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Original Article

Resmetirom for Metabolic Dysfunction-Associated Steatohepatitis: Systematic Review with Meta-Analysis

Resmetirom para esteato-hepatite associada à disfunção metabólica: revisão sistemática com metanálise

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ABSTRACT

Objectives: To evaluate the evidence on the efficacy, safety, and cost-effectiveness of resmetirom for metabolic dysfunction-associated steatohepatitis (MASH). **Methods**: A systematic review with meta-analysis of randomized clinical trials was conducted, comparing resmetirom to placebo or active comparators for the treatment of MASH (PROSPERO: CRD42024557306). Searches were performed in 06/2024 in the Medline, Embase, Lilacs, Cochrane, and Centre for Reviews and Dissemination databases. Two researchers independently selected studies, extracted data, and assessed their methodological quality. Meta-analyses were conducted in R. The risk of bias in randomized clinical trials was assessed using the Cochrane Collaboration's RoB-2 tool, and the level of evidence was evaluated using the GRADE approach. **Results**: The final sample was composed by eight publications. Resmetirom was shown to be effective in resolving MASH, with a 149% improvement compared to the control group. It also significantly improved liver fibrosis and reduced liver fat, with notable effects in long-term studies. However, an increased incidence of diarrhea and nausea was observed among treated patients. Laboratory parameters, such as LDL and triglycerides, also improved with resmetirom. The technology was considered cost-effective at a threshold of $100,000/QALY (ICER ranging from $36,600/QALY to $74,018/QALY) in studies worldwide. **Conclusion**: Resmetirom demonstrated significant and sustained reductions in liver fat and improvements in fibrosis, proving to be effective, safe, and potentially cost-effective for the treatment of MASH.

Keywords: Pharmacoeconomics; Resmetirom; Metabolic dysfunction-associated steatohepatitis; Obesity; Review.

RESUMO

Objetivos: Avaliar as evidências sobre a eficácia, segurança e custo-efetividade de resmetirom para esteato-hepatite associada à disfunção metabólica (EHADM). **Métodos**: Uma revisão sistemática com metanálise de ensaios clínicos randomizados foi realizada comparando o resmetirom ao placebo ou comparador ativo para o tratamento da EHADM (PROSPERO: CRD42024557306). As buscas foram realizadas em 06/2024 nas bases de dados Medline, Embase, Lilacs, Cochrane e Centre for Reviews and Dissemination. Dois pesquisadores selecionaram independentemente os estudos, extraíram os dados e avaliaram sua qualidade metodológica. As metanálises foram conduzidas em R. O risco de viés nos ensaios clínicos randomizados foi avaliado através da escala RoB-2 da Colaboração Cochrane e o nível de evidência foi avaliado pelo método GRADE. **Resultados**: A amostra final foi composta por oito publicações. O resmetirom mostrou-se eficaz na resolução da EHADM, com um aumento de 149% em comparação ao controle. Além disso, promoveu melhorias significativas na fibrose hepática e na redução da gordura no fígado, com efeitos notáveis nos estudos de longa duração. No entanto, foi observado um aumento na incidência de diarreia e náusea entre os pacientes tratados. Os parâmetros laboratoriais, como LDL e triglicerídeos, também apresentaram melhora com o resmetirom. A tecnologia foi considerada custo-efetiva a um limiar de US$100.000/QALY (RCEI entre US$36.600/QALY e US$74.018/QALY) em estudos ao redor do mundo. **Conclusão**: O resmetirom demonstrou uma redução significativa e sustentada na gordura do fígado e uma melhora na fibrose, demonstrando ser eficaz, seguro e potencialmente custo-efetivo para o tratamento da EHADM.

Palavras-chave: Farmacoeconomia; Resmetirom; Esteato-hepatite associada à disfunção metabólica; Obesidade; Revisão.

Introduction

Metabolic dysfunction-associated steatohepatitis (MASH) is considered one of the most severe forms of metabolic dysfunction-associated fatty liver disease (MAFLD).[1,2] The disease is characterized by the accumulation of more than 5% of triglycerides in the cytoplasm of hepatocytes and progressive fibrogenesis, which may evolve into fibrosis, cirrhosis, and fatal complications, such as liver failure and hepatocellular carcinoma.[3–7] Its progression is associated with inflammation and hepatocyte ballooning, often asymptomatic at the beginning, but potentially causing fatigue, abdominal discomfort, and, in advanced stages, jaundice and ascites.[7] Diagnosis involves laboratory tests, imaging exams, and, in some cases, liver biopsy.[7,8] Early identification and control of inflammation are essential to improve prognosis and reduce mortality.[5,8,9]

The global prevalence of MAFLD in adults is estimated at approximately 30%. MASH is diagnosed in 10% to 20% of MAFLD cases.[10,11] In Latin America, the prevalence of MASH is relatively high, around 7%.[10] A global meta-analysis estimated the overall mortality rate for MASH at approximately 25.6/1,000 person-years, with a follow-up period of 4 to 13 years.[12] It has been observed that approximately 20% of patients with MASH and advanced fibrosis or compensated cirrhosis progress to cirrhosis or develop liver failure within about 2 years.[8] In 2019, MASH was the second most common indication for liver transplantation in the United States.[14]

In the United States, MASH-related costs were US$11.61 million in 2020. With a projected increase of 82.6% in cases, this cost could reach US$19.53 million by 2039. Consequently, accumulated direct healthcare costs are expected to reach US$1.208.47 billion in obese patients and US$453.88 billion in non-obese patients.[15] The cost per patient was estimated at US$7,668 per year.[16] O'Hara et al. (2020) reported that direct medical costs, direct non-medical costs, and indirect costs per patient with MASH were €2,763, €4,917, and €5,509, respectively, in Europe and the United States in 2018. A systematic review of 14 studies estimated that direct medical costs attributable to MASH with or without fibrosis ranged from €332 million in Germany to US$7.35 billion in the United States, with an average annual cost per patient of €4,754 (2019 values).[17] Shahinul et al.[16] estimated direct costs for MASH with cirrhosis in Bangladesh at US$1,783.83 per patient. The amount found was US$938.84 per patient in public hospitals and US$3,004.29 per patient in private hospitals.[16]

The goal of MASH management is to slow disease progression and possibly reverse liver damage.[18,19] Standard care for MASH includes lifestyle modifications, such as weight loss, physical exercise, and a balanced diet, to reduce inflammation and regress fibrosis.[1,20–22] It has been shown that weight loss of more than 7% is associated with MASH resolution and fibrosis regression[23]. However, maintaining weight loss remains a challenge for the population. In 2024, the United States Food and Drug Administration (FDA) approved resmetirom as the first targeted pharmacological treatment for non-cirrhotic patients with MASH and moderate-to-advanced liver fibrosis (stage F2 and F3)[24,25] Resmetirom is a thyroid hormone receptor β (THR-β) agonist, with 28 times higher selectivity for THR-β than for thyroid hormone receptor V (THR-β).[2,26] This selectivity provides greater drug concentration and stability in hepatocytes, with lower systemic exposure, avoiding cardiac and bone effects associated with THR-β.[2,25,26] The medication should be used daily in combination with diet and physical activity. According to the Institute for Clinical and Economic Review, projections indicate that resmetirom will be cost-effective if its price ranges between US$39,600 and US$50,100 per year.[27]

To date, there is no standardized medication for MASH within the Unified Health System (SUS).[28] Resmetirom has not yet been registered in Brazil but offers a promising mechanism of action by modulating lipid metabolism and reducing fat accumulation in the liver. In this context, it is important that high-quality information is available for assessment by health managers at all levels. This study is an initiative of the authors to support decision-making when the evaluation of the drug is considered by federal, state, and municipal authorities.

Objectives

The objective of this study is to conduct a systematic literature review on the efficacy, safety, and cost-effectiveness of resmetirom as a treatment for metabolic dysfunction-associated steatotic liver disease.

Methodology

This systematic review with meta-analysis was conducted in accordance with the principles of the Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[29] Its protocol was prospectively registered in the PROSPERO database (CRD42024557306).

Research Question

This study aims to answer the following question: "Is resmetirom effective, safe, and cost-effective for the treatment of metabolic dysfunction-associated steatohepatitis in adults?" The experimental group received resmetirom. The control group could receive either placebo or an active control. The meta-analysis was conducted based on the resmetirom dosage. The PICO-formatted question is presented in Appendix 1.

Literature Search

An electronic search was conducted in the Medline (via PubMed), Lilacs (via BVS), The Cochrane Library, Embase, and Centre for Reviews and Dissemination (CRD) databases for studies that comparatively assessed the efficacy, safety, and cost-effectiveness of resmetirom for MASH. Several descriptors and synonyms were used, such as "Resmetirom," "MGL-3196," "randomized controlled trial," "Cost-Benefit," "Cost-Utility," "economic evaluation," "cost-effectiveness," among others. The complete search strategies are available in Appendix 2. A complementary search was conducted in clinicaltrials.gov, in the references of included studies, in journals and specialized periodicals, in conference abstracts, and in Google Scholar. Searches were carried out in June 2024. The references identified were imported into EndeNote® 20 for duplicate removal and subsequently transferred to the online application Rayyan[30] for the first phase of selection.

Study selection and data collection

Randomized controlled trials (RCTs) and full economic evaluations (EEs) were selected for outcome assessment. The RCT is the gold-standard study design for evaluating the efficacy and safety of health technologies[31],[32]. Since this work is concerned only with comparative results for a meta-analysis, single-arm or phase 1 clinical trials were not included. No restrictions on date, language, or location were applied. In phase 1, records were screened by titles and abstracts. In phase 2, the full texts of the remaining records were retrieved and assessed for inclusion. In phase 3, data related to the outcomes of interest were collected in a spreadsheet created a priori. Phases 1, 2, and 3 were conducted independently by two researchers, and differences were resolved by consensus[33].

Outcomes

The primary outcomes chosen for this analysis were the resolution of metabolic dysfunction-associated steatohepatitis (MASH), improvement in liver fibrosis (change in fibrosis stage observed in liver biopsies or other non-invasive imaging tests), and reduction of liver fat content. Secondary outcomes were divided into four groups: (i) efficacy, (ii) safety, (iii) quality of life, and (iv) pharmacoeconomics. The efficacy outcomes included improvement in fibrosis without worsening of MASH characteristics, improvement of MASH-related symptoms (abdominal pain, fatigue), and improvements in laboratory parameters such as low-density lipoproteins (LDL), high-density lipoproteins (HDL), apolipoprotein B (ApoB), apolipoprotein C-III (ApoC-III), lipoprotein A (LipoA), triglycerides, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyltransferase (GGT). The safety outcomes included adverse

events leading to drug discontinuation, serious adverse events (SAEs), headache, weight loss or gain, diarrhea, and nausea. Improvements in quality of life among patients with MASH were included. Finally, incremental cost-effectiveness ratio (ICER) data were collected for the economic studies.

Data analysis

A qualitative analysis was presented describing the results of the different RCTs and economic studies. The quantitative synthesis of RCTs (direct meta-analysis) was conducted using the inverse variance method. To ensure accuracy and consistency of the collected data, studies in which resmetirom was used in more than one treatment arm with different therapeutic doses were combined. The pooling of data from multiple doses to obtain a single overall estimate followed the guidelines described by Higgins et al.[33] For dichotomous variables, the sample sizes of each resmetirom arm and the number of events were summed to generate a single estimate. Results were expressed as relative risk (RR) and 95% CI. For continuous outcomes, the weighted mean was applied for the estimation of the central effect, and the pooled standard deviation was used to represent data dispersion. Data were expressed as mean difference (MD) and 95% confidence interval (95% CI). Results from the fixed-effect model (FEM) and the random-effects model (REM) were presented. The REM was calculated using the DerSimonian and Laird method.[34] Results with $p<0.05$ were considered statistically significant. Analyses with $I^2>30\%$ were considered to have moderate heterogeneity, $I^2>50\%$ substantial heterogeneity, and $I^2>75\%$ high heterogeneity. Heterogeneity data with $p<0.10$ were considered statistically significant[33]. Publication bias was presented using funnel plots and Egger's test when at least ten studies were included in the meta-analysis.[33,35] All analyses were conducted in R.[36]

Economic studies were analyzed according to their general characteristics, and the results were reported by the ICER. The incremental cost-effectiveness ratio was calculated through the difference in costs between the therapeutic options evaluated, divided by the difference in effectiveness (Equation 1). It is a measure of how much is paid for an additional unit of outcome if the intervention under evaluation is adopted. When its value is negative, dominance is observed in the analysis, i.e., one of the alternatives is both less costly and more effective at the same time.

$$\text{ICER} = \frac{C_1 - C_2}{E_1 - E_{2+}} \quad \#(1)$$

When there is no dominance in the analysis, it is necessary to determine how much one is willing (or able) to pay for an additional unit of outcome. In this case, the ICER value must be compared to a critical value, called the cost-effectiveness threshold (λ). Most authors accept that a technology is recommended when ICER $\leq \lambda$[37].

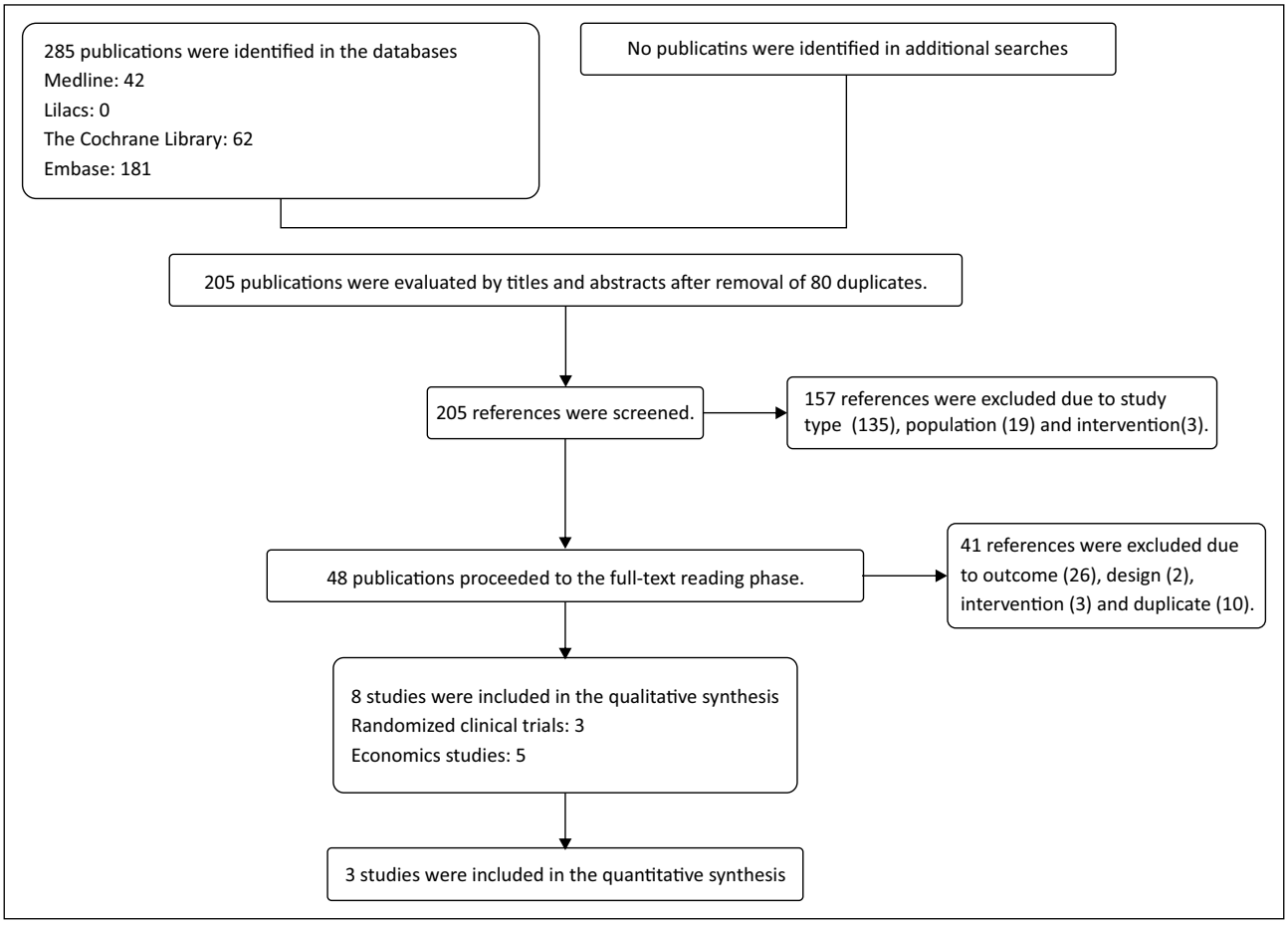
Risk of bias in the included studies and level of evidence

To assess the methodological quality of the RCTs, the Cochrane Collaboration's Risk of Bias-2 (RoB-2) tool was used[33]. The RoB-2 evaluation of the primary studies was conducted in duplicate and disagreements were resolved by consensus. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system was used to assess the level of evidence. The level of evidence was classified into four categories: high, moderate, low, and very low.[38–42] There is no widely accepted method to assess the quality of economic studies.[43]

Results

A total of 285 publications were identified in the search. In phase 1, after the removal of 80 duplicates, 205 records were screened by titles and abstracts. After excluding 157 records, the full content of 48 publications was analyzed. In the end, 8 publications were included in the review (Figure 1).

Figure 1. Study selection flowchart



Source: Author's Elaboration

General characteristics of the included studies

Three RCTs were included in the analysis. These studies were denominated MAESTRO-NAFLD-1,[44] MAESTRO-NASH[45] and MGL-3196-05.[46] The first two had a duration of 52 weeks, while the third lasted 36 weeks. All studies were multicenter, but MAESTRO-NAFLD-1 and MGL-3196-05 were conducted only in centers in the United States. MAESTRO-NASH was conducted across centers in 15 countries. This resulted in a total population of 2,318 participants. All studies compared resmetirom to placebo and used the same protocol for both groups: oral administration once daily. Patients in both study arms received nutritional and exercise counseling according to current recommendations. The mean age of patients in the MGL-3196-05 study was lower than in the other studies. Thus, patients from 2019, being younger, were less exposed to inflammatory factors and possible liver fibrotic activity. All studies excluded patients with uncontrolled diabetes from the sample.

It is noteworthy that in the MAESTRO-NASH study, statistical data from the biopsy endpoint and outcomes were not adjusted for multiplicity and therefore cannot be used for hypothesis testing. Without appropriate adjustment, confidence intervals cannot be fully relied upon to make statistical decisions or conclusions regarding the significance of the results. All RCTs were published by the same team, with the same lead author, and funded by Madrigal Pharmaceuticals, the company holding the resmetirom patent. For MAESTRO-NASH and MAESTRO-NAFLD-1, data from resmetirom 100 mg and 80 mg doses were pooled to obtain a single global estimate for conducting the meta-analysis. Data from the open-label continuation arm with 100 mg of resmetirom from the MAESTRO-NAFLD-1

study were not included, as this arm did not contain a comparator group.

All economic studies were conducted for the United States.[47–51] Markov models with 10 health states and annual cycles were built in at least three studies.[49–51] The studies by Ansaripour et al. (2023) did not report the number of health states or the cycle duration. Only Javanbakht et al.[49,50] reported the discount rate (3%). Methodological differences were observed, such as the drug cost and the data sources used: Fahim et al.[51] relied on phase III trial data (MAESTRO-NASH), while Javanbakht et al.[49,50] used phase II data. Ansaripour et al. (2023) was based on a systematic review and network meta-analysis. It is also noteworthy that only the study by Fahim et al. was not sponsored by Madrigal Pharmaceuticals. Missing data on evaluated outcomes were requested from the authors of the publications, but no response was obtained. Information on the characteristics of the included studies was extracted from each of the publications (Appendices 3 to 5).

Qualitative synthesis of outcomes

The three studies by Harrison et al. (2019) provide a comprehensive overview of the efficacy and safety of resmetirom in the treatment of metabolic dysfunction-associated steatohepatitis. The MGL-3196-05[46] study is a phase 2 trial that demonstrated resmetirom's ability to significantly reduce liver fat and improve markers of inflammation and fibrosis over 36 weeks compared to placebo, with adverse events mainly mild to moderate. The MAESTRO-NAFLD-1[44] study is a phase 3 trial that reinforces these findings, showing that resmetirom, at doses of 80 mg and 100 mg, was safe and well tolerated in patients with MASH. The study suggests that resmetirom significantly reduces liver fat and improves liver stiffness and lipid profiles over 52 weeks. Finally, the MAESTRO-NASH[45] study continues to assess the efficacy of resmetirom, confirming its ability to resolve MASH and improve liver fibrosis without worsening disease activity after 52 weeks of treatment. The study confirms the efficacy and safety of the drug for MASH in multiple populations.

The economic studies by Ansaripour et al.[47,48] indicate that resmetirom is cost-effective for the treatment of MASH in the United States. An ICER of US$74,018 was found compared to placebo and dominance over obeticholic acid (OCA). Fahim et al.[51], using a lifetime horizon and the perspective of the US healthcare system, evaluated resmetirom at a provisional price of US$19,011. The authors considered the intervention dominant compared to standard treatment, with incremental gains of 0.60 QALYs (quality-adjusted life years) and 0.68 evLYs (equal value life-years). The ICER was estimated at between US$39,600 and US$50,100 compared to placebo. Javanbakht et al.[49,50] reinforced these conclusions, demonstrating that resmetirom yielded incremental gains of 1.392 QALYs and an ICER of US$77,348/QALY. Resmetirom was cost-effective at a daily price of up to US$72.00. Costs and benefits were discounted at a 3% rate, as recommended by ICER. All these studies considered λ=US$100,000/QALY.

Quantitative synthesis of outcomes

Resolution of metabolic dysfunction-associated steatohepatitis

Resmetirom was associated with a 149% increase in the resolution of MASH compared to the control group (RR=2.49, 95% CI=1.77-3.51, p<0.01). Substantial and significant heterogeneity was observed in the analysis (I^2=68%, p=0.08) (Figure 2). The random-effects estimate yielded more conservative results (RR=2.08, 95% CI=0.96-4.54, p=0.06). These results are not statistically significant at the 5% level, but they are at the 10% level.

The MAESTRO-NASH study[45] showed that resmetirom promoted improvement in each component of the NAFLD activity score (RR=3.58, 95% CI=2.31–5.54) and that patients in the experimental group were more likely to achieve resolution of MASH and improvement of liver fibrosis by ≥1 stage compared with the control group (RR=3.00, 95% CI=1.74–5.17). Resmetirom was twice as likely to improve the NAFLD activity score by ≥2 points without worsening fibrosis compared with the control group (RR=1.99, 95% CI=1.59–2.48). Heterogeneity in the result was null (I^2=0%, p=0.58).

Improvement of liver fibrosis

Resmetirom was associated with a 66% gain in improvement of liver fibrosis by ≥1 stage without worsening in the activity score compared with the control group (RR=1.66, 95% CI=1.23–2.24, p<0.001). Heterogeneity in the result was null (I^2=0, p=0.35) (Figure 3). Only the MAESTRO-NASH study evaluated the outcome of liver fibrosis improvement by ≥2 stages, showing improvement in fibrosis compared with placebo (RR=3.26, 95% CI=1.56–6.79).[45] Additionally, one of the studies reported improvements in liver stiffness measured by FibroScan VCTE (Vibration Controlled Transient Elastography) (MD=-0.17 kPa, 95% CI=-0.28 to -0.06).[44]

Reduction of liver fat content

Resmetirom showed significant reductions in liver fat compared with the control group, with a greater effect observed in long-term studies (MD=-21.54%, 95% CI=-21.79 to -21.29, p<0.01). Heterogeneity of the result was high and significant (I^2=100%, p=0) (Figure 4). Similarly, the MAESTRO-NAFLD-1[44] study demonstrated, through FibroScan CAP (Controlled Attenuation Parameter), reductions in liver fat with the use of resmetirom (MD=-21.35 dB/m, 95% CI=-22.07 to -20.63).

Other outcomes

Resmetirom showed reductions in LDL (MD=-14.91 mg/dL, 95% CI=-15.15 to -14.68), HDL (MD=1.56, 95% CI=1.34 to 1.77), triglycerides (MD=-20.01 mg/dL, 95% CI=-20.55 to -19.48), ApoB (MD=-18.43 mg/dL, 95% CI=-18.62 to -18.25), Apo C-III (MD=-20.53 mg/dL, 95% CI=-20.95 to -20.11), Lipo A (MD=-29.45 mg/dL, 95% CI=-29.90 to -29.00), ALT (MD=-16.67 U/L, 95% CI=-17.07 to -16.27), AST (MD=-9.36 U/L, 95% CI=-9.70 to -9.02), and GGT (MD=-19.30 U/L, 95% CI=-19.86 to -18.74). All outcomes showed high heterogeneity **(Appendices 6 to 14)**. The phase 2 MGL-3196-05[46] study indicated that the quality-of-life questionnaire results showed no differences between the resmetirom and placebo groups (data not presented).

Figure 2. Meta-analysis of the resolution of metabolic dysfunction-associated steatohepatitis

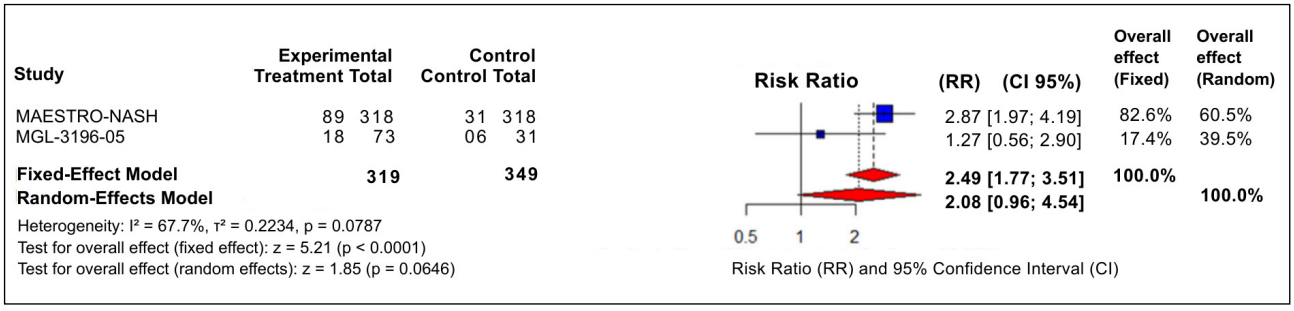
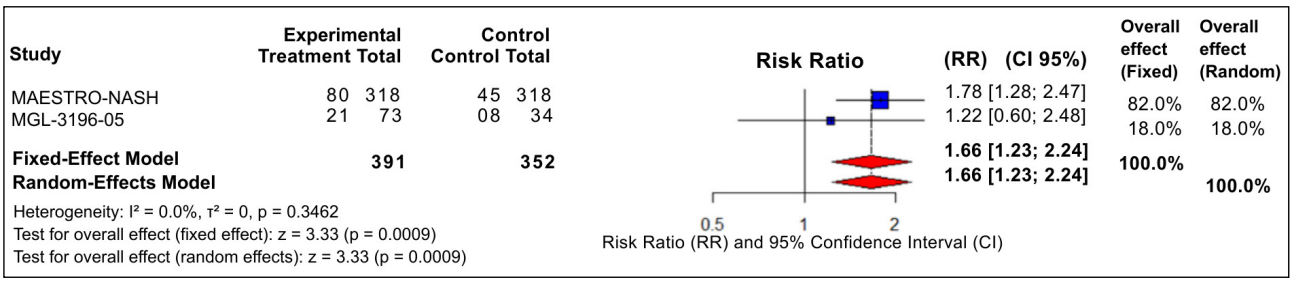
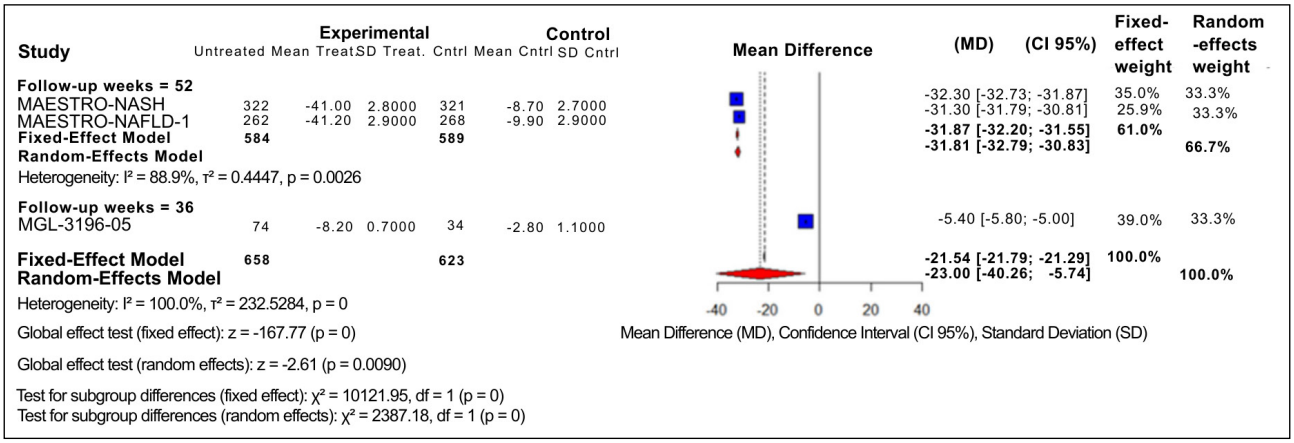


Figure 3. Meta-analysis of liver fibrosis improvement by one stage without worsening of the NAFLD activity score



Source: Author's Elaboration

Figure 4. Meta-analysis of liver fat content reduction (MRI-PDFF test)



Source: Own elaboration

No difference was demonstrated between groups in terms of serious adverse events (RR=1.04, 95% CI=0.69-1.56), headache (RR=0.96, 95% CI=0.60–1.53), or discontinuation of medication due to adverse events (RR=1.71, 95% CI=0.91–3.19). Resmetirom showed a higher incidence of diarrhea (RR=1.91, 95% CI=1.53–2.38) and nausea (RR=1.66, 95% CI=1.25–2.20) **(Appendices 15 to 20)**. A slight trend toward a higher incidence of fatigue was observed in the experimental groups (RR=1.08, 95% CI=0.74–1.59), with no significant heterogeneity (I^2=0%, p=0.66) (Appendix 6). In the MAESTRO-NAFLD-1,[44] study, the incidence of abdominal pain was 7.1% in the Resmetirom 100 mg group, 4.3% in the Resmetirom 80 mg group, and 4.4% in the placebo group. The outcome of weight loss or weight gain was not assessed in the studies.

Risk of bias assessment and level of evidence

The risk of bias assessment using the RoB-2 tool was conducted individually for each outcome. However, since the results were consistent across outcomes within each study, the findings were unified by study **(Figure 5)**. Overall, the assessment indicated some concerns, including multiple imputations that could interfere with the actual outcomes, as well as uncertainty regarding the results in the statistical analyses. The quality of evidence for the outcomes included in the meta-analysis, evaluated using the GRADE methodology, was classified as moderate. The outcomes are presented in the summary of findings table of the included studies **(Appendix 21)**.

Discussion

The meta-analysis demonstrated that resmetirom results in the resolution of MASLD in 2.49 times more cases when compared with placebo. Furthermore, it was associated with a 66% increase in the likelihood of fibrosis improvement by one stage and with a 1.99-fold higher likelihood of liver fibrosis improvement by two stages. However, the data presented substantial heterogeneity (I^2=68%), possibly associated with the follow-up duration of the studies. Regarding the lipid profile, resmetirom promoted significant reductions in LDL-c, HDL-c, triglycerides, apolipoprotein B, and apolipoprotein C-III levels. In addition, it proved effective in reducing ALT, AST, and GGT levels, indicating a beneficial effect on liver inflammation. Concerning biomarkers associated with inflammation and fibrosis, resmetirom demonstrated the ability to reduce them.[44,46]

The findings of the present study corroborate data from the literature. In the MAESTRO-NASH study[45], the resolution rate of MASLD with the use of 100 mg of resmetirom was 29.9%, a higher value than the resolution rate observed in placebo groups in other studies, such as Ng et al.[52], which reported only 11.65% (95% CI: 7.98–16.71). Similarly, fibrosis improvement by one stage was observed in 25.9% of patients treated with resmetirom, compared with 18.82% (95% CI: 15.65–22.47) in the placebo group.[45,52] Furthermore, reductions in liver fat were observed in three studies, with averages ranging between 5.4% and 32%.[44–46]

Figure 5. Methodological risk of bias of the studies included in the meta-analysis

Studies	D1	D2	D3	D4	D5	Final
MAESTRO-NAFLD-1	LRoB	LRoB	SC	LRoB	LRoB	SC
MAESTRO-NASH	LRoB	LRoB	SC	LRoB	LRoB	SC
MGL-3196-05	LRoB	SC	SC	LRoB	LRoB	SC

D1 = Risk of bias in the randomization process; D2 = Risk of bias due to deviations from intended interventions; D3 = Risk of bias due to missing outcome data; D4 = Risk of bias in the measurement of the outcome; D5 = Risk of bias in the selection of the reported result; LRoB: low risk of bias; SC: some concerns. Source: Author's Elaboration.

This reduction is consistent with the findings of Patel et al.,[53] who demonstrated that a reduction of approximately 29% in MRI-PDFF is associated with a favorable histological response in MASLD. Additionally, to adequately position the additional benefits offered by resmetirom, it is essential to evaluate the drug alongside the standard of care, which includes physical exercise and dietary modifications, since these lifestyle changes are an integral part of MASLD treatment.

Another relevant aspect was the improvement in quality of life among patients treated with resmetirom. Younossi et al.[54] reported significant improvements in bodily pain and general well-being scores as early as week 12 of treatment, with continued benefits through week 36. However, these findings contradict the results of the phase 2 MGL-3196-05 study,[46] which found no differences between the resmetirom and placebo groups in quality-of-life questionnaires. Regarding safety, the incidence of treatment-emergent adverse events was similar between resmetirom and placebo groups, with diarrhea and nausea being the most common events within the first 12 weeks, lasting on average 15 to 20 days.[45,46]

Among the limitations of this study, it is noteworthy that all trials were funded by Madrigal Pharmaceuticals, the manufacturer of the drug. The size of the trials did not allow for exploratory subgroup analyses by comorbidities that could strengthen evidence of efficacy. Inclusion and exclusion criteria varied slightly between studies, but all involved adults diagnosed with MASLD. Information regarding whether patients in Harrison et al.[45] were derived from other RCTs was not provided by the author.[44,46] There was also a lack of reporting on the fibrosis staging of patients in the 2023 study..[44] The absence of final post-intervention data stratifying how many patients were at F0, F1, F2, and F3 stages may represent a transparency bias, neglecting to show at which fibrosis stage the greatest statistical benefits occurred. The MAESTRO-NAFLD-1[44] trial was impacted by the COVID-19 pandemic.

Conclusion

Resmetirom demonstrated effects in the resolution of MASLD, reduction of liver fat, and improvement in liver fibrosis, also suggesting an important therapeutic potential with reductions in biomarkers associated with inflammation and fibrosis. However, the methodological limitations of the studies indicate the need for careful approaches when interpreting the results. All studies analyzed the cost-effectiveness relationship from the perspective of the United States health payer, adopting the threshold of US$100,000/QALY, a standard widely used in the country. As all ICER results were below this threshold, resmetirom was considered a cost-effective intervention in the United States.

Author contributions

WHAS and ASMS: Project conception, data analysis and interpretation, article drafting, and final revision of the version to be published. WHAS: Responsibility for all aspects of the text, ensuring the accuracy and integrity of any part of the work.

Conflicts of interest

The authors declare no conflicts of interest that could affect the results of this study.

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Data availability statement
Data will be made available upon request. The datasets generated and analyzed during the present study are available upon request to the corresponding author.

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References

1. Rinella ME, Neuschwander-Tetri BA, Siddiqui MS, Abdelmalek MF, Caldwell S, Barb D, et al. AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease. Hepatology. 2023;77(5):1797–835. doi: 10.1097/HEP.0000000000000323
2. Eslam M, Newsome PN, Sarin SK, Anstee QM, Targher G, Romero-Gomez M, et al. A new definition for metabolic dysfunction-associated fatty liver disease: An international expert consensus statement. Journal of Hepatology. 2020;73(1):202–9. doi: 10.1016/j.jhep.2020.03.039
3. Murag S, Ahmed A, Kim D. Recent Epidemiology of Nonalcoholic Fatty Liver Disease. Gut and Liver. 2021;15(2):206–16. doi: 10.5009/gnl20127
4. O'Hara J, Finnegan A, Dhillon H, Ruiz-Casas L, Pedra G, Franks B, et al. Cost of non-alcoholic steatohepatitis in Europe and the USA: The GAIN study. JHEP Reports. 2020;2(5):100142. doi: 10.1016/j.jhepr.2020.100142
5. Schwabe RF, Tabas I, Pajvani UB. Mechanisms of Fibrosis Development in Nonalcoholic Steatohepatitis. Gastroenterology. 2020;158(7):1913–28. doi: 10.1053/j.gastro.2019.11.311
6. Polyzos SA, Kountouras J, Mantzoros CS. Obesity and nonalcoholic fatty liver disease: From pathophysiology to therapeutics. Metabolism. 2019;92:82–97. doi: 10.1016/j.metabol.2018.11.014
7. Lekakis V, Papatheodoridis GV. Natural history of metabolic dysfunction-associated steatotic liver disease. European Journal of Internal Medicine. 2024;122:3–10. doi: 10.1016/j.ejim.2023.11.005
8. Karim G, Bansal MB. Resmetirom: An Orally Administered, Small-molecule, Liver-directed, β-selective THR Agonist for the Treatment of Non-alcoholic Fatty Liver Disease and Non-alcoholic Steatohepatitis. European Endocrinology. 2023;19(1):60. doi: 10.17925/EE.2023.19.1.60
9. Food and Drug Administration (FDA). Table of Surrogate Endpoints That Were the Basis of Drug Approval or Licensure | FDA [Internet]. [cited July 31, 2024]. Available from: https://www.fda.gov/drugs/development-resources/table-surrogate-endpoints-were-basis--drug-approval-or-licensure
10. Younossi ZM, Golabi P, Paik JM, Henry A, Van Dongen C, Henry L. The global epidemiology of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH): a systematic review. Hepatology. 2023;77(4):1335–47. doi: 10.1097/HEP.0000000000000004
11. Tokushige K, Ikejima K, Ono M, Eguchi Y, Kamada Y, Itoh Y, et al. Evidence□based clinical practice guidelines for nonalcoholic fatty liver disease/nonalcoholic steatohepatitis 2020. Hepatology Research. 2021;51(10):1013–25. doi: 10.1111/hepr.13688
12. Mantovani A, Scorletti E, Mosca A, Alisi A, Byrne CD, Targher G. Complications, morbidity and mortality of nonalcoholic fatty liver disease. Metabolism. 2020;111:154170. doi: 10.1016/j.metabol.2020.154170
13. Taylor RS, Taylor RJ, Bayliss S, Hagström H, Nasr P, Schattenberg JM, et al. Association Between Fibrosis Stage and Outcomes of Patients With Nonalcoholic Fatty Liver Disease: A Systematic Review and Meta-Analysis. Gastroenterology. 2020;158(6):1611-1625.e12. doi: 10.1053/j.gastro.2020.01.043
14. Younossi ZM, Stepanova M, Ong J, Trimble G, AlQahtani S, Younossi I, et al. Nonalcoholic Steatohepatitis Is the Most Rapidly Increasing Indication for Liver Transplantation in the United States. Clinical Gastroenterology and Hepatology. 2021;19(3):580-589.e5. doi: 10.1016/j.cgh.2020.05.064
15. Younossi ZM, Paik JM, Henry L, Yang J, Fernandes G, Stepanova M, et al. The Growing Economic and Clinical Burden of Nonalcoho-

lic Steatohepatitis (NASH) in the United States. Journal of Clinical and Experimental Hepatology. 2023;13(3):454–67. doi: 10.1016/j.jceh.2022.12.005

16. Alam S, Islam Alin MdS, Begum F, Fahim SM, Tasnim Z, Alam MdM. Estimating the cost of illness of non-alcoholic fatty liver disease in Bangladesh. JGH Open. 2023;7(9):629–35. doi: 10.1002/jgh3.12960
17. Witkowski M, Moreno SI, Fernandes J, Johansen P, Augusto M, Nair S. The Economic Burden of Non-Alcoholic Steatohepatitis: A Systematic Review. PharmacoEconomics. 2022;40(8):751–76. doi: 10.1007/s40273-022-01140-y
18. Herring WL, Gould IG, Wittrup-Jensen V, Ertle J, Kuti E, Wolowacz S. Evaluation of emerging NASH therapies: the impact of treatment efficacy profiles on long-term health outcomes. J Comp Eff Res. 2022;11(18):1349–63. doi: 10.2217/cer-2021-0194
19. Petta S, Targher G, Romeo S, Pajvani UB, Zheng M, Aghemo A, et al. The first MASH drug therapy on the horizon: Current perspectives of resmetirom. Liver International. 2024;44(7):1526–36. doi: 10.1111/liv.15930
20. Chang Y, Jeong SW, Jang JY. Recent updates on pharmacologic therapy in non-alcoholic fatty liver disease. Clin Mol Hepatol. 2023;30(1):129–33. doi: 10.3350/cmh.2023.0356
21. Oseini AM, Sanyal AJ. Therapies in non-alcoholic steatohepatitis (NASH). Liver International. 2017;37(S1):97–103. doi: 10.1111/liv.13302
22. Dufour JF, Anstee QM, Bugianesi E, Harrison S, Loomba R, Paradis V, et al. Current therapies and new developments in NASH. Gut. 2022;71(10):2123–34. doi: 10.1136/gutjnl-2021-326874
23. Vilar-Gomez E, Martinez-Perez Y, Calzadilla-Bertot L, Torres-Gonzalez A, Gra-Oramas B, Gonzalez-Fabian L, et al. Weight Loss Through Lifestyle Modification Significantly Reduces Features of Nonalcoholic Steatohepatitis. Gastroenterology. 2015;149(2):367-378.e5. doi: 10.1053/j.gastro.2015.04.005
24. Food and Drug Administration (FDA). FDA Approves First Treatment for Patients with Liver Scarring Due to Fatty Liver Disease | FDA [Internet]. [cited July 31, 2024]. Available from: https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-patients-liver-scarring-due-fatty-liver-disease
25. Kokkorakis M, Boutari C, Hill MA, Kotsis V, Loomba R, Sanyal AJ, et al. Resmetirom, the first approved drug for the management of metabolic dysfunction-associated steatohepatitis: Trials, opportunities, and challenges. Metabolism. 2024;154:155835. doi: 10.1016/j.metabol.2024.155835
26. Moreira RO, Valerio CM, Villela-Nogueira CA, Cercato C, Gerchman F, Lottenberg AMP, et al. Brazilian evidence-based guideline for screening, diagnosis, treatment, and follow-up of metabolic dysfunction-associated steatotic liver disease (MASLD) in adult individuals with overweight or obesity: A joint position statement from the Brazilian Society of Endocrinology and Metabolism (SBEM), Brazilian Society of Hepatology (SBH), and Brazilian Association for the Study of Obesity and Metabolic Syndrome (Abeso). Archives of Endocrinology and Metabolism. 2023;67(6):e230123. doi: 10.20945/2359-4292-2023-0123
27. Tice JA. Resmetirom and Obeticholic Acid for Non-Alcoholic Steatohepatitis.pdf [Internet]. Available from: https://icer.org/wp-content/uploads/2022/10/NASH-Final-Report_For-Publication_053023.pdf
28. Ministério da Saúde. Esteatose hepática - Ministério da Saúde [Internet]. Available from: https://www.gov.br/saude/pt-br/assuntos/saude-de-a-a-z/e/esteatose-hepatica
29. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;n71. doi: 10.1136/bmj.n71
30. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan—a web and mobile app for systematic reviews. Syst Rev. 2016;5(1):210. doi: 10.1186/s13643-016-0384-4
31. Beaglehole R. Epidemiologia Básica. World Health Organization: Santos; 2006. (2 ed.).
32. Toma TS, da Veiga Pereira T, Vanni T. Avaliação de tecnologias de saúde e políticas informadas

por evidências. São Paulo: Instituto de Saúde; 2017. 453p. (Temas em saúde coletiva).
33. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al., organizadores. Cochrane Handbook for Systematic Reviews of Interventions [Internet]. 1st ed. Wiley; 2019 [cited August 20, 2024]. Available from: https://onlinelibrary.wiley.com/doi/book/10.1002/9781119536604
34. DerSimonian R, Laird N. Meta-analysis in clinical trials. Controlled Clinical Trials. 1986;7(3):177–88. doi: 10.1016/0197-2456(86)90046-2
35. Schwarzer G, Carpenter JR, Rücker G. Meta-Analysis with R [Internet]. Cham: Springer International Publishing; 2015 [cited August 20, 2024]. (Use R!). Available from: https://link.springer.com/10.1007/978-3-319-21416-0
36. R CORE TEAM. R: A language and environment for statistical computing [Internet]. 2024. Available from: https://cran.r-project.org/doc/manuals/r-release/fullrefman.pdf
37. Santos AS, Guerra-Junior AA, Godman B, Morton A, Ruas CM. Cost-effectiveness thresholds: methods for setting and examples from around the world. Expert Review of Pharmacoeconomics & Outcomes Research. 2018;18(3):277–88. doi: 10.1080/14737167.2018.1443810
38. Ministério da Saúde - Secretaria de Ciência T e IE. Diretrizes metodológicas: sistema grade: manual de graduação da qualidade da evidência e força de recomendação para tomada de decisão em saúde. Ms; 2014. (ECOS: Economia da Saúde para Gestão do SUS).
39. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336(7650):924–6. doi: 10.1136/bmj.39489.470347.AD
40. Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schünemann HJ. What is "quality of evidence" and why is it important to clinicians? BMJ. 2008;336(7651):995–8. doi: 10.1136/bmj.39490.551019.BE
41. Guyatt GH, Oxman AD, Kunz R, Falck-Ytter Y, Vist GE, Liberati A, et al. Going from evidence to recommendations. BMJ. 2008;336(7652):1049–51. doi: 10.1136/bmj.39493.646875.AE
42. Guyatt GH, Oxman AD, Kunz R, Jaeschke R, Helfand M, Liberati A, et al. Incorporating considerations of resources use into grading recommendations. BMJ. 2008;336(7654):1170–3. doi: 10.1136/bmj.39504.506319.80
43. Motta-Santos A, Noronha K, Reis C, Freitas D, Carvalho L, Andrade M. Cost-Effectiveness of Technologies for the Treatment of Spinal Muscular Atrophy: A Systematic Review of Economic Studies. Value in Health Regional Issues. 2024;42:100985. doi: 10.1016/j.vhri.2024.02.002
44. Harrison SA, Taub R, Neff GW, Lucas KJ, Labriola D, Moussa SE, et al. Resmetirom for nonalcoholic fatty liver disease: a randomized, double-blind, placebo-controlled phase 3 trial. Nat Med. 2023;29(11):2919–28. doi: 10.1038/s41591-023-02603-1
45. Harrison SA, Bedossa P, Guy CD, Schattenberg JM, Loomba R, Taub R, et al. A Phase 3, Randomized, Controlled Trial of Resmetirom in NASH with Liver Fibrosis. N Engl J Med. 2024;390(6):497–509. doi: 10.1056/NEJMoa2309000
46. Harrison SA, Bashir MR, Guy CD, Zhou R, Moylan CA, Frias JP, et al. Resmetirom (MGL-3196) for the treatment of non-alcoholic steatohepatitis: a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. The Lancet. 2019;394(10213):2012–24. doi: 10.1016/S0140-6736(19)32517-6
47. Ansaripour A, Fishman J, Moloney E, Javanbakht M. EE227 The Impact of Treatment-Related Changes in Lipids on the Cost-Effectiveness of Resmetirom and Obeticholic Acid for Treatment of Nonalcoholic Steatohepatitis. Value in Health. 2023;26(6):S100–1. doi: 10.1016/j.jval.2023.03.528
48. Ansaripour A, Fishman J, Bowes K, Brown A, Nasserinejad K, Javanbakht M, et al. EE349 A Systematic Literature Review, Network Meta-Analysis, and Cost-Effectiveness Analysis of Resmetirom for the Treatment of Nonalcoholic Steatohepatitis. Value in Health. 2023;26(6):S123. doi: 10.1016/j.jval.2023.03.650
49. Javanbakht M, Fishman J, Moloney E, Rydqvist P, Ansaripour A. EE313 Cost-Effectiveness Analysis of Resmetirom: An Investi-

gational Treatment for the Management of Nonalcoholic Steatohepatitis. Value in Health. 2022;25(7):S395. doi: 10.1016/j.jval.2022.04.558

50. Javanbakht M, Fishman J, Moloney E, Rydqvist P, Ansaripour A. Early Cost-Effectiveness and Price Threshold Analyses of Resmetirom: An Investigational Treatment for Management of Nonalcoholic Steatohepatitis. PharmacoEconomics Open. 2023;7(1):93–110. doi: 10.1007/s41669-022-00370-2
51. Fahim SM, Tice JA, Suh K, Carlson JJ, Richardson M, Chu JN, et al. Resmetirom for nonalcoholic steatohepatitis: Summary from the Institute for Clinical and Economic Review's Midwest Comparative Effectiveness Public Advisory Council. jmcp. 2023;29(10). doi: 10.18553/jmcp.2023.29.10.1169
52. Ng CH, Xiao J, Lim WH, Chin YH, Yong JN, Tan DJH, et al. Placebo effect on progression and regression in NASH: Evidence from a meta-analysis. Hepatology. 2022;75(6):1647–61. doi: 10.1002/hep.32315
53. Patel J, Bettencourt R, Cui J, Salotti J, Hooker J, Bhatt A, et al. Association of noninvasive quantitative decline in liver fat content on MRI with histologic response in nonalcoholic steatohepatitis. Therap Adv Gastroenterol. 2016;9(5):692–701. doi: 10.1177/1756283X16656735
54. Younossi ZM, Stepanova M, Taub RA, Barbone JM, Harrison SA. Hepatic Fat Reduction Due to Resmetirom in Patients With Nonalcoholic Steatohepatitis Is Associated With Improvement of Quality of Life. Clinical Gastroenterology and Hepatology. 2022;20(6):1354-1361.e7. doi: 10.1016/j.cgh.2021.07.03