Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Bimatoprost

May 2023

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

Active Ingredient: Bimatoprost

Dosage Form; Route: Implant; Ophthalmic

Strength: 10 mcg

Recommended Study: One comparative clinical endpoint bioequivalence study

1. Type of study: Comparative clinical endpoint bioequivalence study
   Design: Randomized, double-blind (evaluator-blind), parallel, two-arm, in vivo study
   Strength: 10 mcg
   Subjects: Males and non-pregnant, non-lactating females with open angle glaucoma or ocular hypertension

Additional comments regarding the comparative clinical endpoint bioequivalence study:

1. FDA recommends conducting a bioequivalence study with clinical endpoint in subjects with confirmed diagnosis of open angle glaucoma or ocular hypertension. Subjects are to be randomized to receive the bimatoprost ophthalmic implant, 10 mcg test product versus the reference product. The study drug is to be administered by a physician. The intracameral injection procedure must be performed under magnification that allows clear visualization of the anterior chamber structures and should be carried out using standard aseptic conditions for intracameral procedures, with the patient's head in a stabilized position. The eye should not be dilated prior to the procedure.

2. Inclusion Criteria (the sponsor may add additional criteria):
   a. Males and non-pregnant, non-lactating females at least 18 years of age
   b. Diagnosis of either open angle glaucoma or ocular hypertension in one or both eyes requiring a treatment for reduction of intraocular pressure (IOP)

c. Patients should be screened for iridocorneal angle eligibility with an appropriate method: (i) Shaffer Grade ≥ 3, and (ii) the Van Herick Grade ≥ 1/2 corneal thickness
d. Baseline (Day 0 at 8:00 a.m.) IOP ≥ 22 mm Hg and ≤ 32 mm Hg in one or both eyes
e. Adequate washout period prior to baseline of any ocular hypotensive medication.
f. Sponsors may add additional criteria

3. Exclusion Criteria (the sponsor may add additional criteria):
    a. Active or suspected ocular or periocular infections
    b. Corneal endothelial cell dystrophy (e.g., Fuchs' Dystrophy)
    c. Prior corneal transplantation or endothelial cell transplants
    d. Absent or ruptured posterior lens capsule
    e. Corneal or other ocular abnormalities that may preclude accurate IOP readings
    f. Functionally significant visual field loss
    g. Significantly reduced visual acuity (e.g., 20/50 or poorer using Snellen equivalent)
    h. Current or history of significant ocular disease (e.g., macular edema, ocular trauma, uveitis, external ocular or intraocular malignancy, or severe blepharitis)
    i. Narrow iridocorneal angles (Shaffer grade < 3) or anatomical obstruction (e.g., scarring) that may prohibit implant settling in the inferior angle
    j. History or evidence of a peripheral iridotomy/iridectomy in the inferior iris
    k. History or evidence of complicated cataract surgery resulting in complicated lens placement or history of phakic intraocular lens implant insertion for refractive error correction
    l. Intraocular surgery and/or any ocular laser surgery within the 6 months prior to baseline exam
    m. Hypersensitivity to bimatoprost or to any other components of the product
    n. Patients were determined to be nonresponsive to topical ophthalmic beta-blockers and/or topical prostaglandins
    o. Use of any ophthalmic, oral, intramuscular, or intravenous corticosteroids within 2 months prior to baseline except for use of postoperative topical ocular corticosteroids after administration
    p. Sponsors may add additional criteria

4. The protocol should include a list of prescription and over-the-counter drug products, procedures, and activities that are prohibited during the study, such as:
    a. Other ocular hypotensive drug products
    b. Ophthalmic over-the-counter or prescription product, other than study treatment and the occasional use of artificial tears
    c. Oral carbonic anhydrase inhibitor
    d. High-dose salicylate therapy
    e. Monoamine oxidase (MAO) inhibitor
    f. Tricyclic antidepressant or any other antidepressant that affects noradrenergic transmission
    g. Adrenergic-augmenting psychotropic drug (e.g., desipramine, amitriptyline)

h. Topical or systemic corticosteroid
i. Intraocular corticosteroid implant
j. Intravitreal or subtenon injection of ophthalmic corticosteroid
k. Systemic beta-adrenergic blocking drug product
l. Change in concurrent treatment or initiation of treatment with agents potentially affecting IOP, e.g., antihypertensive medication
m. Contact lenses
n. Ocular surgery

5. Use of any topical ophthalmic medication containing an ocular antihypertensive is prohibited as concurrent therapy, unless medically necessary due to inadequate control of IOP as determined by the investigator. The protocol should include the minimum washout prior to baseline required for each class of ocular hypotensive medications.

6. Use of soft contact lenses within 3 days and use of rigid gas permeable or hard contact lenses within 1 week prior to a scheduled study visit or administration day is prohibited. Use of contact lenses of any kind within 1 week following bimatoprost administration is prohibited.

7. The eye that meets the inclusion and exclusion criteria is to be selected as the study eye. If both eyes meet the inclusion and exclusion criteria, the eye with the higher IOP at baseline is to be selected as the study eye. If both eyes have the same IOP, then the right eye is to be designated as the study eye. The fellow eye (non-study eye) is to be treated with the reference product.

8. The primary endpoint of the study is IOP of the study eye at Weeks 2, 6, and 12 post-administration visits. All IOP measurements should be obtained at the same time of the day (i.e., 8:00 a.m.) at each visit, including the baseline visit. When both eyes are treated, IOP of the fellow eye should be monitored during the study.

9. IOP of the study eye is to be measured as two consecutive measurements by two blind evaluators using the Goldmann applanation tonometer. If the two measurements for the eye differ by > 1.0 mm Hg, a third measurement for the eye is to be taken and the IOP is to be the median of the three readings. If the two measurements differ by 1.0 mm Hg or less for the eye, the IOP is to be the average of the two readings for the eye. All IOP measurements on each eye should be reported. The mean or median IOP of the study eye at each timepoint is used for the primary endpoint.

10. To establish bioequivalence, the limits of each two-sided 95% confidence interval of the mean difference between the test and reference) for the measured IOP of the study eye at all three follow-up time points (i.e., at approximately 8:00 a.m. at Week 2, Week 6, and Week 12) must be within ± 1.0 mm Hg using per-protocol (PP) population.

11. The results of the primary endpoint at each timepoint by both the test and reference products should be compared to the results that supported the approval of the reference product and any historical results in the literature.

12. Subjects whose condition worsens (e.g., IOP ≥ 36 mm Hg in either eye) and require alternate or supplemental therapy for the treatment of their chronic open angle glaucoma or ocular hypertension during the study should be discontinued and provided with effective treatment.

13. The protocol should clearly define the PP, intent-to-treat (ITT) and safety populations.
    a. The accepted PP population used for bioequivalence evaluation includes all randomized subjects who:
        - Meet all inclusion/exclusion criteria
        - Complete the evaluation within visit window with no protocol violations that would affect the treatment evaluation
    b. The ITT population includes all randomized subjects and analyzed as randomized irrespective of the treatment received
    c. The Safety population includes all enrolled subjects who use at least one dose of product

14. Subjects who are discontinued early from the study due to lack of treatment effect should be included in the PP population using Last Observation Carried Forward (LOCF). Subjects whose condition worsens and who require alternate or supplemental therapy for the treatment of their condition during the treatment phase of the study should be discontinued, included in the PP population analyses using LOCF, and provided with effective treatment. Subjects discontinued early for other reasons should be excluded from the PP population. Applicants should provide a pre-specified definition of lack of treatment effect.

15. The start and stop calendar date (e.g., mm/dd/yyyy) and study day (e.g., Day X) of concomitant medication use should be provided in the data set in addition to the reason for the medication use. The Applicant should clearly note whether the medication was used prior to baseline visit, during the study, or both.

16. All adverse events (AEs) should be reported whether or not they are considered to be related to the treatment. The report of AEs should include date of onset, description of the AE, severity, relation to study medication, action taken, outcome and date of resolution. This information is needed to determine if the incidence and severity of adverse reactions is different between the test product and RLD.

17. The method of randomization should be described in the protocol and the randomization schedule should be provided. It is recommended that an independent third party generate and hold the randomization code throughout the conduct of the study to minimize bias. The applicant may generate the randomization code if not involved in the packaging and labeling of the study medication. A sealed copy of the randomization scheme should be retained at the study site and should be available to FDA investigators at the time of site inspection to allow for verification of the treatment identity of each subject.

18. A detailed description of the blinding procedure is to be provided in the protocol. The packaging of the test product, reference standard and placebo should be similar in

appearance to make differences in treatment less obvious to the subjects and to maintain adequate blinding of evaluators. When possible, neither the subject nor the investigator should be able to identify the treatment. The containers should not be opened by the subject at the study center.

19. It is the applicant's responsibility to enroll sufficient subjects for the study to demonstrate bioequivalence between the products. The protocol should provide the sample size calculation.

20. The protocol should include a section with fully detailed statistical analysis plan.

21. Provide the Subject-Level Analysis Dataset (ADSL), one record per subject, using the following headings, if applicable:
    a. Study identifier
    b. Unique subject identifier
    c. Subject identifier for the study
    d. Study site identifier (if applicable)
    e. Age
    f. Age units (years)
    g. Sex
    h. Race
    i. Iris color
    j. Name of planned treatment
    k. Name of actual treatment
    l. Date/time of treatment
    m. Safety population flag (yes/no)
    n. Reason for exclusion from safety population
    o. Intent-to-Treat (ITT) population flag (yes/no)
    p. Reason for exclusion from ITT population
    q. PP population flag (yes/no)
    r. Reason for exclusion from PP population
    s. End of study date
    t. Subject required additional treatment due to unsatisfactory treatment response (yes/no)
    u. Identification of the study eye (right/left)
    v. Intraocular pressure of the study eye at Baseline, Week 2, Week 6, and Week 12
    w. Concomitant medication (yes/no)
    x. Adverse event(s) reported (yes/no)

22. Provide the basic data structure (BDS) dataset with records per subject, per visit, per analysis timepoint, using the following headings, if applicable:
    a. Study identifier
    b. Unique subject identifier
    c. Subject identifier for the study
    d. Study site identifier (if applicable)
    e. Name of planned treatment

f. Name of actual treatment
g. Safety population flag (yes/no)
h. ITT population flag (yes/no)
i. PP population flag (yes/no)
j. Analysis date
k. Analysis visit
l. Study visit within designated window (yes/no)
m. Analysis timepoint (e.g., Week 2)
n. Intraocular pressure of the study eye and the fellow eye as measured by each evaluator
o. Additional treatment required during the visit (yes/no)
p. Concomitant medication reported during this visit (yes/no)
q. Adverse event reported during this visit (yes/no)
r. Laboratory testing during this visit (yes/no)

23. Study data should be submitted in a standardized format. Refer to the study data standards published at www.fda.gov (Study Data Standards Resources: https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources).

Waiver request of in vivo testing: Not applicable

Dissolution test method and sampling times: Conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application (ANDA).

Additional information:

Device:
The reference listed drug (RLD) is presented as a preloaded, biodegradable, single-dose implant in a sterile, single-use applicator. The implant and the applicator are the device constituent parts. FDA recommends that prospective applicants examine the size and shape, the external critical design attributes, and the external operating principles of the RLD device when designing the Test (T) devices including:

- Size of the biodegradable implant
- Preloaded, sterile, single-use applicator
- Needle features: silicone coating, gauge, and length
- Implant retention mechanism

User interface assessment:
An ANDA for this product should include complete comparative analyses so FDA can determine whether any differences in design for the user interface of the proposed generic product, as compared to the RLD, are acceptable and whether the product can be expected to have the same clinical effect and safety profile as the RLD when administered to patients under the conditions specified in the labeling. For additional information, refer to the most recent version of the FDA

guidance for industry on *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA*.[a]

Unique Agency Identifier: PSG_211911

[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.