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Pharmacokinetic and Statistical Considerations in First-in-Human Clinical Trials

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ABSTRACT

One of the major challenges when undertaking a first-in-human (FIH) clinical trial is how to appropriately plan and analyze the pharmacokinetics (PK) of a new drug. Although PK assessment in the earliest stages of clinical development provides valuable dosing recommendations for further development, only limited recommendations are available in the European Medicines Agency and US FDA guidelines, or in scientific publications, about how to view the statistical analysis and interpretation of PK data and results, respectively.

This presentation will elaborate further on following items:

- How to plan correct PK assessments in a FIH study design to get estimable and appropriate PK parameters
- How to correctly analyze and interpret PK data
- Which statistical analysis to use for PK evaluation in FIH study

INTRODUCTION

One of the major challenges when undertaking a first-in-human (FIH) clinical trial is how to appropriately plan and analyze the pharmacokinetics (PK) of a new drug. Although PK assessment in the earliest stages of clinical development provides valuable dosing recommendations for further development, only limited recommendations are available in the European Medicines Agency and US FDA guidelines, or in scientific publications, about how to view the statistical analysis and interpret the PK data and results .

During FIH studies, it is advantageous to gather sufficient and appropriate information about the PK of the drug, therefore most FIH clinical trial protocols (CTPs) include PK assessment as one of the primary or secondary objectives of the study.

Typically, FIH studies include single ascending dose (SAD) and multiple ascending dose (MAD) components. The SAD part offers an ideal opportunity to investigate dose proportionality, whereas the MAD part gives an insight as to how the PK effect changes with repeated doses when compared to a single dose. Additionally, in complex umbrella FIH protocols, other factors such as any food effects, gender differences, drug-drug interaction (DDI), patient age effect, or other assessments may be added to widen the information on the drug's PK and safety profile.

By their very nature, FIH trials are exploratory. Various PK analysis methods can be used, but there is a lack of consensus on how best to plan the PK assessments and analyze the data to have meaningful results that is useful for further clinical development.

This raises another question as to what - if any - statistical analysis is necessary to foresee for PK data, and how to draw appropriate conclusions, given that statistical tests are not mandatory in the exploratory phases of clinical development?

PK results in a FIH study are required in the registration files submitted to the regulatory authorities. Scientifically rigorous PK analysis methodology and interpretation are required and although there are PK-related sections in different FDA and EMA guidelines related to FIH trials, there are no common requirements or recommendations on precise PK methodology. In many respects, this is not a surprise since the PK properties of drugs vary widely even for those with similar physico-chemical characteristics or identical pharmacological mechanisms of action. So PK analysis may be planned, performed and interpreted by various methods in different FIH studies, which should be justified by the properties of the drug and by pre-clinical observations.



HOW TO PLAN CORRECT PK ASSESSMENTS IN A FIH STUDY DESIGN TO GET ESTIMABLE AND APPROPRIATE PK PARAMETERS

Pharmacokinetics relates to the entire “journey” of a drug in the body and includes its absorption from the site of administration, followed by the distribution in the rest of the body’s metabolism, and its excretion from the body (ADME).

PK is demonstrated by plotting the drug’s profile data against time. Some parameters are mathematically estimated to describe the above mentioned different parts of drug ADME. In FIH studies, PK is evaluated in plasma or serum, since this is the central matrix, and is mandatory to assess for any drug with systemic absorption. Figure 1 shows an example of a plasma PK profile (linear-linear scale in the left and log-linear scale in the right) with some main PK parameters.

PK parameters such as the observed maximum concentration (C_{max}), time when maximum concentration is the observed (t_{max}), area under the concentration-time curve for different time intervals (AUCs) and elimination half-life ($t_{1/2}$) are the primary ones measured in FIH protocols and are very valuable in order to describe for the first time human PK properties of a compound. From these data, other parameters, such as plasma clearance (CL), apparent volume of distribution (V_z) can be derived.

Inappropriately estimated PK parameters will lead to incorrect interpretations of results, and Figure 2 shows how the flow of PK assessments and documents correspond with each other in the clinical workflow. To ensure the correct outcome of results, each step must be correct and planned out.

The frequency and nature of PK sampling within a FIH study design will vary depending on the drug’s pharmacological properties observed in animals and in vitro or predicted by applying PK or PK/PD models. Experience teaches the following key factors in the design of

PK assessments within a FIH study:

- Plan enough PK samples around the expected C_{max}/t_{max} , in order to not miss the real C_{max}/t_{max} .
- Ensure enough PK samples occur at the end of a PK profile to correctly estimate the terminal elimination half-life.
- Allow PK sampling for a period of up to 5-6 times half-life for the final PK assessments.
- If PK is one of the factors involved in the dose escalation review process, it is best to evaluate the PK for a period of up to 3 times half-life, but if this is not possible, then 2 or 3 samples should be taken in the decline phase (after C_{max}).
- Use a suitably sensitive bio-analytical method to ensure as low as possible plasma/serum concentration of the drug can be quantified, in order to not lose the real terminal elimination phase.
- If there are major and/or active metabolites known from preclinical studies or human metabolism predictions, the FIH study is a good opportunity to assess their PK in humans.
- Keep PK sampling time as close as possible to the planned one, preferably within 10%.
- If urinary excretion is involved in drug elimination, plan for the appropriate urinary collections.
- Where possible, harmonize the PK sampling schema with the pharmacodynamics (PD) assessments (such as biomarkers, receptor occupancy) since establishing a PK/PD relationship assessment in a FIH study is an added value.
- Finally, do not plan FIH studies on “similar” methods, or an approximate PK sampling schema. Each should be built by experienced experts based on the available drug pharmacological properties and preclinical data.

HOW TO CORRECTLY ANALYZE AND INTERPRET PK DATA

Review of PK data before starting the analysis is a crucial point for a FIH study. The number of subjects is limited in a FIH study, therefore, we should try to keep the PK analysis population as large as possible.

One of the aspects of the PK data review should be to find an explanation for unexpected PK profiles. The reasons for unexpected or abnormal results may be very simple or more complex in nature. A sample may have been taken with a large time deviation from the planned time, or samples accidentally switched; or it may be indicative of a concomitant medication, some adverse events such as diarrhea or vomiting, or even some pathologies reported in medical history such as Gilbert’s syndrome, or pharmacogenomic reasons (poor or extensive metabolizers).



In addition to the above-mentioned abnormalities in PK data, some PK parameters may just not be correctly estimated, such as the terminal elimination half-life, when there are not enough PK sampling points in the last part of the concentration-time curve. Other examples are an insufficient PK sampling period or an insufficiently sensitive bioanalytical method, making the estimation of extrapolated part of the area under the curve to infinity (AUCinf) inappropriate.

Once the abnormalities are identified, and reasons found for each, it is important to assess the need to either keep or exclude data. Advance thought must be given to foresee the actions to be taken in the official CTP, SAP and PKAP documents so that if exclusion is considered, there is no deviation from them, and no manipulating of the data in the exploratory phase of clinical development takes place.

The PK (and other) data from FIH trials may be analyzed using standard PK analysis methods, such as non-compartmental analysis (NCA).

However, this may not be the most optimal method to describe the PK profile and estimate PK parameters for all the molecules, and it may be beneficial and appropriate to further refine the knowledge by using other methods such as compartmental, population PK and modeling and simulation methods.

Furthermore, when assessing the data for calculation and interpretation in the FIH reports, it is advisable to draw conclusions based on essential and primary PK parameters and rely on dose-normalized PK parameters when appropriate. This will avoid issues around the small dose groups in FIH studies (four to eight patients receiving active treatment) having relatively high inter-subject variability, and any arithmetic mean of the values being an unreliable indicator for the wider population. Using average values is only worthwhile when the inter-subject variability is low, and if the number of subjects is high enough to represent the population.

WHICH STATISTICAL ANALYSIS TO USE FOR PK EVALUATION IN A FIH STUDY

As previously discussed, the PK objectives of a FIH study are not only to describe the PK profiles, but also to learn about the dose proportionality, accumulation, steady-state achievement of the compound and to assess the influence of some factors such as food and gender on PK. Most of these PK objectives are well described using appropriate standard descriptive statistics, such as the mean, standard deviation (SD), coefficient of variation (CV%) as well as median, minimum and maximum values.

A good graphical presentation of the data can be time consuming, but the appropriate selection of ranges for the axes will help to present the important aspects of the data. A longer time frame with the drug concentration on a logarithmic scale is preferable to provide information on the exponential disposition and the terminal half-life, while the maximum concentration and its timing would be better presented on the original scale with a shorter time frame.

Inferential statistical analyses are performed to draw conclusions about general populations and involve statistical models such as analysis of (co)variance and regression. The results from inferential statistical analysis can be reported using estimates of population parameters – for example, least-square means - and their standard errors or confidence intervals, which quantify the variability and uncertainty of the reported estimates.

Some clinical pharmacology trials such as drug-drug interaction and bio-equivalence/bio-availability require a formal power calculation if the objective of the trial is to investigate a specific hypothesis and demonstrate a statistically significant difference between treatments regarding specified study endpoints. FIH trials are exploratory, aiming to quantify mechanisms, rather than trying to prove them, therefore, a formal power calculation is not necessary. However, whenever possible, the chosen sample size should be justified, and importantly, the results from the statistical test should be interpreted with caution, keeping in mind the exploratory nature of the study.

PK measurements and some PK parameters are log-normally distributed, at least approximately, so that the logarithmic transformation is recommended. It is generally not required to perform statistical tests of normality since results of such tests are not always reliable, especially with small sample sizes.

In FIH studies, significance threshold levels larger than the standard 0.05 might be acceptable but the authors of any such study should provide the rationale. Confidence intervals are on the same scale with the same units as the individual values, which make them a preferred choice for reporting PK results. In contrast, p-values should be used to demonstrate whether the difference between two treatments is statistically significant.



Finally, it must be decided which statistical test to choose to assess the various PK questions in FIH studies. The methods often used to assess dose proportionality in FIH studies are the power model or the mixed effect model. Dose proportionality may also be assessed in the MAD part of FIH by adapting the model used in the SAD. The accumulation phenomenon in MAD is assessed by a special PK parameter, R_{ac} (ratio of accumulation), without a particular need to perform inferential statistics. A graphical presentation of trough concentration values is helpful to interpret the steady state achievement in the MAD part, although some exploratory statistical tests have been used by researchers.

If other assessments, such as food effect, gender effect, formulation effect, and DDIs are included in FIH study objectives, then knowing that sample size was not estimated and the statistical test is not powered, it is advisable to highlight the exploratory nature of this assessment and interpret the results accordingly.

CONCLUSION

FIH studies are an exploratory part of clinical development, with sometimes complex protocols including several secondary assessments. PK evaluation is often one of the primary objectives in FIH studies and should be planned, analyzed and interpreted in a manner to make it understandable and acceptable. Deep knowledge of the pharmacological properties of the drug compound and of preclinical results is crucial to design the PK assessments correctly.

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