The efficacy of treatments for PAH in adults is mainly based on improvements in exercise capacity i.e. the six-minute walk distance (6MWD) test. In children >7 y, 6MWD is not well reproducible and peak oxygen consumption (VO2) is used instead. In younger patients an exercise capacity test is not doable and hemodynamic endpoints may be used to assess efficacy [1, 2].

A recent FDA assessment [3] showed a relationship between changes from baseline in 6MWD and an hemodynamic endpoint i.e. pulmonary vascular resistance index (PVR) in the adult PAH population and that this relationship is consistent across different drug classes. From this relationship, a 30% decrease (placebo corrected change from baseline) in PVR corresponds to a 10–15% enhancement in 6MWD.

Sildenafil (REVA50), 20 mg TID, received approval for the treatment of adult PAH in the US based on 6MWD data.

Consistency of Sildenafil data for both adults and pediatrics with predictions from the FDA model has been assessed; Dose selection for sildenafil in adults is consistent across both hemodynamic and exercise based criteria [4].

**METHODS**

A population PK/PD analysis of PVR data from two pivotal sildenafil trials in adult [5] (n=218) and pediatric patients [6] (n=219, 1-17 y) was performed.

Objectives were developed in NONMEM 7 to characterize the relationship between PVR, baseline patho-physiological covariates i.e. age, body surface area (BSA), PAH functional class, PAH etiology, ability for exercise capacity assessment and sildenafil average concentration at steady state (individual empirical Bayesian estimates) obtained using a previously developed population PK model [7]. The model was developed using an exploratory graphical analysis which suggested piece-wise linear relationships between covariates and baseline PVR, between exposure and drug effect, followed by a stepwise inclusion of covariates.

Simulations based on clinically defined success criteria to achieve similar hemodynamic responses in children as seen previously in adults under the labeled dose were conducted to support the dose selection in pediatric patients.

**RESULTS**

PVR was modeled as a function of baseline covariates (functional class, etiology, age, BSA, ability for exercise capacity assessment) and exposure.

**PVR at baseline**

\[
PVR_{\text{baseline}} = c_0 + c_1 \times \text{BASIE} + c_2 \times \text{AGE} + c_3 \times \text{BSA} + c_4 \times \text{PAH} + c_5 \times \text{ETIO} + c_6 \times \text{EXC} + c_7 \times \text{LEA}
\]

**PVR at end of treatment**

\[
PVR_{\text{end C}} = c_0 + c_1 \times \text{BASIE} + c_2 \times \text{AGE} + c_3 \times \text{BSA} + c_4 \times \text{PAH} + c_5 \times \text{ETIO} + c_6 \times \text{ETIO} + c_7 \times \text{ETIO}
\]

Parameter estimates and covariates influence on baseline PVR

![Parameter estimates and covariates influence on baseline PVR](image)

**Distribution of PVR improvement measured as change from baseline**

![Distribution of PVR improvement measured as change from baseline](image)

**Exposure-effect relationship in adults and in pediatric patients**

![Exposure-effect relationship in adults and in pediatric patients](image)

**Simulations in pediatrics**

![Simulations in pediatrics](image)

**Conclusions**

A recent FDA assessment of the relationship between 6MWD and PVR proposes the use of hemodynamic endpoints to support drug development in PAH especially in the pediatric population. Prior to this analysis, the FDA assessment was leveraged and contrasted with Pfizer’s sildenafil data.

A model developed for PVR described the baseline data, the exposure-response relationship and the entire distribution of PVR improvements in both population: adults and pediatrics. Utilities model based simulations of PVR outcomes allowed bridging efficacy from adults to children supporting dose recommendations for sildenafil in pediatric PAH patients at 10 mg TID below 20 kg body weight and 20 mg TID beyond.

**REFERENCES**


