The Dash to Treat NASH, The Next Big Global Epidemic

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NAFLD is Now the Most Common Cause of Chronic Liver Disease in North America

- Non-alcoholic fatty liver disease (NAFLD) encompasses a spectrum ranging from simple steatosis to NASH with increasing levels of fibrosis, and ultimately cirrhosis.

- NASH describes a distinct clinical entity in which patients lack a history of significant alcohol consumption but have liver biopsy findings indistinguishable from alcoholic steatohepatitis.

- NASH is closely associated with insulin resistance and features of the metabolic syndrome such as obesity, hypertriglyceridemia, and type 2 diabetes.

NASH is an Important Cause of Liver-Related Morbidity and Mortality

♦ In the U.S., ~30% of adults and ~10% of children are estimated to have NAFLD.

♦ 10-30% of these patients have NASH and 25–40% of patients with NASH will develop progressive liver fibrosis.
  • NASH patients have an increased liver-related mortality rate.
  • NASH patients have an increased risk of cardiovascular death.

♦ 20–30% of NASH patients with advanced fibrosis will develop cirrhosis which is associated with a poor long-term prognosis:
  • 10-year mortality rate is 20% for patients with Child-Pugh A disease and 45% will decompensate within 10 years of diagnosis.
  • Patients with cirrhosis secondary to NASH are at increased risk of developing hepatocellular carcinoma.

♦ End stage liver disease secondary to NASH is projected to become the most common indication for liver transplant by 2025.

Patients with NAFLD
~81,000,000

Patients with NASH
~16,000,000

NASH Patients with Advanced Fibrosis
~5,000,000

NASH Patients with Cirrhosis
~1,300,000

End Stage Liver Failure, HCC
?

References:
There Are No Drugs Approved for NAFLD and/or NASH

- Management of NAFLD depends largely on the stage of disease:
  - Lifestyle modification (e.g. diet and exercise) treatment of any associated metabolic risk factors.
  - Pioglitazone or vitamin E may be considered for NASH patients with fibrosis.
  - For patients who have progressed to cirrhosis, surveillance for HCC is essential.

With an estimated 16-30 million adults affected in the U.S. alone and no FDA approved treatments, non-alcoholic steatohepatitis (NASH) has been proclaimed “the Next Big Global Epidemic” and “the Next Hepatitis C.” Indeed, analysts now forecast that the market for NASH treatments could reach $35-40 Billion by 2025.
The Number of Patients with NASH is Undoubtedly Large, but the Number that are Currently Being Diagnosed is Likely Much Smaller

- Most patients with NAFLD are asymptomatic and are typically only identified by routine blood tests showing elevations in liver enzymes (i.e. ALT, AST, GGT).
- Liver enzymes are not elevated in all NAFLD patients and many don’t get routine wellness exams, thus many with NAFLD remain undiagnosed.
- Liver biopsy is required to diagnosis NASH and only a small percentage of patients currently undergo liver biopsy.
- Non-invasive methods for detecting advanced fibrosis still have many limitations (e.g. high failure rate, much less sensitive than biopsy).
- The number of NASH patients who are diagnosed may be significantly smaller than population based estimates would suggest.

NASH Represents a Huge Patient Population with a High Level of Unmet Need, but there Are Significant Obstacles to Developing New Drugs

- No drug has received FDA approval for NASH, thus a clinical and regulatory path has not yet been established.
- The pathogenesis of NASH is poorly understood and probably multifactorial.
- NASH progresses very slowly, necessitating long clinical trials.
- The natural history of NASH is often heterogeneous and it is difficult to predict who will progress, necessitating large clinical trials.
- Non-invasive techniques for diagnosing NASH and assessing response to treatment are not yet ready for clinical trials, thus liver biopsies continue to be required.
The Number of Companies Seeking to Develop New Treatments for NASH is Rapidly Growing

<table>
<thead>
<tr>
<th>Company</th>
<th>Drug</th>
<th>MoA</th>
<th>RoA</th>
<th>Phase</th>
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<tr>
<td>Raptor</td>
<td>RP103</td>
<td>Antioxidant - cysteine depleting agent</td>
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<td>Saroglitzazar</td>
<td>PPAR agonist</td>
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<td>SubQ</td>
<td>Phase 2</td>
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<td>Pioglitazone</td>
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<td>Remogliflozin etabonate</td>
<td>SGLT-2 inhibitor</td>
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<td>Ursodeoxycholic acid</td>
<td>Bile acid</td>
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<td>Simtuzumab</td>
<td>LOXL2 antibody</td>
<td>IV and SubQ</td>
<td>Phase 2</td>
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<td>Conatus</td>
<td>Emricasan</td>
<td>Caspase protease inhibitor</td>
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<td>Aramchol</td>
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<td>Cenicriviroc</td>
<td>Dual CCR2/CC5 antagonist</td>
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<td>GFT 505</td>
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<td>OCA</td>
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<tr>
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<td>Sirtuin stimulants</td>
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<td>Cathepsin B inhibitor</td>
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| La Jolla             | LGPC-1010    | Galectin-3        | Oral  | Preclinical
NASH Began Making Headlines Early Last Year When the FLINT Study was Stopped Early After Meeting its Primary Endpoint

UPDATE: Intercept shares dazzle after early success of Phase Ib liver disease drug trial

January 9, 2014 | By John Carroll

Shares of Intercept Pharmaceuticals went into overdrive this morning, soaring more than 250% on the surprise news that a Phase Ib clinical study for its lead drug funded largely by the NIH ended early after achieving the primary endpoint.

The star of Intercept's ($ICPT) show is obeticholic acid, or OCA, which it believes is a "first-in-class agonist of FXR," has broad liver-protective properties. The NIH has nonalcoholic steatohepatitis, or NASH, which bears all three traits. It's seen in alcoholics, but in people who don't drink. The diet is high in fat and sugar, and it's been spreading around the world as a serious health problem in the U.S. and Europe.

The results provide key clinical validation for several prior studies, and investors rushed in to buy shares this morning, adding $8 billion to the biotech's market cap. By midmorning, shares were trading at $148.03, pushing the market cap closing in on $5 billion. Intercept has four programs, including OCA, with a late-stage study for primary biliary cirrhosis in the offing.

Intercept leaps again as deeper NASH data quiet some fears

August 12, 2014 | By Damian Garde

Still riding high on some strong early-year data for its liver disease treatment, Intercept Pharmaceuticals' ($ICPT) shares shot up once more as its lead drug came through in Phase Ib, dismissing some earlier safety worries and setting the stage for late-stage study.

In a 283-patient study, Intercept's drug for nonalcoholic steatohepatitis (NASH) met its primary endpoint of improving fatty-liver disease symptoms without worsening scarring, with 46% of those in the treatment arm showing meaningful improvement compared with 21% on placebo. The treatment, called obeticholic acid (OCA), also met its secondary endpoints of broadly reducing disease scores and significantly improving liver scarring; with 35% of OCA patients reporting a reduction in fibrosis compared with 19% taking placebo.

That last endpoint likely stood out to investors concerned about safety signals in the drug's earlier mid-stage results, and the new data sent Intercept up about 60% in after-hours trading. The company's share value has surged more than 500% since the start of the year, when it first unveiled encouraging results against a disease with no approved treatments.

www.fiercebiotech.com; Lancet, 2014 Nov 7

NASH Insight Briefing
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Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, non-alcoholic steatohepatitis (FLINT): a multicentre, randomised, placebo-controlled trial

Brent A Neuschwander-Tetri, Rohit Loomba, Anuj J Sanyal, Joel E Levine, Mark I. Van Natta, Mansal F Abdelmalek, Naga Chalasani, Srinivasa Sanasar, Anne M Diehl, Khalid Hameed, Kris V Kowdley, Arthur McCullough, Noreh Terrault, Jeanne M Clark, James Tonascia, Elizabeth M Brunt, David E Kleiner, Edward Doo, for the NASH Clinical Research Network*

Summary

Background The bile acid derivative 6-ethylchenodeoxycholic acid (obeticholic acid) is a potent activator of the farnesoid X nuclear receptor that reduces liver fat and fibrosis in animal models of fatty liver disease. We assessed the efficacy of obeticholic acid in adult patients with non-alcoholic steatohepatitis.

Methods We did a multicentre, double-blind, placebo-controlled, parallel group, randomised clinical trial at medical centres in the USA in patients with non-cirrhotic, non-alcoholic steatohepatitis to assess treatment with obeticholic acid given orally (25 mg daily) or placebo for 72 weeks. Patients were randomly assigned 1:1 using a computer-generated, centrally administered procedure, stratified by clinical centre and diabetes status. The primary outcome measure was improvement in centrally scored liver histology defined as a decrease in non-alcoholic fatty liver disease activity score by at least 2 points without worsening of fibrosis from baseline to the end of treatment. A planned interim analysis of change in alanine aminotransferase at 24 weeks undertaken before end-of-treatment (72 weeks) biopsy supported the decision to continue the trial (relative change in alanine aminotransferase −24%, 95% CI −45 to −3). A planned interim analysis of the primary outcome showed improved efficacy of obeticholic acid (p=0.0024) and supported a decision not to do end-of-treatment biopsies and end treatment early in 64 patients, but to continue the trial to obtain the 24-week post-treatment measures. Analyses were done by intention-to-treat. This trial was registered with ClinicalTrials.gov, number NCT01265498.

Findings Between March 16, 2011, and Dec 3, 2012, 141 patients were randomly assigned to receive obeticholic acid and 142 to placebo. 50 (45%) of 110 patients in the obeticholic acid group who were meant to have biopsies at baseline and 72 weeks had improved liver histology compared with 23 (21%) of 109 patients in the placebo group (relative risk 1.9, 95% CI 1.3 to 2.8; p=0.0002). 33 (23%) of 141 patients in the obeticholic acid developed pruritus compared with nine (6%) in the placebo group.

Although FLINT Met its Primary Endpoint, there Was No Resolution of NASH, and Some Potentially Troubling Safety and Tolerability Signals

The good news:

- 45% in the OCA arm had an improvement in disease (i.e. ≥2 point decrease in NAS with no worsening of fibrosis) compared to 21% in the placebo arm.
- Fibrosis was improved in 35% of the OCA arm and 19% of the placebo.

<table>
<thead>
<tr>
<th></th>
<th>Obeticholic acid</th>
<th>Placebo</th>
<th>Relative risks or mean changes from baseline* (95% CI)</th>
<th><em>p value</em></th>
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<tbody>
<tr>
<td>Primary outcome†</td>
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</tr>
<tr>
<td>Number of patients at risk</td>
<td>110</td>
<td>108</td>
<td></td>
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</tr>
<tr>
<td>Patients with improvement</td>
<td>50 (45%)</td>
<td>22 (21%)</td>
<td>1.0 (0.9 to 1.2)</td>
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Although FLINT Met its Primary Endpoint, there Was No Resolution of NASH, and Some Potentially Troubling Safety and Tolerability Signals

The bad news:
- There was no significant difference in resolution of NASH between the OCA and placebo groups.
- There were clear signs that the OCA arm suffered an increase in LDL.
- About one in four in the OCA arm suffered from pruritis, including three cases which were deemed severe or life threatening.

Although FLINT Met its Primary Endpoint, there Was No Resolution of NASH, and Some Potentially Troubling Safety and Tolerability Signals

**UPDATED: Intercept shares tank as investigators question OCA's safety/efficacy for NASH**

November 7, 2014 | By John Carroll

After crunching the data on Intercept’s ($ICPT) clinical study of OCA for non-alcoholic steatohepatitis, investigators say they tracked some distinct improvements for patients suffering from the liver disease. But they also fretted about some troubling safety issues as well as inadequate efficacy endpoints that will have to be carefully considered in follow-up studies, tempering some of the high excitement that has been stoked by some analysts and the biotech's investors ahead of a pivotal Phase III study.

That's not what investors wanted to hear. Intercept's shares slid 30% by the end of the day on Friday--a $74 plunge--as fresh doubts prompted a big sell off.

Here's a look at the data:
In December of 2014, the AASLD and the FDA Published Guidance from a Joint Workshop Focused on Clinical Development of Drugs for NASH

According to the FDA/AASLD guidance “the reversal of steatohepatitis with no evidence of progression to advanced fibrosis (stage 3 or 4), may be an acceptable surrogate endpoint suitable both for phase 2b and 3 trials that enroll patients with NASH and evidence of early fibrosis.”
On January 6, Gilead announced that it will pay Phenex Pharmaceuticals up to $470M for access to its FXR program for NASH.

Gilead buys its way into the blockbuster NASH race with $470M deal

January 6, 2015 | By Damian Garde

Gilead Sciences ($GILD) has shouldered its way into one of the industry’s hottest fields, agreeing to pay as much as $470 million to get its hands on potential treatments for nonalcoholic steatohepatitis (NASH).

Under a deal with German biotech Phenex Pharmaceuticals, Gilead is getting a handful of small-molecule drugs designed to block the build up of bile at the heart of many common liver diseases, agreeing to hand over an undisclosed up-front sum and down-the-road milestone payments. The most promising asset, Px-104, is in Phase II development to treat NASH, a liver-scarring disease that affects as many as 20% of people in the developed world but has no approved therapies.

Each of Phenex’s candidates works by activating the body’s farnesoid X receptors (FXRs), which regulate bile and lipids in the liver. Targeting FXR can help prevent the accumulation of fat and occurrence of inflammation, according to the company, preventing the fibrosis that marks NASH and the related nonalcoholic fatty liver disease (NAFLD).
On January 29th, Intercept Announced that OCA Received “Breakthrough Therapy Designation” for NASH Patients with Liver Fibrosis

Intercept Pharma soars after nabbing 'breakthrough' title for blockbuster NASH contender

January 29, 2015 | By John Carroll

Intercept Pharmaceuticals (ICPT) has nabbed the FDA’s breakthrough therapy designation (BTD) for obeticholic acid (OCA), a closely watched therapy in the pipeline for a blockbuster NASH indication.

The biotech says the BTD win was based on data from a pair of midstage studies of OCA, which persuaded some analysts to tap it as a major new therapy in the clinic for a rapidly growing population of patients suffering from liver disease. While no guarantee of success, the agency has been handing out BTDS as a hall pass for companies looking for quick access and feedback from the agency. In this case, the company says a breakthrough designation should help grease the tracks for the late-stage program.

The biotech's shares were up a whopping 38% this morning, the latest twist in the stock's wild roller coaster ride.
On February 23, Merck Announced it Will Pay NGM Biopharmaceuticals Up to $450M to Collaborate on Pipeline Product Development

Merck bets big on NGM with a $450M handshake
February 23, 2015 | By Damian Garde

Taking a page from famed partners like Sanofi ($SNY) and Regeneron ($REGN) and Roche and Genentech, Merck ($MRK) has signed a sweeping R&D deal with biotech NGM Biopharmaceuticals, promising up to $450 million for 5 years of pipeline-building collaboration.

Under the agreement, **Merck will pay NGM $94 million up front and trade $106 million for a 15% stake in the company.** In exchange, the pharma giant gets the chance to collaborate on NGM's wide range of preclinical biologics, committing up to $250 million to bankroll development.

The collaboration's only thus-far disclosed asset is NP201, a preclinical candidate with potential in obesity, diabetes and nonalcoholic steatohepatitis (NASH), NGM said. Beyond that, the biotech has hinted at a pipeline of potential treatments for other cardiometabolic diseases, cancer, central nervous system disorders and kidney ailments, otherwise keeping details under wraps. NGM's lead asset, the Phase II NASH treatment NGM282, is not part of the Merck deal and remains wholly owned by the biotech.
The NASH Ecosystem Certainly Looks Ready for More Big deals, but Important Questions Remain to be Answered

♦ Which primary endpoint(s) is the FDA most likely to accept for regulatory approval of new treatments for NASH?

♦ What will a label indication for NASH look like?

♦ How will clinicians determine which NASH patients to treat?

♦ When will non-invasive tools for diagnosing NASH and monitoring response to treatment become more widely used in the clinic?

♦ What criteria will payers use to determine which NASH patients are eligible for treatment?

♦ What issues/barriers/obstacles to developing drugs for NASH remain?
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Dr. Brent A. Tetri is the director of the division of gastrointestinal and hepatology and a specialist in liver diseases. A professor of internal medicine, he has been a member of the faculty at Saint Louis University School of Medicine since 1991. Dr. Tetri has been recognized for his expertise in non-alcoholic steatohepatitis (NASH). His outpatient clinical practice focuses on the diagnosis of liver disease and the management of all aspects of liver disease including cirrhosis and associated complications. Dr. Tetri’s clinical research involves treatment trials for NASH and studies to understand the causes of NASH. He also conducts basic laboratory research with an emphasis on understanding how dietary trans-fats damage the liver.

Dr. Tetri often speaks at educational and scientific meetings – nationally and internationally – to promote a better understanding of liver diseases such as NASH, and consults with industry experts to design and interpret clinical trials in liver disease. He is an active member of the American Association for the Study of Liver Diseases (AASLD), and has served on the Practice Guidelines committee of the AASLD to promote evidence-based practices in the care of patients with liver disease.

Dr. Tetri has published over 100 papers with one of his most recent being the Lancet paper published in December of 2014, which reported the full results of the FLINT study of obeticholic acid conducted by the NASH clinical research network.
David J. Lomb, PhD, Senior Consultant, Defined Health

♦ As a Senior Consultant with Defined Health, David participates in and leads opportunity assessments as well as indication prioritization/sequencing, search, and strategy projects. David regularly contributes to projects in the oncology, dermatology, CNS, and autoimmune and inflammatory disease spaces. In addition, David leads most projects involving the fibrosis therapeutic area at Defined Health.

♦ Prior to joining Defined Health in 2010, David was a postdoctoral fellow in the Paul F. Glenn Laboratories for the Biological Mechanisms of Aging at Harvard Medical School. As a scientist at Harvard, David studied a family of enzymes known as sirtuins which have been implicated in the regulation of aging and age-related diseases. Also while at Harvard, David was a fellow in the Early Technology Assessment Program sponsored by the Office of Technology Development. In this position, David was responsible for performing initial commercial assessments of discoveries made by Harvard faculty members.

♦ David earned a PhD in Pharmacology from the University of Rochester, in Rochester, New York, where his thesis work focused on the molecular mechanisms of neuronal programmed cell death. David has also earned Bachelor of Science degrees in both Biochemical Pharmacology and Psychology from the University at Buffalo, in Buffalo, New York. David has published in peer reviewed scientific journals and has presented his work at national scientific meetings.
Defined Health is Pleased to Present:

26th Annual Cancer Progress Conference
March 17 – 18, 2015
New York City
www.cancerprogressbyDH.com

BioEurope Spring
March 9 – 11, 2015
Paris, France
www.therapeuticinsight.com

Defined Health will also be participating in the following industry events:

Cancer Progress by Defined Health
March 17 – 18, 2015 | New York City | http://www.cancerprogressbyDH.com

Therapeutic Insight by Defined Health at BIO-Europe Spring®


