Draft Guidance on Crisaborole

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

Active Ingredient: Crisaborole

Dosage Form; Route: Ointment; topical

Recommended Studies: To demonstrate bioequivalence (BE) for this drug product by conducting two studies with pharmacokinetic (PK) endpoints (one in vitro study evaluating local (cutaneous) PK and one in vivo study evaluating systemic (plasma) PK), the following criteria should be met:

A. The test and Reference Listed Drug (RLD) products are qualitatively (Q1) and quantitatively (Q2) the same as defined in the Guidance for Industry: ANDA Submissions – Refuse-to-Receive Standards.

B. The test and RLD products are physically and structurally similar based upon an acceptable comparative physicochemical characterization of a minimum of three lots of the test and a minimum of three lots (as available) of the RLD product. Comparison of physical and structural similarity for the test and RLD products should include the following physicochemical characterizations for each lot of test and RLD products:

    1. Assessment of appearance
    2. Microscopic characterization of the ointment with representative images at multiple magnifications.
    3. Analysis of the rheological behavior which may be characterized using a rheometer that is appropriate for monitoring the non-Newtonian flow behavior of semi-solid dosage forms. The following evaluations are recommended:
        i. A complete flow curve of shear stress (or viscosity) vs. shear rate should consist of multiple data points across the range of attainable shear rates, until low or high shear plateaus are identified.
        ii. Yield stress values should be reported if the material tested exhibits plastic flow behavior.
        iii. The linear viscoelastic response (storage and loss modulus vs. frequency) should be measured and reported.
    4. Analysis of any other potentially relevant physical and structural similarity characterizations

C. The test and RLD products have an equivalent rate of crisaborole release based upon an acceptable in vitro release test (IVRT) comparing a minimum of one lot each of the test and

RLD products using an appropriately validated IVRT method. Refer to the Draft Guidance on Acyclovir (Topical Cream) for additional information regarding the development, validation, conduct and analysis of acceptable IVRT studies.

D. The test and RLD products are bioequivalent based upon an acceptable in vitro permeation test (IVPT) comparing the rate and extent of crisaborole permeation through excised human skin from a minimum of one lot each of the test and RLD products using an appropriately validated IVPT method.

   Type of study: In vitro (IVPT) BE study with local (cutaneous) PK endpoints
   Design: Parallel, single-dose, multiple-replicate per treatment group study design
   Strength: 2%
   Skin: Barrier-competent skin from male and/or female donors of at least 18 years of age, general population

   Additional comments: The lots of test and RLD products evaluated in the IVPT study should be the same as those evaluated in the IVRT study, and that these lots should be included among those for which the physical and structural similarity is characterized and compared. Refer to the Draft Guidance on Acyclovir (Topical Cream) for additional information regarding the development, validation, conduct and analysis of PK endpoints for acceptable IVPT studies.

E. The test and RLD products are bioequivalent based upon an acceptable in vivo PK study with one lot each of the test and RLD products.

   Type of study: In vivo BE study with systemic (plasma) PK endpoints
   Design: Single-dose, two-way crossover study design
   Strength: 2%
   Subjects: Males and non-pregnant, non-lactating females, general population

   Additional comments: The lots of test and RLD products evaluated in the plasma PK study should be the same as those evaluated in the IVPT study.

Analytes to measure (in appropriate fluid): Crisaborole in plasma (in vivo) or in receptor solution (in vitro)

Bioequivalence based on (90% CI): Crisaborole

Waiver request of in vivo testing: Not applicable (N/A)

Dissolution test method and sampling times: N/A