Modeling and Simulation Strategy to Support the Development of ARS-1 (Intranasal Epinephrine) for Adult and Pediatric Subjects with Systemic Allergies

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RATIONALE

A critical component of any pediatric development plan is the quantitative definition of the therapeutic window across the age range of intended use with some comparison to the existing standard of care including any reference listed drug (RLD) in children and/or adults. This is especially true when an equivalence approach based on similar exposure defines the regulatory path to approval. Along with this objective there is also a need to defend the dose recommendation and support the selection of pharmacodynamic or clinical endpoints used in submission trials. To that end modeling and simulation approaches consistent with a model informed drug development (MIDD) paradigm are highly effective at informing such decisions and supported by FDA, PMDA, EMA and other global regulatory authorities in general.

Physiologically-based pharmacokinetic (PBPK) models have the benefit of addressing both the likelihood that an active drug substance reaches its intended site of action in adequate quantities to elicit the desired therapeutic effect and also the ability to account for size, ontogeny and maturation effects that define the pediatric population across various age strata. Clinical trial simulation (CTS) is an approach that leverages prior knowledge (PK and PK/PD including safety indices) about various treatments (experimental and reference) with consideration for study design constructs (e.g., sampling scheme, dose, strata and sample size) to explore the probability of success based on this prior knowledge, various design scenarios and critical assumptions. Both of these approaches have been conducted with the intention of providing guidance with respect to the therapeutic window of ARS-1 in children relative to the RLD and the potential for any meaningful difference in hemodynamic effects to be observed in future clinical trials or in the marketplace.

METHODS

Both physiologically based pharmacokinetic (PBPK) and pop-PK/PD-informed clinical trial simulation (CTS) models have been developed. The PBPK model addresses the likelihood that epinephrine reaches its intended site of action in adequate quantities to elicit the desired therapeutic effect and also the ability to account for size, ontogeny and maturation effects that define the pediatric population across various age strata. Clinical trial simulation (CTS) leverages prior knowledge (PK and PK/PD including safety indices) about various treatments (experimental and reference) with consideration for study design constructs (e.g., sampling scheme, dose, strata and sample size) to explore the probability of success based on this prior knowledge, various design scenarios and critical assumptions.

PBPK Modeling

The description of the PBPK model is presented in detail in Poster #468. In general, a Pulmonary Compartmental Absorption and Transit™ (PCAT™) model was developed to simulate nasal absorption epinephrine after IN administration. The physicochemical and biopharmaceutical properties for epinephrine were defined using in silico estimates from the ADMET Predictor Module that are based on structure, along with in vitro data obtained from the literature. Leveraging the pharmacokinetics of ARS-1 in adults and adjusting for allometric body weights in the weight distribution of pediatrics, doses of ARS-1 and optimal PK sampling time in proposed trials in pediatric subjects were simulated for pediatric subjects. The simulations included age groups: 4 to <12 and 12 to <18 years. The expected concentrations SBP and HR were also simulated.

METHODS

CTS Model

The PK and PK/PD data were analyzed using a nonlinear mixed effects modeling approach with first-order (FO) or first order conditional estimation (FOCE) method using NONMEM version 7.4. The covariate analysis was conducted using a forward addition method. The population PK/PD model was developed to characterize the relationship of pharmacokinetics of epinephrine with systolic blood pressure (SBP) and heart rate (HR) following administration of ARS-1, intramuscular (IM) with needle/syringe and EpiPen. Various models such as linear direct response, linear direct response model, and saturable-direct response were explored. A time shift between the observed effect and epinephrine concentrations was observed and, thus, models using indirect link models or involving resolution of any clock-wise hysteresis were used (e.g., tolerance models).

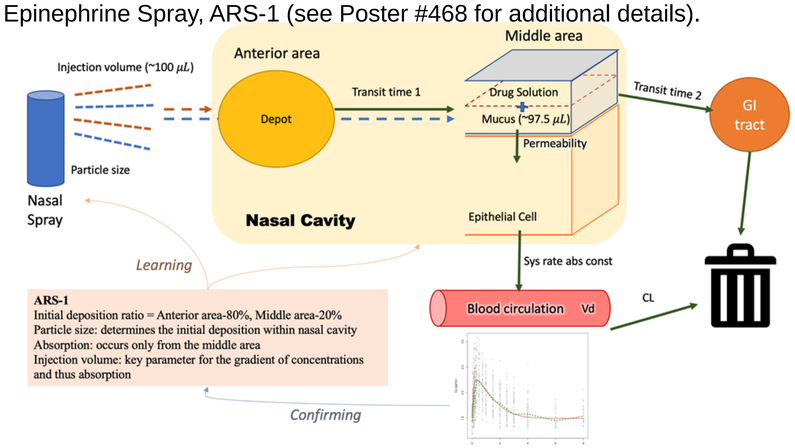
RESULTS

Both physiologically based pharmacokinetic (PBPK) and pop-PK/PD-informed clinical trial simulation (CTS) models have been developed. The PBPK model addresses the likelihood that epinephrine reaches its intended site of action in adequate quantities to elicit the desired therapeutic effect and to account for size, ontogeny and maturation effects that define the pediatric population across various age strata. Clinical trial simulation (CTS) leverages prior knowledge (PK and PK/PD including safety indices) about various treatments (experimental and RLD) with consideration for study design constructs (e.g., sampling scheme, dose, strata and sample size) to explore the probability of success based on prior knowledge, various design scenarios and critical assumptions.

PBPK Model:

The model adequately predicts the nasal PK of epinephrine in adults and its variability. Model robustness to predict epinephrine IN PK was demonstrated with the comparison to available clinical data from studies in healthy subjects and patients. The analysis indicates that there are minimal changes in the predicted exposures between adults and adolescents supporting the use of a standard dose of 1 mg of ARS-1 for these two populations, and that a 0.65 mg is appropriate for children in the younger cohort of patients (i.e., subjects weighting <30 kg which corresponds to ages 4 to 11 years). The model is suitable to answer questions regarding the PK of epinephrine based on physiologically-based differences relating to age or size of patients.

Figure 1. Structure of Physiologically Based Absorption Model for Intranasal Epinephrine Spray, ARS-1 (see Poster #468 for additional details).

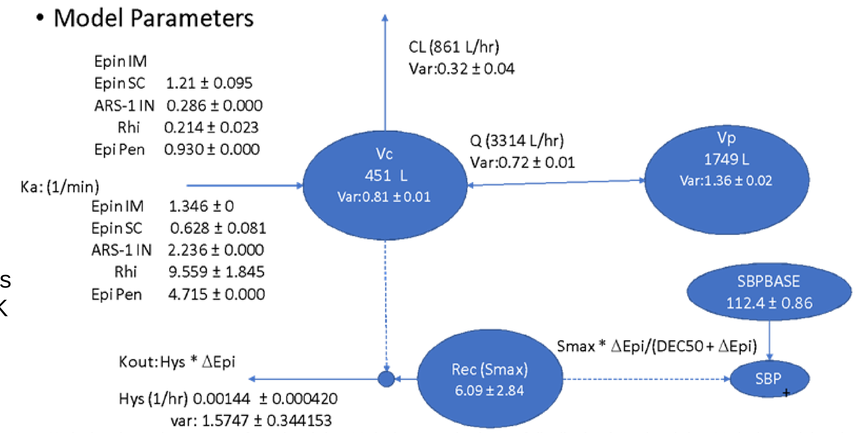


RESULTS

CTS Model

A two-compartment model with absorption compartments for IM, subcutaneous (SC), EpiPen, nasal, and nasal administration in rhinitis subjects was developed. Absorption rate constants and relative bioavailability in reference to epinephrine IM injection were evaluated and suggest that ARS-1 nasal and nasal administration in rhinitis patients have a faster absorption as compared to IM or SC administration. Baseline epinephrine levels were incorporated in the model.

Figure 2. Population-based PK/PD model parameters used for clinical trial simulation of ARS-1 in pediatric patients with systemic allergies.



Note: Ka is the absorption constant for epinephrine; Vc is the central volume of distribution for epinephrine, Vp is the peripheral volume of distribution for epinephrine, Smax is the maximal SBP response, SBP base is the baseline systolic blood pressure Kout is the pharmacodynamic output function, Hys is the hysteresis constant, ΔEpi is the change in epinephrine concentrations.

CONCLUSIONS

- This work highlights quantitative approaches that support dosing and trial design recommendations in support of the development of ARS-1 (Intranasal Epinephrine) for adult and pediatric subjects with systemic allergies.
- Predictability of these complimentary models relative to data generated to date is high and is supportive of the safe and effective dosing of ARS-1 in both adult and pediatric populations.
- Our analyses will be further informed by ongoing trials and ultimately part of the global registration of the ARS-1 product pending regulatory approval.

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