

Draft Guidance on Brimonidine Tartrate

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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:** Brimonidine tartrate
- Dosage Form; Route:** Solution/drops; ophthalmic
- Strength:** 0.025%
- Recommended Studies:** Two options: waiver or in vivo study

Additional Comments: Brimonidine tartrate ophthalmic solution product should have comparable physicochemical properties to the Reference Standard (RS) including but not limited to pH, specific gravity, buffer capacity, viscosity, and osmolality, if applicable. Comparative analysis should be performed on three exhibit batches, if available, of both test and RS products.

I. Waiver option:

To qualify for a waiver of the in vivo bioequivalence (BE) study requirement, a brimonidine tartrate ophthalmic solution product must be qualitatively (Q1)¹ and quantitatively (Q2)² the same as the Reference Listed Drug (RLD).

An in vivo BE study is requested for any brimonidine tartrate ophthalmic solution product that has a different inactive ingredient from the RLD,³ a difference of more than 5% in the amount of any inactive ingredient compared to that of the RLD, or differences in comparative physicochemical characterization data.

II. In Vivo option:

Recommended study:

Type of study: BE study with clinical endpoint

¹ Q1 (Qualitative sameness) means that the test product uses the same inactive ingredient(s) as the reference listed drug product.

² Q2 (Quantitative sameness) means that concentrations of the inactive ingredient(s) used in the test product are within $\pm 5\%$ of those used in the reference listed drug product.

³ For ophthalmic drug products, FDA has determined that, as a scientific matter, any qualitative or quantitative deviations from the RLD, even in inactive ingredients listed in 21 CFR 314.94(a)(9)(iv), should be accompanied by an appropriate in vivo BE study or studies. Guidance for industry: *ANDA Submissions – Refuse-to-Receive Standards*.

Design: Randomized, double-blind, parallel, controlled, in vivo
Strength: 0.025%
Subjects: Males and females with ocular redness

Analytes to measure (in appropriate biological fluid): Not applicable

Bioequivalence based on (95% CI): Clinical endpoint (in vivo option)

Dissolution test method and sampling times: Not applicable

Additional comments regarding the BE study with clinical endpoint:

1. The Office of Generic Drugs recommends conducting a bioequivalence study with a clinical endpoint in the treatment of ocular redness. Subjects are to be randomized to receive brimonidine tartrate 0.025% ophthalmic solution, the RLD or vehicle of brimonidine tartrate ophthalmic solution instilled as one drop into each eye. The primary endpoint is the change in ocular redness score for both eyes from baseline at each individual time point 5, 15, 30 and 60 minutes after drug instillation, using a 0 to 4 unit ocular redness scale and including half units. Reference photographs should be used to define the redness scale.
2. Inclusion Criteria (the sponsor may add additional criteria)
 - a. Male or nonpregnant females aged at least 18 years with redness due to eye irritation.
 - b. Have a baseline redness score ≥ 2 in both eyes on a 0 to 4 unit ocular redness scale.
 - c. Baseline best corrected visual acuity equivalent to 20/40 or better in each eye.
3. Exclusion Criteria (the sponsor may add additional criteria)
 - a. Females who are pregnant, breast feeding, or planning a pregnancy.
 - b. Females of childbearing potential who do not agree to utilize an adequate form of contraception.
 - c. Current or history within two months prior to baseline of significant ocular disease, e.g., corneal edema, glaucoma, uveitis, ocular infection, or ocular trauma in either eye.
 - d. Contraindication to brimonidine therapy or known hypersensitivity to any component of brimonidine therapy.
 - e. Underwent within 6 months prior to baseline any other intraocular or refractive surgery (e.g., cataract surgery).
 - f. Have an intraocular pressure (IOP) of less than 5 mmHg.
4. The protocol should include a list of the prescription and over-the-counter drug products, procedures, and activities that are prohibited during the period indicated prior to during the study, such as:

- a. Ophthalmic over-the-counter or prescription product including artificial tears, vasoconstrictors, decongestants, antihistamines, corticosteroids, contact lenses: 5 days
 - b. Phenylephrine dilating drops: 5 days
 - c. Systemic antihistamines or decongestants: 7 days
 - d. Systemic corticosteroids: 14 days
5. The recommended primary endpoint is the mean difference between the treatment groups in change from baseline in ocular redness score for both eyes from baseline to all four time points of 5, 15, 30 and 60 minutes after drug instillation.
6. The enrolled subjects should have a mixture of light and dark colored irides similar in proportion to the US population.
7. The protocol should clearly define the per-protocol (PP) and safety populations.
 - a. The accepted PP population used for BE evaluation includes all randomized subjects who meet all inclusion/exclusion criteria, instill the scheduled dose of the assigned product, and complete evaluations at 5, 15, 30 and 60 minutes after drug instillation with no protocol violations that would affect the treatment evaluations.
 - b. The safety population includes all randomized subjects who receive study product.
8. The start and stop date of concomitant medication use during the study should be provided in the data set in addition to the reason for the medication use. The sponsor should clearly explain whether the medication was used prior to baseline visit, during study, or both.
9. 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.
10. Generally, a drug product intended for ophthalmic use shall contain the same inactive ingredients and in the same concentration as the RLD. For an ophthalmic drug product that differs from the RLD in preservative, buffer, substance to adjust tonicity, or thickening agent [as permitted by the chemistry, manufacturing and controls (CMC) regulations for abbreviated new drug applications (ANDAs), 21 CFR 314.94(a)(9)(iv)], the regulation specifies that the applicant must identify and characterize the differences and provide information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product.
11. The method of randomization should be described in the protocol and the randomization schedule provided as a SAS data set in .xpt format (created using SAS XPORT). It is recommended that an independent third party generate and hold the randomization code throughout the conduct of the study in order to minimize bias. The sponsor 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.

12. A detailed description of the masking procedure is to be provided in the protocol. The packaging of the test and reference products should be similar in appearance to make differences in treatment less obvious to the subjects and to maintain adequate masking of evaluators. When possible, neither the subject nor the investigator should be able to identify the treatment. If the two treatments differ in appearance, evaluators should not be in the room whenever the treatment is taken out of the external packaging or the subject is dosed with study treatment.
13. Please refer to 21 CFR 320.38, 320.63 and the Guidance for Industry, “Handling and Retention of BA and BE Testing Samples”, regarding retention of study drug samples and 21 CFR 320.36 for requirements for maintenance of records of bioequivalence testing. In addition, the investigators should follow the procedures of ICH E6, “Good Clinical Practice: Consolidated Guideline”, for retention of study records and data in order to conduct their studies in compliance with Good Laboratory Practices (GLP) and Good Clinical Practices (GCP). Retention samples should be randomly selected from the drug supplies received prior to dispensing to subjects. Retention samples should not be returned to the sponsor at any time. Separate shipments sent to a clinical site should each have testing samples retained.
14. It is the sponsor's responsibility to enroll sufficient subjects for the study to demonstrate bioequivalence between the products.
15. To establish bioequivalence, the limits of each two-sided 95% confidence interval of the treatment difference (test – reference) for mean change from baseline in ocular redness score for both eyes at all four time points of 5, 15, 30 and 60 minutes after drug instillation must be within ± 0.75 using the PP population for all time points measured and within ± 0.6 using the PP population for the majority of time points measured.
16. As a parameter for determining adequate study sensitivity, the test product and RLD should both be statistically superior to control ($p < 0.05$, two-sided) for the primary endpoint, using the mITT study population and LOCF.
17. Study data should be submitted to the OGD in electronic format. Please refer to the study data standards published at www.fda.gov⁴
18. Please provide the Subject -Level Analysis Dataset (ADSL), one record per subject, using the following headings, if applicable:

⁴ Study Data Standards for Submission to CDER and CBER available at:
<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

- a. Study identifier
 - b. Subject identifier
 - c. Study site identifier (if applicable)
 - d. Age
 - e. Sex
 - f. Race
 - g. Iris color
 - h. Name of planned treatment
 - i. Name of actual treatment
 - j. Safety population flag (yes/no)
 - k. Completed the study (yes/no)
 - l. Intent-to-Treat (ITT) population flag (yes/no)
 - m. Per Protocol (PP) population flag (yes/no)
 - n. Reason for exclusion from PP population
 - o. Completers populations flag (yes/no)
 - p. Randomized population flag (yes/no)
 - q. Datetime of first exposure to treatment
 - r. Datetime of last exposure to treatment
 - s. End of study date
 - t. End of study status
 - u. Subject required additional treatment due to unsatisfactory treatment response (yes/no)
 - v. Ocular redness score of both eyes at baseline (Day0/hour0)
 - w. Best corrected visual acuity of both eyes at baseline, 20/200 or better (yes/no)
 - x. Compliance rate (%)
 - y. Adverse event(s) reported (yes/no)
 - z. Concomitant medication (yes/no)
19. Please provide the basic data structure (BDS) dataset with records per subject, per analysis timepoint, using the following headings, if applicable:
- a. Study identifier
 - b. Subject identifier
 - c. Study site identifier (if applicable)
 - d. Name of planned treatment
 - e. Name of actual treatment
 - f. Safety population flag (yes/no)
 - g. Intent-to-Treat (ITT) population flag (yes/no)
 - h. Per-Protocol (PP) population flag (yes/no)
 - i. Completers population flag (yes/no)
 - j. Analysis date
 - k. Analysis visit
 - l. Study visit within the designated window (yes/no)
 - m. Analysis timepoint (e.g., hour 0, hour 2)
 - n. Ocular redness score of both eyes
 - o. Additional treatment required during the visit (yes/no)
 - p. Adverse event reported during the visit (yes/no)

q. Concomitant medication during the visit (yes/no)