received open label active treatment with resmetirom. Starting dose was 80 mg and could be adjusted up to 100 mg based on a Week 2 PK sample.

PK in NASH cirrhotics compared to normal NASH showed that at 80 and 100 mg dose, there was no difference in resmetirom exposure

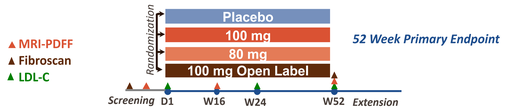
Other than the addition of a Week 2 visit, the NASH cirrhotic protocol is identical to MAESTRO-NAFLD-1 non-cirrhotic protocol.

The primary and key secondary endpoints of MAESTRO-NAFLD-1 include safety, relative percent reduction of MRI-PDFF (week 16), LDL cholesterol (LDL-C) (week 24), Apolipoprotein B and triglycerides, PRO-C3 (week 52). Baseline characteristics were compared between enrolled NASH cirrhotic patients and patients with liver biopsy documented NASH enrolled in the MAESTRO-NASH Phase 3 trial. Initial analyses of safety, imaging and biomarkers were conducted in NASH cirrhotic patients..

RESULTS

105 well-compensated NASH cirrhotic patients were enrolled in the open label arm. Demographics include mean age 62.7 (9.0 (SD)), female 64%, BMI 35.5 (7.5), diabetes 66%, hypertension 71%, dyslipidemia >70%, mean ASCVD score 16%, hypothyroid 30%, 46.3% on statins, MRE (kPa 5.9 (2.2)), fibroscan (kPa 24.5 (15.1)), and mean MRI-PDFF 7.9% (5%), consistent with F4 stage NASH (Table 1). Cirrhotic compared to non-cirrhotic NASH patients (n>1000) had statistically significantly higher MRE (p<0.0001) and lower MRI-PDFF (p<0.0001) (Figure 2). In cirrhotic patients, 34.1% had PDFF ≤5% and 37.8% ≥8% at baseline, unrelated to steatosis grade on biopsy. At baseline (Table 2) NASH cirrhotics with <8% compared with cirrhotics with ≥8% PDFF had higher MELD (p=0.0045), Fib-4 (p=0.012), MRE (p=0.027), baseline SHBG (p=0.0003), and lower ALT (p=0.002), and CAP (p=0.037). In cirrhotics with baseline PDFF ≥8% (Table 3), resmetirom lowered PDFF by mean 30% and MRE by 0.4 kPa at week 16 (# of subjects with week 16 data will be expanded in presentation). In NASH cirrhotics, resmetirom reduced LDL-C (20%), triglycerides (25%), and ApoB (19%) independent of baseline PDFF (Figure 4). Resmetirom was safe and well-tolerated with and AE profile similar to noncirrhotic NASH, ~10% with transient and mild loose stools lasting a few days at the beginning of therapy, not leading to discontinuation.

Figure 1. Phase 3 MAESTRO-NAFLD-1 (presumed NASH) Study Design: Randomized, Double-Blind, PBO Controlled



MAESTRO-NAFLD-1

- 1:1:1:1 resmetirom 80, 100 mg , placebo, open label 100 mg
- MAESTRO-NAFLD-1 1200 F1-F3 NASH patients
- Key inclusion/exclusion

Requires 3 metabolic risk factors; Fibroscan kPa≥ F1, CAP≥280; includes MAESTRO-NASH patients who screen fail at the biopsy stage; MRI-PDFF≥8%

- Endpoints

1º safety objective: to evaluate the safety and tolerability

Key 2º endpoints %change from BL for LDL-C, ApoB and TG lowering Wk 24, reduction in MRI-PDFF and Pro-C3

Figure 2. Baseline MRI-PDFF and MRE in NASH Cirrhotic Compared with Non-Cirrhotic NASH

MRE: Rho = 0.6, highly predictive of F4 compared with all lower stages of fibrosis
Significant decrease in PDFF in F4 compared with earlier fibrosis stages

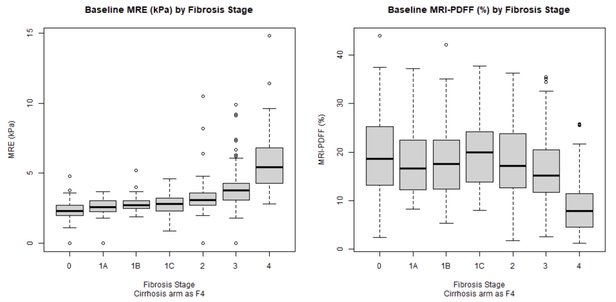


Figure 3. Liver Enzyme reductions in NASH cirrhosis patients

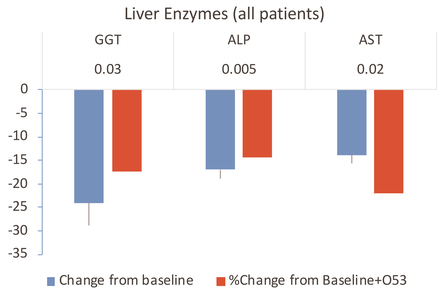


Table 1. Cirrhosis Baseline

MAESTRO-NAFLD-1 NASH Cirrhosis Baseline Characteristics	
N =	105
Mean age, years (SD)	62.7 (9.0)
Male, n (%)	39 (36%)
Female, n (%)	69 (64%)
Hispanic/Latino, n (%)	26 (24%)
Mean Body weight (SD) (kg)	98.2 (24.5)
BMI mean (SD) (kg/m2)	35.4 (7.4)
MELD	8 (1.9)
MRI-PDFF mean (SD) (%FF)	8.1% (5.0%)
MRE mean (SD) (kPa)	5.74 (2.09)
Historical Biopsy if available (n)	67
Fibrosis stage 4 (n, %)	53 (79.1%)
Fibrosis stage 3 (n, %)	9 (13.4%)
Hypertension, n (%)	83 (77%)
Hypothyroid#, n (%)	34 (31%)
T2D, n (%)	76 (70%)
T2D Yrs since diagnosis mean (SD)	12.7 (8.5)
Documented ASCVD@, n	11 (10.2%)
ASCVD score mean (SD)	16.1% (0.1)

MAESTRO-NAFLD-1 NASH Cirrhosis Baseline Characteristics	
Fibroscan TE mean (SD) (kPa)	24.6 (14.9)
Fibroscan CAP mean (SD)	318 (58.9)
PRO-C3 mean (SD) (ng/mL)	33 (20)
HbA1c mean (SD) (%)	6.4 (1.0)
HOMA-IR mean (SD)	10.5 (7.2)
Statin use (n, %)	55 (50.9%)
Thyroxine (n, %)	35 (32.4%)
>75ug (n, %)	23 (21.3%)
GLP-1s (n, %)	25 (23.1%)
SGLT2s (n, %)	26 (24.1%)

Other lab parameters, mean (SD)	
Total bilirubin mean (SD) (mg/dL)	0.9 (0.5)
Direct bilirubin mean (SD) (mg/dL)	0.2 (0.1)
Platelet count mean (SD)	158 (60.7)
Albumin mean (SD) (g/dL)	4.2 (0.4)
INR mean (SD)	1.2 (0.1)
Total Cholesterol mean (SD) (mg/dL)	169 (44.3)
TG mean (SD) (mg/dL)	165 (119.8)
Lp(a) mean (SD) (nmol/L)	44.4 (61.7)
ApoB mean (SD) (mg/dL)	85.1 (24.3)
LDL-C mean (SD) (mg/dL)	95.5 (34.0)
HDL-C mean (SD) (mg/dL)	47.5 (16.7)

Other lab parameters, mean (SD)	
NAFLD fibrosis score	1.1 (1.6)
Fib-4	2.9 (1.7)
ELF	10.8 -(1.2)
ALT (IU/L)	40.3 (26.9)
AST (IU/L)	39.4 (24.9)
GGT (IU/L)	102 (88.8)
CK (IU/L)	101 (65.4)
ALP (IU/L)	102 (52.6)
MCV (fL)	91 (6.3)
CDT (%)	1.7 (0.3)
NAFLD fibrosis score	1.1 (1.6)
Fib-4	2.9 (1.7)
ELF	10.8 -(1.2)
Total bilirubin mean (SD) (mg/dL)	0.9 (0.5)
Direct bilirubin mean (SD) (mg/dL)	0.2 (0.1)
Platelet count mean (SD)	158 (60.7)
Albumin mean (SD) (g/dL)	4.2 (0.4)

Figure 4. Cardiovascular Risk Factor Assessment

- Patients with NASH cirrhosis or advanced liver fibrosis are at high CV risk

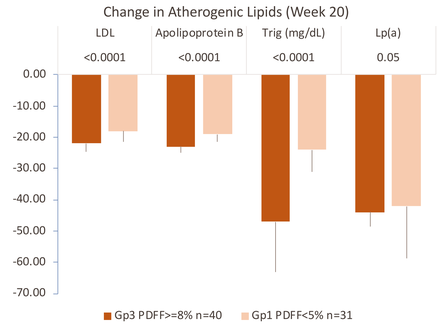


Table 2. Comparison of Cirrhosis Parameters According to Baseline PDFF

NASH cirrhotic patients with lower PDFF<5% at baseline had more progressed cirrhosis based on several parameters of progression

Baseline Parameters	Group 1, PDFF ≤5%	Group 2, PDFF >5%, <8%	Group 3, PDFF ≥ 8%	P-value (diff between Groups 1 and 3)
	N=31	N=28	N=40	
PDFF	3.8%	6.8%	12.8%	p<0.0001
Fib-4	3.7	2.7	2.5	0.006
CAP	299.0	316.0	339.0	0.004
Fibroscan TE (kPa)	27.4	24.9	23.6	NS
MRE	6.1	5.8	5.5	NS
ALT (IU)	32.0	34.2	51.8	0.005
AST (IU)	38.7	33.7	44.6	NS
ELF	11.1	10.8	10.7	0.180
Markers of Cirrhosis Progression				
MELD	8.8	8.0	7.5	0.005
INR	1.2	1.2	1.1	0.030
Bilirubin (mg/dL)	1.08	0.86	0.71	0.004
Platelets	133	152	175	0.002
Albumin	4.0	4.2	4.3	0.030

Table 3. Week 16 Responses in NASH Cirrhosis Patients

16 Week MRI-PDFF and MRE	Value	SD	p-value
MRI-PDFF	-34%	(-29.7)	0.00026
≥30% Responder (%)	60%		
MRE (Baseline >=3.5) (kPa)	-0.5	(-1.1)	0.08
%≥15% reduction responder (%)	35%		

PDFF only assessed in group with >=8% PDFF at baseline

Fibrosis Markers	Value	SD	p-value
M30	-126.00	349.00	0.08
P3NP	-2.90	4.00	0.02
TIMP	-27.00	48.00	0.05
Reverse T3	-21%	21.70	<0.0001

amino terminal type III procollagen peptide (P3NP); TIMP tissue inhibitor metalloproteinases

	Group 1, PDFF ≤5%	Group 3, PDFF ≥ 8%	P-value (all)
BP			
systolic	-8.3	-3.0	0.028
diastolic	-3.3	-1.6	0.14
Body weight	-1.1	-1.2	NS

CONCLUSIONS

NASH cirrhotic have significantly higher MRE and lower PDFF than non-cirrhotic NASH patients. NASH cirrhotics with lower baseline PDFF may represent a more advanced subtype.

Resmetirom appeared to be safe in well-compensated NASH cirrhotic patients.

Resmetirom reduced MRI-PDFF and LDL cholesterol and other atherogenic lipids.

Early readouts of fibrosis markers will be followed by long term data at 52 weeks.

REFERENCES

[1]Harrison SA, et al. Resmetirom (MGL-3196) for the treatment of non-alcoholic steatohepatitis: a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. Lancet 2019;394:2012-2024.

DISCLOSURES

Stephen A. Harrison, Oxford University. Received remuneration from Madrigal for consulting services

Naim Alkhouri, Arizona Liver Health. Study grant support from Madrigal

Rebecca Taub, Management Position: Madrigal Pharmaceuticals

Guy Neff. Covenant Research LLC, Study grant support from Madrigal

Seth J Baum, Excel Medical Clinical Trials, Study grant support from Madrigal

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