Strategies for Successful Market Access in the Untapped NASH Market

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Non-alcoholic fatty liver disease (NAFLD) is the accumulation of triglycerides in the liver cells in the absence of any other specific liver disease. Non-alcoholic Steatohepatitis (NASH) is the severest form of NAFLD, categorized by a buildup of fat in the liver exceeding 5% of its weight [1].

NAFLD is a major potential threat to public health and a huge market access [2] concern. Globally, one out of four is suffering from NAFLD, with the highest prevalence in the Middle East and South America, and the lowest in Africa [3].

The prevalence of NASH in the United States is between 3 to 5% [4], and it increases with the presence of metabolic disorders. NASH is expected to become the leading cause of liver transplantation by 2020 in the United States [5].

Most NAFLD/NASH patients are asymptomatic or have nonspecific symptoms, such as fatigue. The well-known primary causes of NAFLD are obesity, type II diabetes, dyslipidaemia, and insulin resistance. However, diseases other than metabolic disorders also cause NAFLD. These include disorders of lipid metabolism (hypobetalipoproteinaemia, lipodystrophy), nutritional causes (total parenteral nutrition, starvation), medications (anti-HIV medications), and other causes (environmental toxicity). NASH can lead to other severe liver diseases such as fibrosis, cirrhosis, and hepatocellular carcinoma. NASH patients are also at an increased risk of cardiovascular diseases.

Though liver biopsy is the gold standard to diagnose and stage NASH, it has limitations when it comes to patient care [6]. It is an invasive method, it comes at a high cost, and there are chances of sampling errors. There are also risks like bleeding, pain, perforation, infection, and even (on occasion) death. Several studies are currently underway [7] to identify the biomarkers of NAFLD/NASH and non-invasive diagnostic techniques.

Treatment and management options

There is no approved treatment available for NAFLD/NASH. Lifestyle modification is the initial therapeutic option. Pharmacological treatment is considered for biopsy-proven NASH. Bariatric surgery is considered the last option to manage NASH. The current treatment and management options are as follows:

Lifestyle modification

Lifestyle modification (diet and regular exercise) is the main standard of care for NAFLD, and is the initial step to manage NASH.

Pharmacological therapy

- *Anti-obesity drugs:* Some studies on anti-obesity drugs have shown that they may improve NASH symptoms. In a small study on obese patients, Orlistat (inhibitor of fat absorption) caused weight loss and thereby improved NASH symptoms [8]. However, long-term study data on the efficacy of these drugs on liver-related outcomes is not available, and some drugs may have serious central nervous system-related side-effects.

- *Insulin-sensitizing agents:* Several anti-diabetic drugs were *studied for efficacy in NASH [9]*, considering insulin sensitivity is reduced in these patients. Though these drugs increase the insulin sensitivity, none of them were majorly beneficial in improving liver histology.

Lipid lowering agents

- *Statins:* Statins reduce cholesterol biosynthesis, mainly in the liver, and modulate lipid metabolism through the inhibition of the enzyme HMG-CoA reductase. Statins are used to treat NAFLD as dyslipidemia frequently coexists with NAFLD/NASH, and there is an increased cardiovascular risk in these patients. However, there is limited *real world data [10]* on statin efficacy in these patients.

- *Omega-3 fatty acids:* These drugs are assumed to have multiple beneficial effects in NAFLD patients, the important reason being the alteration in the hepatic gene expression, thereby increasing fatty acid oxidation and catabolism. They are also known to improve insulin sensitivity, are anti-inflammatory, and reduce tumour necrosis factor-α levels, thus offering several potential therapeutic mechanisms. However, in a large population-based study, ethyl-eicosapentaenoic acid did *not show any significant effects on NASH symptoms [11]*.

- *Antioxidants*: Oxidative stress is an important step in the pathogenesis of NASH and its progression. Vitamin E has antioxidant properties, and is vastly studied as a potential treatment for NASH. Though Vitamin E demonstrated improvement in steatosis in a clinical study, it *failed to improve the necro-inflammatory activity [12]* or alanine aminotransferase levels.

Bariatric surgery

Bariatric surgery causes massive weight loss and remarkable histological improvement, including partial reversal of cirrhosis. In morbidly obese patients, bariatric surgery improves

the histology, including resolution of NASH in 75% of cases and reduction of fibrosis in 34% of cases after a long follow-up. Massive weight loss associated with the surgery reduces pro-inflammatory mediators, thereby improving the hepatic insulin resistance [13] and inhibiting the hepatic inflammation.

Pipeline molecules under development

The list of drugs under late-stage development to treat NASH are:

Drug name	Company	Mechanism of action	Phase of development	Special designation (FDA)
Obeticholic acid	Intercept Pharmaceuticals	FXR agonist	Phase 3	Breakthrough therapy
Elafibranor (GFT505)	Genfit	PPAR alpha/delta agonist	Phase 3	Fast track designation
Cenicriviroc	Allerga /Tobira	Dual CCR2/CC5 antagonist	Phase 3	Fast track designation
Selonsertib (GS-4997)	Gilead Sciences	ASK-1 inhibitor	Phase 3	-
Aramchol	Galmed Pharma	SCD1 inhibitor	Phase 2 / 3	Fast track designation
NGM282	NGM Biopharmaceuticals	FGF19 hormone modulator	Phase 2	-
TRO19622	Roche	Apoptosis inhibitor	Phase 2	-
BMS-986036 (PEG-FGF21)	BMS	FGF agonist	Phase 2	-
GR-MD-02	Galectin	Galectin-3 inhibitor	Phase 2	Fast track designation
Volixibat (SHP626)	Shire	ASBT inhibitor	Phase 2	Fast track designation
MGL-3196	Madrigal Pharma	THR-β agonist	Phase 2	-

Solithromycin	Cempra	Macrolide antibiotic	Phase 2	-
GS-0976	Gilead Sciences	ACC inhibitor	Phase 2	-
IMM-124E	Immuron	Immunomodulator	Phase 2	-
GS-9674	Gilead Sciences	FXR agonist	Phase 2	-
LJN452	Novartis	FXR agonist	Phase 2	Fast track designation
LMB763	Novartis	Not available	Phase 2	Fast track designation
Emricasan	Conatus / Novartis	Caspase protease inhibitor	Phase 2	Fast track designation
IVA337	Inventiva Pharma	PPAR agonist	Phase 2	-
MT-3995	Mitsubishi Tanabe	Selective mineralocorticoid receptor antagonist	Phase 2	-
Semaglutide	Novo Nordisk	GLP-1 agonist	Phase 2	-
MN-001 (tipelukast)	MediciNova	LT antagonist / PDE inhibitor / 5-LO inhibitor	Phase 2	Fast track designation
DS102	Afimmune	Anti-inflammatory & antifibrotic lipid	Phase 2	Fast track designation
Saroglitazar	Zydus Cadila	PPAR agonist	Phase 2	-
CF102	Can-Fite Biopharma	Adenosine A3 receptor agonist	Phase 2	-

ACC – Acetyl-CoA carboxylase; ASBT – apical sodium dependent bile acid transporter; ASK-1 – Apoptosis signal-regulating kinase 1; CCR – Chemokine receptor; FGF-19 – Fibroblast growth factor; FXR – Farnesoid X receptor; LO – Lipoxygenase; LOXL2 – Lysyl Oxidase-like protein 2; LT – Leukotriene; PDE – Phosphodiesterase E; PPAR – Peroxisome proliferator-

activated receptor; SCD1 - Stearoyl Coenzyme A Desaturase 1; THR-β – Thyroid Hormone Receptor β

The expected early entrants in the NASH market are:

Drug	Year of expected market entry	Key notes
Obeticholic acid	2022/2023	• Leads the race in approval for NASH • In a phase 2 study, the drug, at 10 and 25 mgs, was not statistically significant at the primary endpoints when compared to placebo • Already approved for primary biliary cholangitis (PBC) • Established safety profile in PBC patients may help the drug gain physician acceptance for the treatment
Elafibranor (GFT505)	2023/2024	• Tested as once-daily oral treatment in NASH patients • In a phase-2b trial, Elafibranor showed dose-dependent efficacy on the primary endpoint o Elafibranor also showed significant cardio-metabolic benefits o The drug was well tolerated in the one-year trial • Though the drug is expected to become a second entrant in this space, it may become the first entrant if obeticholic acid falters in its phase 3 studies
Selonsertib (GS-4997)	2024/2025	• Liver disease specialist Gilead's leading bet for NASH therapy • Other Gilead drugs in development for NASH are GS-0976 and GS-9674 • Selonsertib inhibits ASK-1: a protein that promotes inflammation, cell death and fibrosis in settings of oxidative stress • The drug was well tolerated in a phase 2 study, and demonstrated anti-fibrotic activity in NASH patients
Cenicriviroc	2025/2026	• Dual CCR2/CCR5 inhibition plays a key role during inflammation and fibrosis in NASH patients • Also studied in primary sclerosing cholangitis patients • In a phase 2b trial, Cenicriviroc did not meet its primary endpoint of a two-point reduction in the NAFLD Activity Score o However, the drug demonstrated a clinically and statistically significant improvement in fibrosis of at least one stage, without worsening of NASH, after one year of treatment
Aramchol	2024/2025/2026	• Synthetic lipid molecule obtained by combining two natural components, bile acid, and saturated fatty acid • May compete with Cenicriviroc/Selonsertib to become the third marketed drug for NASH • In a phase 2 study, Aramchol was safe, tolerated, and significantly reduced liver fat content in a dose-dependent manner

Challenges for the early entrants in the NASH market

Drug pricing: Payers may be reluctant to cover highly-priced NASH drugs, since the drug has to be taken for a longer duration. So, the price fixed by the early entrants will play a major role in market success. Payers may also be reluctant to cover potentially expensive medications, in part because lifestyle modification is often the first line treatment for NASH.

Physician acceptance: Since lifestyle modification is the initial step to manage NASH, physicians might be reluctant to prescribe the drugs for NASH. Hence, targeting and educating physicians will be crucial for the successful market access of products.

Patients' unwillingness to undergo diagnosis: Although the prevalence of NASH and NAFLD are high, the diagnosis rate is low since liver biopsy is the gold standard to identify the disease. Since liver biopsy is a painful procedure, some patients may opt out of diagnosis, leading to a low diagnosis rate. Hence, patient education on the long-term ill effects of this largely unknown disease is vital for the success of early market entrants.

Diagnosis and staging of NASH: Liver biopsy is the only method available to diagnose and stage NASH. However, this is an expensive and invasive procedure, causing patient discomfort and potential side effects, which can even lead to death. Non-invasive methods are under development. Discovery of easily identifiable biomarker(s) as in patients with diabetes (serum/urine glucose, HbA1c tests) will help monitor/stage the disease, as well as in dose adjustment of the drug thereafter.

Future competition: Many competitors are vying to garner a major share of the untapped NASH market. Considering the unmet needs in this area, the regulators are also promoting the development of promising drugs by providing special designations. A thorough understanding of the strengths and weaknesses of the late-stage pipeline products or next entrants, and their impact on the sales of the early entrants will help in strategizing for the sustained commercial success of products.

Combination therapy: There are a wide variety of compounds with different mechanism of actions in late-stage clinical development to treat NASH. Since NASH is a multifactorial disease, it is most likely that a multifaceted combination therapy will be needed to successfully and effectively treat it. Hence, the collaboration/acquisition of other effective treatments in the pipeline, and testing combination therapies earlier could be one of the incredible strategies for early entrants.

The prevalence of metabolic disorders (including NASH) is increasing at an alarming rate, and the untapped NASH market worth billions is considered as the next big market in the metabolic disorders segment.

Many big (Novartis, Gilead, Allergan, etc.) and small pharma companies (Intercept, Genfit, etc.) are betting big on NASH therapy, considering the large-scale unmet needs and potential financial benefits achievable by being the first entrant in the market.

Some important questions for the new entrants are:

- What should be the optimum prize for the first drug to convince payers, and make it a blockbuster as well?
- How can physician acceptance be increased?

- How can the diagnosis rate be increased to get more patients to treat?
- Are collaborations necessary to develop combination products?

The first entrants of the NASH market should find answers to these questions, which will eventually help them grab a major portion of the potential market. Different market access solutions such as forecasting, pricing strategies, business development/licensing evaluation, and go-to market strategies would help the early entrants for easy access, and increase the potential of their NASH products. Competent partners who have the industry know-how and relevant expertise in this arena can help them strategize better and identify potential avenues.

About the Authors

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