Revised Renal Impairment PK Study Guidance: Key Takeaways

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After 10 years of anticipation, the FDA updated and revised their guidance for renal impairment pharmacokinetic (PK) studies; *Pharmacokinetics in Patients with Impaired Renal Function —Study Design, Data Analysis and Impact on Dosing and Labeling*. The new guidance still describes when to conduct a renal impairment PK study; study design considerations; data analysis and labeling recommendations; however, several significant changes are now suggested compared to the first draft that was introduced in March 2010.

A welcomed modification relates to the design of a reduced study. A reduced study design may be an option when drug elimination is not primarily through the kidneys. For such study, the FDA originally recommended the inclusion of both ends of the renal function spectrum; healthy controls and end-stage renal disease (ESRD) patients with eGFR <15 mL/min and not yet on dialysis to represent the "worst-case scenario" (see review article). However shortly after its release, this stance was overturned.

A dedicated full renal impairment PK study is recommended (i) if the drug is intended for patients with kidney disease and (ii) if the drug or active metabolite is substantially eliminated by the renal route.

An FDA Advisory Committee meeting held on March 17th, 2010 concluded that ESRD patients not yet on dialysis would be difficult to recruit and not feasible for a reduced study design. Moreover, the committee felt that patients with a GFR < 30 ml/min is a sufficient estimate of the worst-case scenario. The newly revised draft guidance issued in September 2020 now includes this recommendation for reduced study designs as well as other key differences related to study design and physiological-based PK (PBPK) modeling and simulation.

Key Changes:

- The current version updates the term end-stage renal disease (ESRD) to *kidney failure,* which is now defined as eGFR or CLcr < 15 mL/min or patients on dialysis during non-dialysis days.

- For a reduced PK study design, severe renal impairment (15-29 mL/min) can represent the worst-case scenario in comparison to a control group. If a clinically relevant PK effect is observed in patients with severe renal impairment, all stages of renal function should be explored.

- For a full PK study with drugs anticipated to have a wide therapeutic range, subjects may be stratified by disease stage as 1) normal to mild: eGFR > 60 mL/min 2) moderate to severe: eGFR = 15-59 mL/min; and 3) kidney failure: eGFR < 15 mL/min or patients on non-dialysis day.

- Sample size justification for each group studied is now required (e.g. 95% confidence interval should fall between 60 and 140% of the geometric mean estimate of relevant pharmacokinetic parameters [e.g. Cmax, AUC] with at least 80% power). This requirement could increase the number of patients for some drugs to more than the 6-10 patients/cohort historically enrolled.

- Physiologically-based modeling can be used to demonstrate that changes in renal function are unlikely to result in any meaningful changes in a drugs pharmacokinetics and thus used as rationale to not perform a study in renally impaired patients. PBPK data can also be used to supplement and support information obtained from studies in renally-impaired patients.

Key Clarifications:

- The 2010 draft recommended cytokines or cytokine modulators with a molecular weight > 69 kDa may be exempt from conducting a PK study in renally impaired patients. The 2020 draft expands this to all therapeutic proteins and peptides > 69 kDa.

- Calculation of unbound drug in plasma and relevant metabolite concentrations are expected for drugs that show high plasma protein binding. This requires collecting at least one sample per patient to determine the unbound fraction. However, the unbound drug calculation may be more frequent (e.g. each plasma sample) if the binding is concentration-dependent or is affected by metabolites or other time-varying factors.

- Population PK analysis from samples collected from patients in phase 2 and 3 studies can be used to assess the impact of changes in renal function on PK but only if a sufficient number of patients with a wide concentration range of renal function markers (e.g. serum creatinine concentrations) are part of the study population.

- For studies involving intermittent hemodialysis therapy, the drug binding to plasma proteins should be assessed in samples collected immediately before dialysis starts and immediately after dialysis. This is to study whether body waste products in uremic plasma have the potential to displace the drug from its plasma protein binding sites.

Key Considerations:

For a successful renal impairment PK study it is important to work with a knowledgeable and experienced CRO, familiar with this unique patient population. Celerion's expert investigators, project managers, and pharmacologists work closely with our Sponsors to provide valuable input on study design and inclusion/exclusion criteria to optimize the clinical trial and realize study timelines.

- *Extensive Site Network*. Celerion has key collaborations and established working processes with expert renal specialists and sites throughout the US and EU. We will recommend a single- or multi- site approach to meet recruitment timelines.

- *Leveraged Experience*. Celerion has conducted over 30 renal insufficient PK studies over the past 5 years. Over 85% of renal studies included severely impaired and/or dialysis patients.

- *Unbeatable Timelines*. On average, it takes only four weeks from the site contract to Institutional Review Board (IRB) approval and typically the study is completed in approximately participants are completed in 16 weeks from First Patient In - Last Patient Last Visit (FPI-LPLV).

Read more about our approach to renal impairment PK studies:
https://www.celerion.com/expertise/renal-hepatic-insufficiency

Putting It All Together:

The updated and revised FDA renal impairment PK guidance was a long time in the making. Several updates and clarifications are commended, such as the reduced study design recommending controls and severely impaired patient rather than patients with ESRD or renal failure. Another considerable improvement is the condensed full study design for drugs with a wide therapeutic window, which may consist of 3 groups (rather than 5 groups previously recommended). This will help increase recruitment rates as patients can be bucketed into three groups, reduce study timelines and may lower costs. Other modifications may prove to be more challenging. While the European Medicine Agency recommends 6-8 participants per cohort (see EMA guidelines), the new FDA guidance indicates sample size calculation should be performed to determine an appropriate cohort size. For drugs with high variability (e.g. interCV% >50%), samples sizes may exceed 14 patients per group. This could exhaust site patients pool, lead to increased recruitment and conduct timelines as well as study costs. Alternatively, population PK during phase 2 and 3 may be a viable options rather than a dedicated renal impairment PK in this scenario. This is where an experienced and knowledgeable CRO team, can help develop the right strategy for your drug program.

Reference:

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