

NASH: The Next Blockbuster Market

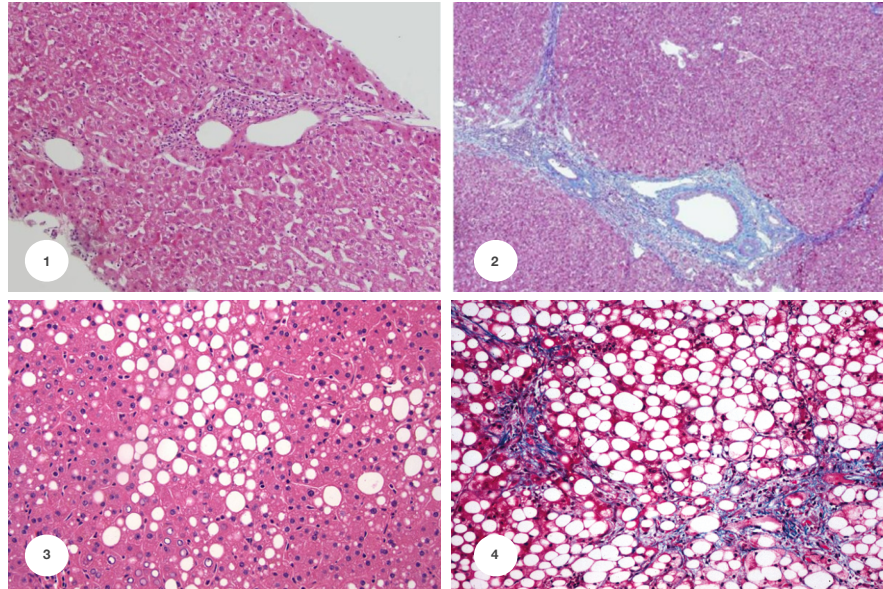
NASH has replaced HCV as the most prevalent nonalcoholic liver disease. The race to tap into this \$35B per year market continues as pharma and biotech companies develop potential candidates for therapy.



Non-Alcoholic Steatohepatitis, abbreviated as ‘NASH,’ is a rapidly growing condition affecting a population that was not previously recognized as high risk. NASH is poised to have a significant impact on the cost of care on the US population as a whole as it is a disease fueled by the rise of obesity and diabetes, both of which are increasingly becoming more prevalent with more than 25 million known cases in the United States. That is about 12% of the adult population.

“NASH is predicted to become the most common liver disease in the future. We’re talking about 3-5% of the general population.”

*-Dr. Brent Tetri,
Gastroenterologist at St.
Louis University*



1. Normal Liver 2. Liver with Mild Fibrosis 3. Liver with Fibrosis 4. Liver with Cirrhosis

NASH is a nonalcoholic fatty liver disease (NAFLD) which is a direct result of the components of metabolic syndrome (i.e. obesity, Type II Diabetes, dyslipidemia, and/or hypertension). The combination of any of these risk factors increase the likelihood of the disease. It has replaced Hepatitis C as the most significant nonalcoholic liver disease in terms of prevalence and cost, although it’s a newly recognized disease, as it was only first named in 1980 by Jurgen Ludwig of the Mayo Clinic in Rochester, Minnesota. In the beginning, many doctors didn’t view fatty liver disease as any different from obesity and diabetes, but soon realized that NASH was a separate and distinct condition.

The disease often goes undetected and undiagnosed as the only current method to verify it is through liver biopsy, a costly, painful, and invasive procedure most doctors tend to avoid unless there is clear cause for concern. Even when diagnosed, there are no FDA-approved therapeutic options for NASH and there is no cure at present other than a liver transplant. At this time, practitioners generally espouse patient lifestyle changes: losing weight by adopting low-carb, low-fat diet to better control diabetes, and/or to address dyslipidemia and hypertension. This is because healthier lifestyle choices have a likely chance of decreasing NASH fibrosis. Therefore, there is an opportunity to decrease risks, minimize symptoms, and perhaps even prevent the disease entirely.

However, since the primary risk factors of NASH are obesity, increased insulin resistance, and Type II diabetes, these risk factors cannot be teased apart. Instead, they combine into a symbiotic relationship where obesity couples with insulin resistance and together these often cause hypertension and hyperlipidemia. “With NASH, you’re dealing with a very complex systemic metabolic condition and not just

the liver,” said Dr. Brent Tetri, a Gastroenterologist at Saint Louis University, during a seminar on managing and identifying NASH patients hosted by Clinical Care Options.

“NASH is predicted to become the most common liver disease in the future. We’re talking about 3-5% of the general population,” says Dr. Tetri. In a 2017 interview with Dr. Aimee Tharaldson, a Senior Consultant for Emerging Therapeutics at Express Scripts, she stated, “Since it’s a huge patient population, some analysts suspect this could be a \$35B per-year market.”

Since liver disease, including complications due to onset of cirrhosis and liver cancer, is the third cause of mortality in NAFLD patients, liver transplantation is commonly indicated for NASH patients with end-stage liver disease. NASH will soon overtake Hepatitis C as the single largest cause of liver transplantation, as many patients have achieved complete resolution of their disease with the introduction of curative anti-viral treatments.

In 2017, the total cost of a liver transplantation in the United States was estimated at \$812,500 per patient versus previous years (2014: \$740,000 and 2011: \$577,000). This could represent an economic burden of \$353B over the next 10 years.

Table 1 | Drugs in Phase III clinical trials for NASH

| Company | Agent | MoA | Main Disease Processes Affected |
|---------------------------|-------------------------------------|---|--|
| Intercept Pharmaceuticals | Ocaliva (obetocholic acid; INT-747) | FXR agonist | Bile acid synthesis and transport, glucose homeostasis, fibrosis, inflammation |
| Gilead Sciences | Selonsertib (GS-4997) | ASK-1 kinase inhibitor | Liver injury, fibrosis |
| Genfit | Elafibranor (GFT-505) | Dual PPAR α and δ agonist | Fatty acid oxidation, inflammation, glucose homeostasis |
| Allergan | Cencriviroc (TBR-652) | CCR2/CCR5 dual agonist | Inflammation, fibrosis |

FXR: farnesoid X receptor; ASK-1: apoptosis signal-regulating kinase 1; PPAR, peroxisome proliferator-activated receptor; CCR: C-C chemokine receptor

As a result, the lack of effective medication in the treatment of NASH is a growing major economic and societal issue. To that end, the race to be first to market in the treatment of NASH has been a rapid dash for biotech and pharmaceutical companies, in particular: Intercept Pharmaceutical’s Ocaliva, Gilead Sciences’ selonsertib, Allergan’s cencriviroc, Genfit’s elafibrinor, and Galmed’s Aramchol.

Recently however, Gilead encountered a setback with selonsertib, an inhibitor of apoptosis signal-regulating kinase 1 in their Phase 3 clinical trial, STELLAR-4, with stage 4 (cirrhosis) NASH patients. Selonsertib failed to meet the primary endpoints of the proportion of participants achieving at least a one-stage improvement, therefore sets back selonsertib as a forefront entrant into the NASH therapy market. The trial

recruited 877 patients who were randomized to receive one of two doses of selonsertib (18 mg or 6 mg) or placebo once daily. After 48 weeks, Gilead examined how many of the trial participants had experienced a 1-stage or more histological improvement in fibrosis without worsening of NASH and found that of the patients who took the higher (18 mg) dose of selonsertib, 14.4% experienced improvement, which compared to the 12.8% in the placebo arm and the 12.5% in the lower dose group, meant that neither dose statistically outperformed the control.

This doesn't mean that Gilead is out of the running. According to public statements, the company intends to initiate a Phase 3 clinical trial with selonsertib for stage 3 (fibrosis) NASH patients, as well as to continue with Phase 2 trials on their combination therapies using GS-0976, an apoptosis signal regulating kinase inhibitor, and GS-9674, an FXR agonist similar to Intercept's Ocaliva. Gilead also entered into strategic collaboration with Scholar Rock Holding Corporation, a biomedical technology firm. This collaboration will explore a pre-clinical program that uses inhibitors of Transforming Growth Factor Beta (TGFβ) activation for the treatment of fibrotic diseases. For as many candidates Gilead has in the running, these assets are nevertheless still in the early stages, and will take many more years before they transition into mid-stage studies.

Table 2 | All FXR Agonists

| Company | Agent | MoA | Main Disease Processes Affected | Current data results | Next Steps |
|---------------------------|-------------------------------------|--------------------------|--|--|--|
| Intercept Pharmaceuticals | Ocaliva (obetocholic acid; INT-747) | FXR agonist | Bile acid synthesis and transport, glucose homeostasis, fibrosis, inflammation | Ocaliva 25mg dose shows improvement of liver fibrosis with no worsening of NASH, significantly greater than placebo | Releasing Phase III data at the National Liver Congress in April 2019; File for FDA approval |
| Gilead Sciences | GS-9674 | Nonsteroidal FXR Agonist | Acts mainly in the intestine | Does not elevate LDL or circulating glucose compared with placebo; 14% of patients on high dose did experience itching | Awaits the results of another Phase 2 trial that tests three Gilead compounds singly and in combination using paired liver biopsies to evaluate efficacy |

| | | | | | |
|------------------------|----------------------|--|--|--|--|
| Novartis | Tropifexor (LJN-452) | Non-Bile Acid FXR Agonist | Marker of target engagement in the gut | Presented interim Phase 2b study results provide evidence for target engagement, anti-inflammatory, and anti-steatotic effects with no important clinically changes in mean LDL-C and HDL-C levels | Jointly launched phase 2 trials with Allergan's cenicriviroc; and separately partnered with Pfizer to test Tropifexor in combination with three different experimental Pfizer NASH compounds |
| NGM Biopharmaceuticals | NGM282 | Targets FGF19 signaling instead of FXR | Eliminates potential cancer risk of activating FGFR4 | Released interim Phase 2 trial results: reduced hepatic fat, fibrosis biomarkers improved, and drug was well tolerated but raised LDL | In clinical development |

FXR: farnesoid X receptor

With the recent release of their pivotal phase 3 studies, Intercept is likely to have the first approved treatment for NASH. The company's candidate, obethocholic acid (Ocaliva), met its primary endpoint by improving liver fibrosis without any worsening of NASH after 18 months of treatment. The trial involved 931 patients with NASH and were randomized to receive daily doses of Ocaliva at 10mg, 25mg, or placebo. The highest dose of Ocaliva showed improved liver fibrosis with no worsening of NASH at 23.1% versus placebo at 11.9%.

However, Ocaliva missed a second efficacy endpoint. While more patients who received Ocaliva in both the doses achieved NASH resolution with no worsening of liver fibrosis against the placebo, it was unfortunately not statistically significant enough. The overall achievement of the primary endpoint allows Intercept to move forward with Ocaliva, presenting data from the study, dubbed REGENERATE, at the International Liver Congress in April and plans to file for FDA approval by the end of 2019. However, some adverse events could be troublesome for Ocaliva down the line, notably some dose-related pruritus (itchy skin), where 19% occurred in placebo, 28% in OCA 10mg and 51% in OCA 25mg. Another is 3% hepatobiliary (liver, bile ducts or bile) events in the 25mg arm. Other serious adverse events were recorded as three patients died during the trials (2 in the placebo arm, and one in the Ocaliva 25mg arm) although none of the deaths were considered treatment-related.

Table 3 | Drugs in Phase II clinical trials for NASH

| Company | Agent | MoA | Main Disease Processes Affected | Status |
|----------------------|---|---|---|---------------------|
| Bristol Myers Squibb | Pegbelfermin (BMS-986036) | Pegylated FGF21 | Regulates metabolism | In Phase II trials |
| CohBar | CB4211 | Optimized analog of MOTS-c | Regulates metabolism | In Phase II trials |
| CymaBay Research | Seladelpar (MBX-802) | PPAR δ agonist | Fatty acid oxidation, inflammation, glucose homeostasis | In Phase II trials |
| Galmed | Arachidyl amido cholanoic acid (Aramchol) | Liver targeted SCD-1 modulator | Fatty acid and bile acid | In Phase II trials |
| Inventiva | Lanifibranor (IVA-337) | PPAR α , δ , and γ agonist | Fatty acid oxidation, inflammation, glucose homeostasis | In Phase IIb trials |
| Zydus Cadila | Lipaglyn (Saroglitazar Magnesium) | PPAR α , and γ agonist | Fatty acid oxidation, inflammation, glucose homeostasis | In Phase II trials |

MOTS-c: mitochondrial-encoded peptide; PPAR, peroxisome proliferator-activated receptor; Pegylated FGF21: recombinant PEGylated human fibroblast growth factor 21

Many other pharmaceutical companies also covet a spot in the NASH treatment market. Another notable candidate is Madrigal Pharmaceuticals' MGL-3196, which is an orally administered, small molecule, liver-directed thyroid hormone receptor THR (β -selective agonist) and is poised to initiate a Phase 3 clinical program.

Novartis has entered collaborations with three different companies in the hopes of identifying a treatment that will work to slow NASH's disease progression. The first collaboration is in co-development with Pfizer, where they are looking to study the impact of combining Novartis' non-bile acid FXR agonist, tropifexor, with one or more of Pfizer's experimental NASH treatments aimed at steatosis/fat accumulation in the liver. Tropifexor is a multi-modal drug that fights inflammation fibrotic scarring and fat accumulation. The second collaboration is with Allergan last year when they jointly launched a phase 2 trial of tropifexor and Allergan's CCR2/CCR5 inhibitor, cencriviroc. And finally, Novartis entered into an exclusive licensing agreement with Conatus Pharma, a biotech focused on liver disease where Novartis is helping fund the development and commercialization of Conatus' emricasan, which helps stop cell death. Unfortunately, recent clinical trial results for emricasan showed the treatment missed its primary endpoint of fibrosis improvement with no worsening of steatohepatitis in early stage NASH fibrosis patients. The companies are still hopeful that future data could show emricasan have a more successful effect on advanced-stage NASH cirrhosis patients.

“We’re only scratching the surface of who has NASH because we only get those who are sent to us, since we are not screening in the community.”


*-Dr. Jonathan Fenkel,
Associate Medical Director
of Liver Transplantation at
Thomas Jefferson University*

While the race to be first to market in NASH therapies continues, the search for reliable, non-invasive markers for diagnostic testing remains elusive. Liver biopsies have often been considered by practitioners as the gold standard for diagnosis in NASH. However, “it is also sort of a bronze standard because it is not perfect,” Dr. Tetri observed. With the risk of bleeding, pain, sampling variability, and limited health insurance coverage for these tests, it is a less than ideal way to get a definitive diagnosis, even though it is currently the best option available to establish diagnosis for NASH, rule out other conditions (e.g. alpha-1 antitrypsin, iron overload, autoimmune component), and assess early fibrosis. The challenge as the healthcare industry gets closer to the approval for potential NASH therapies is to also have non-invasive means of getting diagnosed. “We’re only

scratching the surface of who has NASH because we only get those who are sent to us, since we are not screening in the community,” Dr. Jonathan Fenkel, Associate Medical Director of Liver Transplantation at Thomas Jefferson University, said. According to Dr. Fenkel there remains a large portion of patients that have NASH but are currently undiagnosed. “If you assume that 30% of those with diabetes have fatty liver then about 10-20% of those with fatty liver have NASH,” he said. These are worrisome numbers since it estimates that 1 in 5 Type II diabetics have too much fibrosis in their livers. “I would be interested to see if screening guidelines change when there are finally some available therapies, similar to the way Hep C was screened among the baby boomers,” he continued. Dr. Fenkel refers to the fact that almost a decade ago the diagnostic procedures for Hepatitis C shifted from biopsies to a *Test and Treat* approach upon the arrival of oral agents.

There are existing non-invasive diagnostic tests available that can pick up presence of fatty liver: ultrasound, CT, MRI, *FibroScan* CAP score. However, these tests could only support a preliminary indication of diagnosis, not a medical one. “I’m encouraged that we still do pick-up a lot of NASH by a lot of the noninvasive markers that we have right now, especially some of the lipid species,” Dr Tetri said. “I’m optimistic we’re going to have a blood test to pick-up NASH without a liver biopsy in the coming years; we’re just not there yet,” he continued. Until simplified screening and diagnosis is available, identifying appropriate patients will be a hurdle that all NASH treatments will need to address in their marketing and patient identification activation plans.

The end of 2019 may see some progress with the potential approval of one or two NASH therapies, as the culmination of decades of effort. In the meantime, nutrition and exercise remain at the top of treatment protocol, and for those that get diagnosed early, these lifestyle interventions could achieve a complete reversal of the fibrosis. “About 15-20% of my patients are able to do that,” Dr. Fenkel states, “It can work but it takes the right patient — someone who is really motivated.” As NASH becomes an epidemic of the 21st century, currently the most prevalent liver disease, it must be

treated with nutrition, exercise, and long-term lifestyle change as the foundation of its therapy. Unfortunately, for most patients, it is harder to commit to a treatment plan than it is to take medications. 

REFERENCES:

Attridge, Arran. Lee, Sung. Gilead Announces Topline Data From Phase 3 STELLAR-4 Study of Selonsertib Compensated Cirrhosis (F4) Due to Nonalcoholic Steatohepatitis NASH. *Business Wire*. <https://www.businesswire.com/news/home/20190211005738/en/>. (2019)

Bentley, T.S. et al, U.S. organ and tissue transplant cost estimates and discussion. *Milliman Research Report*. <http://www.milliman.com/uploadedFiles/insight/2017/2017-Transplant-Report.pdf>. (2017)

Chalasini, N. Yonoussi, Z. et al. The Diagnosis and Management of Nonalcoholic Fatty Liver Disease: Practice Guidance from the American Association for the Study of Liver Diseases. *Hepatology*. Vol 67, No 1, 328-357. (2018)

Conatus Pharmaceuticals Inc. Conatus Announces Top-line Results from ENCORE-NF Phase 2b Clinical Trial in NASH Fibrosis. <https://www.globenewswire.com/news-release/2019/03/21/1758961/0/en/Conatus-Announces-Top-line-Results-from-ENCORE-NF-Phase-2b-Clinical-Trial-in-NASH-Fibrosis.html>. (2019)

Dominguez, Christine. NASH Syndrome: The Coming Epidemic. *Gastroenterology Nursing*. Vol 41, No 4, 317-320. (2018)

Frates, Christopher. Vignola, Mark. Intercept Announces Positive Topline Results from Pivotal Phase 3 REGENERATE Study of Obeticholic Acid in Patients with Liver Fibrosis Due to NASH. <http://ir.interceptpharma.com/news-releases/news-release-details/intercept-announces-positive-topline-results-pivotal-phase-3>. (2019)

Garber, Ken. The New Liver Epidemic. *Nature Biotechnology* <https://doi.org/10.1038/s41587-019-0047-9>. (2019)

Ioannou, Lori. The \$35 Billion Race to Cure a Silent Killer that Affects 30 Million Americans. <https://www.cnn.com/2018/12/21/the-35-billion-race-for-a-cure-for-a-liver-disease-that-affects-millions.html>. (2018)