Analysis of baseline PRO-C3 and ELF components in patients with MASH/MASLD and MASH cirrhosis and correlations between change in PRO-C3 and ELF in resmetirom-treated patients from the MAESTRO-NASH trial

POSTER #A17

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INTRODUCTION

- Resmetirom is an oral, liver-directed THR-β–selective agonist approved for the treatment of adults with MASH and liver fibrosis consistent with F2 to F3 stages1
- MAESTRO-NASH (NCT03900429) is an ongoing 54-month, randomized, double-blind, placebo-controlled Phase 3 trial in adult patients with biopsy-confirmed MASH and fibrosis1-3
- Both resmetirom doses were superior to placebo with respect to MASH resolution and ≥1-stage fibrosis improvement at Week 52 (dual primary endpoints)2
- Noninvasive tests including ELF and PRO-C3 have been used to characterize fibrosis stage in MASH and predict liver outcomes4
  - ELF is a highly sensitive and specific FDA-approved fibrosis biomarker combining serum biomarkers TIMP-1, P3NP, and HA5
  - PRO-C3 reflects formation of type III collagen and has a notable capability for distinguishing between mild and moderate fibrosis4
- In MAESTRO-NASH, resmetirom reduced ELF and its components P3NP and TIMP-1 but not HA2
- This study evaluated (1) baseline ELF and its individual components according to biopsy fibrosis stage and (2) correlations between baseline and Week 52 ELF/P3NP with PRO-C3 and effect of resmetirom vs placebo on PRO-C3 and P3NP/ELF in MAESTRO-NASH

OBJECTIVE

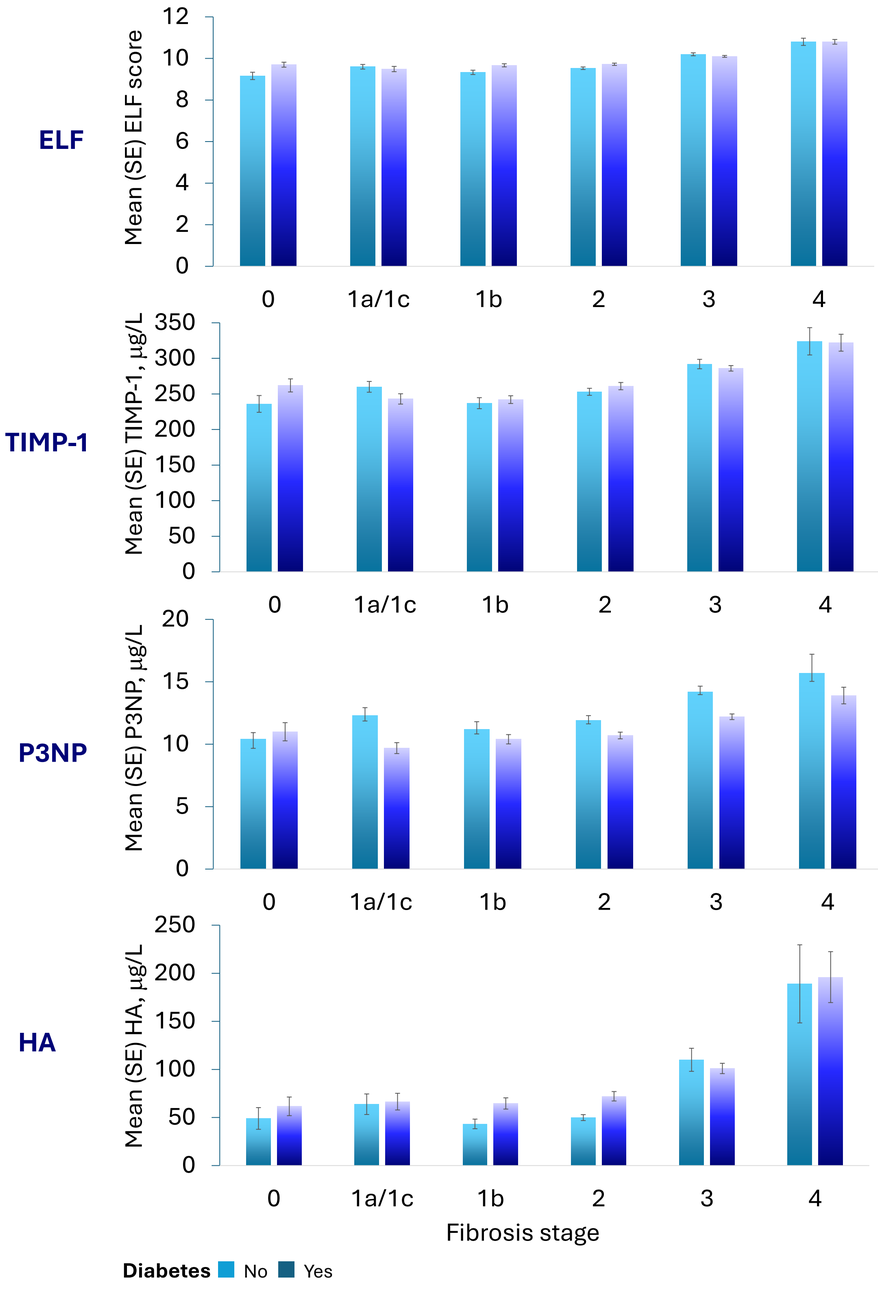
- Mean baseline ELF and ELF components were determined by a central laboratory in a large biopsy-proven cohort comprising patients from MAESTRO-NASH and MAESTRO-NAFLD-1 (F0: n=101; F1a/1c: n=126; F1b: n=126; F2: n=356; F3: n=540; F4: n=107)
  - MAESTRO-NAFLD-1 (NCT04197479) was a 52-week phase 3 double-blind, randomized, placebo-controlled study evaluating resmetirom 100 mg and 80 mg in patients with MASH as documented by historical biopsy or noninvasive techniques
- Correlations were assessed between baseline P3NP/ELF and PRO-C3 and the correlation between change from baseline to Week 52 in P3NP/ELF and PRO-C3 in MAESTRO-NASH
- Changes from baseline to Week 52 in PRO-C3 and ELF were compared between resmetirom 80 mg or 100 mg and placebo
- PRO-C3 was quantified using the ELISA GEN2 assay

RESULTS

Correlation between ELF components and fibrosis stage (MAESTRO-NASH and MAESTRO-NAFLD-1)

- TIMP-1 and P3NP did not show an increase from stages F0-F2 but increased by 20% between F2 and F3/F4 (Figure 1)
- HA was variable and higher in people with diabetes among those with fibrosis stages F0-F2. HA increased 1.9-fold between F3 and F4, explaining the increase in ELF in patients with F4 fibrosis (Figure 1)“

FIGURE 1. ELF and ELF components by fibrosis stage.



Correlation of ELF/P3NP and PRO-C3 and impact of resmetirom on PRO-C3 in MAESTRO-NASH

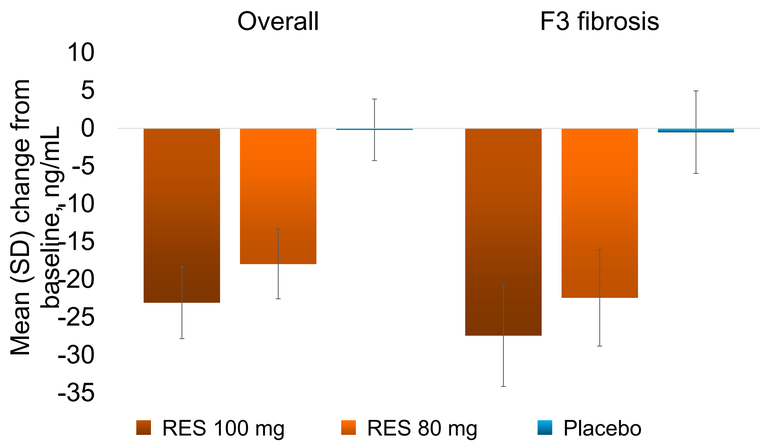
Baseline

- Overall, baseline P3NP and ELF correlated with baseline PRO-C3 (correlation coefficients ρ=0.563 and ρ=0.458, respectively)

Week 52

- Reductions were observed in PRO-C3 from baseline to Week 52 in both resmetirom groups compared with the placebo group (**Figure 2**)
  - Larger reductions in mean (SD) PRO-C3 were observed in the patients with F3 fibrosis in the resmetirom arms

FIGURE 2. Change from baseline to Week 52 in PRO-C3 (MAESTRO-NASH).



- Positive correlations of similar magnitude were observed between the changes from baseline to Week 52 in P3NP and ELF and the change from baseline to Week 52 in PRO-C3 in all treatment groups (**Table 1**)

TABLE 1. Correlation with PRO-C3: change from baseline to Week 52 (MAESTRO-NASH).

Test	Correlation coefficient (ρ)		
	Resmetirom 100 mg	Resmetirom 80 mg	Placebo
P3NP	0.557	0.548	0.524
ELF	0.483	0.484	0.487

CONCLUSION

- **The increase in ELF in patients with F3/F4 fibrosis is explained by the increase in HA, an extracellular matrix protein made outside the liver and cleared from blood by liver sinusoidal endothelial cells, which are dysfunctional in F4 fibrosis**
- **Liver fibrosis markers PRO-C3 and P3NP were correlated and reduced by resmetirom versus placebo, with the reduction being more pronounced in patients with F3 fibrosis**
- **Evaluation of changes in ELF with treatment in MASH should include assessment of individual ELF components**

ABBREVIATIONS

ELFTM, Enhanced Liver Fibrosis test; FDA, US Food and Drug Administration; HA, hyaluronic acid; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; P3NP, amino terminal of type III procollagen peptide; PRO-C3, N-terminal type III collagen propeptide; RES, resmetirom; SD, standard deviation; SE, standard error; THR-β, thyroid hormone receptor-beta; TIMP-1, tissue inhibitor of metalloproteinase-1.

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