Comparative Clinical Endpoint in Bioequivalence Studies

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Outline

- Reasons for conducting comparative clinical endpoint bioequivalence (BE) studies
- Role of product specific guidance (PSG)
- Comparative Clinical Endpoint Study:
    - Study Design
    - Endpoints
    - Analysis Populations
- Types of Hypothesis Testing:
    - Equivalence
    - Superiority

Why Clinical Endpoint BE Studies?

- Conducted when more informative than other approaches
  - Dosage form is intended to deliver the drug locally
    - Topical products (cream, gel, ointment)
    - Ophthalmic products
  - The drug substance does not reach the site of action through the systemic circulation
    - Metered-dose inhalers
    - Nasal spray

Product Specific Guidance (PSG)

- FDA publishes PSGs for generic products
  - Ensure consistency across generic applications for the same Reference Listed Drug (RLD)
- The PSG outlines recommendations
  - Study Design
  - Endpoints
  - Study Population
  - Criteria to establish Bioequivalence
- PSGs can be found at: https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm

Comparative Clinical Endpoint BE Study

- Study Design
- Endpoints
- Analysis Populations

Study Design

- Randomized Parallel-arm studies
  - Test/Reference/Placebo
- Compare Test and Reference products to establish BE
- Compare Test and Reference separately to placebo for assay sensitivity

Analysis Populations

- Modified Intent-to-Treat (MITT)
  - used to assess assay sensitivity
  - randomized subjects, at least one dose of products
- Per Protocol (PP)
  - used to assess Bioequivalence
  - randomized subjects, at least one dose of products, met protocol

Clinical Endpoints

- Continuous
  - Examples:
    - lesion counts (mean percent reduction from baseline)
    - average scales over several assessments
- Binary
  - Examples:
    - cure/no cure
    - success/failure

Types of Statistical Hypothesis Tests

- Equivalence
- Superiority

Hypothesis Testing: Equivalence

- To establish BE, the following compound hypothesis is tested

H_0: **Test is either worse than Reference by θ_1 or Test is better than Reference by θ_2**
H_1: **Test is not worse than Reference by θ_1 and Test is not better than Reference by θ_2**

- Rejection of the null hypothesis supports the conclusion of equivalence of the two products

- This is the Two-One Sided Test (Schuirmann, 1987)

Hypothesis Testing: Equivalence

- For a continuous endpoint

$$H_0: \frac{\mu_T}{\mu_R} \leq \theta_1 \; or \; \frac{\mu_T}{\mu_R} \geq \theta_2 \; vs$$

$$H_1: \theta_1 < \frac{\mu_T}{\mu_R} < \theta_2$$

μ_T = mean of the primary endpoint for the Test group
μ_R = mean of the primary endpoint for the Reference group

- H_0 is rejected if the 90% confidence interval for the ratio of the means between T and R products ($^{\mu_T}/_{\mu_R}$) is contained within the interval $[\theta_1, \theta_2]$

Hypothesis Testing: Equivalence

- For a binary endpoint

$$H_0: \pi_T - \pi_R \leq \Delta_1 \; or \; \pi_T - \pi_R \geq \Delta_2 \; vs$$

$$H_1: \Delta_1 < \pi_T - \pi_R < \Delta_2$$

π_T = the success rate of the primary endpoint for the Test group
π_R = the success rate of the primary endpoint for the Reference group

- H_0 is rejected if the 90% confidence interval for the difference of the success rates between T and R products $(\pi_T - \pi_R)$ is contained within the interval $[\Delta_1, \Delta_2]$

Hypothesis Testing: Superiority

- Superiority: To show that Test and Reference are superior to Placebo
- Done to establish assay sensitivity
  - Let Drug A be Test or Reference

H_0: Drug A is not better than Placebo
H_1: Drug A is better than Placebo

- Rejection of the null hypothesis supports the conclusion that Drug A (Test or Reference) is superior to Placebo

Hypothesis Testing – Superiority

- For a continuous endpoints we test

$$H_0: \frac{\mu_A}{\mu_{pbo}} = 1 \; vs$$
$$H_1: \frac{\mu_A}{\mu_{pbo}} \neq 1$$

μ_A = mean of the primary endpoint for the Drug A
μ_{pbo} = mean of the primary endpoint for the placebo

- Rejecting the null at 5% level of significance supports the superiority of Drug A over Placebo

Hypothesis Testing – Superiority

- For a binary endpoints we test

$$H_0: \pi_A - \pi_{pbo} = 0 \; vs$$
$$H_1: \pi_A - \pi_{pbo} \neq 0$$

π_A = the success rate of the primary endpoint for Drug A
π_{po} = the success rate of the primary endpoint for Drug B

- Rejecting the null at 5% level of significance supports the superiority of Drug A over Placebo

Conclusion

- Reason for conducting comparative clinical endpoint bioequivalence (BE) studies
- Role of product specific guidance
- Study Design/Endpoints/Analysis Population
- Types of Hypothesis Testing