Complexities involved in conducting patient PK/PD/CE studies and alternate proposals to have simplified study designs

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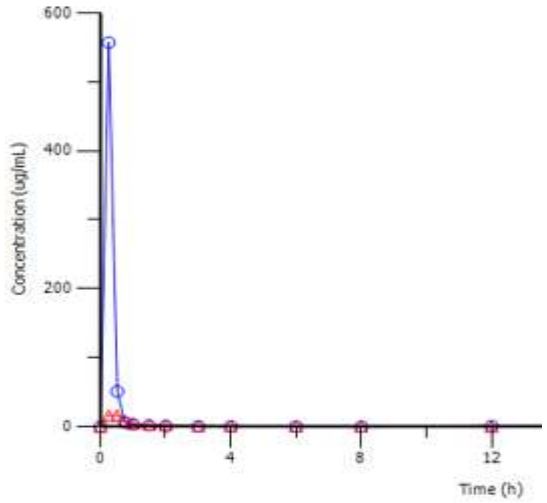
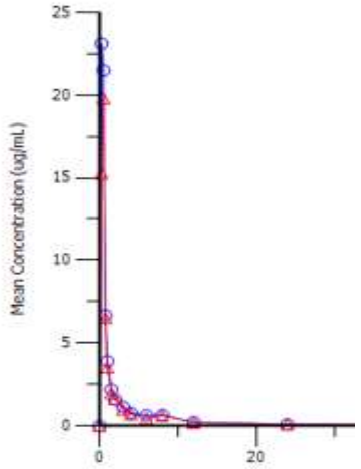
Presentation Contents

LAI Products – Challenges with Steady State Studies in Patients

- Challenges:
  - No guidance from FDA on how to statistically determine steady state (SS), various methods can be applied.
  - Individual subject variability presents challenges in design for SS (selection of the number of doses).
  - Dealing with very long study durations and large sample size (need to account for higher number of dropouts to account for those not meeting individual SS)
- Approaches to consider:
  - Steady state evaluation on the overall dataset without requirement for individual steady state (if mean SS is met or the majority of subjects meet SS, then keep all subjects in BE dataset as per pre-defined criteria in the study protocol)
  - PK modeling approaches to reduce sample size and establish BE with simulated data
  - Establish BE using a single sub-therapeutic dose in healthy subjects (IRBs have approved these studies and single dose studies for these products are standard in EU)

Outlier Example

One patient identified with extremely high levels following administration of the RLD via IV infusion (over 25 times higher than the mean Cmax for both test and RLD; also much higher than levels reported in literature) – determined to be a statistical outlier for all PK parameters using Lund's (studentized residual) method

Outlier Subject (snapshot to see levels): Blue = reference Red = test	Mean Graph (snapshot to see levels):
	

Outlier Example & Analysis Considerations

- No adverse events reported for this patient during the time at which these levels were observed
- Clinical and bioanalytical investigations did not yield a reason for the high levels
- Clearly some unidentified reason is attributed to these high levels for the RLD. The study did not pass with this subject included and FDA did not accept the removal of this statistical outlier. The multi-site patient study needed to be repeated.
- Unless there is a clinical or analytical reason identified for the outlier, the removal of statistical outliers from the dataset is discouraged. In the event that an investigation does not determine a reason, FDA requests for the study to be repeated.
  - Would a blinded review of the analytical data prior to statistical analysis resolve the issue?

PD/CE Study Design Challenges(tough to predict FDA thinking)

- Multiple primary end points
- Sometimes secondary end point of innovator study becomes primary end point for generics
- Different study duration for innovator vs Gx. CE studies
- Dichotomous end point vs continuous end points (Innovator vs Generic studies)
- Because of these changes sample size increases (lot of times Gx study sample size is higher than innovator study)
- Too tight I/E criteria
- Overall it is becoming tough to predict FDA expectations on study designs
- General guidance needed when product is prescribed for multiple indications i.e. how to select the indication or patient population

Alternate Approaches with PD/CE study designs

- To reduce the burden on Generics we need simplified PD/CE study designs
- Maybe wider CI approach for high variable molecules similar to PK studies
- Reducing the number of primary end points
- Totality of evidence approach
- Post Hoc analysis and justifications
- Flexibility in ANCOVA model
- Study duration and number of study visits

Retention sample challenges with respective multicenter trials

- New guidance is helpful but further clarity is needed for multi center trials
- When the same lot number used throughout the study the number of samples should meet minimal requirements as per guidance (eg. single dose product – at least 30 units across all sites for each IP, not per shipment)
- Reducing the burden of retention samples for each shipment (central independent location?), reduce the shipment costs and other burden
- Length of storing these retention samples: Can it be disposed once FDA picks the retention samples during the inspections (high storage costs)?

Interaction with FDA

- Controlled correspondence timelines vs product development timelines
- Flexibility to ask the new questions during the pre development meetings like NDA and BLA meetings
- Availability of Innovator data as soon as product is approved

Acknowledgements

- Elizabeth Rody
- Craig Trexler
- Amanda Valente
- Corrine Dias

Thank you.