A Population Pharmacokinetic Model and Exposure-Response Model of Repeated Time Event (RTTE) to Justify a Dose Increase in Patients with Sickle Cell Disease

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Synopsis
Simulations with a repeated time-to-event (RTTE) model, including a drug effect on the base hazard, showed IMR-687 could substantially reduce vaso-occlusive crises (VOCs) in subjects with sickle cell disease (SCD) when dosed above 200 mg, daily, for 24 weeks.

Objectives
- Develop a population PK model of IMR-687 in healthy subjects and patients with SCD.
- Use patients’ individual exposure metrics to drive efficacy and define a therapeutic dose range.
- Develop an exposure-response (ER) model of VOC events to justify use of a higher dose in future clinical trials.

Methods

Data & Covariates
The PK model was developed using data from Phase 1 and 2a studies. The analysis dataset included 112 subjects. Covariates included weight, age, gender, race, study, time, and baseline VOCs (i.e., number-v0, 1, 2, 3, 4). A one-compartment model with first-order absorption (Ka) and the following covariate effects: body weight on CL/F and V/F, and capsule formulation, capsule dose and a high-fat meal effect with capsule on absorption.

Model Development
The efficacy endpoint was the reduction of VOC events. VOC events were modeled with a parametric hazard model, where cumulative hazard was estimated at each observation [4] (RTTE). Dropout rate was not considered as part of the model structure. The PK-ER model was used to simulate doses higher than those tested in the Phase 2a study (100, 300, 400, and 600 mg once daily) (QD) for 24 weeks) to determine if greater efficacy could be achieved.

Simulations
For the virtual predictive checks (VPCs), 500 simulations were performed in NONMEM using estimates from the PK-ER model and a maximum time of 250 days. Data was summarized by dose cohort and plotted with the observed data. For the effect curve, 200 body weights were sampled with replacement, for each simulated dose cohort, from the analysis dataset. Average concentration (Cavg at 24 weeks) was calculated using area under the concentration-time curve (AUC) as: 

\[ C_{avg} = \frac{AUC}{24} \]

The final RTTE model was an exponential hazard model with a saturable (Michaelis-Menten) drug effect:

\[ h(t) = \lambda \cdot \text{EFFECT} = \left(1 - \frac{C_{avg}}{\text{Cmax}}\right) \]

Where \( h(t) \) is the hazard at time t, \( \lambda \) is the base hazard parameter, \( \text{EFFECT} \) is the exponential individual random effect, \( N \) (\( \text{Ka}, \text{Cmax} \)), and \( C_{avg} \) is concentration at time t. The RTTE model was a Weibull hazard function and the addition of hydroxyurea (HU) adjunct therapy on IMR-687 effect on the hazard, modeled as discrete, categorical covariates, was also attempted but did not improve the model fit. The model estimated the EC50 for IMR-687 as 574 ng/mL. (1.266 95% CI). This exposure represented the very high end of exposures seen in the Phase 2a study. The base hazard estimate was 0.511 (0.1440.849 95%CI).

PDg Inhibitors for Sickle Cell Disease

VOCs occur when vasodilatation is inhibited by aggregating sickle RBCs, occluding microcirculation, and other vascular events. IMR-687, a highly selective PDE9 inhibitor, prevents degradation of cGMP, reducing the risk of VOCs and other complications associated with SCD.

Results - Validation & Simulations

Higher simulated doses approached the estimated EC50, although there was a lot of overlap between the doses due to variability in the PK. The IMR-687 effect curve (i.e., the effect on base hazard for VOCs to the Cavg at 24 weeks) demonstrated that higher doses, greater than the 200 mg QD administered in the Phase 2a study, were likely to achieve greater reductions in VOC events (Figure 3).

VPCs indicate the model was able to closely predict the observed data for the first event. The predictions were not as good (higher variability and less evenly distributed around observed median) for the second event, due to there being considerably fewer observed second VOC events (Figure 2).

References

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