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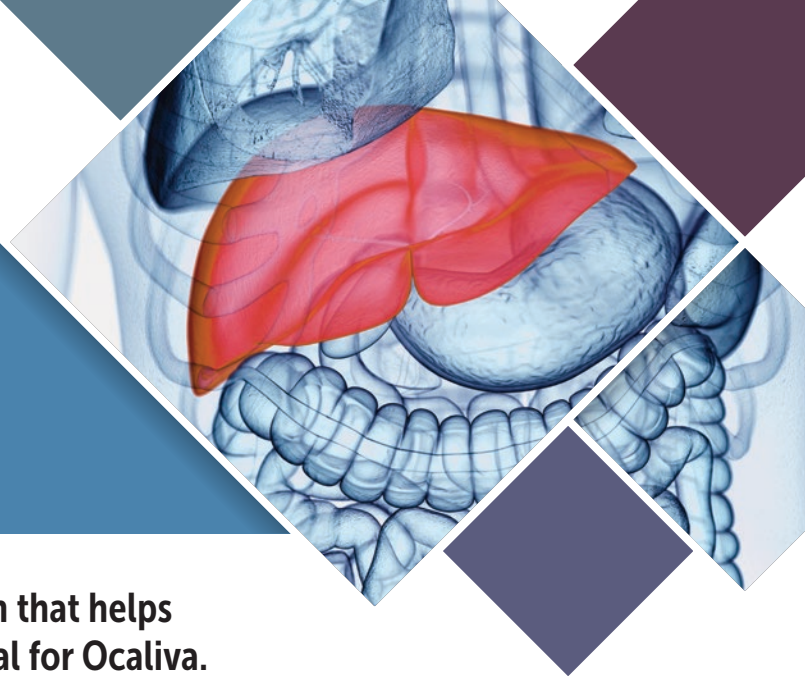


Pharmacokinetic Modeling Supports the Approval of a Rare Liver Disease Treatment

Certara scientists deliver an integrated solution that helps Intercept Pharmaceuticals achieve FDA approval for Ocaliva.

Background

Primary biliary cholangitis (PBC) is a chronic, rare disease characterized by cholestasis—the impaired flow of bile from the liver.[1] The resulting increased bile acid concentrations cause cellular injury. Untreated PBC can lead to liver failure and death. The only currently approved treatment for PBC was ursodeoxycholic acid (UDCA). However, not all patients respond to UDCA.

Intercept Pharmaceuticals—an emerging global biopharmaceutical company—sought to develop obeticholic acid (OCA) as an alternative treatment for PBC. OCA is a semi-synthetic analogue of the primary bile acid chenodeoxycholic acid with similar pharmacokinetic (PK) properties.[2] Like other bile salts, OCA is metabolized via conjugation to glycine acid and taurine.

OCA is a selective and potent farnesoid X receptor (FXR) agonist.[2] FXR activation decreases the concentration of bile acids in the liver to reduce cellular injury. FGF-19 was used as a biomarker for OCA pharmacological activity.

Challenge

Because liver damage is a consequence of disease progression in PBC patients, the Intercept team needed to develop a dosing strategy for OCA in PBC patients with and without hepatic impairment. They conducted a small clinical study wherein a single dose of OCA was given to healthy volunteers and patients with mild, moderate, and severe hepatic impairment and intensive PK sampling was performed for 24 hours.[2]

Study results revealed that systemic OCA concentrations increased with worsening hepatic impairment.[2] Yet, plasma FGF-19 levels were increased with the administration of OCA for subjects with and without hepatic impairment suggesting similar activation of FXR. Clearly, systemic exposure of OCA failed to correspond to its pharmacological effects in the liver. Developing a robust dosing strategy required understanding the relationship between systemic and hepatic exposure of OCA in patients with and without hepatic impairment.

Challenge

Intercept Pharmaceuticals needed to develop a dosing strategy for obeticholic acid (OCA) to treat patients with primary biliary cholangitis (PBC).

Solution

Certara scientists used Phoenix NLME to build a physiologic PK model to define the relationship between systemic and hepatic exposure of OCA in PBC patients with and without liver impairment.

Benefit

Modeling results demonstrated the safety and efficacy of the OCA dosing regimen in PBC patients with and without cirrhosis.

Solution

Certara consulting scientists used their population PK/PD modeling software, Phoenix NLME, to perform mechanistic modeling and simulations.[1,2] That model was based on a previously reported model for chenodeoxycholic acid.[3] The model for OCA was calibrated using the plasma concentration-time profiles of OCA, glyco-OCA and tauro-OCA in healthy volunteers who received a single dose of OCA. Then, the model was recalibrated for patients with hepatic impairment taking a single dose of OCA. Hepatic impairment involves the following mechanisms which were incorporated into the model: decreased hepatic update of OCA and its metabolites, portal systemic shunting, decreased functional liver volume, and increased taurine conjugation.

Benefit

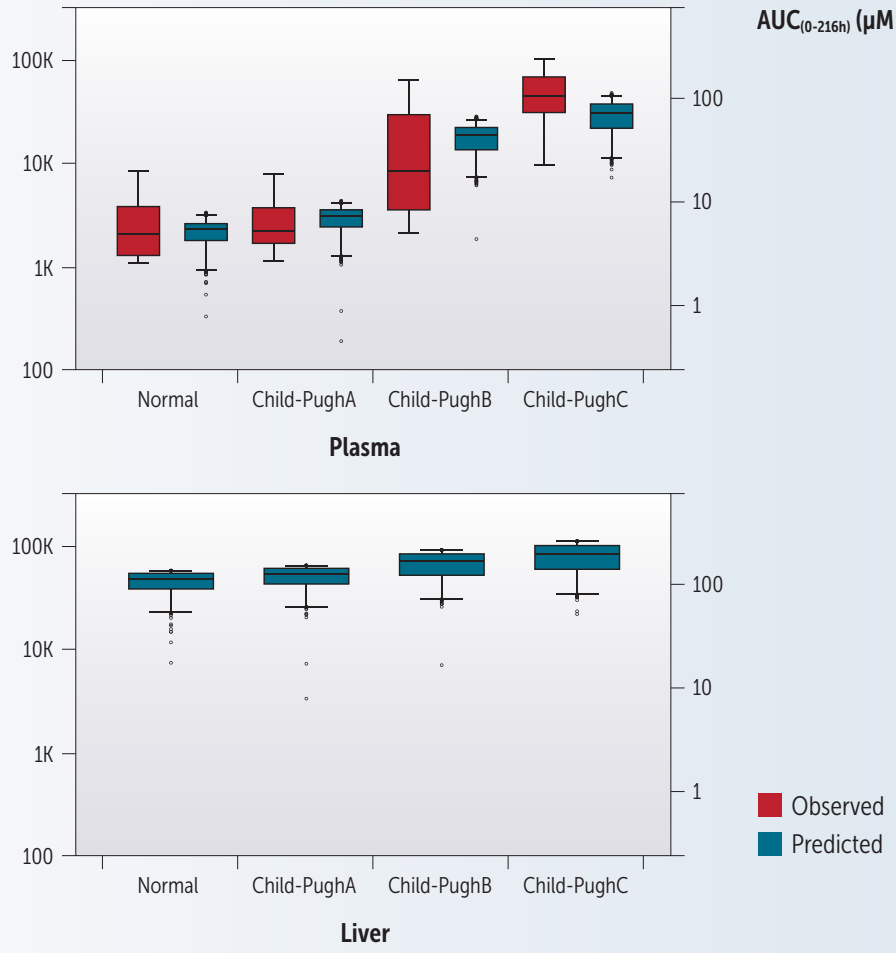
The physiologic PK model was validated when its predicted OCA-plasma exposures were found to be comparable to observed exposures in healthy volunteers and patients with hepatic impairment.[2] Both the model and clinical data showed a significant increase in systemic exposure of OCA in patients with hepatic impairment. Yet, liver exposure of OCA was predicted to only increase modestly in patients with mild, moderate, and severe hepatic impairment compared to healthy volunteers. The modeling results and clinical trial data supported the safety and efficacy of the OCA dosing strategy. Dosing reductions were only required for PBC patients with moderate and severe hepatic impairment.[1,4]

Impact

In May 2016, the FDA approved Ocaliva (obeticholic acid) for the treatment of PBC in combination with UDCA in adults who show inadequate response to UDCA alone or as a single therapy in adults who cannot tolerate UDCA.[5] It is the first new drug for PBC in almost 20 years.

Because of Ocaliva's potential to address an unmet medical need, the FDA granted it fast track designation.[5] Ocaliva also received orphan drug designation which entitles its sponsor to tax credits, user fee waivers, and market exclusivity rights. The case of Ocaliva demonstrates how sponsors can accelerate their drug approvals through pharmacometric modeling.

Plasma OCA Concentrations are a Poor Surrogate for Liver OCA Concentrations



n=8 for observed values. Predicted values were estimated using a 200 replicate simulation from the physiologic PK model of OCA (n=1600). Boxplot whiskers represent 1st to 99th percentile.

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