Workshop on ICH M10

PG-02: Is it allowed to re-analyse positive predose in BE study?

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From the Guideline

- 3.3.4 and 4.3.4 Reanalysis of study samples

"Some examples of reasons for study sample reanalysis are:…. Identification of quantifiable analyte levels in pre-dose samples, control or placebo samples"

But also:

"For comparative BA/BE studies, reanalysis of study samples for a PK reason (e.g., a sample concentration does not fit with the expected profile) is not acceptable, as it may bias the study result."

Pre-meeting survey

	the question	Yes	No
Q1	Is it allowed to re-analyse positive predose in BE study?	22	3
Q2	If no, why not?		
Q3	if yes, what are the limitations or communication requirements/limitations?		
free text			

Feedback from the round table: 84% is performing re-analysis

Key message from the pre-meeting survey and round tables (in red = recommendations/conclusions from the round tables)

- Is it allowed to re-analyse positive predose in BE study?
  - Not clear if this is a PK repeat
  - Yes, because it does not impact the comparison of Cmax/AUC
  - Yes, but confirmatory repeat of the anomalous result only (wouldn't apply if possible positive due to not enough time for wash out between treatments)

- If no, why not?
  - reanalysis for PK reason is not allowed
  - only analytical repeats are allowed and a positive predose is not considered an analytical repeat but is it a PK repeat by definition?
  - It is opening a can of worms

- When confirmatory analysis?
  - Dependent on the level (near LLOQ or high concentration)
  - Dependent on the amount of positive pre-dose samples

Key message from the pre-meeting survey comments

- if yes, what are the limitations or communication requirements/limitations?
  - Majority performs first bioanalytical investigation and reach out to clinical site; rest will first perform confirmatory analysis (two independent repeats)
  - Have a process for re-analysis: communication/approval to sponsor-trial lead-PK, decision tree, clear documentation in report
  - Be mindful of potential for unblinding when communicating
  - Only predose from 1st period can be reanalyzed

- Why bother to analyse a pre-dose sample as it is not part of the PK evaluation
  - Yes
  - it is important to measure whether any matrix interference exists,
  - people still have drug from previous trial,
  - Quality check, ...

Raw data from the pre-meeting survey comments

- In the next slides we provide the unredacted details from 56 survey files reaching us prior to the deadline.
- Surveys that have arrived after the deadline could not be included anymore, for logistic reasons. Please speak up if your comment wasn't already captured in the other 56 files

On Q1: Is it allowed to re-analyse positive predose in BE study?

- Y, Check for technical errors
- NA, we are not involved in BE studies and has therefore not experience with this (and is therefore not on top of the guidelines in this area)
- N/A - No BE Experience
- I would say yes but others say no; example of positive predose is given when reassay could be done but further down for BE studies it says samples should not be reanalyzed for a PK reason
- Not clear if this is a PK repeat or not
- not sure, we have not analysed a BE study in many years. would have to look it up
- Y, because it does not impact the comparison of Cmax/AUC
- Yes - section 3.3.4 and 4.3.4 'Identification of quantifiable analyte levels in pre-dose samples, control or placebo samples'
- y, but confirmatory repeat of the anomalous result only (wouldn't apply if possible positive due to not enough time for wash out between treatments)

On Q2: If no, why not?

- it is stated that reanalysis for PK reason is not allowed
- Because only analytical repeats are allowed to be re-analysed
- We follow wording in the ICH M10 that we do not conduct PK repeats in BA/BE studies, and a positive predose is not considered an analytical repeat but is it a PK repeat by definition?
- open an internal investigation and depending on the outcome re-analysis

On Q3: if yes, what are the limitations or communication requirements/limitations?

- Process (decision tree) should be in place
- Sponsor is informed, Direct or via report
- Maintain blind
- only for technical reasons (to exclude technical errors), prompt communication to Clin Trial Lead and PK
- This is unexpected and raise a concern that the study has not been conducted according to the protocol or if the staff was sufficiently trained to sample in a correct manner. Data not related to PK
- Communication stays internal to avoid any blinding issues.
- No limitations
- lack of clarity of definition of PK repeat for positive pre-dose and what is allowed for BE studies
- communication with sponsors, only re-analyse if an analytical issue occurred
- Reason needs to be documented, e.g. to check that there is no contamination.

On Q3: if yes, what are the limitations or communication requirements/limitations?

- If redosing is carried out in accordance with the SD, and the justification for redosing is documented in the phase report
- Depends on SOP
- seek team approval before
- Analyse in duplicate, so you have three results. Report median
- replicate determination if volume allows
- Communication of the below
- justification (e.g. (technical) outlier)
- to be clearly reported in the BA report”
- If reanalysis, communication between CRO and Sponsor should be done in a timely manner, final decision by Sponsor, and should be documented in TMF/Report.
- in case a BE was performed with wash out periods too short - but this implies that there is another issue with that study. Data must be listed and discussed with clinicians and in the report, if there were an influence on PK profiling

On Q3: if yes, what are the limitations or communication requirements/limitations?

- Based on our experience, Pre-dose samples containing drug are mainly contaminated on site, or samples are inverted during aliquoting, re-analysis only confirm that no error occurs in the BA lab.
- Could not be possible to exclude one abnormal profile in a BE study where number of patients is high?"
- limited to SOP application and communicate according to plan, discussed in BA report
- sample is analysed in duplicate to confirm or not the previous obtained result
- re-analysis of the 2 aliquots (main and back up) and follow pre-defined decision tree
- redefined in the protocol, study plan and SOP / multiple determination
- Positive predose (>LLOQ) in first period can be reanalysed.
- Reporting of original and repeat results. Justification for re-analysis and result reported
- limited to SOP application and communicate according to plan, discussed n BA report

Free text

- Potential points for discussion as PK reason is not clearly defined (is positive pre-dose a PK reason? As it may bias the study result but is most likely an analytical or sampling error). Positive predose is safety - not for PK reasons
- "Two different opinions in our team for Q1:
  - N - ICH M10 not allowed reanalyse “for comparative BA/BE studies, reanalysis of study samples for a PK reason (e.g., a sample concentration does not fit with the expected profile) is not acceptable, as it may bias the study result”
  - Y - It is not for a sample concentration that does not fit the PK profile - rather indicates sampling issue/potential misdosing"
- "I have no experience to encounter the positive predose in BE study.
- However, I think that re-analysis in BE study is NOT allowed under any cases."
- no work in BE studies
- question not clear