In F0-F1 and F2-F3 MASH, ≥5% weight loss significantly lowers VCTE and ELF™ independent of biopsy fibrosis improvement; resmetirom and not placebo reduction of ELF and VCTE are associated with biopsy improvement of fibrosis, independent of weight loss

POSTER #2357

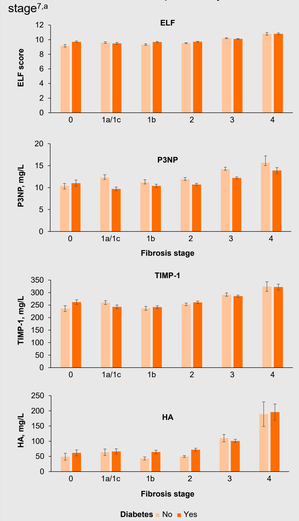
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INTRODUCTION

- Resmetirom is a once-daily, oral, liver-directed thyroid hormone receptor β–selective agonist approved for the treatment of adults with noncirrhotic metabolic dysfunction–associated steatohepatitis (MASH) with moderate to advanced liver fibrosis (consistent with stages F2 to F3), in conjunction with diet and exercise, in the US and EU[1-2]
- Changes in liver stiffness measurement (LSM) (e.g., by vibration-controlled transient elastography [VCTE]) and enhanced liver fibrosis test (ELF), a prognostic test for advanced fibrosis to cirrhosis (F3-F4), are proposed as surrogate endpoints for histological fibrosis response in MASH[3-5]
- ELF and its components (hyaluronic acid [HA], amino terminal of type III procollagen peptide [P3NP], and metalloproteinase inhibitor 1 [TIMP-1]) are generally similar across F0-F2 fibrosis stages in people with metabolic dysfunction–associated steatotic liver disease (MASLD), with higher levels observed in F3-F4 fibrosis
  - ELF of ≥9.8 is proposed as a measure of advanced liver fibrosis[6]
  - HA appears to be the major driver of the increase in ELF during progression to cirrhosis (**FIGURE 1**),[7] due to dysfunction of sinusoidal epithelial cells, which normally metabolise serum HA[8]
- ELF is reduced by 5%-6% in some MASH studies and is mechanism of action–dependent; several liver-directed MASH therapies that reduce liver fibrosis reduce ELF moderately or nonsignificantly,[9-11] while others (e.g., glucagon-like peptide [GLP]-related) significantly decrease ELF, irrespective of fibrosis stage, in F2-F3 and F0-F1 MASH[12-19]
- Weight loss (WL) has been shown to reduce liver stiffness and collagen markers in patients without significant liver fibrosis (F0-F1) who have obesity/metabolic risk, in whom serum markers of fibrosis may be elevated[20-22]

FIGURE 1. ELF and ELF components by fibrosis stage[7,a]



[a]From an analysis correlating baseline ELF score with fibrosis stage in patients from phase 3 resmetirom trials. Data is presented as mean±SE.
ELF, enhanced liver fibrosis test; HA, hyaluronic acid; P3NP, amino terminal of type III procollagen peptide; TIMP-1, metalloproteinase inhibitor 1.

AIM

- To examine the impact of ≥5% WL on VCTE and ELF and the association of changes in VCTE and ELF with WL and biopsy-assessed fibrosis improvement (FI) in resmetirom- and placebo-treated patients with MASH with F0-F1 and F2-F3 fibrosis from phase 3 MAESTRO trials

METHODS

Study design

- MAESTRO-NAFLD-1 and MAESTRO-NASH were phase 3, randomized, double-blind, placebo-controlled, multicenter studies in which participants were randomized to receive resmetirom 80 mg, resmetirom 100 mg, or placebo for 52 weeks

Study population

- Adults with MASH with F0-F1 fibrosis from MAESTRO-NAFLD-1 and with F2-F3 fibrosis from MAESTRO-NASH were included in the analysis

Baseline characteristics

- VCTE, ELF, and ELF components were assessed at baseline and Week 52 in both studies
- Liver biopsies were performed at baseline and Week 52 in MAESTRO-NASH

Outcomes

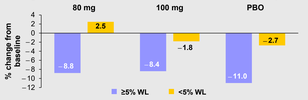
- In MAESTRO-NASH (F2-F3) linear and logistic regression models were used to explore the associations between resmetirom- and placebo-mediated changes in both VCTE (log-transformed) and ELF (absolute) and
  - WL (≥5% vs <5%)
  - Histological FI

RESULTS

Associations between changes in ELF or liver stiffness (VCTE) and WL in the F0-F1 population

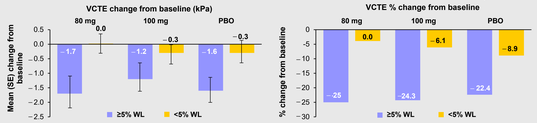
- Resmetirom did not significantly reduce ELF compared with placebo in the overall F0-F1 population[10]
- Approximately 14% of patients in the F0-F1 population had ≥5% WL at Week 52; ELF score showed greater reduction in those with ≥5% WL, with the P3NP component showing the greatest reduction in patients with WL, independent of treatment (**FIGURE 2**)
  - P3NP is the major fibrogenesis biomarker in ELF[23]
- In F0-F1, mean baseline VCTE was 7.4 kPa (median, 6.5 kPa)
- Resmetirom did not significantly reduce VCTE compared with placebo in the MAESTRO-NAFLD-1 F0-F1 population[10]
- VCTE was significantly reduced in those with ≥5% weight loss versus those with <5% weight loss, independent of treatment (**FIGURE 3**)

FIGURE 2. Median percentage change from baseline in P3NP at Week 52 (F0-F1 population)



F, fibrosis stage (F0: no fibrosis, F1: mild fibrosis); P3NP, amino terminal of type III procollagen peptide; PBO, placebo; WL, weight loss.

FIGURE 3. Mean and percentage change from baseline in VCTE at Week 52 (F0-F1 population)

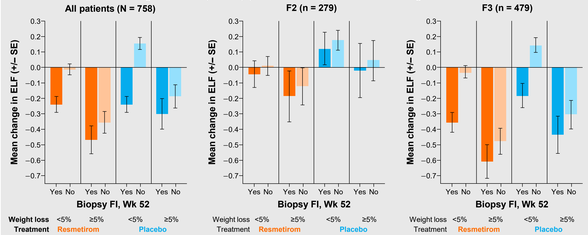


F, fibrosis stage (F0: no fibrosis, F1: mild fibrosis); PBO, placebo; VCTE, vibration-controlled transient elastography; WL, weight loss.

Associations between changes in ELF or liver stiffness (VCTE) and WL or FI on liver biopsy in the F2-F3 population

- In the F2-F3 population, mean baseline ELF score was 9.8
- At Week 52, 17% (80 mg resmetirom), 22% (100 mg resmetirom) and 12% (placebo) had ≥5% WL
- Absolute changes in ELF were evaluated using observed and modelled data from a cohort of 758 patients with F2-F3 fibrosis (MAESTRO-NASH) with paired fibrosis, weight, and ELF data
- There were independent associations of WL and FI with changes in ELF, and associations of change in ELF with WL were more pronounced than associations of change in ELF with FI; most noticeable effects were observed in the F3 population (**FIGURE 4**)
- Interaction statistics showed that the effect of ≥5% WL on ELF attenuated a significant relationship between ELF and FI that was observed in resmetirom- and placebo-treated patients with <5% WL (**TABLE 1, FIGURE 5**)
- The association of change in ELF with fibrosis improvement was more pronounced in those with <5% WL versus those with ≥5% WL (**FIGURE 5**)
- Changes in ELF were strongly associated with fibrosis improvement only in patients with F3 fibrosis with <5% WL (**FIGURE 5**)

FIGURE 4. Absolute changes in ELF (F2-F3) (N = 758 with paired fibrosis/weight/ELF data)[a]



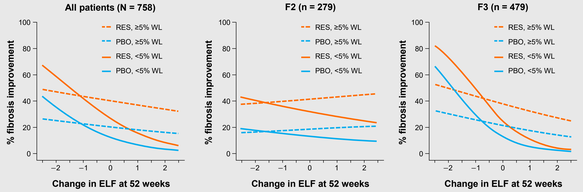
[a]Based on modelled data from linear regression: Change in ELF ~ Treatment + WL (WL, ≥5% vs <5%) + FI at Week 52 (FI, Y/N) + WL × FI.
ELF, enhanced liver fibrosis test; F, fibrosis stage (F2: moderate fibrosis, F3: advanced fibrosis); FI, fibrosis improvement; Wk, Week; WL, weight loss.

TABLE 1. Modelled associations on FI, binary change in weight, and changes in ELF[a]

	All Patients		F2		F3	
Predictor	**Estimate**	***P* value**	**Estimate**	***P* value**	**Estimate**	***P* value**
Intercept	3.945	0.0012	−0.751	0.7305	6.524	0.0001
Treatment	0.973	<0.0001	1.157	0.0005	0.839	0.0020
BL ELF	−0.538	<0.0001	−0.088	0.6860	−0.776	<0.0001
BL Weight	−0.007	0.0993	−0.003	0.6074	−0.009	0.0995
≥5% WL (vs < 5%)	0.588	0.0138	0.414	0.2711	0.660	0.0405
Δ ELF	−0.686	<0.0001	−0.182	0.4451	−1.071	<0.0001
≥5% x Δ ELF	0.546	0.0956	−0.255	0.6622	0.821	0.0520

[a]Based on multivariate logistic regression: logit(Prob(FI)) ~ RES/PBO+ BL ELF + BL Weight + ≥/< 5% WL + Δ ELF + (≥5% WL × Δ ELF).
BL, baseline; ELF, enhanced liver fibrosis test; F, fibrosis stage (F2: moderate fibrosis, F3: advanced fibrosis); FI, fibrosis improvement; PBO, placebo; RES, resmetirom; VCTE, vibration-controlled transient elastography; WL, weight loss.

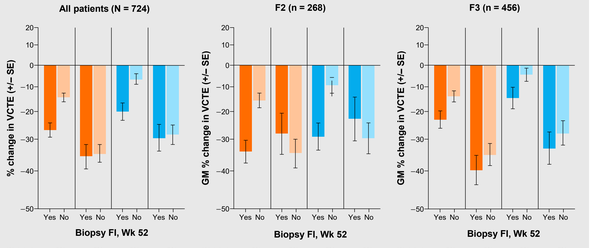
FIGURE 5. Effects of WL and changes in ELF on fibrosis improvement (N = 758 with paired fibrosis/weight/ELF data)[a]



[a]Based on modelled data from logistic regression: Probability FI ~ Treatment + WL (WL, ≥ 5% vs < 5%) + Change in ELF + WL × FI.
ELF, enhanced liver fibrosis test; F, fibrosis stage (F2: moderate fibrosis, F3: advanced fibrosis); FI, fibrosis improvement; PBO, placebo; RES, resmetirom; WL, weight loss; Wk, week.

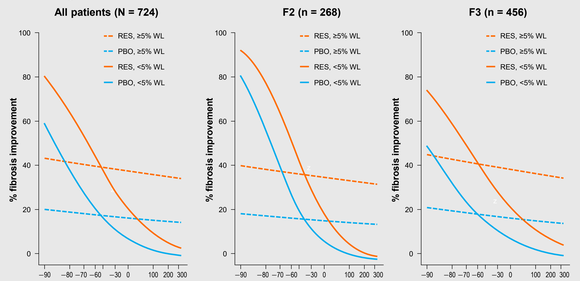
- In the F2-F3 population, baseline VCTE was 13.3 kPa
- Relative changes in VCTE were evaluated using observed and modelled data from a cohort of 724 patients with F2-F3 fibrosis (MAESTRO-NASH) with paired fibrosis, weight, and VCTE data
- There were independent associations of WL and FI with changes in VCTE, and associations of change in VCTE with WL were more pronounced than associations of change in VCTE with fibrosis improvement (**FIGURE 6**)
- The association of VCTE with fibrosis improvement was pronounced in those with <5% WL versus those with ≥5% WL in both resmetirom- and placebo treated-patients (**FIGURE 7**)
- Change in liver stiffness by VCTE predicted fibrosis improvement on biopsy in both F2 and F3 patients without WL (**FIGURE 7**)

FIGURE 6. Percentage changes in VCTE (F2-F3) (N = 724 with paired fibrosis/weight/VCTE data)[a]



[a]Based on modelled data from linear regression: log(fold change in VCTE) ~ Treatment + WL (WL, ≥5% vs <5%) + FI at Week 52 (FI, Y/N) + WL × FI.
F, fibrosis stage (F2: moderate fibrosis, F3: advanced fibrosis); FI, fibrosis improvement; VCTE, vibration-controlled transient elastography; Wk, Week; WL, weight loss.

FIGURE 7. Effects of weight loss and percentage changes in VCTE on FI (N = 724 with paired fibrosis/weight/VCTE data)[a]



[a]Based on modelled data from logistic regression: Probability FI ~ Treatment + WL (WL, ≥5% vs <5%) + log(fold change in VCTE) + WL × log(fold change in VCTE).
FI, fibrosis improvement; PBO, placebo; RES, resmetirom; VCTE, vibration-controlled transient elastography; WL, weight loss.

CONCLUSIONS

- **In patients with F2-F3 MASH, weight loss ≥5% and fibrosis improvement were independently associated with reductions in VCTE and ELF**
- **Fibrosis improvement was clearly associated with VCTE and ELF reduction in patients without weight loss treated with resmetirom or placebo**
- **Confounding effects of weight loss on ELF and VCTE, independent of histological fibrosis improvement, should be considered when evaluating MASH treatments**

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DISCLOSURES

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