

EARLY PHASE CLINICAL TRIALS IN PATIENTS WITH HEPATIC OR RENAL IMPAIRMENT: FROM DESIGN TO DATA ANALYSIS

AUTHOR: NARINE BARIRIAN, PHARM.D, PK EXPERT, SGS LIFE SCIENCES - CLINICAL RESEARCH

FDA ^[1, 2] and EMA ^[3, 4] guidances are intended to help companies evaluate the need for conducting pharmacokinetic (PK) studies in renal impaired and hepatic impaired patients and to provide guidance on how to best assess the influence of renal impairment (RI) or hepatic impairment (HI) on the pharmacokinetics of an investigational drug. Although there exist many procedural recommendations, some key questions still need to be investigated case-by-case at the early stage of the project development.

GUIDELINES

Most drugs are likely to be administered to RI or HI patients and should be investigated in that population, however, the available guidelines for industry are relatively old (EMA and FDA guidelines for HI, 2005 and 2003, respectively), still draft version (FDA guideline for RI, draft since 2010) or not sufficiently detailed (EMA guideline for RI, 2014). And although many recommendations regarding the design, conduct and data analysis of early phase RI or HI trials are available in the guidelines, some key questions still need to be investigated case-by-case at a very early stage of the clinical development.

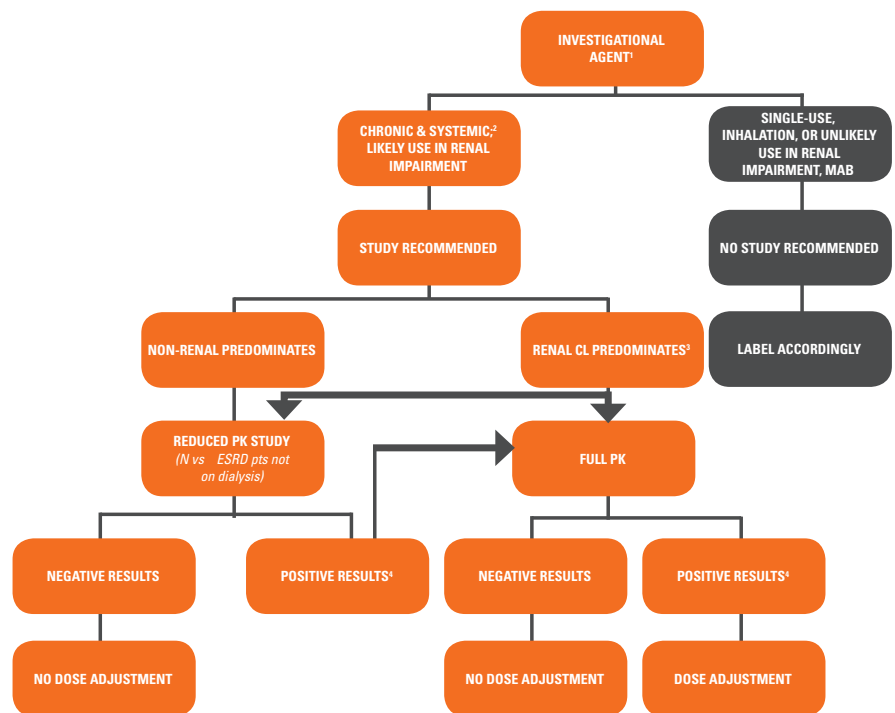
KEY OPEN QUESTIONS

Full or reduced study design?

A decision tree for determining when and how RI or HI studies should be conducted is given in the FDA guidelines. ^[1, 12]

As a general approach, when renal or hepatic elimination is not the major route of elimination of parent drug and/or active metabolites, a "reduced" study can be sufficient in RI and HI, respectively. So, the sponsor has the option of conducting a "reduced" or "full" study, and the choice should be based on the PK prop-

FIGURE 1: WHEN AND HOW RENAL IMPAIRED STUDIES SHOULD BE CONDUCTED IS GIVEN IN THE FDA GUIDANCES ^[1]



¹ Metabolites (active/toxic) – same decision tree

² Includes cytokines or cytokine modulators with MW <69 kDa

³ Option to do either full or reduced study or Pop PK Analysis of Ph 2/3 data

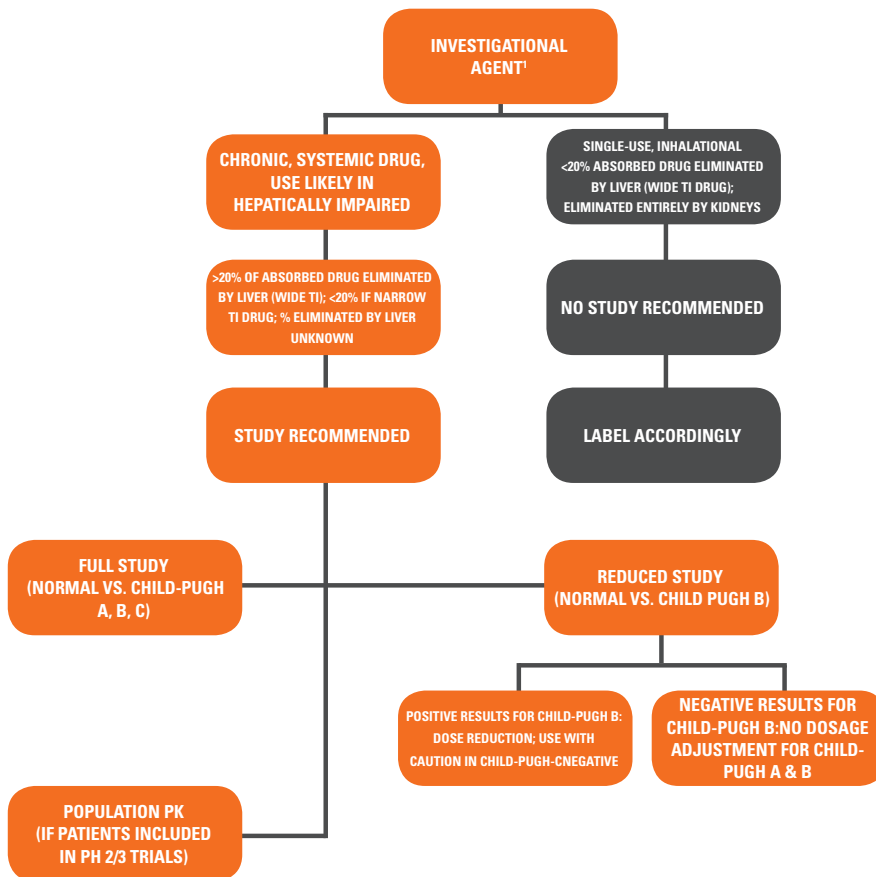
⁴ >50% increase in AUC; < for Narrow TI drugs

erties of the drug including all data from *in vitro*, pre-clinical and clinical studies.

The FDA also advises that if a "reduced" PK study shows a substantial effect

on PK in the patients with RI, a "full" RI study should be conducted. While for patients with HI, the findings in the moderate category in a "reduced" study would be applied to patients with a mild

FIGURE 2: WHEN AND HOW HEPATIC IMPAIRED STUDIES SHOULD BE CONDUCTED IS GIVEN IN THE FDA GUIDANCES^{1, 2, 7}



Child-Pugh category, and dosing in the severe category would generally be contraindicated.

Moreover, FDA and EMA guidelines are not consistent in the definition of “reduced” design for RI studies: according to FDA End Stage Renal Disease (ESRD) subjects who are not undergoing dialysis should be compared to matched healthy volunteers (HVs), while according to EMA, patients with severe RI should be compared to matched HVs.

What about recruitment of ESRD patients not under dialysis? This type of patient is quite difficult to find, therefore, often a “full” study (including all the stages of RI) is preferred by sponsors in order to meet the timelines and also to avoid possible restart of a “full” study in case of a substantial effect on PK in patients with RI in the “reduced” study. Additionally, the minimum number of subjects required in “reduced” design (at least 8 per group) is higher than in “full” design (at least 6 per group).

STATISTICAL CONSIDERATIONS AND MATCHING STRATEGY

The control group of HV should be comparable (matched) to the RI/HI patient population with respect to age, gender, race and weight. Depending on the drug, other factors with significant potential to affect the PK should also be taken into consideration. Matching prevents confounding by increasing precision of estimates (reduction in standard errors). When the sample size is small, such as RI/HI studies, without a good matching, control for confounding in the analysis will result in many strata with sparse data. There are no recommendations in the guidelines about the matching method, but two strategies are known to be used.

When individual matching is used, controls are matched to patients one by one for each of matching criteria. The advantages of the method are the simultaneous recruitment of pairs of patient-HV and the possibility of reuse of HV data

among RI/HI groups. The most important advantage is the guarantee of statistically robust results compared to the only disadvantage of the need of more HVs compared to other matching strategies.

The second matching is group matching. In this approach all patients with RI/HI are completed, HV will be selected (matched) based on the defined distribution (percentiles) of each matching criteria. The advantage of this method is that a lower number of HVs is required, which should be equal to the number of patients in one group of RI/HI patients. However, this method cannot be considered as the first choice in early phase RI/HI trials because it is less statistically robust when comparing PK results between RI/HI groups and HVs.

PARTICULARITIES OF DIALYSIS EFFECT ASSESSMENT IN RI TRIALS

Dialysis may affect the PK of a drug to an extent that dosage adjustment is needed. In general, a study of the effect of dialysis on PK may be omitted if the drug is unlikely to be administered to ESRD patients treated with dialysis, or if the dialysis procedure is unlikely to result in significant elimination of drug or active metabolites.

If dialysis is assessed, PK should be studied in such patients under both dialysis (DTP) and non-dialysis (IDTP) conditions to determine the extent to which dialysis contributes to the elimination of the drug and potentially active metabolites. Venous blood samples during IDTP and blood from both arterial and venous sides of fistula during DTP should be collected. Drug concentration in dialysate, total plasma proteins and drug free fraction in arterial and venous sides should be measured at several time points during the DTP. Some key hemodialysis parameters should also be reported, such as blood flow through the dialyser (Q_B) and rate of ultrafiltration (Q_{UF}).

Taking into account special hemodialysis parameters such as (extraction coefficient by the dialyser (E), hemodialysis clearance (CL_{HD}), and the amount of drug removed by dialysis (A_R)), will provide answers to the main questions:

- Was the drug removed through the hemodialyser?
- How effectively can the dialyser remove the drug from the blood?
- Is it removed through the membrane?

Common PK parameters have to be calculated during the IDTP, as well during the DTP, using drug concentration data from venous side. This will allow comparing the PK behavior of the investigational drug between IDTP and DTP.

DOSING ADJUSTMENT RECOMMENDATIONS

The principal objective of an early phase RI/Hi study is to advise on dosing recommendations. When applicable, it is also important to point out in dosing recommendations that HI/RI does not alter a drug's PK. If the effect of HI/RI on the PK of the drug is obvious, dosage adjustments should be recommended in the

Clinical Study Report (CSR) of the early phase study. It is also possible that the effect of HI/RI on the PK is only partial, i.e., significantly altered only in one or more groups but not in all groups compared to HVs.

To reach a conclusion about the significance of altered PK, a confidence interval approach, rather than a significance test, is preferred in HI studies according to FDA guideline^[2]. The no effect boundaries are defined prior to conducting the studies, based on information available for the investigational drug PK, or a standard 90% confidence interval of 80-125% for AUC and C_{max} . FDA recognizes that providing evidence that a PK parameter remains within an 80-125% no effect boundary would be very difficult given the small numbers of subjects usually entered into HI studies. If a wider boundary is fixed, it should be supported clinically (no safety issue) and confirmed by formal sample size calculation based

on inter-subject variability observed in HVs. However, it may be more probable to conclude that there is no need for dose adjustment with the wider boundaries; therefore, this choice should be taken into consideration when observing the PK properties of the drug.

In RI studies, significance test is used without statistical flexibility, which can often make it difficult to draw conclusions about the RI effect on the drug PK with the low number of subjects. The conclusion in this case should be evidence-based, and if needed confirmed by a PK/PD study in a much larger patient population.

Extra caution is needed when developing a drug with narrow therapeutic index (NTI). Some general approaches to estimate the exact dose adjustment are available using relatively simple equations. Since some conditions should be fulfilled to apply those equations and

FIGURE 3 : SCIENTIFIC ADVICE TO INTERPRET THE PK RESULTS

The following are some scientific recommendations to be considered when interpreting the PK results:

AN UNDERSTANDING OF THE FUNDAMENTAL PK PRINCIPLES RELATED TO RENAL AND HEPATIC DRUG CLEARANCE WILL BE HELPFUL TO CORRECTLY INTERPRET THE RESULTS OF PK OBSERVATIONS IN RI/HI TRIALS

EXTRA CAUTION IS NEEDED WHEN INVESTIGATING A DRUG WITH NTI IN PATIENTS WITH RI/HI

FOR SOME PARTICULAR DRUGS, PD CHANGES IN PATIENTS WITH RI/HI ARE POSSIBLE WITHOUT THE POTENTIAL CONTRIBUTION OF ALTERATION IN THE PK PARAMETERS OF THE DRUG

SEVERE HEPATIC DYSFUNCTION IS USUALLY ACCOMPANIED BY RI (HEPATO-RENAL SYNDROME)

HEMODIALYSIS IN ESRD MAY REMOVE THE DRUG, URAEMIC TOXINS, THEREBY COMPLICATING DRUG EFFECT IN PATIENTS WITH RI

PATIENTS WITH RI/HI REQUIRE MULTIPLE MEDICATIONS, THEREFORE THE INFLUENCE OF CONCOMITANT MEDICATIONS ON INVESTIGATIONAL DRUG'S PK SHOULD BE ASSESSED

IT IS MANDATORY TO INVESTIGATE PLASMA PROTEIN BINDING IN THE EVALUATION OF THE EFFECT OF RI/HI ON DRUG PHARMACOKINETICS

THE ACTIVITY OF VARIOUS PHASE I/II METABOLIC ENZYMES OR CELLULAR TRANSPORTERS CAN BE DIFFERENTLY ALTERED IN HI

SEVERAL GASTRO-INTESTINAL DYSFUNCTIONS MAY RESULT TO THE ALTERED ABSORPTION OF AN ORALLY ADMINISTERED DRUG IN HI

CHILD-PUGH CLASSIFICATION IS SIMPLE AND OFTEN NOT SENSITIVE ENOUGH TO DISTINGUISH MILD AND MODERATE HI

DRUG METABOLISM ALTERATION MAY DIFFER ACCORDING TO THE ETIOLOGY OF CIRRHOSIS

since they are still not optimized, modeling and simulation (M&S) are highly recommended. M&S takes into account drug PK/PD properties, administration particularities and indicates the best approach of dosing adjustment.

RECOMMENDATIONS TO CORRECTLY INTERPRET THE RESULTS FROM EARLY PHASE RI/HI TRIALS

Several scientific review articles have concluded that there is remarkable variation in definitions and recommendations

and lack of scientifically relevant interpretation and used method's description, making the available results from early phase RI and HI trials not unsuitable for clinical use. RI and HI are very complex pathologies so, the particular patho-physiological changes in these patients, together with the PK properties of the drug should be carefully considered when interpreting the observed results.

Some scientific recommendations to be considered when interpreting the PK results are presented in Figure 3.

CONCLUSIONS

At an early stage of drug development, studies in RI/HI special populations are almost always required for drugs with systemic absorption. Conclusions from early phase RI/HI trials are very difficult, variable and often not clear. The best solution is the development of a robust study design by clinical and scientific experts. The study design, as well the interpretation of results, should be based on PK/PD properties of the drug and with an understanding of the fundamental on the PK principles related to RI and HI pathologies.

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CONTACT INFORMATION

EUROPE

+32 15 27 32 45

clinicalresearch@sgs.com

NORTH AMERICA

+ 1 877 677 2667

clinicalresearch@sgs.com

WWW.SGS.COM/CRO

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