Comparison of MAESTRO-NASH and ESSENCE: effects of resmetirom and semaglutide relative to placebo on primary and secondary liver biopsy endpoints using aligned endpoints and statistical methods

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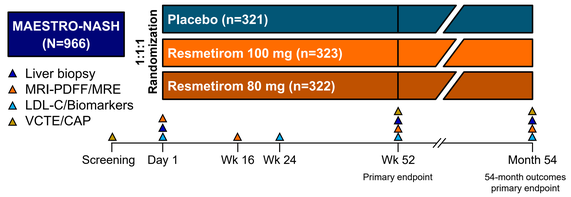
INTRODUCTION

MAESTRO-NASH: Resmetirom in MASH

- MAESTRO-NASH (NCT03900429) is an ongoing 54-month, randomized, double-blind, placebo-controlled Phase 3 trial evaluating the efficacy of resmetirom in patients with biopsy-confirmed MASH (**Figure 1**)[1]
  - A total of 917 patients with fibrosis stages 2-3 (F2F3) were randomized in MAESTRO-NASH

FIGURE 1. MAESTRO-NASH trial design.[1]



- Dual primary endpoints at Week 52 were achieved with both resmetirom 80 mg and 100 mg[1]:
  - NASH resolution with no worsening of fibrosis (NR) with ≥2-point reduction in NAS
  - ≥1-stage improvement in fibrosis with no worsening of NAS (FI)

ESSENCE: Semaglutide in MASH

- ESSENCE is an ongoing 54-month Phase 3 trial evaluating the efficacy of semaglutide 2.4 mg weekly in patients with MASH[2]
  - A total of 800 patients with F2F3 MASH were randomized 2:1 to semaglutide or placebo in ESSENCE
- Dual primary endpoints (NR and FI) were achieved after 72 weeks[2]

Objective

- We compared the responses to drug treatment and placebo in MAESTRO-NASH and ESSENCE using aligned biopsy endpoints and statistical methods

METHODS

- **All cross-trial comparisons are exploratory, unanchored and not evidence of comparative efficacy.**
- Biopsy assessments were similar in both trials, with both employing a biopsy eligibility read requiring F2F3 and NAS ≥4 with all 3 NAS components plus a re-read of baseline biopsies and read of the post-treatment biopsied at 52 or 72 weeks, respectively, by 2 pathologists
- Statistical analyses were conducted according to the statistical plans, and subsequent analyses of MAESTRO-NASH data were conducted using the statistical assumption from ESSENCE (placebo response imputation for missing data in the placebo and resmetirom groups)

RESULTS

- Baseline F2F3 characteristics were similar in the 2 trials:
  - MAESTRO-NASH: RES 80 mg: mean (SD) age: 55.8 (11.2) years; 56.5% female; mean (SD) BMI: 35.6 (6.4) kg/m^2; 35.0% F2 and 63.4% F3. RES 100 mg: mean (SD) age: 57 (10.8) years; 56.5% female; mean (SD) BMI: 36.1 (7.2) kg/m^2; 32.0% F2 and 55.9% F3
  - ESSENCE[2]: mean (SD) age 56.0 (11.6) years; 57.1% female; mean (SD) BMI 34.6 (7.2) kg/m^2; 31.3% F2 and 68.8% F3
- Using a placebo response imputation for missing data, resmetirom 100 mg showed a ~2.4-fold OR and 15% increment relative to placebo in achieving FI, compared with a ~2-fold OR and a 14% increment relative to placebo with semaglutide (**Figure 2**)
- NR versus NR with ≥2-point reduction in NAS (**Figure 2**):
  - 83% of resmetirom 100 mg-treated patients in MAESTRO-NASH had ≥2-point improvement in NAS components to achieve NR, and 17% had <2-point reduction
  - In ESSENCE, 31% of semaglutide-treated patients and 45% of placebo-treated patients with NR had <2-point reduction in NAS components, decreasing the rate of NR from 63% to 44% and 34% to 19% in the semaglutide and placebo arms, respectively
- Ballooning reduction was achieved in a numerically higher percentage of resmetirom 100 mg-treated patients in MAESTRO-NASH (66%) compared with semaglutide-treated patients in ESSENCE (61%), with a larger numerical difference from placebo for resmetirom 100 mg (35%) versus semaglutide (21%; **Figure 3**)[1,2]

Safety

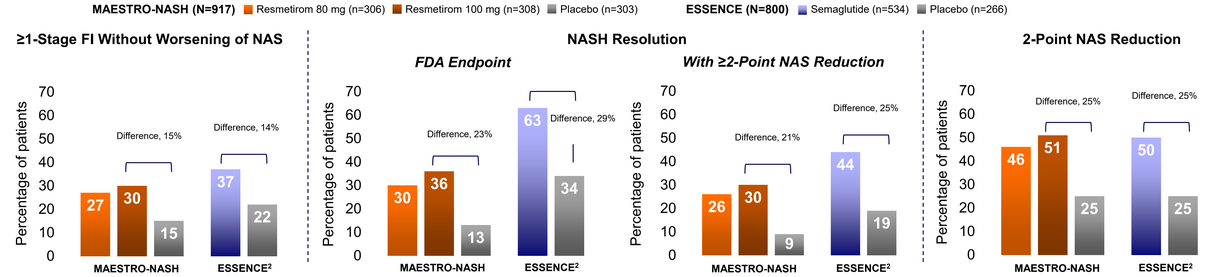
MAESTRO-NASH

- Diarrhea and nausea were more frequent with resmetirom vs placebo[1]
- The incidence of SAEs was similar across the resmetirom 80 mg, resmetirom 100 mg, and placebo groups[1]

ESSENCE

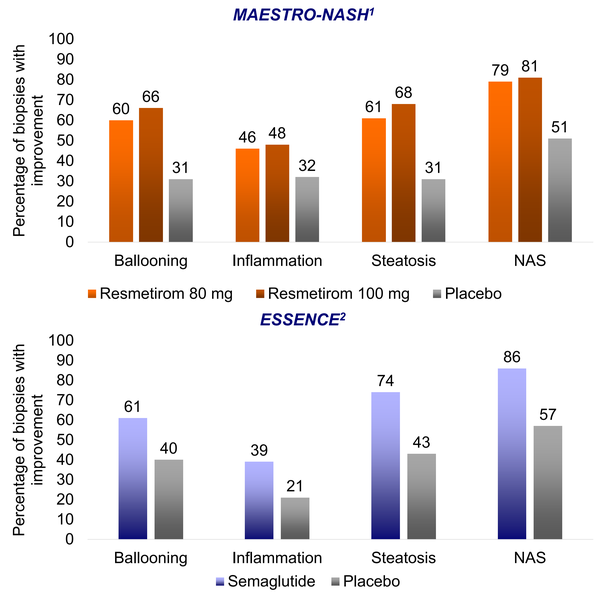
- Nausea, diarrhea, constipation, and vomiting were more common in the semaglutide versus placebo group[2]
- The incidence of SAEs was similar between the semaglutide and placebo groups[2]

FIGURE 2. Achievement of biopsy endpoints: F2F3 populations.[a]



[a]Missing data set as placebo response; presented between-group differences may not equal the differences between the percentages shown for each group due to rounding.

FIGURE 3. Improvements in NAS components.[a]



[a]Observed data, biopsy completer analysis.

CONCLUSIONS

- **Achievement of ≥1-stage fibrosis improvement was similar in ESSENCE and MAESTRO-NASH, showing about 15% improvement with drug treatment relative to placebo**
- **When evaluated for a 2-point change in NAS, the placebo groups had a similar response in both studies, suggesting that the high NR rate (34%) in placebo-treated patients in ESSENCE was due to low NAS in the re-read baseline biopsies**
- **Using more stringent endpoints, resmetirom had a NASH resolution response that was similar to semaglutide, with a higher percentage of resmetirom-treated patients showing a reduction in ballooning compared to placebo-treated patients**

BMI, body mass index; CAP, controlled attenuation parameter; FDA, US Food and Drug Administration; FI, fibrosis improvement; LDL-C, low-density lipoprotein cholesterol; MASH, metabolic dysfunction-associated steatohepatitis; MRE, magnetic resonance elastography; MRI-PDFF, magnetic resonance imaging proton density fat fraction; NAS, nonalcoholic fatty liver disease activity score; NASH, non-alcoholic steatohepatitis; NR, NASH resolution; OR, odds ratio; RES, resmetirom; SAE, serious adverse event; SD, standard deviation; VCTE, vibration-controlled transient elastography; Wk, Week.

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REFERENCES

1. Harrison SA, et al. *N Engl J Med.* 2024;390(6):497-509. 2. Sanyal AJ, et al. *N Engl J Med.* 2025;392(21):2089-2099.

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