INTRODUCTION

Drug development in Rare Diseases is challenging given the prevalence, limited data and understanding of relevant biomarkers, pharmacodynamics (PD) and clinical endpoints.

Applying a Model Informed Drug Development (MIDD) framework by leveraging published data from clinical studies can therefore provide critical insights into efficacious clinical study designs.

OBJECTIVE

The current work describes considerations when leveraging literature data to design clinical studies and estimate the probability of pharmacological success (PoPS) for drugs with similar mechanisms of action.

An example of hematopoietic-prostaglandin D synthase (HPGDS) inhibitors in Duchenne muscular dystrophy therapy is presented.

METHODS

Reduction in urinary tetranor-prostaglandin-D metabolite (tPGDM) from baseline can establish desired proof of pharmacology for HPGDS inhibitors.

Data extraction: Mean and standard deviations of change in 1-tPGDM from baseline across placebo and four dose levels of active drug were digitized from the published Phase 1 and Phase 2 studies of TAS-106, a HPGDS inhibitor under development (Takahashi et al., 2018; Komai et al., 2020). Key study features are provided in Table 1.

RESULTS

A pharmacokinetic-pharmacodynamic (PK-PD) model was developed to describe the relationship between plasma drug concentration and change in urinary tPGDM (Figure 1). The model, which included a saturable inhibition of tPGDM for the drug effect, was used to predict the percent change in urinary tPGDM for a range of different dose levels (Figure 2).

RESULTS

A biomarker inhibition increased with dose. Due to high variability in the data, the two dose levels lack clear separation in their PD effects.

RESULTS

Counterintuitively, using the 90% success criteria, PoPS decreased with increasing sample size and was <15% at 24 h for both high- and low-dose groups. This could potentially be a trial design artifact, with a greater number of possible combinations resulting in trial failures as sample size increases (Figure 5). No order trends with 4-9 subjects were observed in PoPS (>200% at 24 h) (Figure 6).

CONCLUSIONS

Trial simulations conducted with smaller sample sizes may result in potentially erroneous PoPS conclusions.

Although increasing trial sample size naturally improves power to estimate the true PoPS, such trials may be impractical in rare diseases.

Trial to trial and population differences between studies, variability in PD response and sample size have significant impact on PoPS estimation.

REFERENCES


DISCLOSURES

This work is supported through a University of Florida College of Pharmacy Post-Doctoral Fellowship. H.D. Iwata is an employee/consultant of GlaxoSmithKline plc. D.A. and R.D. are employees and shareholders of GlaxoSmithKline plc.