Supplementary Materials

Does the Estimand Framework Add Value to Clinical Pharmacology Trials?

Abstract

Can the estimand framework add clarity in pharmacokinetic (PK) trials and will regulators require estimands to be stated in clinical pharmacology trials?

We apply the estimand framework of ICH E9(R1) "Addendum on estimands and sensitivity analysis"[1,2] to a bioequivalence (BE) study[3] and consider other PK questions of key importance to drug labelling.

PK is what the body does to the drug through the processes of absorption, distribution, metabolism, and excretion. Interest is in the profile of drug or metabolite concentrations in plasma over time summarised by the coprimary parameters: area under curve (AUC) and maximum plasma concentration (C_{max}).

Generally, the goal of bioequivalence trials is to confirm the ratio of geometric means (test/reference) of AUC and C_{max} with 90% confidence intervals lies within equivalence margins. Although regulators have detailed guidelines for bioequivalence and interaction trials, their scientific question(s) of interest are not clearly stated.

We explore the most common intercurrent events expected to impact the PK processes, and hence affect interpretation of the PK parameters. We also discuss the most relevant target population.

We will conclude by reflecting on existing guidelines and on how these may be adapted to incorporate the principles outlined in ICH E9(R1).

Introduction

The following steps of the ICH E9(R1) training slides[2] guided our thinking in considering BE[3] of a new formulation of pirfenidone (film coated 801 mg tablet) which could replace taking three 267 mg capsules three times per day:

Step 1: Therapeutic setting and intent of treatment determining a trial objective
Step 2: Identify intercurrent events
Step 3: Discuss strategies to address intercurrent events
Step 4: Construct the estimand
Step 5: Align choices on trial design, data collection and method of estimation
Step 6: Identify assumptions for the main analysis and suitable sensitivity analyses to investigate these assumptions

Document the Estimand

Step 7 of the thinking process is "Document the estimand" is described in detail on page 3 of this supplement online, and summarised as:

In healthy adults able to tolerate 801 mg pirfenidone, the test formulation of one 801 mg film-coated tablet is compared to the reference of 3 x 267 mg capsules administered with food, by geometric mean ratio (test/reference) of pirfenidone C_{max} and $AUC_{0-\infty}$ after a single dose, as though dosed correctly, without intake of interacting substances or unrelated intercurrent illness affecting absorption or other PK processes.

Justification of Principal Stratum Strategy

It is envisaged that only those able to tolerate 3 x 267 mg capsules of pirfenidone with food would be transitioned to the 801 mg tablet, and thus tolerability of pirfenidone is an important consideration for our principal stratum. Furthermore, differences in tolerability may be reflected in different PK properties (such as increased absorption or decreased clearance). In clinical practice, the dose of pirfenidone is up titrated to 3 x 267 mg capsules three times per day but approximately 40% of patients have tolerability issues (e.g., nausea and rash) and do not tolerate the top 801 mg dose level. The new film-coated tablet is anticipated to have similar PK profile to the three

capsules and thus it is designed for convenience rather than to alleviate any gastro-intestinal tolerability issues. We will study healthy adults able to tolerate 801 mg pirfenidone (in either formulation) as a good surrogate for the patient population able to tolerate 3 x 267 mg pirfenidone capsules; we study healthy adults rather than very sick patients since we can take full PK profiles and control other substances/interacting drugs more easily.

Justification of Hypothetical Strategy

This is a bioequivalence study comparing different formulations and thus sensitivity to pick up any differences between how these formulations are absorbed is paramount. In healthy volunteer PK studies, it is possible to minimize dosing errors and use of interacting drugs or substances. Sometimes, issues emerge such as being unwell with tummy bug (unrelated nausea) or needing to take a prohibited medicine for a new condition. These factors introduce noise to a subsequent PK profile which should be excluded but they do not define a principal stratum which justifies complete exclusion of these people; thus, PK profiles prior to these events may provide informative data and a later PK profile after washout/recovery would also be relevant data if the design allows.

Comments on Analysis Approaches

Fixed effect ANOVA analysis of completers is still considered the benchmark analysis of 2x2 cross-over BE studies and advocated as the preferred analysis by regulatory guidance[4-7] "despite its proneness for biased results"[8]. "The fixed-effects analysis provides sensible results only under MCAR and overestimates the effect under MAR"[8]. In the case, where all subjects who can tolerate pirfenidone complete the study with no issues then the mixed model we advocate would provide identical results to the fixed effects approach. However, should there be data available in Period 1 for someone who has an (unrelated) tummy bug in Period 2 or other medical issue requiring prohibited medication, we consider their Period 1 data is still relevant for use.

Recommendations on Regulatory Guidance

Currently, guidelines on bioequivalence studies[4-7] provide detailed information on trial design and statistical analysis. They advocate complete exclusion of subjects who have vomited[6,7] without mentioning if interest is in the principal stratum able to tolerate the drug?

We challenge the regulators to reconsider their guidance and to state the estimand they have in mind and justify an analysis approach aligned to their estimand.

References with Links

1. ICH E9(R1) Addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials (Effective in EMA 30 July 2020)
2. ICH E9(R1) training slides: E9(R1) Training Material - PDF 0.pdf (https://database.ich.org) (accessed 23 May 2022)
3. Lin Pan et al. A Pharmacokinetic Bioequivalence Study Comparing Pirfenidone Tablet and Capsule Dosage Forms in Healthy Adult Volunteers. Adv Ther (2017) 34:2071–2082.
4. FDA Draft Guidance for Industry: Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an Abbreviated New Drug Application (ANDA) (August 2021)
5. FDA Guidance for Industry: Statistical Approaches to Establishing Bioequivalence (FINAL January 2001)
6. FDA Draft Guidance for Industry: Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs - General Considerations (March 2014)
7. EMA Guideline on the Investigation of Bioequivalence (Effective 1 August 2010)
8. Gerd K Rosenkranz. Analysis of cross-over studies with missing data. Statistical Methods in Medical Research (2015) Vol. 24(4) 420-433

Contacts

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Supplementary Materials

Step 7: Document the Estimand

Estimand Description	In healthy adults able to tolerate 801 mg pirfenidone, the test formulation of one 801 mg film-coated tablet is compared to the reference of 3 x 267 mg capsules administered with food, by geometric mean ratio (test/reference) of pirfenidone C_{max} and $AUC_{0-\infty}$ after a single dose, as though dosed correctly, without intake of interacting substances or unrelated intercurrent illness affecting absorption or other PK processes.
Target Population	Healthy adults able to tolerate 801 mg pirfenidone (either formulation, since no tolerability differences expected) administered with food.
Treatment Conditions	**Test:** 1 x 801 mg film-coated tablet compared to **Reference:** 3 x 267 mg capsules Administered with food as per drug label (to reduce side effects), dosed correctly and without intake of interacting substances
Population-Level Summary	Ratio of geometric means (test/reference)
Endpoint	Pirfenidone C_{max} and $AUC_{0-\infty}$ after a single dose
Intercurrent Event Strategies	1. **Principal Stratum** of healthy adults **able to tolerate** 801 mg pirfenidone administered with food 2. **Hypothetical -** Without any effects from incorrect dosing, interacting substances and without any unrelated intercurrent illness affecting absorption or other PK processes.
Rationale for Intercurrent Event Strategies Please refer to justification of principal stratum and hypothetical strategies outlined earlier.	

Comments on Intercurrent events in a Clinical Pharmacology Trial
Consider the intercurrent events in a clinical pharmacology trial as those things that impact the processes of absorption, distribution, metabolism, and excretion. For example, consider the route of administration when considering absorption. For an inhaled product, there may be a tendency (particularly in healthy volunteers not used to inhalers) to swallow part of the dose; for a patch, it may come loose. Other intercurrent events may impact the elimination processes such as interacting drugs which induce or inhibit metabolism.

Good study conduct and potentially a training period (e.g. to reliably inhale) may be able to alleviate some of these intercurrent events. Other intercurrent events such as needing to discontinue doses because of inability to tolerate, are a characteristic of the population and thus lend themselves to strategies considering the principal stratum.

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