

## ORAL PRESENTATIONS

### LB005

#### Primary data analyses of MAESTRO-NAFLD-1 a 52 week double-blind placebo-controlled phase 3 clinical trial of resmetirom in patients with NAFLD

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**Background and aims:** Approval of a drug therapy for NASH requires a very good safety/tolerability profile and acceptable therapeutic index. MAESTRO-NAFLD-1 (NCT04197479) is a randomized double-blind (DB) Phase 3 clinical trial of placebo (PBO) versus resmetirom (RES), a once-a-day oral selective thyroid hormone receptor  $\beta$  agonist, in >1100 patients with NAFLD with safety as the primary end point.

**Method:** Enrollment was Dec 2019 to Oct 2020 at 79 US sites. Requirements included 3 metabolic risk factors, fibroscan (FS)  $\geq 5.5$  kPa/CAP  $\geq 280$  dBm, MRI-PDFF  $\geq 8\%$ . Randomization was 1:1:1:1 to 3 DB arms, PBO, 80 or 100 mg RES (n = 972) or an 100 mg open label (OL) arm (n = 171). The primary objective was to evaluate the safety and tolerability of 80 or 100 mg RES versus PBO measured by the incidence of adverse events (AEs).

**Results:** At baseline the DB safety population (n = 969) was age 55.9 (11.8); female, 54.4%, white 88.6%; hispanic 34.7%; BMI 35.3 (6.0) type 2 diabetes 49%, hypertension 76.1%, dyslipidemia 87.9%; FS 7.4 (4.7) kPa. Discontinuations (22.5%) did not differ by treatment, most patient decision (pandemic related). DB compliance was impacted by COVID drug kit delays. AE withdrawals were 80 mg, 2.4%; 100 mg, 2.8%; PBO, 1.3%. The primary objective was met. TEAEs were 80 mg, 88.4%; 100 mg, 86.1%; PBO, 81.8%. TEAEs  $\geq$  grade 3 severity were 80 mg, 7.6%; 100 mg, 9.0%; PBO, 9.1%. AEs in excess of PBO were grade 1–2 AEs of diarrhea (80 mg, 23.5%; 100 mg, 31.2%; PBO, 13.8%) and nausea (80 mg, 11.9%; 100 mg, 18.2%; PBO, 7.9%), in the first few weeks. ALT increases  $\geq 3$ XULN were 80 mg, 0.61%; 100 mg, 0.31%; PBO, 1.6%. There were no changes in body weight or HR. BP decreased by 2–3 mmHg in the RES arms. Key 2<sup>o</sup> end points were met (Table). Comparative mean reduction in FS VCTE was not significant; a responder analysis of FS and MRE showed significant reductions with RES treatment.

**Conclusion:** RES achieved the primary safety end point in this 52-week Phase 3 NAFLD clinical trial that identified patients by metabolic risk and non-invasive imaging. Key 2<sup>o</sup> end points were met including LDL-C, ApoB, triglycerides, MRI-PDFF, FS (CAP).

	RES 100 mg OL	p value	RES 100 mg DB	p value	RES 80 mg DB	p value	PBO
n	171		314		320		309
LDL-C %CFB (SE) (Wk 24)	-21 (1.9)	<0.0001	-14.4 (2.1)	<0.0001	-12.7 (2.1)	<0.0001	-1.7 (2.0)
ApoB %CFB (SE) (Wk 24)	-22 (1.5)	<0.0001	-16.6 (1.6)	<0.0001	-14.6 (1.5)	<0.0001	-0.1 (1.5)
MRI-PDFF %CFB (Wk 16)	-48.9%	<0.0001	-47.7%	<0.0001	-40.8%	<0.0001	-6.0%
MRI-PDFF %CFB (Wk 52)	-52.5%	<0.0001	-48.2%	<0.0001	-42.5%	<0.0001	-7.9%
Triglycerides BL > 150 %CFB	-25 (3.1)	<0.0001	-21.5 (-28.0, -14.3)	<0.0001	-19.5 (-27.0, -11.1)	0.0005	-2.1 (-10.6, 7.4)
FS CAP	-52.9 (4.6)	<0.0001	-42.2 (4.1)	<0.0001	-36.2 (4.0)	<0.0001	-17.8
FS VCTE	57.1%	0.0005	42.7%	0.020	31.9%	0.38	24.7%
BL $\geq 7.2$ kPa %, $\geq 2$ kPa reduction							
MRE BL $\geq 2.9$ kPa, % $\geq 19\%$ reduction	25.7%		22.6%	0.024 <sup>1</sup>	21.7%		11.4%
ALT (%CFB) (BL $\geq 30$ IU)	-29.4 (3.3)	<0.0001	-17.9 (5.0)	0.0010	-18.5 (4.8)	0.0015	-2.1 (5.1)

<sup>1</sup>MRE combined RES groups.

### LB006

#### Reduction of intra-hepatic Z-AAT synthesis by fazirsiran decreases globule burden and improves histological measures of liver disease in adults with alpha-1 antitrypsin deficiency

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**Background and aims:** Adults homozygous for PiZZ synthesize mutant alpha-1 antitrypsin (Z-AAT) that accumulates in hepatocytes leading to progressive liver disease and fibrosis. Fazirsiran, an investigational RNAi therapeutic, silences liver Z-AAT mRNA to reduce Z-AAT synthesis. This analysis assessed histological changes in patients (pts) with PiZZ AATD liver disease receiving fazirsiran in an ongoing, open-label, phase 2 study.

**Method:** Fazirsiran (200 mg [n = 12] or 100 mg [n = 4]) was administered subcutaneously on Day 1, Week (wk) 4 and then every 12 wks. The primary end point was change in liver Z AAT as measured by LC-MS/MS at Wk 24 or 48. Three pathologists blinded to subjects and time points assessed and adjudicated histological parameters including globule burden (periodic acid-Schiff with diastase [PAS +D] staining for extent of portal tract and periportal hepatocyte involvement and zonal location; total score of 0–9), globule size (scored by comparing % of total granules or size of largest globule to the size of a red blood cell; total score of 0–6), portal inflammation (score of 0–3), and METAVIR fibrosis (F0–F4).

**Results:** Fazirsiran reduced liver Z-AAT in all pts by a mean of 85% at Wk 24/48, with concomitant reductions in histological globule burden (mean score 7.4 at baseline and 2.3 at Wk 24/48). All 16 pts also showed reductions in globule size (mean score 3.0 at baseline and 1.0 at Wk 24/48). Removal of Z-AAT improved histological assessments of portal inflammation, a key feature of AATD liver disease; approximately two-thirds (8/13) of pts with a baseline score of  $\geq 1$  in portal inflammation showed improvement at Wk 24/48. In particular, portal inflammation on biopsy has been shown in previous observational studies to be strongly associated with fibrosis progression. Overall, 7/15 pts (7/12 subjects receiving 200 mg dose and 0/3 subjects receiving 100 mg dose) had a  $\geq 1$ -point improvement in fibrosis. Fazirsiran was well tolerated, with no adverse events leading to study/drug discontinuation.

**Conclusion:** By reducing Z-AAT synthesis, fazirsiran improved histological features of AATD liver disease, including reductions in globule burden/size and severity of portal inflammation, leading to fibrosis regression.