1. INTRODUCTION

Obetricolic acid (OCA) is a selective and potent farnesoid X receptor (FXR) agonist in development for several chronic liver diseases. OCA is a semi-synthetic analogue of chenodeoxycholic acid (CDCA) with similar pharmacokinetic (PK) properties. There was a significant increase in systemic exposure of OCA in patients with hepatic impairment. A proportionally similar increase in systemic exposure of endogenous bile acids was also observed in patients with hepatic impairment. A physiologic PK model was developed based on previously reported model for CDCA to define the relationship between systemic and hepatic exposure of OCA (and its pharmacologic active conjugates) in patients with and without hepatic impairment (cirrhosis).

2. METHODS

Figure 1. Study Design in Patients with Hepatic Impairment for Model Recalibration

3. RESULTS

Figure 2. Total OCA Concentrations Increase with Worsening Hepatic Impairment

Table 2. Pharmacokinetic Parameters

Table 3. Plasma Endogenous Bile Acids Increase with Worsening Hepatic Impairment

Figure 3. Plasma Endogenous Bile Acids Concentrations Increase with Worsening Hepatic Impairment

Figure 4. Plasma FGF-19 Concentration Consistent Regardless of Hepatic Impairment

Table 1. Demographic Summary for Model Development

Figure 5. Physiologic PK Model Diagram

Figure 6. Plasma OCA Concentrations are a Poor Surrogate for Liver OCA Concentrations

4. CONCLUSIONS

The physiologic PK model for OCA-predicted plasma exposures showed good agreement with observed exposures in healthy volunteers and patients with hepatic impairment. Systemic exposure of OCA was predicted to be 1.4, 8.0, and 13-fold greater in patients with mild, moderate, and severe hepatic impairment, based on Child-Pugh score, than in healthy patients which is consistent with observed results. Liver exposure of OCA was predicted to be ~2-fold greater in patients with end-stage liver disease relative to healthy patients.

5. REFERENCES


6. DISCLAIMER

Obetricolic acid (OCA) is an investigational drug. It is not approved for use by the FDA or any other regulatory body. No conclusions can be drawn concerning the safety or efficacy of OCA at this time.