Population PK Analysis of C1 Esterase Inhibitor in Adult and Pediatric Patients for the Prevention and Treatment of Hereditary Angioedema Attacks

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Objectives: CINRYZE® (C1 esterase inhibitor [human]; C1INH) is a normal constituent of human blood and primarily regulates activation of the coagulation, contact, and complement pathways. Intravenous administration of 1000 units (U) of CINRYZE every 3-4 days is currently approved in the US and EU for routine prophylaxis of hereditary angioedema (HAE) and in the EU for treatment of HAE in adolescents and adults. A population PK analysis of C1INH was performed to support dosing recommendations in younger pediatric patients for the prevention and treatment of HAE.

Methods: Concentration-time data of functional C1INH from 8 clinical (prevention or treatment of HAE attacks) were included in the population PK analysis. Of the 278 patients included in the analysis, a total of 3, 32, and 26 subjects were in the 2-5, 6-11 and 12-17 years of age cohorts, respectively. Sources of variability (age, sex, race, baseline C1INH, indication, HAE attacks, and dose) were explored and formally tested using a full model approach (NONMEM Version VII).

Results: A one-compartment model with baseline C1INH resulted in adequate goodness-of-fit of functional C1INH. Typical clearance and volume of distribution (V) were 0.105 L/h and 3.13 L, respectively. Pediatric patients between 2-5 and 6-11 years of age are expected to have V values 1.38- and 1.22-fold higher than adults, respectively. Mean area under the curve up to 4 h (AUC₀-₄) and maximum concentrations (Cₘₐₓ) following dosing of 500 U every 3-4 days in patients 2-5 years of age were within 5% of adults treated with 1000 U. Mean AUC₀-₄ and Cₘₐₓ following dosing of 500 U in patients 6-11 years of age were within 20% of adults treated with 1000 U.

Conclusions: The exposure to C1INH following CINRYZE 500 U in patients 2-5 and 6-11 years of age every 3-4 days are expected to closely match those observed in adults treated with 1000 U.