Translational Modelling and Estimation of the Probability of Molecule Success on Balance of Pharmacology Benefit and Safety Risk

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Background

- An early understanding of a molecule's potential is important to tackle the high failure rate of clinical proof of concept studies.
- The estimation of probability of pharmacological success (PoPS) has been proposed as a framework for early prediction of the benefit-risk ratio, as PoPS quantifies the overall pharmacological strength and safety risk of a molecule.
- Here, a PoPS framework based on translational pharmacology modelling was applied to a molecule approaching first-in-human.

Methods

PoPS evaluation settings were as follows:

- Simulations including parameter translational uncertainty and variability were performed via the human pharmacokinetic (PK)-target engagement (TE) model:
  - Ex vivo data for concentration-blood biomarker response were analyzed to describe biomarker's dynamics and drug effect.
  - The model was translated into human by combining it with the predicted in vivo human PK, derived via allometry from three preclinical species.
- Success was defined as "≥90% of patients with adequate pharmacology, and ≤5% exceeding safety limit".
  - The in vivo PK-pharmacology relationship for a surrogate efficacy endpoint, based on a preclinical model, allowed identification of the efficacious range of the biomarker response, thus defining "adequate pharmacology".
  - The molecule's exposure at the no-observed-adverse-effect level (NOAEL) in three preclinical species was used as the safety limit.

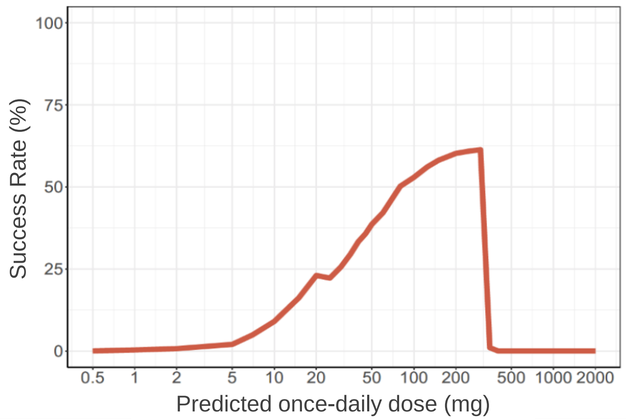
Results

- The human PK was bi-compartmental. TE was described via a transduction model; production was driven by PK via an Emax model.
- The in vivo concentration-efficacy Emax model was an Emax function; adequate pharmacology was achieved at doses providing ~2-10 fold increase in TE biomarker.
- Initially, different weights (60:30:10) were assigned to the three preclinical species NOAELs based on the knowledge about species relevance at the time.
- Later, based on emerging in vitro and in vivo toxicology data, the NOAEL from one species only was deemed to be relevant for translation into human.

Overall PoPS

Uncertainty on adequate pharmacology and the safety limit were included via a beta-distribution prior and weighted sampling respectively (see Figure 1 for result).

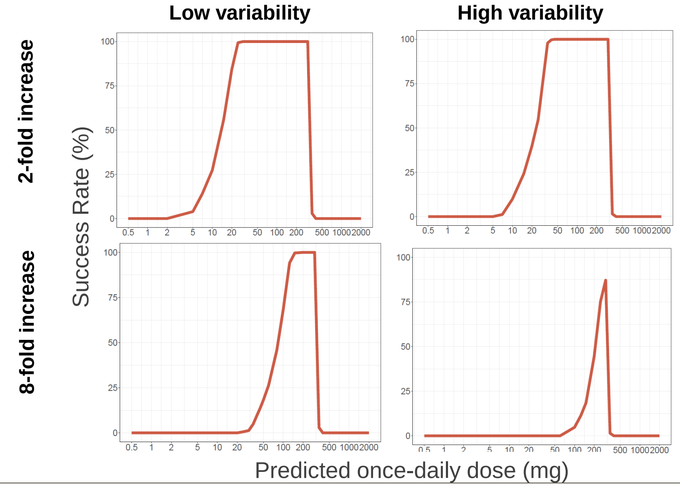
Figure 1. Initial overall PoPS considering NOAEL in all three species



PoPS scenario analysis

Considered scenarios were: (i) adequate pharmacology being 2- or 8-fold increase in the TE biomarker, and (ii) TE variability being low or high. Safety limit was the single relevant species NOAEL (see Figure 2 for representative results).

Figure 2. Scenario assessment of final PoPS using a single species NOAEL



Conclusions

- This work illustrates the general principles for situational application of the PoPS framework, which considers both the molecule's pharmacological properties and the intervention needs for the intended indication.
- Through effective integration of multi-source data and transparent description of key assumptions, the PoPS captures multiple uncertainties in a single probability term. This methodology has the potential to enhance the confidence and clarity of investment decisions for drug candidates.

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