SMARTANALYST®
an Ashfield Advisory Company

Updates in Hepatology

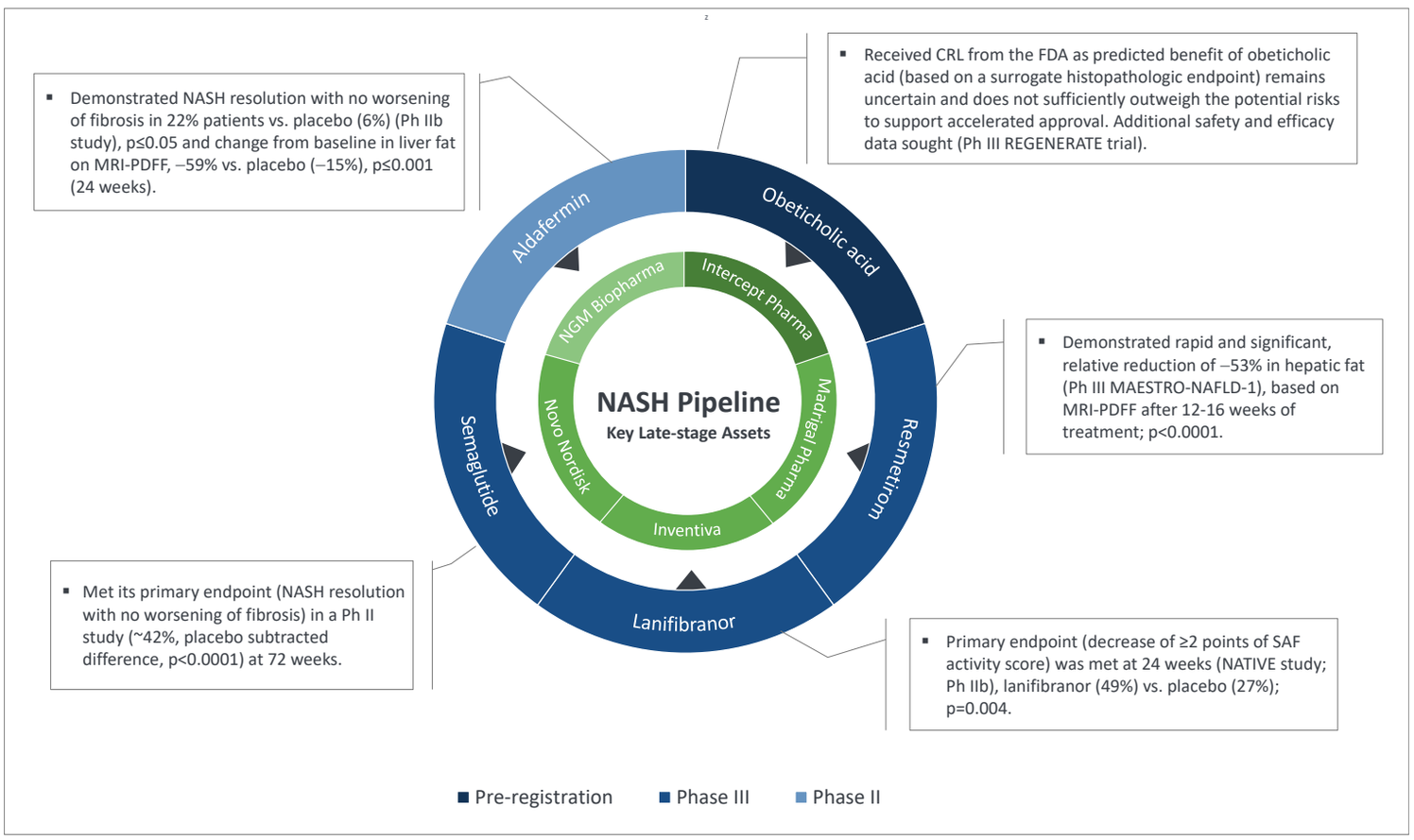
Focus on Nonalcoholic Steatohepatitis (NASH)

NASH has intense pipeline activity with more than 100 assets in development, including 10 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, in both early as well as in late-phase clinical trials, have been reported over the past year.

NASH is an indication with high unmet need since underlying steatosis, inflammation, cellular damage, and fibrosis manifest as cirrhosis and liver failure. There are no approved therapies and liver transplantation remains the only curative treatment option for NASH. Metabolic syndrome, including 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.

Therapies targeting metabolism (glucose, fat, cholesterol), inflammation, and fibrosis hold promise in NASH. Engagement of multiple targets simultaneously could increase the likelihood of success. Monotherapies such as FXR agonists, PPAR agonists, FGFR agonists, or combination therapies such as Semaglutide + Firsocostat + Cilofexor; Cenicriviroc + Tropifexor; Tropifexor + Licogliflozin etc. that tackle multiple pathways are aimed at addressing the complex nature of NASH. Given its ability to improve fibrosis, obeticholic acid (OCA), if approved, is likely to see use in clinical practice, but concerns regarding its long-term safety are likely to influence prescribing decisions. Resmetirom is another promising therapy to watch due to its ability to significantly reduce hepatic fat and fibrosis.

Key late-stage assets

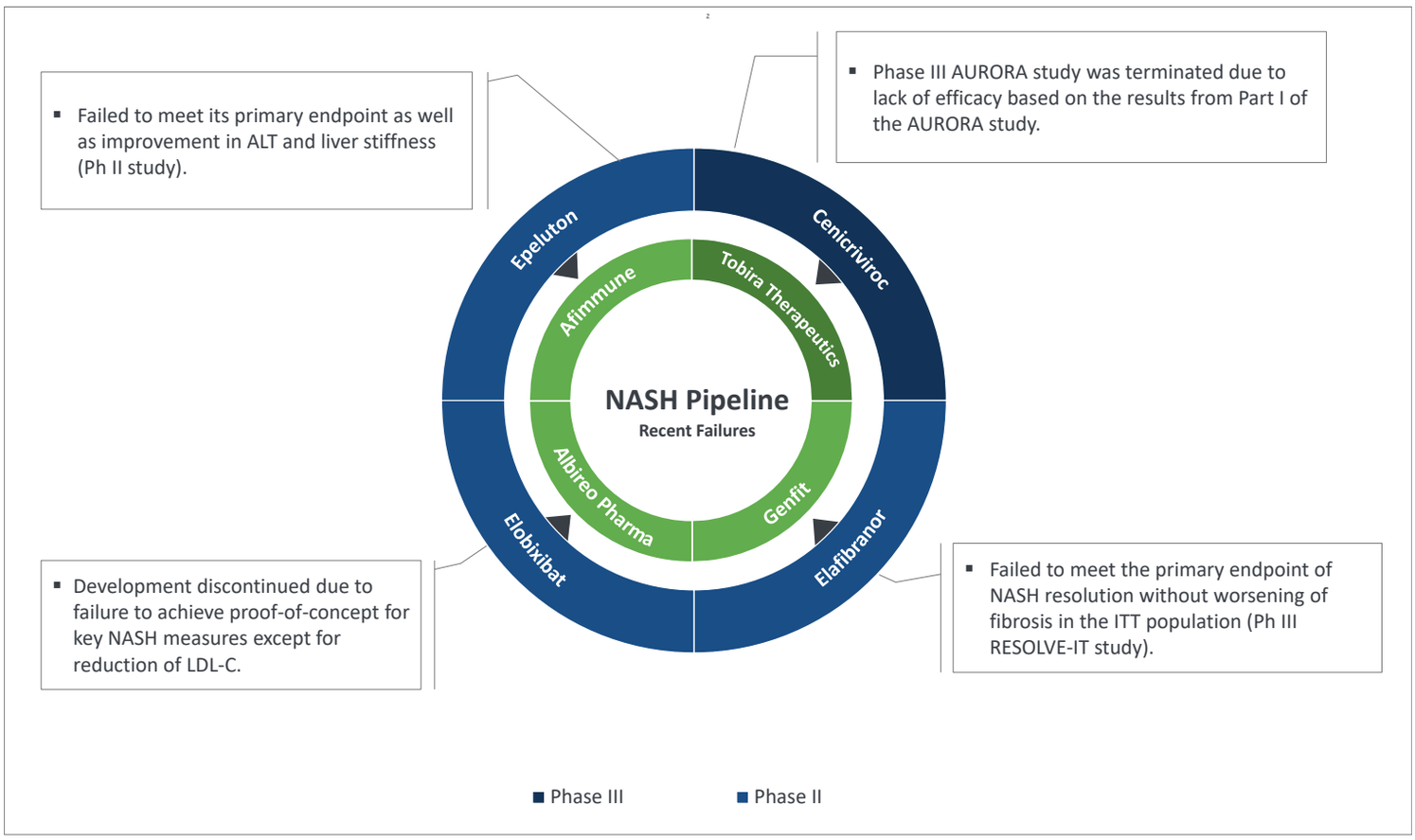


Combination approaches

Addressing the inflammation and fibrosis of NASH has been challenging. Given the encouraging efficacy signals demonstrated by semaglutide - GLP 1R agonist and resmetirom - Thyroid hormone receptor agonist in NASH, combinations are an emerging trend and multiple trials including Semaglutide + Firsocostat + Cilofexor; Cenicriviroc + Tropifexor; Tropifexor + Licogliflozin etc. are underway.

- Combinations, in comparison to monotherapies, may produce greater efficacy or benefit a greater proportion of patients.
  - ➢ However, the combinations are likely to be used as second-line treatment options in patients not responding to monotherapies, to minimize safety issues that may be associated with combination therapies.

NASH: Multiple failures in the past year



Key questions that remain to be answered:

1. Which treatment strategies are going to emerge successful?
2. What are the key asset combinations that could increase the likelihood of success?
3. What is the acceptable extent of trade-off between efficacy and safety of therapies to achieve significant reduction in liver fat and fibrosis?

Sources: 1. ClinicalTrials.gov; 2. Company Websites

Please contact:
John.L'Ecuyer@smartanalyst.com

GLOBAL HEADQUARTERS
(New York, USA)
285 Madison Ave
22nd Floor, New York
NY 10017
Mobile: +1 (646) 852-5097

EUROPE
(London, UK)
1.04 Power Road Studios
114 Power Road, Chiswick
London W3 5PY
Mobile.: +44-(0)-752-163-8242
Mobile.: +44-(0)-772-574-4296

ASIA PACIFIC
(Gurgaon, INDIA)
First Floor, DLF Plaza Tower
DLF Qutub Enclave, DLF City
Phase-I, Gurgaon 122002
Haryana, India
Tel.: 91-124-4313800