Exposure-Response Analyses 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 highly purified, viral-inactivated, nanofiltered concentrate of C1 inhibitor (C1 INH) produced from human plasma. The objectives of this project were to perform exposure-response analyses to support dosing of intravenous Cinryze in pediatric patients for the prevention and treatment of HAE attacks.

Methods: Exposures to C1INH derived with a population PK model previously constructed were merged with the probability of preventing HAE attacks (whereby response was defined as ≤1.0 HAE attack/month) to ultimately assess exposure-response relationships (n=166). Logistic regressions for the probability of response and time-to-event modeling of the first HAE attack as a function of exposure was performed for the prevention of HAE. For subjects treated with Cinryze for an acute HAE attack, dose- and exposure-response relationships were explored. Exposure-response analyses (i.e., logistic regression and time-to-event) were performed using R® version 3.2.2.

Results: A positive relationship was observed between minimum concentrations (Cmin) of functional C1INH and the probability of preventing HAE attacks (p=0.0004). Typical Cmin values of 0.285, 0.425 and 0.955 U/mL (corresponding to 1st, 2nd, and 3rd tertiles, respectively) were associated to 85.5%, 86.8%, and 90.9% probabilities of preventing HAE attacks, respectively. Time to a 50% probability of HAE attack for the 1st, 2nd and 3rd tertiles of Cmin were 2.43, 9.79, and 15.7 weeks, respectively. For treatment of an acute attack, relief of defining symptoms within 4 h of dosing (1000 U) was observed in 95.2% of patients. No exposure-response relationship was observed. For patients who did not show improvement within 1 h of dosing, an additional dose (1000 U) resulted in symptom relief within 4 h in 84.2% of patients.

Conclusions: A 500 U dose of CINRYZE in patients 2-5 years of age and 1000 U dose in patients 6-11 years of age are expected to result in optimal prevention and treatment of HAE attacks.