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 analysis 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 pharmacokinetic and critical 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 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.

RESULTS
Both physically 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 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 dose will be further informed by ongoing trials and ultimately part of the drug development trajectory.

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