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

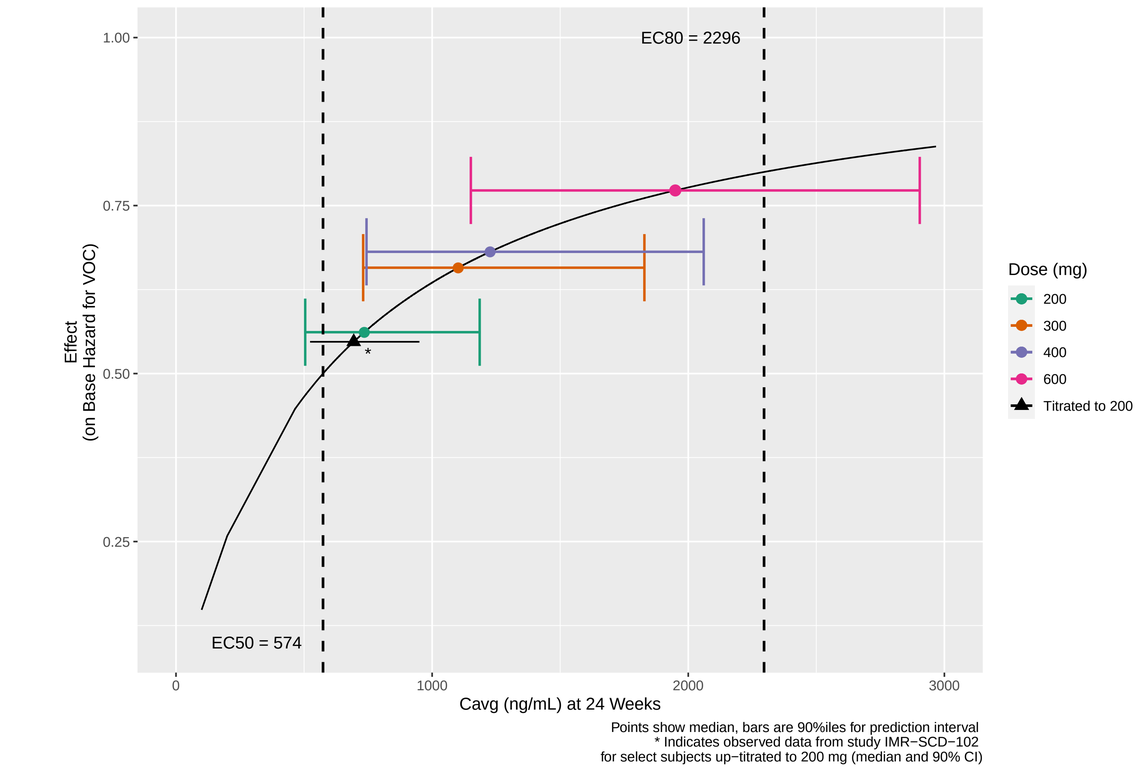

Figure 1: Concentration-effect curve for the hazard of VOC. EC50 = IMR-687 concentration that yields half of the maximum response. EC80 = IMR-687 concentration that yields 80% of the maximum response

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

Observed Data & Covariates

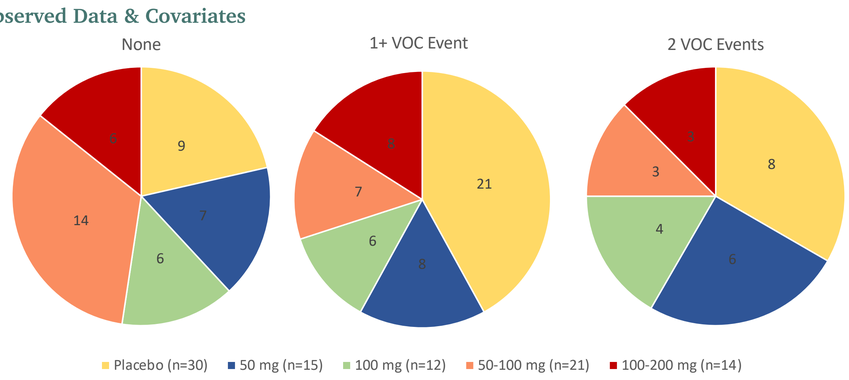

Figure 2: Pharmacodynamic (PD) dataset consisted of 92 subjects from the Phase 2a study

The PPK model was developed using data from Phase 1a and 2a studies. The analysis dataset included 112 subjects.

Covariates considered included weight, age, gender, disease state, dose, food status and formulation (tablet or capsule).

Model Development

The efficacy endpoint was the reduction of VOC events. VOC events were modeled with a parametric hazard model, where cumulative hazard was subtracted 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 (300, 400 and 600 mg once daily [QD] for 24 weeks) to determine if greater efficacy could be achieved.

Simulations

For the visual 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 of QD dosing at 200, 300, 400 and 600 mg was calculated using area under the concentration-time curve (AUC)/time and effect = Cavg /(EC50 + Cavg).

Results - PK-ER Model

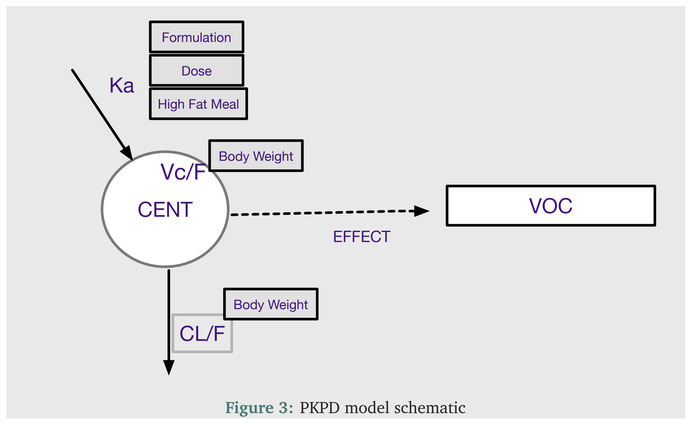

Figure 3: PKPD model schematic

The final population PK model was a one-compartment model with first-order absorption (Ka) and the following covariate effects: body weight on clearance (CL/F) and volume (V/F); and capsule formulation, capsule dose and a high-fat meal effect with capsule on absorption.

Parameter estimates were CL/F: 14.6 (13.8, 15.4 95% confidence intervals [CI]) L/h, V/F: 104 (98.8, 109) L, Ka: 4.90 (3.12, 7.70) 1/h, formulation effect: 0.239 (0.143, 0.401), dose effect: -0.602 (-0.908, -0.296), and high fat meal effect: 0.176, (0.121, .254). Random effect % coefficient of variations (CVs) were 22.3, 16.2 and 77.0% for CL/F, V/F, and Ka, respectively. Residual proportional error was 40.9% CV.

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

$$h(t) = \lambda \cdot^{\eta_i} \cdot EFFECT$$
$$EFFECT = (1 - (Cavg_t/(Cavg_t + EC50)))$$

Where $h(t)$ is the hazard at time t, λ is the base hazard parameter, η is the exponential individual random effect, N $(0,\omega^2)$, $Cavg_t$ is average drug concentration at time, t, and $EC50$ is concentration at half of the maximum effect of drug on hazard.
A RTTE model with a Weibull hazard function and the addition of hydroxyurea (HU; adjunct therapy) or IMR-687 effect on the hazard, modeled as discrete categorical covariates, were also attempted but did not improve the model fit. The model estimated the EC50 for IMR-687 as 574 ng/mL (0, 1266 95%CI). This exposure represented the very high end of exposures seen in the Phase 2a study. The base hazard estimate was 0.0311 (0.0140,0.0481 95%CI).

PDE9 Inhibitors for Sickle Cell Disease

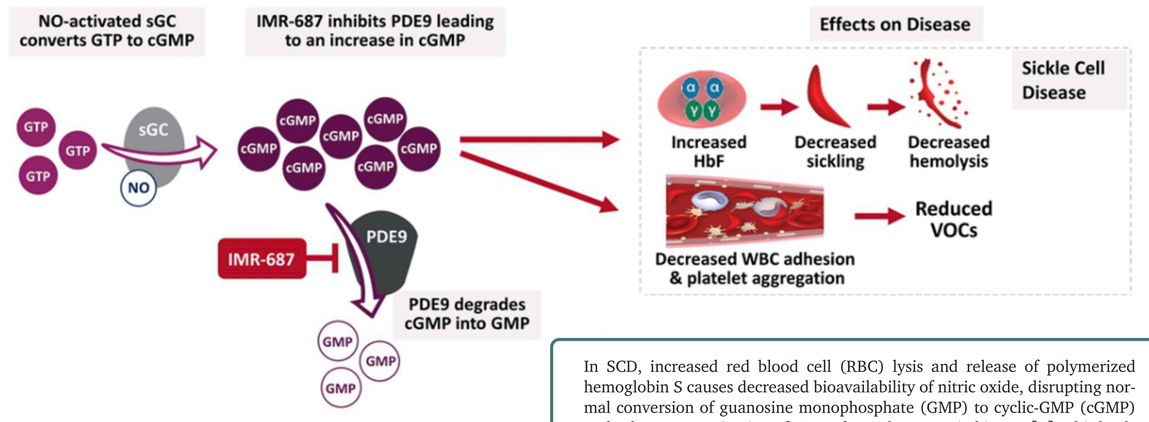

Figure 4: PDE9 inhibitor intervention in SCD pathology. Adapted from [1]

In SCD, increased red blood cell (RBC) lysis and release of polymerized hemoglobin S causes decreased bioavailability of nitric oxide, disrupting normal conversion of guanosine monophosphate (GMP) to cyclic-GMP (cGMP) and subsequent activation of cGMP-dependent protein kinases [2]. This leads to vasoconstriction, increased inflammation and greater cell adhesion.

A highly selective PDE9 inhibitor, IMR-687, prevents degradation of cGMP, leading to increased hemoglobin F and decreased white blood cell (WBC) and platelet aggregation, and decreased hemolysis and VOC events [1].

VOCs occur when vasodilation is inhibited and aggregates of sickled RBCs, activated WBCs, and other vascular elements, block blood vessels, causing downstream inflammation.

VOCs are painful, can occur multiple times per year, and are a leading cause of emergency room visits, hospitalization, and mortality.

Endothelial Cells - line interior surface of blood vessels; These adhere to RBCs and RBCs, become inflammed and recruit cytokines.
Platelets - express higher levels of adhesion factors and bind to RBCs, WBCs and endothelial cells.
WBCs - become activated and adhere to endothelial cell wall and drive downstream inflammation.

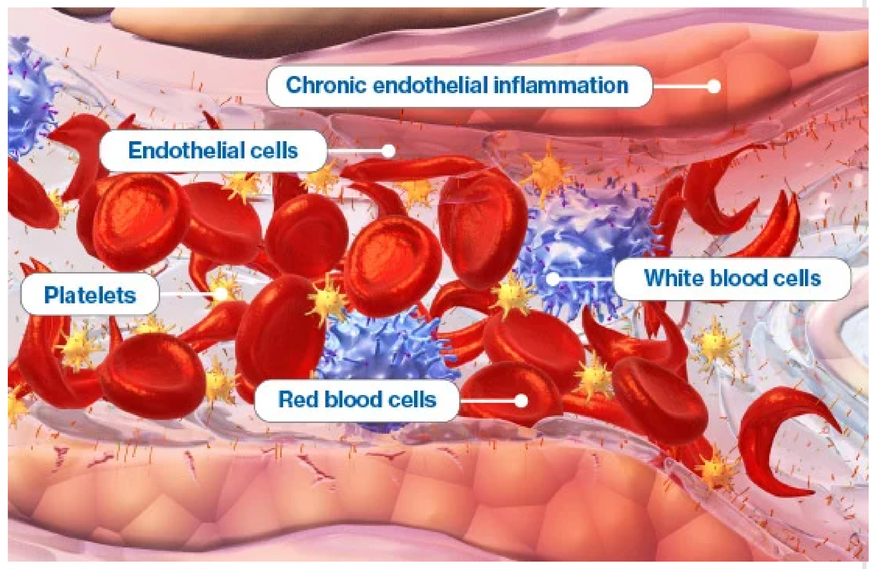

Figure 5: Pathology of VOCs. Adapted from [3]

Results - Validation & Simulations

Higher simulated doses approached the estimated EC80, 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 VOC vs 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 1).

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).

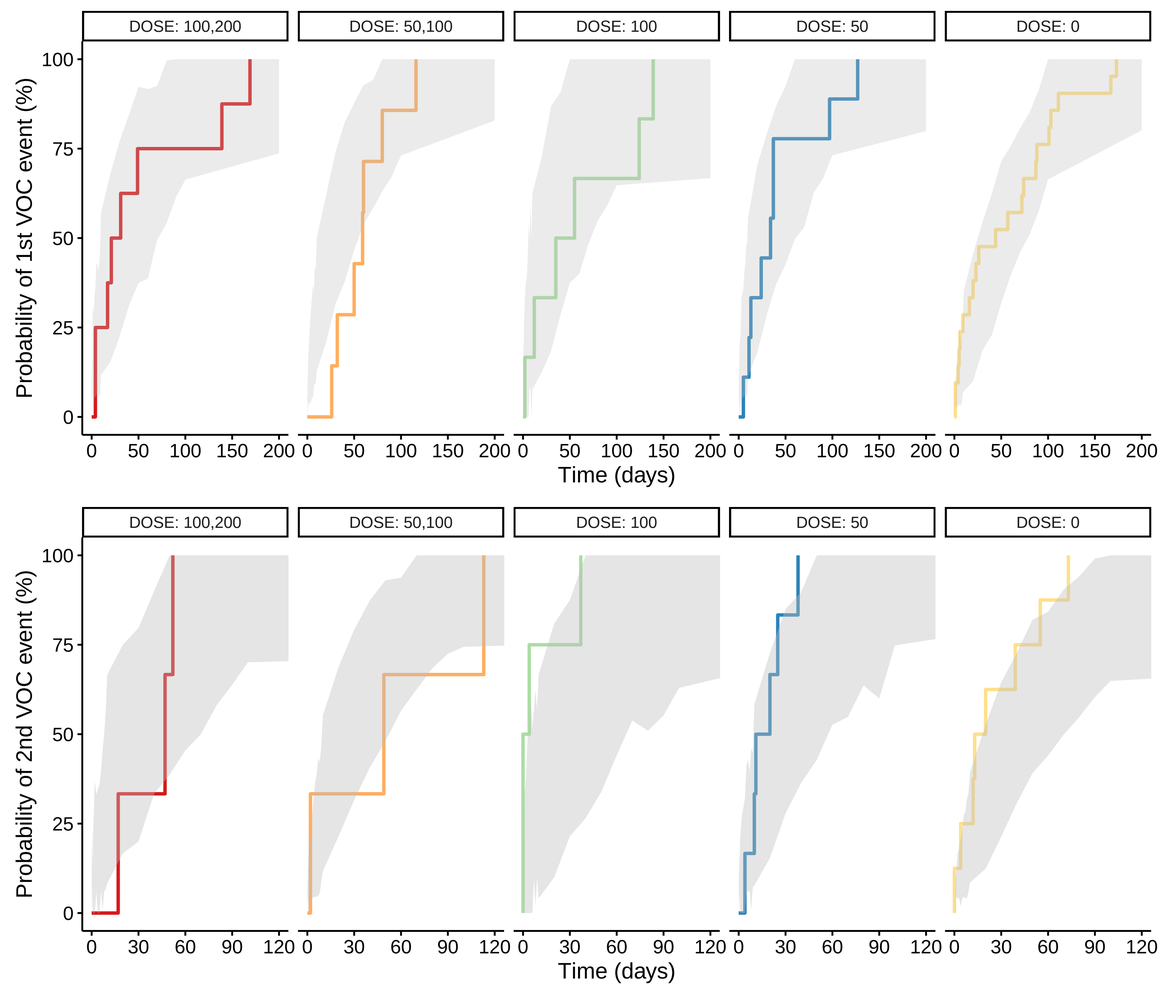

Figure 6: VPCs of the probability of a first VOC event (top figure) and probability of a second VOC event (bottom figure) over time, by dose cohort

References

[1] Advancing Novel Treatments for Hemoglobin Disorders. Corporate Presentation (2021).

[2] Conran, N. and Torres, L. cGMP modulation therapeutics for sickle cell disease. *Exp. Biol. Med.* **244** (2019):132–146.

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[4] Karlsson, K.E., Plan, E.L. and Karlsson, M.O. Performance of three estimation methods in repeated time-to-event modeling. *AAPS J.* **13** (2011):83–91.

Acknowledgements

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