Allucent's Expertise in Predicting Human Exposure From Nonclinical Data

Several different approaches can be used to predict human drug exposures and exposure-response relationships from nonclinical data. Four possible approaches are described below. Scope and budget for actual project requests may differ, depending on specific client objectives (including which and how many dosing regimens to simulate) and the amount and format of the nonclinical data used for analyses and modeling.

Approach 1: Allometric Scaling of Nonclinical PK Data

This is the simplest approach, in which PK data from one or more nonclinical studies is used to predict human exposures for a given dose or range of doses. With this approach, allometric scaling will be performed using nonclinical PK data provided by the client. A brief written report will be provided as a final deliverable.

The advantage of this approach is that it is a quick, low cost option that should provide the information needed to make well-informed dosing decisions regarding the progression of the compound.

Approach 2: IVIVE (In Vitro/In Vivo Extrapolation), Allometric Scaling, and Inclusion of Pharmacodynamic (PD) Data

This approach is similar to Approach 1, but it may also incorporate in vitro metabolism, plasma protein binding, permeability, solubility or other relevant in vitro data, as applicable. A brief written report will be provided as a final deliverable.

The advantage of this approach is that, in addition to nonclinical PK data, it incorporates additional properties of the molecule along with pharmacodynamics to predict an efficacious dose for humans.

Approach 3:
PK/PD Modeling Using Phoenix® WinNonlin®

This approach uses more formal modeling tools in Phoenix® WinNonlin® to guide first-in-human doses by predicting a human PK/PD model based on all available non-clinical data (PK, PD and in vitro data). This approach involves dataset generation, model development, and simulations to predict exposure and exposure-responses in humans receiving various dosing regimens. A summary report will be provided as a final deliverable.

The advantage of this approach is that a human PK/PD model will be developed, which can be used to simulate various dosing scenarios. Additional functionalities such as intra-subject, inter-subject, and model prediction variability and error can be introduced as well.

Approach 4:
PK/PD Modeling in NONMEM

This approach is similar to Approach 3 but involves the use of NONMEM, the pharmaceutical industry and health authorities' standard software for conducting PK/ PD modeling, to predict and simulate human PK. This approach involves dataset generation, model development, and simulations to predict exposure and exposure-response relationships in humans receiving various dosing regimens. A summary report will be provided as a final deliverable.

The advantage of this approach is that NONMEM provides greater flexibility and complexity in model development. The NONMEM model developed at this stage may also be further developed into a population PK model used during clinical development and ultimately included as part of the final submission.

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