Resmetirom – A Potential Novel Therapy for NASH

Nonalcoholic fatty liver disease (NAFLD) is a general term for a range of conditions characterized by extra fat that is not caused by alcohol. NAFLD is the most common liver condition in the United States and it is estimated that about 25% of adults in the U.S. have the disease. There are two different types of NAFLD; Simple fatty liver and nonalcoholic steatohepatitis (NASH). Simple fatty liver is sometimes referred to as nonalcoholic fatty liver (NAFL) and has little or no inflammation of the liver or damage to liver cells and typically does not progress to cause liver damage. NASH is the most severe form of NAFLD and causes the liver to swell and become damaged. NASH tends to develop in individuals who are overweight, have diabetes, high cholesterol or high triglycerides and typically occurs between 40-60 years of age. It is estimated that about 20% of NAFLD patients have NASH which is approximately 5% of the adults in the U.S. The inflammation and liver damage of NASH can cause fibrosis of the liver and may lead to cirrhosis and potentially lead to liver cancer. NASH is becoming the leading cause of liver transplantation in the U.S.

Chronic liver disease progresses through varying stages of fibrosis to cirrhosis. The accepted "gold standard" for diagnosis of cirrhosis is liver biopsy. Measurement of the amount of fibrosis is called staging. There are five stages (F0: no scarring (no fibrosis); F1: minimal scarring; F2: scarring has occurred and extends outside the liver area (significant fibrosis); F3: fibrosis spreading and forming bridges with other fibrotic liver areas (severe fibrosis); F4: cirrhosis or advanced scarring).

Traditional approach to therapy is recommended weight loss to treat NAFLD, either NAFL or NASH, and physical activity. Weight loss can reduce fat, inflammation and fibrosis in the liver. It is generally recommended to gradually lose weight to improve NAFLD. Rapid weight loss and malnutrition may make liver disease worse. Currently, there are no approved drug therapies for NAFLD—either NAFL or NASH.

Resmetirom may become the first FDA-approved therapy in March 2024 for the treatment of NASH. Resmetirom, from Madrigal Pharmaceuticals, is an oral, once daily thyroid receptor beta agonist that acts by decreasing liver fat and reducing lipotoxicity. Madrigal announced topline results in December 2022 of their Phase 3 trial, MAESTRO-NASH, for the treatment of NASH with liver fibrosis. In this on-going Phase 3 trial, 966 patients with liver biopsy-confirmed NASH were randomized to two different doses of oral resmetirom or placebo. The baseline liver biopsy fibrosis scores were approximately 60% F3, 35% F2 and 5% F1B. The primary efficacy analysis assessed histological response by a second liver biopsy after 52 weeks of treatment through two primary endpoints [NASH resolution with a ≥ 2-point reduction in nonalcoholic fatty liver disease activity score (NAS) and no worsening of fibrosis and ≥ 1 stage improvement in fibrosis with no worsening of NAS].

In the analysis, the primary endpoint of NASH resolution with ≥2-point reduction in NAS and no worsening of fibrosis was achieved by 26%, 30%, and 10% of patients taking 80 mg resmetirom, 100 mg resmetirom, and placebo respectively. The second primary endpoint, a ≥1-point decrease in fibrosis with no worsening of NAS, was achieved in 24%, 26%, and 14% of patients taking 80 mg resmetirom, 100 mg resmetirom, and placebo respectively. Low-density lipoprotein cholesterol (LDL-C) levels at 24 weeks, a secondary outcome measure, were reduced by 12% and 16% for 80 mg and 100 mg resmetirom, respectively, and increased by 1% in the placebo arm. Madrigal also reported that multiple other secondary endpoints were achieved including statistically significant reduction from baseline in liver enzymes (ALT, AST and GCT) as well as reductions in atherogenic lipids and lipoproteins, fibrosis biomarkers and imaging tests in the resmetirom treatment arms as compared to placebo.

Resmetirom was safe and well-tolerated in the trial, showing similarly low rates of serious adverse events to placebo. The rates of study discontinuation were higher in the 100mg resmetirom treatment group as compared to the 80mg and placebo arms (7.7% as compared to 2.8% and 3.7%, respectively). All patients enrolled in MAESTRO-NASH are continuing treatment after the initial 52-week period for up to 54 months to evaluate additional outcomes, including progression to cirrhosis on biopsy, hepatic decompensation events, and all-cause mortality.

Resmetirom has three additional Phase 3 trials ongoing (MAESTRO-NAFLD-1, MAESTRO-NAFLD-OLD and MAESTRO-NASH-OUTCOMES) to further demonstrate the safety and efficacy for the treatment of NASH. The MAESTRO-NAFLD-1 study is not including a liver biopsy and may more closely resemble clinical practice diagnosis of NASH by non-invasive techniques and adding additional NASH biomarker endpoints. In initial reported results in October 2023, resmetirom showed reductions of over 40% in a measure of liver fat. MAESTRO-NASH-OUTCOMES is focused on early NASH cirrhosis to allow for noninvasive monitoring of progression to liver decomposition events and if this 700-patient study shows positive outcomes, may support the use in well-compensated NASH cirrhosis (F4).

The Institute for Clinical and Economic Review (ICER) published an Evidence Report on NASH treatments in May 2023 prior to any FDA product approval. In their report, ICER concluded that for adult patients with NASH with significant fibrosis (Stage 2 or 3) and not cirrhosis, a majority of the ICER panelists found that the current evidence is adequate to demonstrate a net health benefit for resmetirom when compared to lifestyle management alone and calculated a health-benefit price benchmark to be between $39,600-$51,100 per year. The report also recommended that payers should develop coverage criteria based upon non-invasive testing and integrate coverage of NASH products with obesity management.

While resmetirom may be the first product for NASH, other product applications were not approved by the FDA. In June 2023, Intercept Pharmaceuticals received a Complete Response Letter (CRL) from the FDA for obeticholic acid (OCA). As part of the Advisory Meeting, the majority of the Committee voted against OCA, citing the risk of drug-induced liver damage and the modest efficacy of the product. This CRL followed an earlier CRL in June 2020 in which the FDA requested longer-term, post-interim analysis efficacy and safety from their Phase 3 trial. Intercept has discontinued all NASH related work on OCA. Lower dose OCA still remains available as Ocaliva® for the treatment of adult patients with primary biliary cholangitis.

There are a large number of other products in the pipeline for NASH. It appears that the potential next products that would likely be approved for NASH would be in 2025. One interesting potential upcoming product is semaglutide. Semaglutide is a glucagon-like peptide-1 (GLP-1) agonist that is currently approved for use in diabetes (Ozempic®, Rybelsus®) and weight loss (Wegovy®) and received a Breakthrough Designation from the FDA. Phase 2 results in patients with stage 4 compensated cirrhosis demonstrated improvements in NASH resolution and reducing triglycerides, along with weight reduction and improvements in A1c in diabetic patients. Other ongoing trials include patients with F2 & F3 NASH as monotherapy and combination therapy with empaglifozin for patients with NASH and type 2 diabetes. Given the impact of semaglutide on weight loss, this would be an attractive treatment option for NASH, if approved. Other potential therapies that could be approved in 2025 include azemiglitzone, a thiazolidinedione, being studied in pre-type or type 2 diabetes and belapectin, an IV galectin inhibitor, being studied for NASH cirrhosis.

Resmetirom will likely be the first of many products that will be available to treat NASH. This is a significant new pharmaceutical market and costs are expected to be high for treatment and likely above the ICER cost benefit projections. With no current approved drug therapies, these new products will be added costs for

payers to consider with a hopeful medical cost offset to long-term complications of the disease. Given the different mechanisms of action of the upcoming products, combination therapy is likely going to be a consideration for physicians in treating this disease and will add to the treatment paradigm and costs. Efficacy has been modest in the available clinical trials and with biopsy being an inclusion criteria, may limit the use until acceptance is gained or publication of on-going clinical trials on non-invasive diagnostic criteria as a surrogate measure by the medical community.

References:

https://www.niddk.nih.gov/health-information/liver-disease/nafld-nash/treatment
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5944985/#:~:text=Fibrosis%20stage%3A%20stratified%20on%20liver,fibrosis%2C%20F4%E2%80%94cirrhosis)
https://www.cochrane.org/CD010542/LIVER_transient-elastography-for-measurement-of-liver-fibrosis-and-cirrhosis-in-people-with-alcoholic-liver-disease#:~:text=There%20are%20five%20stages%20(F0,%3A%20cirrhosis%20or%20advanced%20scarring)
https://liverfoundation.org/liver-diseases/fatty-liver-disease/nonalcoholic-steatohepatitis-nash/nash-definition-prevalence/
https://www.niddk.nih.gov/health-information/liver-disease/nafld-nash/definition-facts#:~:text=People%20with%20NASH%20can%20develop,dying%20from%20liver%2Drelated%20causes.
https://ir.madrigalpharma.com/news-releases/news-release-details/madrigal-announces-positive-topline-results-pivotal-phase-3
https://www.nature.com/articles/s41591-023-02603-1
Bedossa P, Guy CD, Schattenburg JM, Loompa R, et al. 2463-C: Resmetirom Treatment Helps Restore Thyroid Hormone Levels in Patients with Nonalcoholic Steatohepatitis: 52-Week Data from the Phase 3 MAESTRO-NASH Trial. Paper presented at: The Liver Meeting. Boston, MA. November 10 - 14, 2023
Bedossa P, Guy CD, Schattenburg JM, Loompa R, et al. 2462-C: Resmetirom Improves the Atherogenic Lipid/Lipoprotein Profile in Patients with Nonalcoholic Steatohepatitis: 52-Week Data from the Phase 3 MAESTRO-NASH Trial. Paper presented at: The Liver Meeting. Boston, MA. November 10 - 14, 2023
https://icer.org/news-insights/press-releases/icer-publishes-final-evidence-report-on-treatments-for-non-alcoholic-steatohepatitis/