Impact of the FDA's Revised Draft Guidance on Renal Impairment PK Studies —Trends, Challenges and Solutions

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OBJECTIVE

- Kidney dysfunction can affect drug elimination resulting in adverse events and safety concerns, therefore it is imperative to understand an investigational drug's disposition under conditions of renal impairment (RI), especially when the drug is cleared by the kidneys and/or if the target population includes patients with kidney disease.
- In September 2020, the FDA updated the draft RI pharmacokinetics (PK) guidance, impacting study design and sample size (1).
- Changes include adaptions to reduced and full study designs, as well as a recommendation to perform a sample size justification (**Table 1**), which could **increase sample size to 14 or more** patients per group (2).
- An analysis of RI PK studies conducted before and after the guidance release was performed to address how the pharmaceutical industry has responded to these recommendations.

Table 1. **Summary of Key Design Elements from the Revised Draft Guidance**

Design Elements	Previous Draft Guidance (March 2010)	Revised Draft Guidance (September 2020)
End-Stage Renal Disease (ESRD) Patients	GFR <15 mL/min not on dialysis or patients requiring dialysis.	Updated term to Kidney Failure (KF), GFR <15 mL/min or patients on dialysis during non-dialysis days.
Reduced PK Design	Worst-case scenario originally described as ESRD patients not yet on dialysis and suitable control group. Advisory Committee recommended hemodialysis patients on off-dialysis periods or patients with GFR <30 mL/min can be considered as worst-case scenario.	Severe RI (GFR 15–29 mL/min) can represent worst-case scenario vs control group.
Full PK Design	All stages of RI i) control/normal; ii) mild; iii) moderate; iv) severe; v) ESRD.	New consideration for drugs with a wide therapeutic range, can stratify disease stage as i) normal-mild; ii) moderate-severe; iii) KF.
Sample Size	Must be sufficient to determine a meaningful PK difference between patients and controls (typically 6–8 patients per group).	Justification based on drug PK variability (95% confidence interval should fall between 60 and 140% of the geometric mean estimate of relevant PK [e.g. Cmax, AUC] with at least 80% power.

METHODS

- Phase I, Industry-sponsored, RI study details were obtained from ClinicalTrials.gov in January 2023.
- Total trial number, duration, subjects per cohort and clinical sites as well as geography were compared for studies starting before and after the revised guidance was issued.
  - **Pre-guidance completed trials:** 01/01/2018–12/31/2019
  - **Post-guidance completed trials:** 01/01/2021–12/31/2022
  - **Ongoing trials:** 01/01/2021–12/31/2022
- Results are presented as average (range) or count (percent).
- Studies with a start date in 2020 were omitted from the analysis due to pandemic related delays and cancellations.

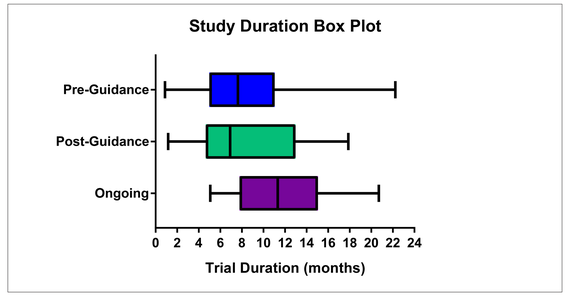
RESULTS

Table 2. **Uptick in Renal Impairment PK Studies Enrolling KF Patients Post-Guidance Release**

Trial Characteristics	Summary of All Trials		RI Disease Stages Investigated [Number of Trials (%)]				
Groups	Total Trial Number	Ave. Subjects per Trial (range)	Normal	Mild	Moderate	Severe	ESRD / KF
Pre-Completed	37	28 (14–48)	37 (100%)	25 (68%)	31 (84%)	32 (86%)	10 (27%)
Post-Completed	24	28 (12–48)	24 (100%)	13 (54%)	19 (79%)	14 (58%)	10 (42%)
Post-Ongoing	33	33 (12–64)	33 (100%)	19 (58%)	23 (70%)	26 (79%)	14 (42%)

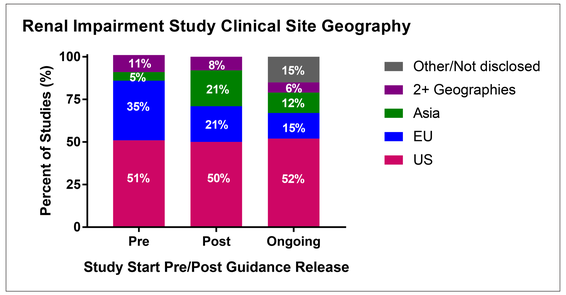
- The number of trials enrolling KF patients increased from 27% Pre-Guidance to 42% Post-Guidance.
- Total number of subjects enrolled in a RI PK study was similar for Pre- & Post-Completed studies, with an average of 28 participants (approximately 8 per cohort).
- For Ongoing studies, the **average subjects per trial jumped to 33 (12–64)**, with 9 (6–16) patients enrolled per cohort.
- Majority of KF patients were part of a full RI PK study rather than a reduced design.

Figure 1. **Average Study Duration is Two Months Longer Since the Guidance Release**



- Study duration was calculated as the difference between the primary completion date and start date as listed in ClinicalTrials.gov.
- Ongoing dates applied the estimated completion date, and average trial duration is expected to be **2–3 months longer** than previous studies.

Figure 2. **Nearly Half of Renal Impairment Studies are Conducted in the US with Fewer Trials Run in the EU**



- The US remains the most popular geography for RI PK studies while **studies run in the EU seem to be declining.**
- A substantial number of studies are now being conducted in Asia sites Post the guidance release compared to Pre guidance years, while fewer trials are being run in more than one geography.

PERSPECTIVE

Factors Influencing Renal Impairment PK Study Trial Designs and Geography:

- Time lag between guidance issuance implementation of design changes.
- Impact of COVID—study pauses, cancellations, difficulty enrolling severe patients, travel restrictions affecting site selection.
- Trial design guided by intended drug use in severe or KF renal impairment patients.
- New EMA clinical trial submission system may deter engaging EU sites.
- Study limitations: Not all studies reported on ClinicalTrials.gov, and very few had results for Post-completed studies.

CONCLUSION

- The revised guidance recommends to perform sample size justification based on drug PK variability, which can drive number of patient per cohort to 14 or more (1, 2).
- While the updated guidance did not seem to have an immediate impact on sample size, **ongoing studies are enrolling 5 more participants** than previously. This is extending study duration by several months, which can potentially delay phase II/III study initiation.
- Higher enrollment rates continue into 2023 as currently planned studies intend to enroll an average of 32 (20–48) participants for a RI PK study.
- Overall, this analysis can assist drug developers plan their future RI studies, as data can be leveraged to set **realistic study timelines** and give insight into **clinical site geography**, to comply with the revised FDA guidance.
- For instance, this analysis suggests there is **capacity at EU sites** which can be as part of a single- or multi-geography solution to facilitate speedy enrollment.

REFERENCES

1. Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER). Guidance for Industry Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling. Draft. September 2020. www.fda.gov/media/78573/download
2. Revised Renal Impairment PK Study Guidance: Key Takeaways. Paglialunga, S; Benrimoh, N; Pritchard, J.F. Celerion Whitepaper. October 2020. https://live-celerion.pantheonsite.io/wp-content/uploads/2020/10/Microsoft-Word-Whitepaper3.docx.pdf

DISCLOSURE

Sabina Paglialunga – Noting to disclose

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