# MASH IN FOCUS

Current Developments in the Management of Metabolic Dysfunction-Associated Steatohepatitis

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## Recent Data From the ESSENCE Trial on Semaglutide in Metabolic Dysfunction-Associated Steatohepatitis

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### G&H What is the rationale for studying semaglutide for the treatment of metabolic dysfunction-associated steatohepatitis?

**NA** Semaglutide is a glucagon-like peptide-1 receptor agonist (GLP-1 RA) that has been approved to treat both type 2 diabetes (Ozempic and Rybelsus, Novo Nordisk) and obesity (Wegovy, Novo Nordisk). The drug has pleiotropic effects, as it works on the pancreas and increases insulin sensitivity; affects the stomach and delays gastric emptying, inducing satiety; and works on the central nervous system to decrease appetite. Semaglutide has been a success story in treating both type 2 diabetes and obesity with very effective weight loss, approximately 17% total body weight loss with around 1 year of treatment. It is well known that patients with metabolic dysfunction-associated steatotic liver disease and metabolic dysfunction-associated steatohepatitis (MASH) benefit from weight loss. Studies of lifestyle interventions have shown that losing around 10% of total body weight can induce both MASH resolution and fibrosis regression. However, the success rate of lifestyle interventions is only approximately 10%, which means that 90% of patients do not achieve that threshold. We have learned that semaglutide can induce 10% weight loss in approximately 75% of patients, so there was speculation that this agent would be an effective treatment strategy to induce both MASH resolution and fibrosis improvement by 1 stage, which are the 2 primary endpoints that are approved by the US Food and Drug Administration (FDA). In a phase 2b trial that tested semaglutide in a relatively large cohort of patients (320) with biopsy-proven MASH and fibrosis, MASH resolution occurred with a high dose of semaglutide in approximately 59% of patients after 72 weeks of treatment, which was significantly better than with placebo. However, there was no significant signal on fibrosis improvement. One of the biggest questions to be answered in the ESSENCE trial was whether semaglutide induces fibrosis improvement.

### G&H What was the study design of the ESSENCE trial, including the baseline characteristics of the participants?

**NA** The ESSENCE trial is a phase 3 trial that has 2 parts. Part 1 enrolled 800 patients with biopsy-proven MASH and stage 2 or 3 fibrosis. Patients were randomized in a 2:1 fashion to either placebo or semaglutide with dose escalation to the high dose of 2.4 mg weekly. All patients underwent biopsy at baseline, were treated for 72 weeks, and then underwent a second liver biopsy. Those results were presented at the American Association for the Study of Liver Diseases 2024 Liver Meeting.

The study included a typical cohort of patients with MASH with significant fibrosis: middle-aged adults, approximately 55% female, around 55% with type 2 diabetes, and a high prevalence of obesity (mean body mass index around 35). Approximately two-thirds of the patients had stage 3 fibrosis, whereas one-third had stage 2 fibrosis. Liver stiffness was measured to noninvasively determine the presence of significant and advanced fibrosis, with the mean liver stiffness being around 12.8 kPa. Similarly, the mean Enhanced Liver Fibrosis (ELF) score, a serologic test to determine the stage of fibrosis, was 10.

**G&H** What were the primary and secondary endpoint data that were recently presented?

**NA** Semaglutide 2.4 mg weekly achieved both of the primary endpoints. MASH resolution was achieved in approximately 63% in the semaglutide arm and 34% in the placebo arm, with an approximately 29% delta from placebo or what is known as absolute risk reduction or estimated difference in responder proportions (EDP). The number needed to treat to achieve MASH resolution in 1 patient was around 3 patients. The second primary endpoint, fibrosis improvement by 1 stage, was achieved in 37% of patients receiving semaglutide compared with 22.5% receiving placebo, with a 14.5% delta or EDP. This means that the number needed to treat was around 7 patients to achieve fibrosis improvement by 1 stage in 1 patient. Both of these results were significantly better in the semaglutide arm than the placebo arm, and this was a large cohort in a phase 3 trial, giving us confidence that the difference from placebo was real and will translate into benefit to patients.

Additionally, there were several secondary endpoints. One evaluated the proportion of patients that achieved both MASH resolution and improvement in liver fibrosis. This was achieved in approximately 33% in the semaglutide arm. Change in body weight was around 10.5% total body weight loss, demonstrating the efficacy of semaglutide in inducing weight loss. There was also improvement in several serologic tests, including liver enzymes. Alanine aminotransferase was reduced by 40% from baseline, which was a significant decrease. Aspartate aminotransferase was decreased by 30%, and gamma-glutamyl transferase was decreased by 40%. Noninvasive tests were also examined. Liver stiffness by transient elastography was reduced by 20% from baseline. There was also a reduction in the ELF score, by 0.6 unit. These findings are very encouraging; not only were benefits seen on biopsy, but in measures that providers routinely use in clinics, such as improvements in liver enzymes, transient elastography, and serologic biomarkers for fibrosis.

**G&H** What adverse events were reported?

**NA** Because semaglutide has been approved for type 2 diabetes and obesity for several years now, a lot is known about what to expect in terms of adverse events. The adverse events in the ESSENCE trial were similar to what has been seen in patients with type 2 diabetes and obesity. The main adverse events were typically gastrointestinal: nausea, constipation, diarrhea, and vomiting in some patients. Overall, from my perspective, there were no surprises.

**G&H** When viewing these positive results, what study limitations should be kept in mind?

**NA** It should be kept in mind that the delta on fibrosis improvement was only 14.5%. It is important to understand that although these data are very encouraging, many of the patients will probably need to be on combination therapy. Some patients will probably not respond to semaglutide in terms of improving their fibrosis and will need other medications. That has been seen with resmetirom (Rezdiffra, Madrigal) phase 3 data from the MAESTRO-NASH trial. Approximately 15% of patients started the trial on a stable dose of a GLP-1 RA and still had stage 2 or 3 fibrosis on their liver biopsy, indicating that they were nonresponders to that drug. However, they were either receiving lower doses of semaglutide (up to 1 mg weekly, not the 2.4-mg weekly dose from the ESSENCE trial), or received different GLP-1 RAs. Nevertheless, we know clinically that not everyone is going to be a responder to semaglutide and may benefit better from either combination therapy or switching to other agents.

Additionally, more granularity is needed in terms of the effects of weight loss. Was there weight loss–dependent response in terms of histology and noninvasive tests? Not everyone is going to lose a significant amount of weight on semaglutide. Were the patients who did not lose weight nonresponders? This information will help providers determine when to continue or discontinue treatment and whether there are benefits below a certain threshold of weight loss. Results of part 1 of the ESSENCE trial will be published in the near future, which will provide more granularity in terms of the data.

**G&H** What are the implications and clinical relevance of the ESSENCE findings?

**NA** GLP-1 RAs have been game changers in obesity and type 2 diabetes, and now there is a rationale to utilize these agents in patients with MASH and significant fibrosis. I suspect that, hopefully with approval from the FDA this year, semaglutide will make a large impact in our clinics. I think many specialists will be eager to use it because there are now proven effects on the liver, in addition to metabolic syndrome and its components, and all of these conditions can be treated together with semaglutide. This will be exciting for patients. Unfortunately, many patients with obesity and clear indications for semaglutide get denied access to the drug by insurance because obesity is not covered. When there is an indication for MASH and significant fibrosis, these patients will have a better chance of being able to access this beneficial drug.

It is also important to remember that there were no pharmacologic treatments for MASH with fibrosis for

decades. The approach was to try to lose weight and go on an intensive lifestyle intervention, which, as discussed, has a low success rate. Although resmetirom was approved with promising results in its phase 3 trial, there was hesitation by some specialists to start patients on treatment. There was always the argument that perhaps patients would benefit more from semaglutide or tirzepatide (Zepbound and Mounjaro, Lilly) as a first-line therapy to treat their comorbidities. If semaglutide is approved for the indication of MASH and stage 2 or 3 fibrosis, I think most specialists will feel obligated to pick one treatment between resmetirom or semaglutide, monitor for response, and then either continue with their first choice or perhaps add a second drug or switch. Hopefully, having 2 FDA-approved medications will change the attitude toward MASH and induce providers to be more aggressive to change the natural history of this progressive disease and prevent progression to cirrhosis.

Last year was historic for the field of MASH with the approval of resmetirom, the first FDA-approved medication. I suspect 2025 will also be a great year in the field with a second drug likely being approved by the FDA, specifically for MASH with stage 2 or 3 fibrosis. I think the future will belong to combination therapy and optimization of the management of liver disease, as well as cardiovascular risk reduction and the management of metabolic syndrome. As a hepatologist, by the end of 2025, I feel like I will have the tools to achieve these goals.

### **G&H** What is planned for part 2 of the ESSENCE trial?

**NA** Part 2 will have a larger cohort. The sample size will increase from 800 to 1200 patients. These patients will be followed for a longer period of time (up to week 240), so they will undergo a third liver biopsy after a little less than 5 years. We have been looking at the clinical outcomes of MASH resolution and fibrosis improvement, which are surrogate endpoints based on histology. However, on the week 240 biopsy, researchers will look at hard outcomes, including progression to cirrhosis, especially in patients with stage 3 fibrosis. Other hard outcomes will include decompensating events such as development of ascites, encephalopathy, or variceal bleeding; need for liver transplant; and overall mortality. It is anticipated that by the third or fourth quarter of this year, the FDA will grant accelerated approval of semaglutide based on part 1 of the ESSENCE trial. This will not be full approval, just like resmetirom is only approved under accelerated approval. I think full approval will come if part 2 of the ESSENCE trial shows a significant difference between semaglutide and placebo in terms of the hard outcomes of progression to cirrhosis, decompensation, or overall mortality.

### **G&H** What other research is needed and underway in drug development for MASH?

**NA** One of the urgently needed areas for research is looking at the efficacy of combination therapy, at least between the drugs that are likely to be FDA-approved by the end of 2025. Researchers should look into designing a trial combining semaglutide and resmetirom to see if that improves the delta on both MASH resolution and fibrosis improvement. Additionally, there are several other promising therapeutic targets with different mechanisms of action, including fibroblast growth factor–21 agonists. There are also dual and triple agonists being studied, including the glucagon/GLP-1 RA survodutide and tirzepatide, which is a GLP-1/gastric inhibitory polypeptide agonist. There are also many therapeutic targets under investigation that work on silencing certain genes that can predispose individuals to MASH and progressive disease. Additionally, there is research underway on several targets that work on the de novo lipogenesis pathway. Combination therapy has the potential to prevent patients from progressing to cirrhosis. There are also several trials looking at whether cirrhosis can be reversed, which would be the holy grail in hepatology and would change the natural history of this aggressive disease. The future is bright. So much is going on in this space, and I am excited to be part of it.

***Disclosures***

*Dr Alkhouri is a consultant/speaker for and has received research support from Novo Nordisk.*

## Suggested Reading


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