PHARMACOKINETIC AND PHARMACODYNAMIC MODEL OF SYNTHETIC HUMAN HEPcidin LJPC-401 FOLLOWING SINGLE DOSE ADMINISTRATION IN DOGS

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Objectives: LJPC-401 is a synthetic human hepcidin drug product intended for the treatment of iron overload. A pharmacokinetic/pharmacodynamic (PK/PD) model was developed to describe serum concentrations of LJPC-401 and serum iron following a single escalating subcutaneous (SC) and intravenous (IV) dose administration in dogs.

Methods: LJPC-401 serum concentration (PK) and serum iron (PD) data were obtained from SC injection and IV infusion studies in dogs. A two-compartment model with first-order absorption and zero-order endogenous hepcidin production rate was applied to describe the PK data. An indirect response model with a precursor was selected to characterize the PD data. The precursor pool represents iron stores in macrophages, and the response is the serum iron concentration. LJPC-401 inhibits iron release from the precursor pool into the serum at the maximal inhibition \(I_{\text{max}}\) and potency \(I_{\text{50}}\). The PK and PD data were fitted simultaneously resulting in estimates of model parameters and their variances in the population.

Results: LJPC-401 exhibited linear kinetics with clearance = 256 mL/h/kg, volume of distribution = 178 mL/kg, and a half-life of ~ 2 h. The absorption rate of \(k_a = 0.15 \, \text{h}^{-1}\) for SC administration was slower than the elimination rate of \(k_{el} = 1.4 \, \text{h}^{-1}\) resulting in the flip-flop kinetics and the terminal half-life of 4.6 h. Bioavailability was 60%. Estimated endogenous hepcidin concentration was 3.1 ng/mL. Baseline serum iron was 162 µg/dL. Serum iron decreased in a dose-dependent manner with maximal ~88% decrease at ~ 5-8 h followed by a return to the baseline within 24-48 h. The \(I_{\text{50}}\) was determined as 8.0 ng/mL, implying a 25% inhibition of the iron release from the precursor pool at the baseline conditions.

Conclusions: This PKPD model developed from acute dose PKPD data in dogs can be used to design LJPC-401 repeat dose studies as well as the data analysis.

References: