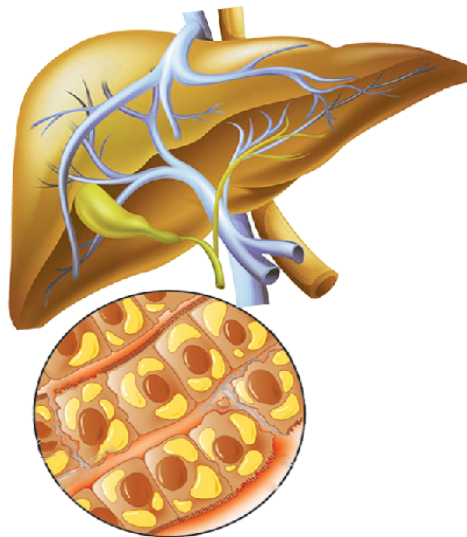


Obeticholic Acid Success in NASH – A Game Changer or Not?

Non-alcoholic fatty liver disease (NAFLD), a global epidemic and the most common cause of slowly progressive chronic liver disease, affects ~25% of the world population, including children and adults. The spectrum of NAFLD ranges from non-alcoholic fatty liver (NAFL) to non-alcoholic steatohepatitis (NASH) and occurs in the absence of excessive alcohol consumption. The majority of NAFLD patients have simple steatosis/NAFL, but ~30% of patients develop NASH, which is projected to be the leading cause of liver failure requiring liver transplant by 2020.

NAFL is characterized by the presence of $\geq 5\%$ hepatic steatosis (accumulation of triglycerides in the liver cells) without evidence of hepatocellular injury in the form of ballooning of the hepatocytes or evidence of fibrosis. The risk of progression to cirrhosis and liver failure is minimal with NAFL. NASH is usually asymptomatic and is distinguished by the presence of $\geq 5\%$ hepatic steatosis with inflammation and hepatocyte injury (ballooning) with or without fibrosis. Advanced fibrosis (Stage ≥ 2) is the most



important predictor of liver-related morbidity and mortality in NAFLD patients.

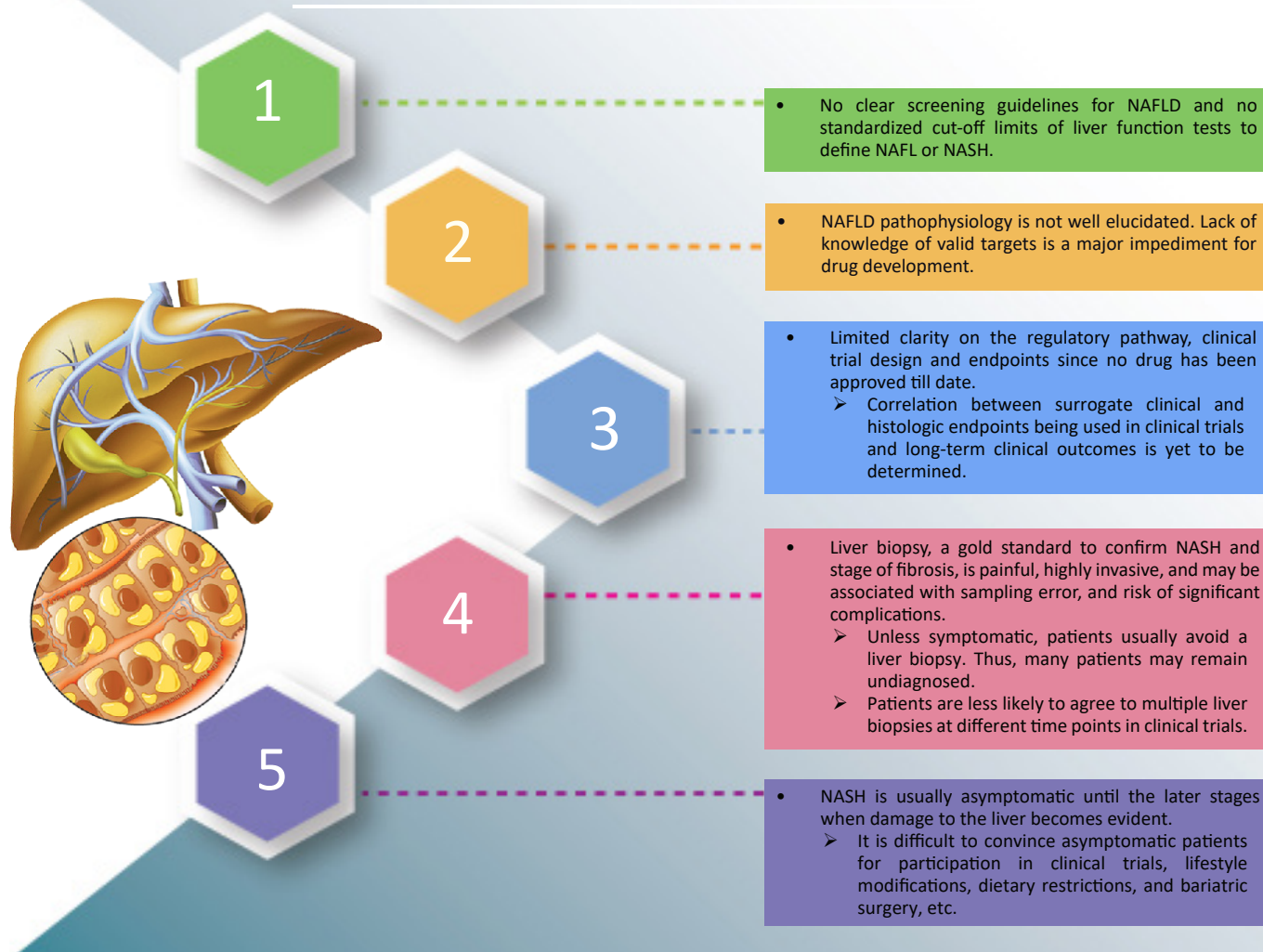
NASH may progress to cirrhosis, liver failure, and rarely liver cancer. Approximately 25% of NASH patients are at risk of progression to cirrhosis over 9 years and ~10% of the patients develop decompensated liver by 13 years. NASH is currently the second most common cause of liver transplant in industrialized nations and is projected to be the leading cause of liver failure requiring liver transplant by 2020.^{1,2,3}

Unmet Needs

There are no approved therapies for NASH, treatment is largely symptomatic, and drug development continues to remain challenging. Lifestyle modifications and treatment of underlying metabolic abnormalities including insulin resistance provide limited benefit. Multiple therapies have failed in clinical trials for NASH over the last 5 years,

including Selonsertib (Gilead), Volixibat (Mirum Pharma), Simtuzumab (Gilead), Cysteamine (Raptor), and Ezetimibe (Merck). Over the last 4 years, development of at least 11 assets, in different phases of development, have been discontinued for various reasons.^{4,5}

Key Challenges in Drug Development for NASH



Obeticholic Acid (OCA) – The Most Advanced Pipeline Asset

OCA (Ocaliva, Intercept Pharmaceuticals, Inc.) is a selective agonist of the Farnesoid X receptor (FXR), a bile acid nuclear receptor, approved for primary biliary cholangitis (PBC). Based on its activity on lipid and glucose metabolism as well as hepatic inflammation, it has been studied extensively as a therapeutic agent for NASH. OCA, a first-in-class selective FXR agonist with anticholestatic and hepatoprotective properties, is a derivative of the primary human bile acid (BA), chenodeoxycholic acid. OCA stimulates FXR activity approximately 100-fold more intensely than chenodeoxycholic acid, the natural FXR agonist in humans. FXR is involved in the synthesis and enterohepatic circulation of BAs. It represses hepatic BAs uptake and synthesis, promotes bile secretion, and induces BAs elimination via alternative export systems at the hepatic basolateral (sinusoidal) membrane. In 2015, OCA received the FDA breakthrough designation for

treatment of NASH with liver fibrosis. Intercept Pharma intends to file for approval in the US and Europe in the H2 2019.^{4,6,7}

Multiple pre-clinical studies have revealed the FXR-mediated activities of OCA including increased insulin sensitivity, reduced lipid synthesis, and fat accumulation, hepatocyte protection against bile acid-induced cytotoxicity, anti-inflammatory, and anti-fibrotic effects in the liver.

Clinical trials of OCA have provided encouraging efficacy data but tempered with some safety concerns. Common side effects include mild-to-moderate pruritus, elevated LDL levels, fatigue, headache, and gastrointestinal symptoms such as pain, discomfort, and constipation. Serious adverse events (SAEs) were observed in 20% of patients on OCA 25 mg vs. 13% for placebo and treatment-emergent adverse events (TEAEs) leading to

drug discontinuation were observed in 13% of patients on OCA 25 mg vs. 6% for placebo in the RE-GENERATE trial. In the Phase III RE-GENERATE trial, OCA 25 mg demonstrated statistically significant efficacy on improvement in liver fibrosis with no worsening of NASH endpoint but only numerical improvement on the co-primary endpoint of NASH resolution with no worsening of liver fibrosis vs. placebo. The efficacy of OCA 10 mg was not encouraging. In the Phase II FLINT trial, OCA 25 mg demonstrated statistically significant efficacy on decrease of at least 2 points in NAS score and no worsening of fibrosis endpoint. OCA is approved for PBC but has a black box warning. In post-marketing reports, hepatic decompensation and failure, in some cases fatal, have been reported in patients with PBC with decompensated cirrhosis or Child-Pugh Class B or C hepatic impairment when OCA was dosed more frequently than recommended. Dose titration could be a strategy in NASH but the maximum dose of OCA for PBC is

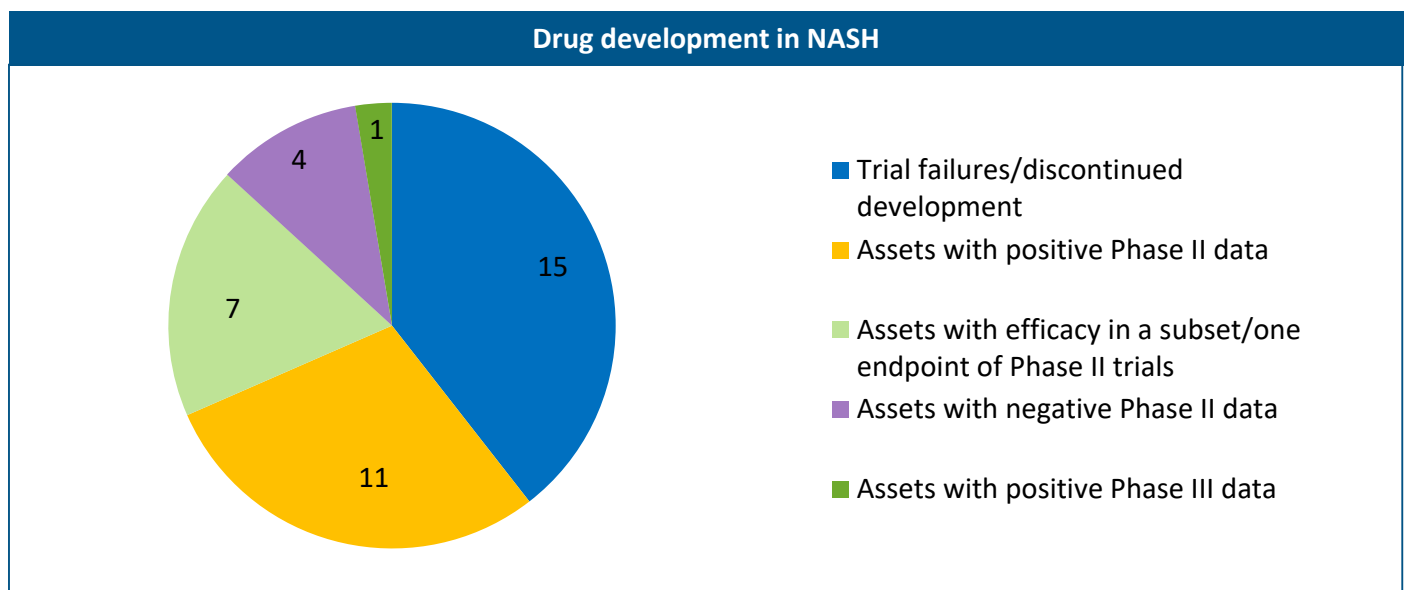
10 mg, which is less than the efficacious dose for NASH.^{8,9}

- Pruritus is the most common side effect, especially at higher doses, which may need dose adjustment, antipruritic medications, and short periods of withholding treatment in some patients or discontinuation of OCA.
 - In the FLINT trial, 23% of patients in the OCA group developed pruritus compared to 6% in the placebo group. Treatment discontinuation was needed in one patient.
 - In the RE-GENERATE trial, 51% of patients on OCA 25 mg developed pruritus compared to 19% in the placebo group.
- Treatment with OCA has been associated with an increase in LDL-cholesterol and decrease in HDL-cholesterol and triglycerides.
 - In the RE-GENERATE trial, LDL increased in 17% of patients on OCA 25 mg vs. 7% in the placebo group.

Other Pipeline Assets in Clinical Development

OCA is the only therapy to demonstrate statistically significant efficacy on the improvement in liver fibrosis endpoint in NASH in a Phase III trial. Recently, Seladelpar (CymaBay Therapeutics), a PPAR agonist, has shown negative data at 12 weeks in a 52 weeks, Phase II study. Reduction in the liver fat was less compared to placebo (14.2% with Seladelpar 20 mg vs. 20.8% with placebo) although the expectation was to see a 20-30% placebo adjusted change in the liver fat. Investor confidence is low in PPARs as a class since Elafibranor (Genfit), Phase III, was

unable to show a reduction in the liver fat in an earlier trial and Lanifibranor (Inventiva Pharma), a PPAR agonist, failed in a Phase II trial. Ceniciviroc (CVC) efficacy, in a Phase IIb CENTAUR study, was numerically better than placebo at two years on improvement in fibrosis ≥ 1 Stage with no worsening of NASH endpoint (26% vs. 19%) but inferior to the crossover arm that received placebo for the first year and CVC in the second year (26% vs. 29%). Thyroid hormone receptor- β agonism has generated significant interest in NASH management and could be a mechanism



While there are a number of promising assets in Phase II development, the history of trial failures and discontinued development suggests that many of these may not be successful in Phase III trials

Randomized Clinical Trials of OCA in NAFLD/NASH¹⁰⁻¹⁴

Trials	Phase of Development	Patient Population	Duration	Primary Endpoints	Result
RE-GENERATE trial NCT02548351	III	Patients with non-cirrhotic NASH with liver fibrosis (Stage 2 and 3) (N=2,370)	18 months	Percent of patients with at least 1 Stage of liver fibrosis improvement with no worsening of NASH OR NASH resolution with no worsening of liver fibrosis	Improvement in liver fibrosis with no worsening of NASH: OCA 25 mg: 23.1% (p = 0.0002), OCA 10 mg: 17.6% (p = 0.0446), Placebo: 11.9% NASH resolution with no worsening of liver fibrosis: OCA 25 mg: 11.7% (p = 0.1268), OCA 10 mg: 11.2% (p = 0.1814), Placebo: 8.0%
REVERSE trial NCT03439254	III	Patients with compensated cirrhosis due to NASH (N=900)	12 months	Percent of patients with improvement in fibrosis by at least 1 Stage with no worsening of NASH	Not available
FLINT trial NCT01265498	II	Biopsy proven NASH (N=283)	72 weeks	Histological improvement in NAFLD activity score (NAS – a decrease of at least 2 points) with no worsening of fibrosis	Decrease of at least 2 points in NAS score and no worsening of fibrosis: OCA 25 mg: 45% (p = 0.0002), Placebo: 21%
NCT00501592	II	Type 2 diabetes patients with presumed NAFLD (N=64)	6 weeks	Insulin resistance and glucose homeostasis	Increase in insulin sensitivity from baseline: OCA 25 mg: 28.0%, OCA 50 mg: 20.1%, Placebo: Insulin sensitivity decreased by 5.5%
CONTROL trial NCT02633956	II	Biopsy proven NASH with fibrosis (Stage 1-4) (N=84)	16 weeks	Effect on LDL concentration (Least squares mean change from baseline at week 16)	Mean LDL change from baseline at week 16: OCA 5 mg: -40 mg/dL; OCA 10 mg: -40 mg/dL; OCA 25 mg: -45 mg/dL; Placebo: -48 mg/dL

to watch out for in the near future. Resmetirom (Madrigal Pharma), thyroid hormone receptor- β agonist, an oral agent in Phase III, demonstrated significant improvement on the primary endpoint of mean relative change in liver fat at week 36 (MRI-PDFF), -37% (p < 0.0001) vs. -8.9% with placebo, in a Phase II trial. It also demonstrated significant improvement on the secondary endpoints of

NASH resolution and ≥ 2 point decrease in NAS at 36 weeks vs. placebo. A numerical trend in reduction of fibrosis with negligible worsening of fibrosis was also observed. Most of the side effects were mild-to-moderate and SAEs were not related to Resmetirom. Another thyroid hormone receptor- β agonist asset, VK2809 (Viking Pharma), is in Phase II of development.¹⁵⁻¹⁹

NASH pathophysiology is complex and multiple pathways are at play. Combination therapies could be the way forward to enhance efficacy and limit toxicity. Multiple combination therapies including Sildenafil/Leucine/Metformin (NuSirt Biopharma), Tropifexor/Ceniriviroc (Novartis/Allergan), Selonsertib/Firsocostat/Cilofexor (Gilead), and Semaglutide/Firocostat/Cilofexor (Novo Nordisk/Gilead) are in Phase II of clinical development. Intercept plans to use an in-licensed pan-PPAR agonist, Bezafibrate in combination with OCA in PBC, and may likely replicate this approach for NASH as well.

Conclusion

NAFLD is a multifaceted systemic disease, with a significant healthcare burden. At present, the only recommended treatment for NAFLD in obese patients is lifestyle changes to

reduce weight with dietary restrictions and physical activity. FXR is a promising molecular target for NAFLD therapy and OCA is the only drug to demonstrate statistically significant efficacy in a Phase III trial. However, it is associated with several adverse effects such as elevated LDL levels, itching, and abdominal discomfort. Based on promising Phase III data, OCA has the potential to be the first approved therapy for NASH management, given the high unmet need in the disease. However, this still leaves room for new agents that can provide meaningful efficacy and acceptable tolerability. Even after the approval of a first therapy for NASH, identification of patients with advanced fibrosis, duration of treatment, assessing response to treatment and determining the need to add-on or switch therapies, would remain as key issues to be addressed for successful long-term management of NASH patients.

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