Matching-adjusted indirect comparison (MAIC) of resmetirom and semaglutide for patients with metabolic dysfunction-associated steatohepatitis (MASH)

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INTRODUCTION

- Metabolic dysfunction-associated steatohepatitis (MASH) is a progressive liver disease affecting approximately 5% of the global population.[1]
  - Symptoms reported frequently by patients include pain, anxiety, depression, and sleep disturbance.[2]
- In 2024, resmetirom was approved by the United States (US) Food and Drug Administration (FDA) for patients with MASH with moderate-to-advanced liver scarring,[3] based on results from the MAESTRO-NASH trial.[4]
- Semaglutide was approved by the US FDA in 2025 for the treatment of MASH,[5] based on results from the ESSENCE trial, published earlier this year.[6]
- Due to differences between the two trials in study design, methods, and patient populations, a matching-adjusted indirect comparison (MAIC) approach was needed.

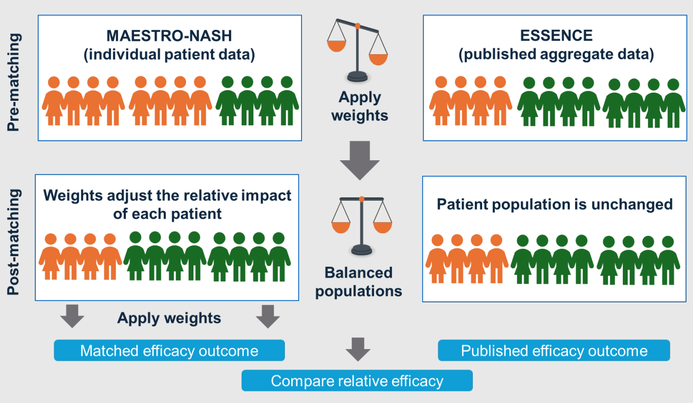
OBJECTIVES

- An MAIC was conducted to evaluate the relative efficacy of oral resmetirom (80 mg and 100 mg once daily [QD]) vs. subcutaneous semaglutide (2.4 mg once weekly [QW]).
- The analysis focused on two primary endpoints:
  - Resolution of steatohepatitis and no worsening of fibrosis
  - Fibrosis improvement by ≥1 stage without worsening of non-alcoholic steatohepatitis activity score (NAS)

METHODS

- A feasibility assessment was conducted with the studies deemed comparable, and the following actions were taken:
  - ESSENCE endpoint definitions were used due to the availability of MAESTRO-NASH patient-level data vs. aggregate data for ESSENCE.
  - Risk ratios (RR, i.e., the ratio of two probabilities) were estimated using weighted binomial regression with a log-link and a robust variance estimator.
  - For continuous treatment effect modifiers (TEM), the second moment was also matched.
  - The MAIC applied is illustrated in Figure 1.
- Patient-level data from MAESTRO-NASH were weighted for comparison with aggregate data from ESSENCE, using mutually reported baseline characteristics identified as TEMs or prognostic variables (Table 1).
- Patients with missing endpoints were considered non-responders (MAESTRO-NASH imputation method).
- Results are reported for the modified intent-to-treat (mITT) (base case) and license (sensitivity analysis) populations.
  - For the sensitivity analysis, the following patients were excluded to reflect the approved labels:
    - Patients with baseline fibrosis stage 1b or 4
    - Patients with weight ≥100 kg in the 80 mg group
    - Patients with weight <100 kg in the 100 mg group
- Outcome assessment timepoints were week 52 for MAESTRO-NASH and week 72 for ESSENCE.

FIGURE 1. MAIC methods



RESULTS

TABLE 1. Pre- and post-match* baseline characteristics comparison

Study characteristics	ESSENCE	MAESTRO-NASH (Resmetirom 80 mg QD and placebo)		MAESTRO-NASH (Resmetirom 100 mg QD and placebo)	
		Pre-match	Post-match	Pre-match	Post-match
mITT, N	800	634	NA	639	NA
ESS, N (%)	800	609	503.89 (82.70%)	616	520.23 (84.40%)
BMI kg/m^2, mean (SD)	34.60 (7.20)	35.50 (6.44)	34.60 (7.20)	35.90 (7.02)	34.60 (7.20)
Type 2 diabetes^	55.50%	67.20%	55.50%	65.30%	55.50%
Liver stiffness VCTE, mean (SD)	12.80 (6.90)	13.14 (6.21)	12.80 (6.90)	13.27 (6.39)	12.80 (6.90)
Age, mean (SD)	56.00 (11.60)	56.32 (10.86)	56.00 (11.60)	56.87 (10.59)	56.00 (11.60)
Fibrosis stage 3^	70.00%	58.50%	70.00%	60.20%	70.00%

*Matched on BMI, type 2 diabetes, VCTE, age, and fibrosis stage 3.
^SMD absolute value >0.2. SMD are used to describe imbalances in patient characteristics between the two trials. SMD absolute values >0.2 are deemed a considerable difference.[7]
Abbreviations: BMI, body mass index; ESS, effective sample size; mITT, modified intent to treat; NA, not applicable; SD, standard deviation; SMD, standardized mean difference; VCTE, vibration-controlled transient elastography

- In the base-case analyses using the mITT population, resmetirom demonstrated numerical advantages vs. semaglutide (Table 2).
  - For resolution of steatohepatitis with and no worsening of fibrosis, the RR for resmetirom vs. semaglutide was 1.14 for 80 mg QD (effective sample size [ESS]: 503.89, 95% confidence interval [CI]: 0.73, 1.76; p=0.564) and 1.24 for 100 mg QD (ESS: 520.23, 95% CI: 0.81, 1.89; p=0.332).
  - For fibrosis improvement by ≥1 stage without worsening of NAS, the RR for resmetirom vs. semaglutide was 1.01 for 80 mg QD (ESS; 503.89, 95% CI: 0.63, 1.61; p=0.969) and 1.18 for 100 mg QD (ESS: 520.23, 95% CI: 0.75, 1.86; p=0.473).
- In the sensitivity analyses using the license population, the results were largely consistent with the base-case analyses; however, these point estimates did not achieve statistical significance (Table 2).

TABLE 2. MAIC results

	RR* (95% CI)			
	N/n/ESS	Resmetirom 80 mg QD vs. semaglutide 2.4 mg QW	N/n/ESS	Resmetirom 100 mg QD vs. semaglutide 2.4 mg QW
mITT population (base-case analysis)				
Resolution of steatohepatitis and no worsening of fibrosis				
ESSENCE	800	Reference	800	Reference
MAESTRO-NASH (unadjusted)	634	1.16 (0.78, 1.75)	639	1.33 (0.89, 1.98)
MAESTRO-NASH (matched)	503.89	1.14 (0.73, 1.76)	520.23	1.24 (0.81, 1.89)
Fibrosis improvement by ≥1 stage without worsening of NAS				
ESSENCE	800	Reference	800	Reference
MAESTRO-NASH (unadjusted)	634	0.90 (0.59, 1.39)	639	0.99 (0.65, 1.52)
MAESTRO-NASH (matched)	503.89	1.01 (0.63, 1.61)	520.23	1.18 (0.75, 1.86)
License population (sensitivity analysis)				
Resolution of steatohepatitis and no worsening of fibrosis				
ESSENCE	800	Reference	800	Reference
MAESTRO-NASH (unadjusted)	456	1.43 (0.93, 2.21)	442	1.51 (0.98, 2.33)
MAESTRO-NASH (matched)	305.98	1.07 (0.64, 1.78)	317.14	1.33 (0.82, 2.18)
Fibrosis improvement by ≥1 stage without worsening of NAS				
ESSENCE	800	Reference	800	Reference
MAESTRO-NASH (unadjusted)	456	1.03 (0.65, 1.61)	442	0.96 (0.60, 1.52)
MAESTRO-NASH (matched)	305.98	0.93 (0.55, 1.56)	317.14	1.13 (0.67, 1.91)

*RR=1 indicates no difference between treatments. RR <1 favors semaglutide. RR >1 favors resmetirom.
Abbreviations: CI, confidence interval; ESS, effective sample size; mITT, modified intent to treat; NAS, non-alcoholic steatohepatitis activity score; QD once daily; QW, once weekly; RR, risk ratio

CONCLUSION

- **The comparative efficacy of resmetirom vs. semaglutide was evaluated via MAIC due to differences in study design and patient characteristics, as well as a lack of head-to-head trial data.**
- **Although limited by differences in assessment timepoints (i.e., week 52 vs. week 72), these MAIC analyses based on all available randomized controlled trial evidence showed statistically similar placebo-adjusted response rates for resmetirom (week 52) and semaglutide (week 72).**
  - **No statistically significant differences in efficacy were observed between these two treatments, although MAIC-adjusted point estimates generally favored resmetirom.**
- **The findings provide additional support for the clinical benefit of resmetirom, reinforcing its role as a standard of care for MASH.**
- **The research underscores the importance of using rigorous cross-trial comparisons, instead of naïve, unadjusted comparisons.**

ABBREVIATIONS

BMI, Body mass index; ESS: Effective sample size. FDA: Food and Drug Administration, MAIC: Matching-adjusted indirect comparison. mITT: Modified intent to treat. MASH: Metabolic dysfunction-associated steatohepatitis. NAS: Non-alcoholic steatohepatitis activity score. RR: Risk ratio. TEM: Treatment effect modifier. VCTE: Vibration-controlled transient elastography.

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