## Product Discovery & Development

# Dainippon intercepts bile acids

**By Tim Fulmer**
**Senior Writer**

By acquiring Asian rights to **Intercept Pharmaceuticals Inc.**'s FXR agonist, **Dainippon Sumitomo Pharma Co. Ltd.** hopes to expand its reach in the liver diseases space to include two new indications with large unmet need: fatty liver disease and primary biliary cirrhosis.

Bile acids are synthesized in the liver and stored in the gallbladder. They act as biological solubilizers that enhance the body's absorption of dietary lipids and fat-soluble nutrients in the intestine.

Beginning in the 1990s, a second role for bile acids emerged: signaling molecules with functions similar to hormones. In that role, bile acids bind their receptors in tissues such as the liver, intestine and kidney to regulate multiple cellular pathways, including bile homeostasis, lipid and glucose metabolism, and inflammation.

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>
> **Mark Pruzanski, Intercept Pharmaceuticals**

Intercept was founded in 2002 to exploit the signaling function of bile acids. Thus far, the company has singled out two bile acid receptors as potential therapeutic targets in liver and metabolic diseases: farnesoid X receptor (FXR; NR1H4) and G protein-coupled bile acid receptor 1 (TGR5; GPBAR1).

The company's lead program, an FXR agonist called obeticholic acid (OCA, formerly INT-747), is in Phase II testing for primary biliary cirrhosis (PBC) and Phase II/III testing for non-alcoholic steatohepatitis (NASH). The latter study is being run by the **National Institute of Diabetes and Digestive Kidney Diseases**.

In March, OCA met the primary endpoint of lowering alkaline phosphatase levels in the Phase II PBC trial. Alkaline is a marker of disease progression and high levels correlate with risk of liver transplant and death.

"By activating FXR in the liver, OCA has multiple therapeutic effects," Intercept President and CEO Mark Pruzanski told BioCentury. "OCA reduces accumulation of bile acids in the liver, which is a key therapeutic benefit in primary biliary cirrhosis and other cholestatic liver diseases where excess buildup of bile acids causes liver damage that can eventually lead to cirrhosis."

Pruzanski noted OCA also lowers production of cholesterol and triglycerides in the liver, which can be beneficial in treating fatty liver diseases such as NASH and non-alcoholic fatty liver disease (NAFLD).

"But it is probably the anti-fibrotic mechanism that OCA triggers through FXR that is the most important basis for its promise as a hepatoprotective drug," he said. "The potential is there for OCA to prevent or even reverse fibrosis – or scarring – in the liver that eventually leads to cirrhosis and organ failure in any chronic liver disease."

OCA's ability to target multiple disease mechanisms attracted the attention of Dainippon, which last month received exclusive rights in Japan and China to develop and commercialize OCA for chronic liver diseases.

Intercept received $15 million up front and is eligible for up to $300 million in milestones plus royalties. Dainippon has an option to add other Asian countries and other indications to the deal.

The pharma markets two drugs to treat liver-related diseases: Sumiferon interferon-alpha to treat HCV and Miripla miriplatin to treat hepatocellular carcinoma (HCC).

Katsumi Tanaka, manager of the licensing group in Dainippon's business development office, said the pharma plans to begin Phase I Japanese trials of OCA in PBC and NASH this year.

"There is a high unmet medical need in Asia for both diseases," he said.

The one approved drug for PBC is Urso ursodiol, a bile acid derivative from **Axcan Pharma Inc.** However, according to Pruzanski, up to 50% of PBC patients show an inadequate response to the drug and are thus at risk of disease progression. There are no approved drugs for NASH.

Meanwhile, Intercept is in discussions with **FDA** on the design of the Phase III program for use of OCA in PBC, having already reached a consensus on trial design with **EMA**.

"Our plan in Phase III will be to study OCA as an add-on therapy to Urso in patients with an inadequate response and known to be at significant risk of progressing to cirrhosis," Pruzanski said.

Intercept also plan to start a clinical trial of OCA to treat portal hypertension.

"Portal hypertension — high blood pressure in the liver's portal vein — is the main cause of morbidity and mortality in all advanced chronic liver diseases," said Pruzanski. "We have preclinical evidence that our compound can reduce portal pressure acutely and independent of the anti-fibrotic effects we see later on in treatment. We therefore plan to start a Phase II proof-of-concept trial to study OCA in this indication."

He declined to disclose when the trial is expected to begin.

Intercept's next most advanced compound is INT-777, a cholic acid-based agonist of TGR5 in preclinical development for Type II diabetes. In 2009 Intercept published in *Cell Metabolism* that the compound prevented weight gain in mice on a high fat diet, as well as reduced steatosis, fibrosis and serum markers of liver damage.

### COMPANIES AND INSTITUTIONS MENTIONED

**Axcan Pharma Inc.** (TSX:AXP; NASDAQ:AXCA), Mont-Saint-Hilaire, Quebec
**Intercept Pharmaceuticals Inc.**, New York, N.Y.
**Dainippon Sumitomo Pharma Co. Ltd.** (Tokyo:4506; Osaka:4506), Osaka, Japan
**European Medicines Agency** (EMA), London, U.K.
**National Institute of Diabetes and Digestive Kidney Diseases** (NIDDK), Bethesda, Md.
**U.S. Food and Drug Administration** (FDA), Bethesda, Md.