NASH – A Growing and Costly Disease

Non-alcoholic fatty liver disease (NAFLD) is the build-up of extra fat in liver cells and is not associated with alcohol use. Similarly, non-alcoholic steatohepatitis (NASH) is a more severe type of NAFLD in which more than 5 to 10 percent of the liver's weight is fat. The Food and Drug Administration (FDA) estimates that 16.8 million adults in the United States have NASH. Hispanics, Asians, and Caucasians who are obese or have type 2 diabetes are most likely to develop the disease. Symptoms often include loss of appetite, swelling in the legs, and jaundice. However, many patients do not have symptoms and are unaware the disease is progressing.

NASH patients are more likely to develop other comorbid conditions. For example, people living with NASH are at increased risk of developing cardiovascular disease and have a higher risk for heart attack or stroke. Approximately 20% of patients with NASH go on to develop cirrhosis in which the liver is scarred and permanently damaged. Patients with cirrhosis also have a significantly greater chance of developing liver cancer. Due to its high prevalence, NASH is the second leading cause of liver transplant in the United States and remains the fastest growing indication for liver transplantation.

Despite significant research over the last decade, the underlying development and progression to NASH is not fully understood. Genetics, metabolic changes including insulin resistance, and changes to the microorganisms in the gut may all play a role in NASH. Because there are multiple pathways that can lead to buildup of fat in the liver, a successful FDA approved treatment option is not yet available. Drug development has also been limited by the need for multiple liver biopsies to monitor disease progression. Good, non-invasive, biomarkers are in development but not yet available. As a result, current treatment options focus on preventing further fibrosis and other liver-related and cardiovascular complications. Hepatologists usually manage NASH by recommending lifestyle modifications including a healthy diet, exercise, weight loss, and abstaining from alcohol. In addition, vitamin E supplementation may be recommended for patients without diabetes. Vitamin E is an antioxidant that can sometimes improve markers of liver health in non-diabetic patients. Pioglitazone, a medication currently approved to treat Type II diabetes, is considered a potential treatment for NASH patients with diabetes to help control blood sugar levels. Obese patients may consider taking weight loss medications or bariatric surgery.

Until recently, there were two investigational medications for NASH in late-stage development. However, in June, the FDA rejected Intercept Pharmaceutical's second attempt at approval of obeticholic acid (OCA) for the treatment of NASH with stage 2 or 3 fibrosis. OCA is currently available as Ocalvia® and is FDA approved to treat primary biliary cholangitis (PBC). Intercept first attempted FDA approval for NASH with OCA in 2019 and received a complete response letter. The company refiled a new drug application this past December. The FDA decision follows the recommendation from the FDA Gastrointestinal Drugs Advisory Committee meeting where members voted 15 to 1 against approval. Intercept's clinical trial data demonstrated only a moderate benefit over placebo in improving fibrosis in NASH patients and there were also notable safety concerns including an increased risk for drug-induced liver injury. In response, Intercept has decided to discontinue all NASH-related investments. Ocalvia will remain available to treat PBC.

As a result of OCA's FDA rejection, resmetirom (MGL-3196), from Madrigal Pharmaceuticals, now has the potential to be the first approved therapy for NASH. This investigational medication is a once daily, oral thyroid hormone receptor (THR) beta-selective agonist designed to treat one of the underlying causes of the disease. Thyroid hormone, through activation of its β-receptor in liver cells, plays a central role in liver function impacting blood levels of cholesterol and triglycerides as well as the buildup of fat in the liver. Patients with NASH often have reduced levels of THR-β receptor activity in the liver. Ultimately, resmetirom works by increasing hepatic fat metabolism and therefore decreasing liver fat.

On June 30th, Madrigal Pharmaceuticals announced that it initiated a rolling submission for the accelerated approval of resmetirom. The filling is supported by positive results from the MAESTRO-NASH trial, a Phase 3 study in 955 patients with liver biopsy-confirmed NASH. Participants were randomized 1:1:1 to receive 80 mg resmetirom, 100 mg resmetirom, or placebo orally once daily. The primary efficacy analysis assessed histological response by liver biopsy at 52 weeks. In the analysis, the primary endpoint of NASH resolution with ≥2-point reduction in nonalcoholic fatty liver disease activity score (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. Both primary endpoints are surrogate endpoints that were previously proposed by the FDA as being reasonable likely to predict clinical benefit to support in the drug's accelerated approval. In addition, low-density lipoprotein cholesterol (LDL-C) levels at 24 weeks, a key 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. The most common adverse event seen in the trial was generally mild diarrhea or increased stool frequency at the beginning of resmetirom therapy. This occurred in 9% and approximately 17% over the placebo rate in the 80 mg and 100 mg dose groups, respectively. All patients enrolled in MAESTRO-NASH have continued 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. If priority review is granted, resmetirom approval could occur in the first quarter of 2024. The Institute for Clinical and Economic Review (ICER) issued a draft evidence report earlier this year indicating that resmetirom would need to be priced between $39,600 and $50,100 per year to be cost effective assuming that short-term effects on liver fibrosis translate into longer-term reductions in cirrhosis. Pricing will not be available until market approval, but it is anticipated that the ICER benchmark will likely be surpassed as a starting price.

Given the multifaceted nature of NASH, it is possible that future successful treatment strategies may require combining medications that have different mechanisms of action or target different disease components. One such combination currently being studied is efruxiferim (EFX) and Ozempic® (semaglutide). EFX is an investigational subcutaneous once weekly fibroblast growth factor being studied for the treatment of NASH on its own. It works to regulate fibroblast growth factors because of the essential role they play in lipid and carbohydrate metabolism. In September 2022, results from the Phase 2b Harmony study demonstrated EFX was effective at improving fibrosis and reducing liver fat. There were also improvements in liver enzymes, noninvasive fibrosis markers, glycemic control, and body weight. While EFX seems to be effective at treating NASH on its own, better results were seen when combined with Ozempic. Ozempic is currently approved by the FDA to improve glycemic control and reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes. It is particularly effective at improving insulin resistance, which is a core issue for NASH patients. In a recent Phase IIb study, EFX and Ozempic were tested against Ozempic alone in a small cohort of 31 patients with type 2 diabetes and liver fibrosis due to NASH. Study results indicate that patients receiving the EFX-Ozempic combination had a 65% relative reduction in liver fat, compared to just 10% for patients only receiving Ozempic. In addition, 88% of patients treated with the combination therapy had normalized liver fat of less than 5% at week 12, compared to 10% of patients only treated with Ozempic. The patients treated with EFX also showed statistically significant improvements in liver enzymes and non-invasive markers of liver scarring, as well as reduced levels of blood sugar. Similar adverse events were reported in both treatment groups and no serious drug-related adverse events were noted. This new positive data may increase future utilization of Ozempic which already has blockbuster sales for its diabetes indication. The same drug, semaglutide, is marketed for obesity under the name Wegovy®. Both are currently experiencing availability issues due to their increasing popularity for use as a weight loss therapy.

With the recent FDA rejection of OCA, resmetirom will likely be the first NASH therapy to market in 2024. Several other investigational monotherapy and combination therapies for NASH are in phase 2 and phase 3 trials, but their approvals are likely a few years away. Meanwhile, the number of patients with NASH is predicted to grow significantly over the next 5 to 10 years due to increases in obesity and the growing prevalence of Type 2 diabetes. NASH patients are at risk for liver fibrosis, cardiovascular disease, and cancer. Future NASH pharmacotherapy is anticipated to fill a significant therapy gap and help to alleviate the clinical and economic burden NASH currently places on the healthcare system.

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