Outlook For NASH Therapy & Market Dynamics

Presentation by:
Hannah Cohen, Datamonitor Healthcare & Joseph Haas, Informa Pharma Intelligence
31 October, 2019
## Agenda

<table>
<thead>
<tr>
<th>Section</th>
<th>Topics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction</td>
<td></td>
</tr>
<tr>
<td>NASH background</td>
<td>• NASH definition&lt;br&gt;• Epidemiology&lt;br&gt;• Clinical trial landscape&lt;br&gt;• FDA approvable endpoints</td>
</tr>
<tr>
<td>Research &amp; development</td>
<td>• Unmet needs&lt;br&gt;• Timeline of approvals&lt;br&gt;• Pipeline landscape</td>
</tr>
<tr>
<td>Business development</td>
<td>• NASH business development&lt;br&gt;• Our expectations, predictions&lt;br&gt;• Gilead, Pfizer, Novartis, others</td>
</tr>
<tr>
<td>Pricing strategies</td>
<td>• Uncertainties in the market&lt;br&gt;• Manufacturer pricing strategies&lt;br&gt;• Payer responses</td>
</tr>
<tr>
<td>Second-To-Market &amp; Combination Strategies</td>
<td>• Who will follow Intercept?&lt;br&gt;• Evolving standard of care</td>
</tr>
<tr>
<td>Conclusions and Q&amp;A</td>
<td></td>
</tr>
</tbody>
</table>
What Is NASH & What's Being Done To Address It?
Non-alcoholic steatohepatitis (NASH)

Definition

- Progressive form of non-alcoholic fatty liver disease (NAFLD)
- NASH is the presence of ≥5% hepatic steatosis and inflammation with hepatocyte injury, with or without fibrosis
- Presence of fibrosis not required for diagnosis, though fibrosis is present in over 80% of NASH patients
- Multifactorial pathogenesis of NASH:
  - Hepatic steatosis
  - Inflammation
  - Fibrosis

Source: Datamonitor Healthcare, 2019
NASH Epidemiology

Diagnosed prevalence projected to grow significantly in the US

In 2018 there were 26.2m diagnosed prevalent cases of NASH in the US, Japan, and five major EU markets

Increase by 12.6% to 29.5m cases by 2038, due to increase in US cases

Increase in prevalence due to:
- Western diet
- Sedentary lifestyle
- Metabolic syndrome: obesity, type II diabetes, dyslipidemia, hypertension

Source: Datamonitor Healthcare
Unmet Needs in NASH

Increasing prevalence creates significant need for treatment

1. No disease-specific approved therapy for NASH

2. Alternate reliable diagnostic tool to liver biopsy
   - No reliable way to predict the magnitude of risk of disease progression
   - Genfit developing NIS4 in-vitro diagnostic tool

3. Clinical trials in F4 cirrhosis patients

“Many companies are appropriately scared off by the fact that cirrhosis is viewed as irreversible, there are examples where the patient’s cirrhosis can reverse, but usually it takes five years or longer, at least in the hepatitis B and hepatitis C experience”

- US Key Opinion Leader

Source: Datamonitor Healthcare
Non-alcoholic Fatty Liver Disease (NAFLD) Clinical Trial Landscape

Interest in NAFLD has spiked since 2014

434
Number of Trials

103
Number of Ongoing Trials

287
Number of Drugs

123
Number of Companies

Source: Trialtrove
FDA approvable endpoints for noncirrhotic NASH

Slow progression of NASH creates need for surrogate endpoints

1. **Resolution of steatohepatitis** on overall histopathological reading and no worsening of liver fibrosis on NASH CRN fibrosis score. Resolution of steatohepatitis is defined as absent fatty liver disease or isolated or simple steatosis without steatohepatitis and a NAS score of 0–1 for inflammation, 0 for ballooning, and any value for steatosis.

2. **Improvement in liver fibrosis** greater than or equal to one stage (NASH CRN fibrosis score) and no worsening of steatohepatitis (defined as no increase in NAS for ballooning, inflammation, or steatosis).

3. **Both resolution of steatohepatitis and improvement in fibrosis** (as defined above).

Source:
FDA draft guidance, 2018; Pink Sheet
NASH Pipeline

Diverse pipeline, numerous players

- 65 candidates in clinical development
- 53 companies, six with multiple candidates
- 5 in Phase III
- Gilead no longer lists selonsertib as a NASH candidate, although it reported Phase III data
- 40 candidates in Phase II
- 20 candidates in Phase I or Phase I/II

Source: Biomedtracker
An Overview Of NASH R&D
NASH Research and Development

Phase III pipeline and timeline to approval

- **Ocaliva** (Intercept) - Farnesoid x receptor agonist
- **Elafibranor** (Genfit) - Peroxisome proliferator-activated receptor alpha/delta agonist
- **Cenicriviroc** (Allergen) - Chemokine receptor 2/5 antagonist
- **Resmetirom** (Madrigal Pharmaceuticals) - Thyroid hormone receptor agonist
- **Aramchol** (Galmed) - Stearoyl-coA desaturase 1 (scd1) inhibitor

Source: Datamonitor Healthcare
Intercept's Ocaliva (obeticholic acid/OCA)

Will Ocaliva’s efficacy profile outweigh the safety risks?

Fibrosis Improvement by ≥1 Stage with No Worsening of NASH

*Primary Endpoint: ITT Population, N=931*

- Placebo (n=311): 11.9%
- OCA 10 mg (n=312): 17.6%
- OCA 25 mg (n=308): 23.1%

NASH Resolution with No Worsening of Fibrosis

*Additional Primary Endpoint: ITT Population, N=931*

- Placebo (n=311): 8.0%
- OCA 10 mg (n=312): 11.2%
- OCA 25 mg (n=308): 11.7%

Source: Intercept, 2019
 Intercept’s Ocaliva (obeticholic acid/OCA)

Ocaliva’s safety concerns will not likely impact approval

- Dose-dependent increase in pruritis
- 9% of patients in 25mg Ocaliva arm discontinued due to pruritis
- Potential for CV events due to elevated LDL-cholesterol
- Phase III REVERSE trial in F4 patients, with enrolment completion in Q4 2019
- Potential combination with pan-PPAR agonist bezafibrate

![Changes in Lipid Parameters Over Time](image)

*Safety Population: N=1968*

Source: [EASL, 2019; Datamonitor Healthcare](#)
Genfit's elafibranor

Elafibranor’s strong safety and tolerability profile will likely make it a commercially attractive choice

- Failed to meet protocol-defined primary outcome of NASH resolution with no worsening fibrosis
- Met primary endpoint with modified definition in post-hoc analysis
- Greater response rate with more advanced fibrosis patients (F2/F3)
- Phase III RESOLVE-IT results in Q4 2019
- Launch of combination therapy clinical program

Response rates of all patients according to protocol-defined and modified definitions

<table>
<thead>
<tr>
<th>NAFLD Activity Score (NAS)</th>
<th>n</th>
<th>Placebo (%)</th>
<th>Elafibranor 80mg (%)</th>
<th>Elafibranor 120mg (%)</th>
<th>P value (Elafibranor 120mg vs placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protocol-defined primary endpoint</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>274</td>
<td>17</td>
<td>23</td>
<td>21</td>
<td>0.280</td>
</tr>
<tr>
<td>NAS ≥4</td>
<td>234</td>
<td>11</td>
<td>20</td>
<td>20</td>
<td>0.018</td>
</tr>
<tr>
<td>Modified definition of response</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>274</td>
<td>12</td>
<td>13</td>
<td>19</td>
<td>0.045</td>
</tr>
<tr>
<td>NAS ≥4</td>
<td>234</td>
<td>9</td>
<td>13</td>
<td>19</td>
<td>0.013</td>
</tr>
</tbody>
</table>

Source: Ratziu et al., 2016; Datamonitor Healthcare
Allergan's cenicriviroc (CVC)
Poor efficacy results cast doubt over success in Phase III trial

- Failed to meet primary endpoint of a two-point improvement in NAS with no worsening fibrosis
- Failed to show reduction in fibrosis with no worsening NASH after two years of treatment
- Pooled results show greatest impact in F3 patients
- Ongoing Phase III AURORA study in F2/F3 patients
- Opportunity to combine cenicriviroc with Novartis’s FXR agonist, tropifexor

"The relatively low proportion of efficacy may limit this as a monotherapy drug, the Phase III trial will help answer what that magnitude will be, I do not expect to see higher results in Phase III than in Phase II"
- US Key Opinion Leader

Source: Friedman et al., 2018; Datamonitor Healthcare
Madrigal’s resmetirom (MGL-3196)

Strong efficacy and safety data could overcome resmetirom’s late entry to market

- Strong decrease in hepatic fat (-36.3%) compared to baseline (9.6%) at week 12

- 77% resmetirom-treated patients showed ≥30% reduction in liver fat (MRI-PDFF responder) at week 36

- Favorable rates of NASH resolution, 39% in MRI-PDFF responders

- Robust safety profile with positive effects on LDL-cholesterol

- Initiated Phase III MAESTRO-NASH trial in biopsy-confirmed F2/F3 patients

"The molecular problem is to demonstrate that it is a full and exclusive agonist of the beta subtype of the receptor THR, because otherwise there will be too many effects, especially cardiovascular“

- US Key Opinion Leader

Source: The International Liver Congress, 2019; Datamonitor Healthcare
Galmed's Aramchol (arachidyl amido cholanoic acid)

Aramchol’s inconsistent results are concerning

Mean absolute change from baseline in liver fat

Placebo (N=41)  Aramchol 400 (N=90)  Aramchol 600 (N=83)

Aramchol 400 vs. Pbo  p=0.0450
Aramchol 600 vs. Pbo  p=0.0655

≥5% reduction in absolute change from baseline in liver fat

Aramchol 600 vs. Pbo  p=0.0279
OR 2.77 (95% CI: 1.12-6.89)

Source: AASLD, 2018
NASH Business Development
NASH Business Development
Active deal-making space; pace should increase

• Currently 53 companies with candidates in clinical development

• 21 deals recorded by Strategic Transactions since January 2015

• Won’t drive major M&A but could lead to some larger-scale acquisitions: *Unsure how much weight NASH carries in AbbVie/Allergan merger*

### Deals:

<table>
<thead>
<tr>
<th>License/Option Transactions</th>
<th>M&amp;A Deals:</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>Gilead/Nimbus Apollo 2016</td>
<td>Allergan/Akarna 2016</td>
</tr>
<tr>
<td></td>
<td>Allergan/Tobira 2016</td>
</tr>
<tr>
<td></td>
<td>Genentech/Jecure 2018</td>
</tr>
<tr>
<td></td>
<td>Altimmune/Spitfire 2019</td>
</tr>
<tr>
<td>5 trial collaborations, 1 technology pact</td>
<td>5 M&amp;A deals:</td>
</tr>
<tr>
<td></td>
<td>Gilead/Nimbus Apollo 2016 $400m</td>
</tr>
<tr>
<td></td>
<td>Allergan/Akarna 2016 $50m</td>
</tr>
<tr>
<td></td>
<td>Allergan/Tobira 2016 $534m</td>
</tr>
<tr>
<td></td>
<td>Genentech/Jecure 2018 (undisclosed)</td>
</tr>
<tr>
<td></td>
<td>Altimmune/Spitfire 2019 $5m</td>
</tr>
</tbody>
</table>

Source: Strategic Transactions, Scrip
Gilead

Looking to replicate HCV success

• Has been a frequent deal-maker in the NASH space: One buyout – Nimbus Apollo; two licenses; one trial collaboration; one biomarker partnership

• May look for a strategic M&A to try to replicate its hepatitis C success with Pharmasset: Viking or Madrigal could offer a complementary MOA

• For Pharmasset, paid $11bn for essentially a single Phase II asset, yet yielded substantial return for Gilead, sofosbuvir catalyzed its dominance in the space

• NASH likely to too diverse in terms of disease pathology, patient base to repeat that success

Source: Strategic Transactions, Scrip
Pfizer and Novartis

Big pharmas combine their strengths

- Have pursued multi-candidate, multi-MOA strategies apart and together

- Novartis’ boondoggle with Conatus & emricasan: Pharma paid $50m up front in 2016 for option to pan-caspase inhibitor; shelved June 2019

- The two pharmas signed trial collaboration late in 2018: Effort combines tropifexor with three Pfizer fat-reducing MOAs

- Could be hugely influential if they come up with a strong combo comprising just their candidates

Source: Scrip
Crowded Field Adds AbbVie

Boehringer Ingelheim ramping up R&D

- AbbVie now in thru merger with Allergan: viability of CVC is questionable, although AbbVie brings added liver expertise with its HCV success

- Boehringer Ingelheim, license deal with Yuhan, doing internal combo work

- To date, Intercept and Genfit, the clear R&D leaders, largely have gone it alone

- Genfit is partnered with LabCorp on its NIS4 diagnostic, licensed Chinese rights to elafibranor to Terns in both NASH and PBC

- Intercept not partnered with anyone

Source: Scrip
Pricing Strategies For NASH: Multiple Uncertainties To Consider
Pricing Strategies

The future of the NASH market is uncertain

• Debate over suitable and sustainable pricing strategy that satisfies every party involved

• Lack of an approved therapy creates ambiguity over what the market will be able to bear

• “Budget-busting” drugs face usage restrictions to limit impact on payer budgets

• Manufacturers should learn from market access challenges experienced by PCSK9 inhibitors

“PCSK9s were highly restricted when they came out, the prior authorization criteria were well beyond the label, and I think that is a challenge, if you can avoid that it will be much better for the manufacturers, and the manufacturers of PCSK9 learned the hard way and reduced their prices, but it would be smart for the NASH manufacturers to start off lower, and use those lessons.”

- US payer

Source:
Datamonitor Healthcare, 2019
Pricing Strategies

Payers discretion to determine value of NASH therapy

• No marketed analogs available to act as price benchmarks

• Limited epidemiology data due to unreliable diagnostic tools

• No formal report on NASH’s economic burden on healthcare systems

• Uncertainty over clinical relevance of surrogate endpoints

“We are going to have to understand what those surrogate endpoints mean, and how that affects outcomes. So, what is that going to mean for a downstream cost? What are we achieving by improving those surrogate markers?”

-US payer

Source: Datamonitor Healthcare, 2019
Pricing Strategies

Manufacturers likely to strive for premium price

- Two pricing options for manufacturers
  1. Conservative - wider patient population
  2. Aggressive - restricted patient population

- Regulatory bodies likely to restrict approval to F2/F3 patients

- F4 patients – high priority, low attraction as difficult-to-treat

- F1 patients – low priority, compliance issue as often asymptomatic, with multiple comorbidities

Source: Datamonitor Healthcare, 2019
## Pricing Strategies

Manufacturers will likely to strive for premium price

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Payer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fulfilling an unmet need</td>
<td>No clinical outcomes data</td>
</tr>
<tr>
<td>Long-term cost savings through prevention of hepatic outcomes</td>
<td>Timeframe of disease progression unclear</td>
</tr>
<tr>
<td></td>
<td>Chronic medication</td>
</tr>
<tr>
<td></td>
<td>Large market size</td>
</tr>
</tbody>
</table>

### Potential pricing hurdles

Payers will likely restrict access if dealing with premium prices. Reimbursement hurdles may include:

- Prior authorization forms
- Biopsy-confirmed NASH patients requiring documented proof
- F4 patients kept off formulary
- Pay-per-performance plan
- Placed on the speciality tier
- High financial burden for patients

Source: [Datamonitor Healthcare, 2019](#)
Who Will Follow Intercept?
Combo Therapy Expected
Ultimately
Who Will Follow Intercept?

After Genfit, many possibilities

- **Genfit** likely second to market, field unclear after that
- No clear third place, given the clinical trial stumbles of Gilead, Allergan/Tobira, Conatus/Novartis
- **Madrigal** was fifth to enter Phase III, just underway, data 2H21
- **Galmed** followed into Phase III in September
- **Galectin** filed a Phase III protocol with FDA in August

Source: Scrip
Second-To-Market, Followers Should Have Solid Opportunity

**Efficacy/Safety Improvement Sought Immediately**

- With size of patient base, multi-factorial disease, likelihood of chronic rather than curative therapy, NASH should offer treatment niches for several MOAs, therapies, companies
- Intercept expects to have anti-fibrotic market to itself for two years or more; Genfit will have a NASH-resolution claim.
- Both drugs thought to offer modest benefit, so market will seek efficacy advances. Intercept's tolerability profile also may be limiting - pruritus, raised LDL
- Intercept and Genfit could end up being like Vertex and Merck & Co. with Incivek, Victrelis for HCV; quick launches; equally fast decline
- Vertex launched 2011; blockbuster 2012; out of HCV by 2014
Others To Watch

Madrigal, Viking

- **Madrigal** also will initiate Phase III study in NAFLD patients w dyslipidemia, diabetics, w endpoint of lowering LDL
- **Madrigal** and its direct competitor in THR agonism Viking could be M&A targets. Viking does not anticipate Phase IIb date for VK2809 until 2021
- Cirrhotic patients likely an important treatment niche; Intercept already targeting for a potential sNDA with REVERSE trial of Ocaliva; data in 2021
- Too many players in mid-stage development to get a clear handle on who’s next into Phase III, showing particular development
- **Inventiva, Cirius, NGM** may be ones to watch as they near Phase IIb data readouts; **Novartis and Gilead** also
Standard Of Care Eventually Combos

SOC Evolution May Mimic HCV, HIV Therapy

• Expected to mimic the evolution of the HIV and HCV spaces
• Gilead, Pfizer, Novartis, Boehringer among the companies pursuing combo strategies; in-house or with partners
• Intercept hopes Ocaliva will be a backbone therapy, is considering studying combo with PPAR bezafibrate, GLP1, THR beta agonists, FGF21. "like metformin for diabetes"
• Genfit also wants to be backbone, will explore combo of elafibranor with GLP1, SGLT2 classes
• Novartis/Pfizer collaboration looks into teaming former’s FXR agonist with latter’s ACC, DGAT2, KHK inhibitors
• Yuhan and BI partnered on dual GLP1/FGF21 candidate

Source: Scrip
Conclusions and Q&A
Concluding thoughts

Huge untapped potential, however, aggressive pricing could hamper commercial prospects

The lack of an approved therapy creates a significant unmet need
• Large market size, high clinical and economic cost increase the need for NASH therapy
• Complicated pathophysiology of NASH disease progression has contributed to multiple trial failures

The NASH space continues to evolve
• Ocaliva will dominate the market as the first-approved therapy for NASH, but be more of a starting point
• NASH will likely mirror the constant change seen in HCV between 2011 and 2016

Business development will also evolve
• Novartis seems especially committed to deal-making and may begin pushing toward the front of the pack; the Swiss firm seems focused on developing a standard-of-care combo regimen

Pricing strategies will determine ease of market access
• Companies will initially strive for premium pricing
• High pricing will result in strong reimbursement criteria, which will limit patient access

Source: Datamonitor Healthcare
Questions?

Pharma@informa.com