Population PK and Exposure-Response Analyses of Icatibant in Pediatric Patients for the Treatment of Hereditary Angioedema

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Objectives: Icatibant is a synthetic decapeptide with a structure similar to bradykinin that acts as an antagonist of the bradykinin B2 receptor. Population PK and exposure-response analyses were performed to support dosing of icatibant in pediatric patients for the treatment of HAE.

Methods: Population PK modeling of icatibant was performed based on data collected in 172 subjects enrolled in four Phase I studies (healthy subjects), a Phase IIa study in adults with HAE, and a Phase III study in children and adolescents with HAE. Sources of variability (weight, age, sex, race, HAE attacks) were explored and tested using a full model approach (NONMEM V7). Exposure-response analysis of time of onset of symptom relief (TOSR) was performed (R® version 3.2.2).

Results: A 2-compartment model with first-order absorption and lag-time resulted in an adequate quality-of-fit. The population PK model included the effect of body weight on apparent clearance (CL/F) and volume of distribution (Vc/F). Typical CL/F and Vc/F were 15.4 L/h and 20.4 L, respectively. Maximum concentration in children (2-<12 years old) and adolescents with HAE (12-17 years old) following a single 0.4 mg/kg dose (capped to 30 mg) were similar (737 and 734 ng/mL, respectively) but approximately 34% lower than those derived in adults less than 75 kg (1116 ng/mL). The clinical relevance of the lower icatibant exposure in pediatric patients was evaluated in light of the exposure-response of TOSR. Patients with exposure in the lower tertiles displayed the slowest onset of symptom relief. Overall, median Time to Onset Symptom Relief (TOSR) was 1.0 h (95% CI 1.0-1.1) and all subjects displayed resolution of symptoms within 4 hours of icatibant administration.

Conclusions: The exposure to icatibant in children and adolescents was generally lower than that observed in adults. The lower exposure did not affect clinical response, based on the TOSR and complete symptom resolution within 4 hours of icatibant administration.