A Systematic Literature Review, Network Meta-analysis, and Cost-effectiveness Analysis of Resmetirom for the Treatment of Nonalcoholic Steatohepatitis

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BACKGROUND

- Resmetirom is a potential treatment for nonalcoholic steatohepatitis (NASH)

OBJECTIVES

- A systematic literature review (SLR) and network meta-analysis (NMA) were conducted to assess the efficacy of resmetirom compared with obeticholic acid (OCA) and placebo
- An economic evaluation was subsequently performed to explore the cost-effectiveness of resmetirom versus OCA and placebo from a US healthcare payer perspective

METHODS

Systematic literature review

- To identify eligible studies, a comprehensive search of MEDLINE/PubMed, EMBASE, the Cochrane library (including the Cochrane Central Register for Controlled Trials [CENTRAL] and Cochrane Databases of Systematic Reviews [CDSR]), and clinical trial registries (clinicaltrials.gov and clinicaltrialsregister.eu) was conducted up to May 5, 2022
- The search strategy incorporated key terms for NASH, nonalcoholic fatty liver disease (NAFLD), clinical trials, and a broad range of terms for NASH pharmacological therapies
- Included studies were randomized controlled trials (RCTs) comparing any of the pre-specified interventions head-to-head with placebo or a combination of these interventions in participants where ≥80% of the individuals (aged ≥18 years) were diagnosed with NASH or suspected of having NASH

Statistical analysis for indirect treatment comparison

- A Bayesian NMA was conducted for each outcome unless the effect estimate was not reported for the resmetirom arm
- Both fixed-effect and random-effect models were applied, with the latter considering the between-trials inherent heterogeneity. The smaller deviance information criterion (DIC) was used to choose the models with the best performance
- Outcomes reported by ≥2 RCTs with 1 shared arm were pooled; odds ratios (ORs) for dichotomous outcomes and posterior probability of success (PPS) of resmetirom versus comparators were calculated
- The NMA within the Bayesian framework was performed using Jag's embedded R-package [bnma]
- The Markov Chain Monte Carlo (MCMC) sampling method was used to execute the model

Cost-effectiveness analysis

- We used a previously-developed cost-effectiveness model which applied a Markov model to simulate the clinical pathways of patients with NASH with liver fibrosis; no fibrosis (F0) and fibrosis (F1-F3) stages, compensated cirrhosis (CC or F4) as well as other hepatic complications including decompensated cirrhosis (DCC), hepatocellular carcinoma (HCC), and liver transplant (LT); hospitalizations; and mortality were included[1]

RESULTS

Systematic literature review

- 3,536 studies were retrieved through the literature search; **64 publications** (24 interventions with 37 full-text articles, 16 conference abstracts, 11 trial records) fulfilled the inclusion criteria and were included in the current analysis
- Ultimately, 5 studies were selected for the NMA to assess the comparative efficacy of resmetirom versus **placebo**, **vitamin E**, **OCA**, and **pioglitazone**
  - Those studies covered 1,562 participants; median follow-up duration was 69.6 weeks; 47.1% of participants were male; mean age of participants was 50.9 years[2-6]

Statistical analysis for indirect treatment comparison

- The analysis was restricted to 5 efficacy endpoints due to the lack of data for other clinical outcomes; these endpoints included:
  - NASH resolution
  - Fibrosis improvement
  - Fibrosis stabilization
  - Fibrosis-at least stable (stable and improved)
  - Fibrosis worsening
- Network diagrams comparing directed and undirected interventions are depicted in **Figure 1**

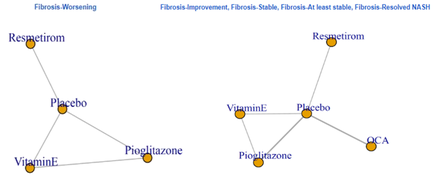

Figure 1. Network diagrams

- When compared with placebo, resmetirom demonstrated ORs 0.33, 1.23, 1.62, 3.76, and 1.44 for fibrosis worsening, stable fibrosis, fibrosis improvement, fibrosis-at least stable, and NASH resolution, respectively
- The NMA yielded ORs of 0.91, 1.29, 3.37, and 0.98, respectively, for fibrosis worsening, stable fibrosis, fibrosis improvement, fibrosis-at least stable, and NASH resolution for resmetirom in comparison to OCA
- The results of resmetirom PPS are shown in **Table 1**

Cost-effectiveness analysis

- Results from the base-case probabilistic sensitivity analysis (PSA) showed that costs/patient in the resmetirom arm were $319,686 over a lifetime time horizon, which was $8,859 more costly than placebo and $258,390 less costly than OCA on an individual patient basis
- The results of the base-case analysis also showed that resmetirom (10.52) leads to more quality-adjusted life-years (QALYs) than placebo (8.87) and OCA (9.79) over a lifetime (incremental QALYs gained of 1.65 and 0.729, respectively)
- The incremental cost-effectiveness ratio (ICER) was $5,380 vs placebo, which is below the $100,000 per QALY US threshold of cost-effectiveness
- On the other hand, OCA showed a high ICER of $291,373 in comparison to placebo
- The PSA showed that resmetirom was cost-effective, with a probability of 99% and OCA was not cost-effective against placebo or resmetirom (**Figure 2**)

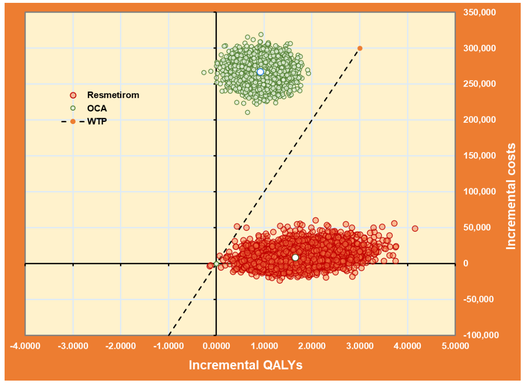

Figure 2. Cost-effectiveness plane – incremental costs ($) vs incremental QALYs (resmetirom or OCA vs placebo)

Table 1. Posterior probability of resmetirom success -NMA

Comparison	PPS (%)
Fibrosis Worsening*	
Resmetirom vs Placebo	71
Resmetirom vs Pioglitazone	63
Resmetirom vs Vitamin E	65
Fibrosis Stabilization	
Resmetirom vs Placebo	56
Resmetirom vs Pioglitazone	60
Resmetirom vs OCA	49
Resmetirom vs Vitamin E	58
Fibrosis Improvement	
Resmetirom vs Placebo	68
Resmetirom vs Pioglitazone	45
Resmetirom vs OCA	58
Resmetirom vs Vitamin E	49
Fibrosis-At Least Stable	
Resmetirom vs Placebo	74
Resmetirom vs Pioglitazone	65
Resmetirom vs OCA	68
Resmetirom vs Vitamin E	65
NASH Resolution	
Resmetirom vs Placebo	70
Resmetirom vs Pioglitazone	11
Resmetirom vs OCA	45
Resmetirom vs Vitamin E	37

*Since the response is negative, 1-posterior probability, had been reported.

Study limitations

- Trial comparability may be impacted by heterogeneity reflecting underlying variations in study/patient demographics. The heterogeneity was attempted to be minimized by limiting the eligibility criteria
- The follow-up period for the resmetirom trial was shorter than other trials. Resmetirom's long-term efficacy may be challenged as a result, but it may also be indicated by the fact that it outperforms other therapies for a wide range of endpoints over a shorter period

CONCLUSIONS

- **In an SLR and NMA including eligible RCTs, resmetirom was superior to OCA and placebo for the outcomes of fibrosis improvement and fibrosis-at least stable**
- **An economic evaluation showed resmetirom would be cost-effective for treatment of NASH, improving clinical outcomes and reducing costs**

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