

Partner Content

Bile acid modulators in discovery: Identifying cholestasis candidates with the best chance of success

Unmet needs are high in cholestatic liver disease, where bile acid modulators show real potential. With smart DMPK strategies, cross-domain collaboration, and strong CDMO support, companies are pushing past the challenges of discovery biology.

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Disrupted bile flow, or cholestasis, is a key feature of various chronic liver diseases such as primary biliary cholangitis (PBC) and primary sclerosing

primary cholangitis (PBC) and primary sclerosing cholangitis (PSC). As bile accumulates in the liver and backs up into the bloodstream, progressive liver damage, fibrosis, and inflammation occurs. The disease often advances slowly but, if untreated, may progress to liver failure.

The prognosis of patients with liver failure is poor since no treatment options are available beyond transplantation, meaning early diagnosis and therapeutic interventions are pivotal. Cholestatic liver disease treatment options are severely limited, however, with an absence of truly disease-modifying drugs and very limited approved treatments for paediatric patients.

According to GlobalData's Drugs Intelligence platform, there are currently 54 drugs in active development for PBC and PSC, the majority of which are small molecules. Targeted bile acid receptor modulators have emerged as a promising method of suppressing bile acid synthesis and reabsorption in the liver and ileum. Certain bile acid modulators are advancing in the pipeline, with key candidates nearing or broadening approval, while several novel modulators are in the early stages of discovery and preclinical.

Bile acid modulator challenges in discovery

Early in drug development, companies developing bile acid modulators face challenges driven by the biological complexity of bile acids, which function not only as toxic metabolites but also as essential signalling molecules in the metabolic system and gut microbiome. Many candidate drugs closely mimic bile acid structures, creating formulation difficulties.

These compounds tend to have poor solubility, while distribution and exposure can be hard to predict and control due to reabsorption and enterohepatic recycling. In addition, bile acid receptors are expressed across the intestine, gallbladder, and immune system, increasing the risk of off-target effects such as diarrhoea.

These challenges mean that, despite their therapeutic potential in cholestatic liver diseases, bile acid modulators are at risk of failure because the chemistry is intrinsically difficult to optimise into a reliable, safe medicine. Careful candidate selection therefore depends on robust DMPK and ADME profiling to identify molecules with the highest likelihood of success.

Discovery biology in action

Case study: Identifying the best candidate

Syngene's world-class team of scientists drives cost-effective, reproducible and high-quality data that helps reduce compound failure, identify those with optimal safety profiles, and minimise drug-drug interactions in later stages. In one example, Syngene partnered with a biopharmaceutical company that needed to evaluate two bile acid modulators for treating orphan paediatric liver diseases and other liver and gastrointestinal disorders.

To understand the candidate with the superior pharmacokinetics and pharmacodynamics (PK/PD) profile, a 7-day repeat-dose PK study in mice was essential. The study design included three

experimental groups – for Compound A, Compound B, and the control – each consisting of five mice. Three independent teams within Syngene's Discovery Biology division collaborated on the data. Firstly, the DMPK *in vivo* team administered the diet, collected samples, and computed the PK parameters. Then, the bioanalytical team quantified the test compound exposure in plasma and assessed serum C4 levels (a bile acid precursor). Finally, the *in vivo* pharmacology team evaluated total bile acid concentrations and conducted gene expression analyses for CYP7A1 and FGF-15.

The results revealed that total bile acid levels and serum C4 levels were consistent or similar across all groups, showing that both compounds play a role in bile acid modulation. However, data for Compound B showed significantly higher systemic exposure, indicating better therapeutic potential. The comprehensive data generated by Syngene's teams gave the client the confidence to advance Compound B into the next stage of development, and the case study stands as a great example of Syngene's ability to integrate three distinct domains (PK, PD, and molecular expression) into a cohesive study, providing comprehensive insights that informed the client's development decisions.

Case study: Developing a novel molecule

In another example, a mid-sized biotech collaborated with Syngene to identify a novel candidate for cholestatic liver disease. The company sought to prevent the reabsorption of bile acid through inhibition of apical sodium-dependent bile acid transporter (ASBT) and sodium/taurocholate co-

transporter (ABT), and sodium taurocholate co-transporting polypeptide (NTCP) targets found in the ileum and liver respectively. Inhibition of these targets leads to decreased bile acid absorption and, subsequently, higher elimination through faeces.

Using a ligand-based design approach, Syngene's medicinal chemistry team developed several lead analogues, conducting extensive studies to understand the structure-activity relationship and how the ADME profile could be improved. Analogues were screened through various cell-based activity, ADME profiling, and PK/PD studies measuring various biomarkers in animal models. At the end of the work, a lead compound was successfully selected with single digit nanomolar potency and an excellent *in vitro* PK profile with improved bioavailability. The first-in-class bile acid modulator has now progressed to preclinical development.

DMPK is a significant opportunity in discovery, with insights and optimisation helping teams identify the molecule with the right balance of efficacy, exposure, and safety. But DMPK can also be a source of key challenges and roadblocks, from PK-based drug-drug interactions to CNS exposure. To learn more about DMPK strategies and challenges, please download the whitepaper below.

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