Updates in Hepatology

Focus on Nonalcoholic Steatohepatitis (NASH)

NASH has intense pipeline activity with ~120 assets in development, including 8 assets in Phase III and 1 asset in Pre-registration. While new assets continue to be added to the pipeline, most assets have thus far demonstrated modest efficacy and drug development continues to be challenging. Multiple failures have been reported over the past 6 months.

Steatosis, inflammation, cellular damage, and fibrosis manifest over time as cirrhosis and eventually liver failure in NASH patients. With no approved therapies, liver transplantation remains the only curative treatment option for NASH. Co-morbidities such as metabolic syndrome (obesity, dyslipidemia, and type 2 diabetes mellitus) can hasten the worsening of NASH outcomes. NASH drug development is challenging due to disease heterogeneity, limited understanding of disease pathophysiology, and multiple disease pathways at work.

Given the complex pathophysiology of NASH, diverse pathways including metabolism (glucose, fat, cholesterol), inflammation, and fibrosis are being targeted by therapies in development. Engagement of multiple targets simultaneously could increase the likelihood of success. Monotherapies (FXR agonists, FGF21 agonists, THR-β agonists, PPAR agonists etc.) or combination therapies (Semaglutide + Firsocostat + Cilofexor; Lanifibranor + Empagliflozin; Tropifexor + Licogliflozin etc.) that tackle multiple pathways are aimed at addressing the complex nature of NASH.

Obetcholic acid/FXR agonist/Intercept Pharma/Pre-registration:

In response to the FDA CRL, efficacy and safety data from the ongoing REGENERATE Phase III study will be used to support resubmission.
The goal of the company is to have a pre-submission meeting with the FDA by the first half of 2022.

TERN-101/ FXR agonist/Terns Pharma/Phase II:

In a Phase IIa study, TERN-101 10 mg demonstrated significant reduction in cT1 at week 12 in patients with presumed NASH

- % patients with reduction in cT1 from baseline at week 12: 36.8% (p<0.05)
- Mean change in cT1 at week 12 (msec): –57.7 (p=0.002)

Resmetirom/THR-β agonist/Madrigal Pharma/Phase III:

In the Phase III open label part of MAESTRO-NAFLD1, resmetirom demonstrated significant efficacy on key secondary endpoints including reduction from baseline in hepatic fat, liver volume, low-density lipoproteins (LDL), and atherogenic lipids at week 52

- Reduction in MRI-PDFF at week 52: –53% (p<0.0001)
- Reduction in LV at week 52: –23% (1.0%) (p<0.0001)

LPCN-1144/Testosterone receptor agonist/Lipocine/Phase II:

In a Phase II study, LPCN 1144 + d-alpha tocopherol, significantly reduced hepatic fat, resolved NASH with no worsening of fibrosis and improved liver injury markers

- Mean absolute decrease in hepatic fat at week 12: 9.4% (p<0.05)
- % patients with NASH resolution and no worsening of fibrosis: 69% (p< 0.001)

Vonafexor/FXR agonist/Envyo Pharma/Phase II:

In the Phase II LIVIFY study, vonafexor 100 mg, demonstrated significant reduction in absolute liver fat content (LFC)vs. placebo

- % patients with >5% absolute (LFC) reduction at week 12: 57% (p<0.05 vs. placebo)
- % patients with >30% absolute (LFC) reduction at week 12: 50% (p<0.05 vs. placebo)

NASH: Trial Failures/Discontinuations in 2H 2021

- **CC-90001 (JNK 1 inhibitor)/Celgene:**
  Phase II study terminated due to strategic business decisions and CC-90001 is not being developed for NASH
- **Cenicriviroc (Dual CCR2/CCR5 inhibitor) + Tropifexor (FXR agonist)/Novartis:**
  Phase II study failed to meet its endpoints, and the combination asset is no longer in development for NASH
- **LY-3478045/Eli Lilly:**
  According to Eli Lilly current pipeline, LY-3478045 is no longer in development for NASH

Aldafermin/FGF 19 analog/ NGM Biopharma:

- Aldafermin failed to meet its primary endpoint – Response rate by MCP-MOD (fibrosis improvement of ≥1 stage with no worsening of NASH) in the Phase IIb ALPINE2/3 study
- The development of aldafermin has been discontinued in NASH fibrosis F2/F3; however, the ALPINE 4 study is ongoing for NASH fibrosis F4

Pegbelfermin/FGF 21 agonist/BMS:

The Phase IIb FALCON1 study failed to meet its primary endpoint:

- Fibrosis improvement without worsening of NASH or NASH improvement without fibrosis worsening in NASH liver fibrosis F3

The Phase IIb FALCON2 study failed to meet its primary endpoint:

- Fibrosis improvement without worsening of NASH in NASH with compensated liver cirrhosis

Combination Therapies

Multiple combination approaches are in development in view of the complex pathophysiology of NASH and involvement of multiple disease pathways including fibrosis and inflammation:

- Danuglipron (PF-06882961) (GLP-1R Agonist) + Ervogastat (DGAT2 Inhibitor)/Phase I/Pfizer
- Semaglutide (GLP-1 analogue) + Firsocostat (ACC inhibitor) + Cilofexor (FXR agonist)/Phase II/(Novo Nordisk/ Gilead Sciences)
- Lanifibranor (pan-PPAR agonist) + Empagliflozin (SGLT2 inhibitor)/Phase II/(Inventiva)
- Tropifexor (FXR agonist) + Licogliflozin (SGLT1/2 inhibitor)/Phase II/Novartis
- Clesacostat (ACC inhibitor) + Ervogastat (DGAT2 Inhibitor)/Phase II/Pfizer
- NNC0174-0833 (Amylin receptor agonist) + Semaglutide (GLP-1 agonist)/Phase II/Novo Nordisk
- LYS006 (LTA4 hydrolase inhibitor) + Tropifexor (FXR agonist)/Phase II/Novartis

However, some combinations including Cenicriviroc (Dual CCR2/CCR5 inhibitor) + Tropifexor (FXR agonist)/Phase II and Selonsertib (ASK1 inhibitor) + Firsocostat (ACC inhibitor) + Cilofexor (FXR agonist)/Phase II have failed in clinical trials, so the combination approach is not without its own challenges. The potential efficacy benefit of combinations may be tempered by the risk of safety issues that may be associated with combination therapies.

Key questions that remain unanswered

Which monotherapies or combination therapies will be successful for the treatment of NASH?

Which disease pathways modulation in the liver (inflammation vs. fat deposition vs. fibrosis) will improve the likelihood of success?

Which combinations are likely to have maximal impact on the improvement in disease outcomes in NASH?

Sources: 1. ClinicalTrials.gov 2. Company Websites

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