Summary of 2nd GBHI Workshop Session IV: Exclusion of Pharmacokinetic Data in Bioequivalence Assessment

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2016 Session IV: Exclusion of Pharmacokinetic Data in Bioequivalence Assessment

Regulatory Perspective

- European Regulatory Authority's perspective

Jan Welink, Medicines Evaluation Board, The Netherlands

- US Food and Drug Administration (FDA)'s perspective

Hao Zhu, US FDA

- Brazilian Regulatory Authority's perspective

Gustavo Mendes Lima Santos, The Brazilian Health Regulatory Agency (ANVISA), Brazil

2016 Session IV: Exclusion of Pharmacokinetic Data in Bioequivalence Assessment

Pharmaceutical Industry Examples

- Potential reasons for exceptional product performance ("outlier profiles") in BE studies

Keith D. Gallicano, Novum Pharmaceutical Research Services, USA

- How to deal with "event"-related outliers (e.g., caused by AEs/Non-compliance)

Fethi Trabelsi, Biopharma Services Inc., Canada

- How to deal with individual "implausible" PK-data in BE studies?

Mohammad Khalil Mohammad, ACDIMA Biocenter, Jordan

- Pros and cons for re-dosing in case of outliers

Yu Chung Tsang, Apotex, Canada

European Medicines Agency (EMA)

General Considerations for Subject Exclusion

- All subjects are observed and treated according to the same rules
- Decision to exclude a subject must be made before bioanalysis and specified in the protocol

Exclusion of Subjects/Pharmacokinetic Data Unacceptable

- Statistical analysis alone
- Pharmacokinetic reasons alone

Exclusion of Subjects/Pharmacokinetic Data Acceptable

- Vomiting (within reasonable time from administration)
- Diarrhea
- Concomitant medication influencing pharmacokinetics
- A subject with lack of any measurable concentrations or only very low plasma concentrations for reference medicine (e.g. the AUC of the subject < 5% geometric mean of the AUC of the reference)
- Subjects with non-zero baseline concentration > 5% of Cmax

Jan Welink, Medicines Evaluation Board, The Netherlands

Guideline on the investigation of bioequivalence, EMA, 2010, http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500070039.pdf

FDA

Outliers

- Subject data for one or more bioavailability (BA) measures that are discordant with corresponding data for that subject and rest of subjects in a study

Take home message

- Outliers can be informative and should not be ignored.

Case I: Comparison of early clinical trial formulation and to-be-marketed formulation

- Subgroup of patients with elevated gastric pH had lower drug exposure

Case II: Alcohol dose dumping for Palladone

- Some individual showed about 16-fold increase in Cmax while average is about 6-fold increase when co-administered with 40% alcohol

ANVISA

For discrepant Pharmacokinetic profiles

- Evaluation of possible errors (Design? Analytical?)
- Difference in bioequivalence conclusion?
- Proper justifications for exclusions of subjects ?

For single data in a Pharmacokinetic profile

- Exclusion established in standard operating procedure (SOP)?
- Exclusion criteria adequate?
- Possible errors properly investigated?

Gustavo Mendes Lima Santos, ANVISA, Brazil

Potential Reasons for Exceptional Product Performance ("Outlier Profiles") in BE Studies

Subject Event Outliers

- Interference from structural isomer(s) of phentermine
- Vaginal ring removal

Study Process Event (Clinic) Outliers

- Sample interchange at clinic
- Swallowing volume and rate control for suboxone sublingual film
- Inadvertent extravasation during intravenous administration

Study Process Event (Lab) Outliers

- Sample process queue error

Subject-by-Formulation Outliers

- Genetic polymorphism
- Test treatment show below the limit of quantitation (BLOQ) concentrations in replicated study

Outlier and Reference Scaled Bioequivalence (RSABE)

- RSABE is appropriate for highly variable drug products but not appropriate for highly variable study procedures
  - Outliers for Reference product will inflate reference within subject variability and lead to unjustified scaling, which may
    - Increase consumer risk of incorrectly concluding the products are BE when they are truly not BE
    - Increase sponsor risk of incorrectly concluding the products are not BE when they are truly BE

Investigation of Outliers

- Challenging
- Call for standardized procedures

How to Deal with "Event"-related Outliers (e.g., Caused by Adverse Events (AEs)/Non-compliance)

Subjects exclusion/withdrawal

- Exclusion of data cannot be accepted on the basis of statistical analysis or for pharmacokinetic reasons alone
- The decision to exclude data from this subject from the statistical analysis must be made before performing the bio-analysis to avoid bias
- Subjects could be excluded if
  - Adverse events (e.g. vomiting and diarrhea) may impact the reliability of the Pharmacokinetic profile
  - They met pre-specified reasons in the protocol (e.g. vomiting within 2 median Tmax for immediate release (IR) or dosing interval for extended release (ER)
  - …..

Take home messages

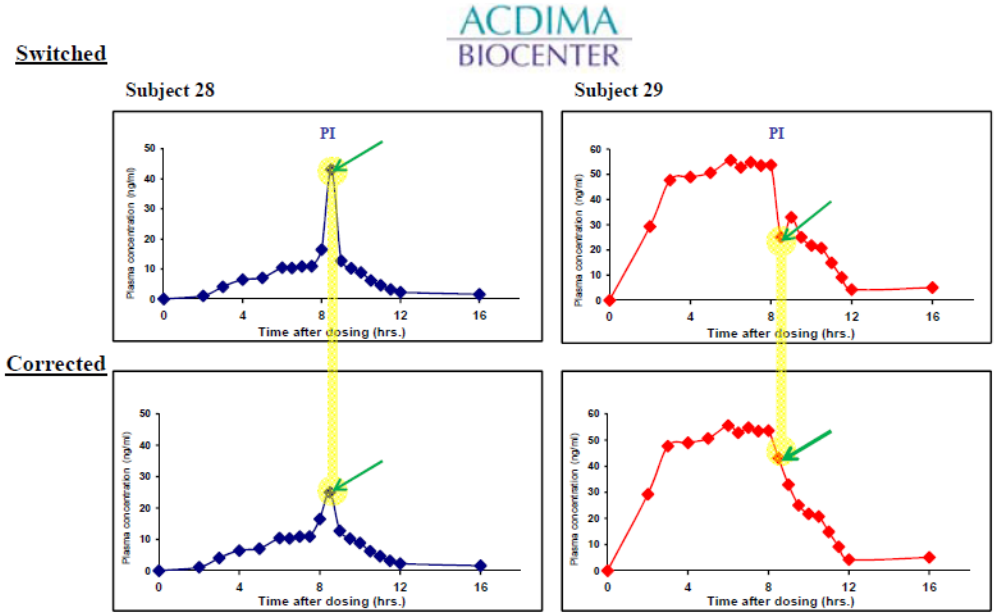
- Subjects having experienced significant AEs (other than vomiting) and withdrawn could have similar pharmacokinetic profiles as others (two case examples)
- It might be advisable in some cases (e.g. headache, migraine attack) to look retrospectively into the data and decide to exclude a subject. However, the decision criteria should be set in the protocol to avoid unbiased assessment.
- More research on the topic is needed.

How to Deal with Individual "Implausible" Pharmacokinetic Data in BE studies?

Possible Reasons For Implausible PK Data

- Product related
  - Real formulation differences
  - Lack of homogeneity
  - Stability issues
- Study related
  - Clinical conduct
  - Analytical execution
  - Sample integrity during clinical and analytical procedures
    - o Proper labeling
    - o Storage conditions
    - o Right container and light-protection
    - o Good documentation and record keeping

Case Study on Suspected Inadvertent Sample Switching



- Proper investigation has been conducted and evidence of sample switching is proven.
- No difference in bioequivalence conclusion with different analysis
- Switching is not overly recurrent in the study samples.

Pros and Cons for Redosing in Case of Outliers

Methodology of Re-dosing

- Suspected aberrant T/R ratios of AUC and/or Cmax should be first identified as statistical outliers
- The statistical outlier subject (s) is re-dosed along with a few “normal” subjects from the original study with both the test and reference products

Case Examples

- Ketoconazole tablet
- Bisphosphonate drug A
- Nasally administered drug B
- Antidepressant drug C

Challenges for Redosing

- Regulatory, statistical and practical

Pros of Re-dosing: Cost-effective to confirm outliers and provide justification for data exclusion

- Reduce drug exposure to healthy subjects
- Not delay drug approval time

Cons of Re-dosing: value of the redosing interpreted differently by different reviewers without formal policy or guidance on re-dosing

- May not know the interpretation of redosing data until the ANDA review
- Eventually may cause longer time and higher cost for drug approval

Verdict: Pros outweigh Cons especially if agencies can formalize their policy and provide clear guidance on the procedure and acceptance criteria

Yu Chung Tsang, Apotex, Canada

Summary

Regulatory Perspective

- Discourage the dropping of outlier subjects from in vivo BE studies in general
- No clear standards for pre-hoc definition of outlier subjects
- Outlier are handled differently among different regulatory agencies

Pharmaceutical Industry Examples

- Demonstrate a wide variety of outlier examples
- Call for harmonized procedures and acceptance criteria to handle outliers
- Need regulatory research on pharmacokinetic outliers