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Draft Guidance on Tirbanibulin

October 2022

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Active Ingredient: Tirbanibulin

Dosage Form; Route: Ointment; topical

Recommended Studies: Two options: (1) one in vitro bioequivalence study and other characterization tests or (2) one in vivo bioequivalence study with clinical endpoint

I. Option 1: One in vitro bioequivalence study and other characterization tests

To demonstrate bioequivalence for tirbanibulin topical ointment, 1% using in vitro studies, the following criteria should be met:

1. The test product should contain no difference in inactive ingredients or in other aspects of the formulation relative to the reference standard that may significantly affect the local or systemic availability of the active ingredient. For example, if the test product and reference standard are qualitatively (Q1) and quantitatively (Q2) the same, as defined in the most recent version of the FDA guidance for industry on *ANDA Submissions – Refuse-to-Receive Standards*[a] and the criteria below are also satisfied, the bioequivalence of the test product may be established using a characterization-based bioequivalence approach.

2. The test product and reference standard should have the same physicochemical and structural (Q3) attributes, based upon acceptable comparative Q3 characterization of a minimum of three batches of the test product and three batches (as available) of the reference standard. The test product and reference standard batches should ideally represent the product at different ages throughout its shelf life. Refer to the most recent version of the FDA guidance for industry on *Physicochemical and Structural (Q3) Characterization of Topical Drug Products Submitted in ANDAs*[a] for additional

information regarding comparative Q3 characterization tests. The comparison of the test product and reference standard should include characterizations of the following Q3 attributes:

a. Characterization of visual appearance and texture
b. Characterization of phase states and structural organization of matter
    - Microscopic examination with representative high-resolution microscopic images at multiple magnifications
c. Characterization of 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:
    - A characterization of shear stress vs. shear rate and viscosity vs. shear rate. At minimum, this should consist of numerical viscosity data at three shear rates (low, medium, and high).
    - A complete flow curve across the range of attainable shear rates, until low or high shear plateaus are identified.
    - Yield stress values should be reported if the material tested exhibits plastic flow behavior.
d. Characterization of specific gravity
e. Characterization of any other potentially relevant Q3 attributes

3. The test product and reference standard should have an equivalent rate of tirbanibulin release based upon an acceptable in vitro release test (IVRT) comparing a minimum of one batch each of the test product and reference standard using an appropriately validated IVRT method.

    Type of study: Bioequivalence study with IVRT endpoint
    Design: Single-dose, two-treatment, parallel, multiple-replicate per treatment group study design using an occluded pseudo-infinite dose, in vitro
    Strength: 1%
    Test system: A synthetic membrane in a diffusion cell system
    Analyte to measure: Tirbanibulin in receptor solution
    Equivalence based on: Tirbanibulin (IVRT endpoint: drug release rate)
    Additional comments: Refer to the most recent version of the FDA guidance for industry on *In Vitro Release Test Studies for Topical Drug Products Submitted in ANDAs*[a] for additional information regarding the development, validation, conduct and analysis of acceptable IVRT methods/studies. The batches of test product and reference standard evaluated in the IVRT bioequivalence study should be included among those for which the Q3 attributes are characterized.

II. Option 2: One in vivo bioequivalence study with clinical endpoint

1. Type of study: Bioequivalence study with clinical endpoint
    Design: Randomized, double blind, parallel, placebo-controlled, in vivo study
    Strength: 1%
    Subjects: Males and non-pregnant, non-lactating females with clinically typical, visible, and discrete actinic keratosis (AK) lesions on the face or scalp

Additional comments: Specific recommendations are provided below.

Additional comments regarding the bioequivalence study with clinical endpoint:

1. FDA recommends conducting a bioequivalence study with a clinical endpoint in the treatment of AK. Subjects are to be randomized to receive the tirbanibulin topical ointment, 1% test product, the reference standard, or placebo vehicle. The study drug is to be applied once daily for 5 days with an amount of ointment sufficient to evenly cover up to 25 cm^2 treatment field on the face or scalp using one single-dose pack, left on the skin for approximately 8 hours, and then removed by washing with mild soap and water. Applications near and around the mouth, lips, and periocular area should be avoided. Hand washing with soap and water immediately after ointment application is recommended.

2. Inclusion criterion (the sponsor may add additional criteria):
    a. Males and non-pregnant, non-lactating females at least 18 years of age with four (4) to eight (8) clinically typical, visible, and discrete AK lesions in a contiguous area of 25 cm^2 on the face or scalp

3. Exclusion criteria (the sponsor may add additional criteria):
    a. Clinically atypical and/or rapidly changing AK lesions on the treatment area: hypertrophic, hyperkeratotic, recalcitrant disease with previous cryosurgery and/or cutaneous horn.
    b. Location of the treatment area is 1) on any location other than the face or scalp or 2) within 5 cm of an incompletely healed wound and 3) within 5 cm of a suspected basal cell carcinoma or squamous cell carcinoma.
    c. Use within 8 weeks prior to the screening visit, 1) 5-fluorouracil, 2), imiquimod, 3) ingenol mebutate, 4) diclofenac, 5) photodynamic therapy, or 6) other treatments for AK within the treatment area or within 2 cm of the treatment area.
    d. Use within 4 weeks prior to the screening visit, 1) immunomodulators, 2) cytotoxic drugs, 3) interferons/interferon inducers, or 4) systemic medications that suppress immune system.
    e. Use of systemic retinoids within 6 months prior to the screening visit.
    f. Use within 2 weeks prior to the screening visit, 1) cosmetic or therapeutic procedures, 2) acid-containing therapeutic products, 3) topical retinoids, 4) light chemical peels, 5) topical salves, 6) topical steroids, or 7) artificial tanner.
    g. Known allergy to tirbanibulin or any excipient in the test product or reference standard.
    h. Skin disease (e.g., atopic dermatitis, psoriasis, eczema) or condition (e.g., scarring, open wounds) that might have interfered with the study conduct or evaluations.
    i. Other significant uncontrolled or unstable medical diseases or conditions that might have interfered with the study conduct or evaluations.

4. The protocol should include a list of the prescription and over-the-counter drug products, procedures, and activities that are prohibited during the study, such as cytotoxic drugs, immunomodulators or immunosuppressive therapies, interferon/interferon inducers, topical or systemic steroids, 5- fluorouracil, ingenol mebutate, imiquimod, diclofenac, topical or systemic retinoids, topical salicylic acid, bichloroacetic acid, trichloroacetic acid, acid-containing therapeutic products, benzoyl peroxide, chemodestruction, medicated/therapeutic topical salves, photodynamic therapy, psoralen plus ultraviolet A or ultraviolet B therapy, artificial tanner, and excessive or prolonged exposure to ultraviolet light source.

5. Subjects should not apply lotions, creams, ointments, moisturizers, sunscreen, artificial tanners, make-up, or any topical product other than the assigned treatment to the treatment area. Subjects should avoid excessive sunlight or ultraviolet light exposure, including the use of tanning beds, to the face or scalp. They should not use any type of bandage or occlusive dressing on the treatment area and not allowing the ointment to come in contact with the mouth, lips, or eyes.

6. The primary endpoint of the study is the proportion of subjects in the per protocol population with treatment success (100% clearance of all AK lesions within the treatment area) at Day 57. All AK (i.e., baseline AK and any new AK) lesions within the treatment area are to be treated and included in the efficacy lesion count for each visit.

7. Subjects are recommended to return to the study site for investigatory assessment on Day 5, 8, 15, 29, and 57. If subjects have unresolved treatment emergent adverse events, hypo- or hyperpigmentation, scarring, or local skin responses, site visits are recommended every 7 to 28 days until resolution or until investigator deemed clinically stable.

8. Refer to the most recent version of the FDA product-specific guidance on *Adapalene; Benzoyl Peroxide Topical Gel* (NDA 207917)[b] for a recommended approach to statistical analysis and study design for bioequivalence studies with clinical endpoint.

9. Refer to the study data standards resources, https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources.

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[a] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[b] For the most recent version of a product-specific guidance, check the FDA product-specific guidance web page at https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm.