Contains Nonbinding Recommendations

Draft Guidance on Brimonidine Tartrate

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Recommended Study: One study

1. Type of study: bioequivalence (BE) study with clinical endpoint
   Design: Randomized, double-blind, parallel, three-arm, placebo-controlled in vivo
   Strength: EQ 0.33% Base
   Subjects: Healthy males and nonpregnant females with moderate to severe persistent facial erythema of rosacea
   Additional comments: See specific recommendations provided below

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

Bioequivalence based on (90% CI): Clinical endpoint

Dissolution test method and sampling times: N/A

Additional comments regarding the BE study with clinical endpoint:

1. The Office of Generic Drugs (OGD) recommends conducting a BE study with clinical endpoint in the treatment of moderate-to-severe persistent (nontransient) facial erythema of rosacea. The study should compare the test product versus the reference listed drug (RLD) and placebo (vehicle) control, each administered by applying a pea-size amount of the assigned study treatment to each of the five areas of the face (forehead, chin, nose, each cheek)—avoiding the eyes and lips—once daily for 15 days.

2. A placebo (vehicle) control arm is recommended to demonstrate that the test product and RLD are active and as a parameter to establish that the study is sufficiently sensitive to detect differences between products.

3. Inclusion criteria (the sponsor may add additional criteria):
   a. Healthy male or nonpregnant females aged at least 18 years with a clinical diagnosis of facial rosacea.
   b. A clinical diagnosis of facial rosacea

c. A Clinician Erythema Assessment (CEA) score of ≥3 at Screening and on Baseline/Day 1 prior to study drug application (per Table 1)
d. A Patient Self Assessment (PSA) score of ≥3 at Screening and on Baseline/Day 1 prior to study drug application (per Table 2)
e. Subject's willingness to minimize external factors that might trigger rosacea flare-ups (e.g., spicy foods, thermally hot foods and drinks, hot environments, prolonged sun exposure, strong winds, alcoholic beverages)

Table 1: Sample CEA Scale for Rosacea

Grade	Description
0	Clear skin with no signs of erythema
1	Almost clear; slight redness
2	Mild erythema; definite redness
3	Moderate erythema; marked redness
4	Severe erythema; fiery redness

Table 2: Sample PSA Scale for Rosacea

Grade	Description
0	No redness
1	Very mild redness
2	Mild redness
3	Moderate redness
4	Severe redness

4. 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. Particular forms of rosacea (rosacea conglobata, rosacea fulminans, isolated rhinophyma, isolated pustulosis of the chin) or other concomitant facial dermatoses that are similar to rosacea such as peri-oral dermatitis, demodicidosis, facial keratosis pilaris, seborrheic dermatitis, acute lupus erythematosus, or actinic telangiectasia.
   d. Presence of ≥3 facial inflammatory lesions of rosacea.
   e. Subjects with Raynaud's syndrome, thromboangiitis obliterans, orthostatic hypotension, severe cardiovascular disease, cerebral or coronary insufficiency, renal or hepatic impairment, scleroderma, Sjögren's syndrome, or depression
   f. Presence of any skin condition on the face that would interfere with the diagnosis or assessment of rosacea
   g. Excessive facial hair (e.g., beards, sideburns, moustaches, etc.) that would interfere with the study treatments or study assessments
   h. Dermatologic or surgical procedure on the face within four weeks prior to baseline
   i. Known hypersensitivity reaction to any component of brimonidine therapy

j. Current use of monoamine oxidase (MAO) inhibitors, barbiturates, opiates, sedatives, systemic anesthetics, alpha-agonists, cardiac glycosides, beta blockers, other antihypertensive agents, or brimonidine tartrate ophthalmic solution
k. Use within six months prior to baseline of oral retinoids (e.g., Accutane®) or therapeutic vitamin A supplements of greater than 10,000 units/day (multivitamins are allowed)
l. Use within 12 weeks prior to baseline of systemic immunomodulators
m. Use within four weeks prior to baseline of 1) topical immunomodulators, 2) systemic antibiotics, 3) systemic corticosteroids, 4) systemic anti-inflammatory agents, 5) systemic treatment for rosacea, or 6) systemic treatment for acne (other than oral retinoids, which require a 6-month washout)
n. Use within two weeks prior to baseline of 1) topical corticosteroids, 2) topical retinoids, 3) topical antibiotics, 4) topical anti-inflammatory, 5) topical treatment for rosacea, or 6) topical treatment for acne
o. Use within 1 week prior to baseline of niacin ≥500 mg per day

5. 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:
   a. Any other topical products applied to face
   b. Medicated soaps used on face
   c. Dermatologic or surgical procedure on face
   d. MAO inhibitors, barbiturates, opiates, sedatives, systemic anesthetics, alpha-agonists, cardiac glycosides, beta blockers, other antihypertensive agents, or brimonidine tartrate ophthalmic solution
   e. Systemic treatment for rosacea
   f. Systemic corticosteroids, systemic antibiotics, systemic immunomodulators, systemic anti-inflammatory agents, oral retinoids, or other systemic treatment for acne vulgaris
   g. Use of tanning booths, sunbathing, or excessive exposure to the sun
   h. Subjects should be instructed to wash their hands with soap and water before and after applying treatment and to avoid contact of the study product with the eye or lips.

6. The CEA and PSA should be performed at the screening visit, the Baseline/Day 1 visit, and the End of Study/Day 15 visit. The screening visit and the Day 1 visit should be on separate days. During the screening visit, the CEA and PSA should be performed once. During the Day 1 and Day 15 visits, the CEA and PSA should be performed five times: prior to dosing and at 3, 6, 9, and 12 hours post-application.

7. The recommended primary endpoint is the proportion of subjects with treatment success at Hour 3, 6, 9, and 12 post-application on Day 15, where treatment success is defined as a 2-grade improvement from pre-dose on Day 1 on both the CEA and PSA scales at each time point.

8. The recommended secondary endpoint is the proportion of subjects with treatment success at Hour 3, 6, 9, and 12 post-application on Day 1, where treatment success is defined as a 2-grade improvement from pre-dose on Day 1 on both the CEA and PSA scales at each time point.

9. The protocol should clearly define the per-protocol (PP), modified intent-to-treat (mITT), and safety populations.
    a. The accepted PP population used for BE evaluation includes all randomized subjects who met all inclusion/exclusion criteria, applied a pre-specified proportion of the scheduled doses (e.g., 75% to 125%) of the assigned product for the specified duration of the study, did not miss the scheduled applications for more than 1 consecutive day, and completed the evaluation within the designated visit window (+/- 2 days) with no protocol violations that would affect the treatment evaluation. The protocol should specify how compliance will be verified, e.g., by the use of subject diaries.
    b. The mITT population includes all randomized subjects who applied at least one dose of assigned product.
    c. The safety population includes all randomized subjects who received study product.

10. Subjects who are discontinued early from the study due to insufficient or lack of treatment effect should be included in the PP population as treatment failures. Subjects discontinued early for other reasons should be excluded from the PP population, but included in the mITT population, using Last Observation Carried Forward (LOCF).

11. The start and stop dates 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 the study, or both.

12. 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 AE, severity, relation to study medication, action taken, outcome, and date of resolution. This information is relevant to FDA's determination of whether the incidence and severity of adverse reactions is different between the test product and RLD.

13. If the inactive ingredients of the test product are different from those contained in the RLD or in significantly different amounts, the sponsor must clearly describe the differences and provide information to show that the differences will not affect the safety, efficacy, and/or systemic or local availability of the drug.

14. 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). The Agency recommends 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 the site inspection to allow for verification of the treatment identity of each subject.

15. A detailed description of the blinding procedure is to be provided in the protocol. The packaging of the test, reference, and placebo products 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.

16. 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 BE testing. In addition, the investigators should follow the procedures of 21 CFR 58 and 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.

17. It is the sponsor's responsibility to enroll sufficient subjects for the study to demonstrate bioequivalence between the products.

18. To establish bioequivalence for a dichotomous endpoint, FDA recommends applicants test the following compound hypotheses using the per protocol population:

$$H_O: \pi_T - \pi_R \leq \Delta_1 \text{ or } \pi_T - \pi_R \geq \Delta_2 \quad \text{versus} \quad H_A: \Delta_1 < \pi_T - \pi_R < \Delta_2$$

where π_T = the success rate of the primary endpoint for the treatment group, and
π_R = the success rate of the primary endpoint for the reference group.

The null hypothesis, H_O, is rejected with a type I error (α) of 0.05 (two one-sided tests) if the estimated 90% confidence interval for the difference of the success rates between test and reference products ($\pi_T - \pi_R$) is contained within the interval $[\Delta_1, \Delta_2]$, where $\Delta_1 = -0.20$ and $\Delta_2 = 0.20$. Rejection of the null hypothesis supports the conclusion of equivalence of the two products.

19. To establish sensitivity within the study for either a dichotomous or continuous primary endpoint, the test and reference products should both be statistically superior to the placebo. Conduct an appropriate inferential test with a type I error (α) of 0.05, using the mITT population and the primary endpoint.

20. Study data should be submitted to OGD in electronic format. All data should be submitted as a SAS .xpt file, created using SAS XPORT (not CPORT).
    a. Include a list of file names, a description of the content of each file, an explanation of the variables within each file, and a description of all variable codes (for example, for the treatment variable, A = TEST and B = RLD).
    b. Provide a SAS program to open the SAS .xpt files.

c. Provide two primary data sets, one with No Last Observation Carried Forward (NO-LOCF - pure data set) and one with the Last Observation Carried Forward (LOCF - modified data set).
d. Provide a separate data set for demographic, vital sign, adverse event, disposition (including reason for discontinuation of treatment), concomitant medication, medical history, compliance, and comment variables.

21. Sponsors should provide a summary data set that contains a separate line listing for each subject (if data exist) using the following headings, if applicable:
    a. Study identifier
    b. Site identifier: study center
    c. Subject identifier
    d. Age
    e. Age units (years)
    f. Sex
    g. Race
    h. Name of actual treatment (exposure): test product, RLD, placebo control
    i. Duration of treatment (total exposure in days)
    j. Completed the study (yes/no)
    k. Reason for premature discontinuation of subject
    l. Subject required additional treatment for rosacea due to unsatisfactory treatment response (yes/no)
    m. Per Protocol (PP) population inclusion (yes/no)
    n. Reason for exclusion from PP population
    o. Modified Intent to Treat (mITT) population inclusion (yes/no)
    p. Reason for exclusion from mITT population
    q. Safety population inclusion (yes/no)
    r. Reason for exclusion from safety population
    s. CEA score at screening visit
    t. CEA score at Day 1 visit at pre-dose
    u. CEA score at Day 1 visit at 3 hours post-application
    v. CEA score at Day 1 visit at 6 hours post-application
    w. CEA score at Day 1 visit at 9 hours post-application
    x. CEA score at Day 1 visit at 12 hours post-application
    y. CEA score at Day 15 visit at pre-dose
    z. CEA score at Day 15 visit at 3 hours post-application
    aa. CEA score at Day 15 visit at 6 hours post-application
    bb. CEA score at Day 15 visit at 9 hours post-application
    cc. CEA score at Day 15 visit at 12 hours post-application
    dd. PSA score at screening visit
    ee. PSA score at Day 1 visit at pre-dose
    ff. PSA score at Day 1 visit at 3 hours post-application
    gg. PSA score at Day 1 visit at 6 hours post-application
    hh. PSA score at Day 1 visit at 9 hours post-application
    ii. PSA score at Day 1 visit at 12 hours post-application
    jj. PSA score at Day 15 visit at pre-dose

kk. PSA score at Day 15 visit at 3 hours post-application
ll. PSA score at Day 15 visit at 6 hours post-application
mm. PSA score at Day 15 visit at 9 hours post-application
nn. PSA score at Day 15 visit at 12 hours post-application
oo. Final designation of treatment success (yes/no)
pp. Treatment compliance: number of missed doses per subject
qq. Concomitant medication (yes/no)
rr. Adverse event(s) reported (yes/no)

Table 3 provides an example. Note: this table may contain additional information not applicable to the study and/or it may not contain all information applicable to the study.

Table 3: Example of a Summary Data Set Containing One Line Listing for Each Subject

STUDYID	SITEID	SUBJID	AGE	AGEU	SEX	RACE	EXTRT	EXDUR	completd	disc_rs	add_trt	pp	pp_rs	mitt	mitt_rs	safety	safe_rs
101	01	1	30	YEARS	F	1	A	56	Y		N	Y		Y		Y	
101	01	2	28	YEARS	F	1	B	56	Y		N	Y		Y		Y	

cea_s	cea1_p	cea1_3	cea1_6	cea1_9	cea1_12	cea15_p	cea15_3	cea15_6	cea15_9	cea15_12	psa_s	psa1_p	psa1_3	psa1_6	psa1_9	psa1_12	psa15_p	psa15_3
3	3	2	1	1	1	3	2	1	1	1	4	4	2	1	1	1	3	2
3	3	1	0	0	0	3	1	0	0	0	4	4	1	0	0	0	3	1

psa15_6	psa15_9	psa15_12	success	complian	CM	AE
1	1	1	N	0	Y	Y
0	0	0	Y	0	N	N

Note: Capitalized headings are from the Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) Implementation Guide (IG) for Human Clinical Trials V3.1.2 Final, dated 11/12/08.

STUDYID: Study Identifier
SITEID: Study Site Identifier

SUBJID:	Subject Identifier for the Study
AGE:	Age
AGEU:	Age units (years)
SEX:	Sex, e.g., M=Male, F=Female, U=Unknown
RACE:	Race, e.g., 1=White, 2=Black or African American, 3=Asian, 4=American Indian or Alaska Native, 5=Native Hawaiian or Other Pacific Islanders
EXTRT:	Name of Actual Treatment (exposure), e.g., A=test product, B= RLD
EXDUR:	Duration of treatment (total exposure in days)
completd:	Subject completed the study, e.g., Y=Yes, N=No
disc_rs:	Reason for premature discontinuation from the study, e.g., A=adverse event, B=death, C=lost to follow-up, D=non-compliance with treatment, E=treatment unmasked, F=subject moved out of area, G=unsatisfactory treatment response, H=withdrew consent, I=protocol violation, K=other event
add_trt:	Subject required additional treatment for rosacea to unsatisfactory treatment response, e.g., Y=Yes, N=No
pp:	Per Protocol (PP) population inclusion, e.g., Y=Yes, N=No
pp_rs:	Reason for exclusion from PP population, e.g., A=prematurely discontinued, B=lost to follow-up, C=subject moved out of the area, D=noncompliant, etc.
mitt:	Modified Intent to Treat (mITT) population inclusion, e.g., Y=Yes, N=No
mitt_rs:	Reason for exclusion from mITT population, e.g., A=never treated, etc.
safety:	Safety population inclusion, e.g., Y=Yes, N=No
safe_rs:	Reason for exclusion from Safety population, e.g., A=never treated, etc.
cea_s:	CEA score at screening visit, e.g., 3 or 4
cea1_p:	CEA score at Day 1 visit at pre-dose, e.g., 3 or 4
cea1_3:	CEA score at Day 1 visit at 3 hours post-application, e.g., 0, 1, 2 or 3
cea1_6:	CEA score at Day 1 visit at 6 hours post-application, e.g., 0, 1, 2 or 3
cea1_9:	CEA score at Day 1 visit at 9 hours post-application, e.g., 0, 1, 2 or 3
cea1_12:	CEA score at Day 1 visit at 12 hours post-application, e.g., 0, 1, 2 or 3
cea15_p:	CEA score at Day 15 visit at pre-dose, e.g., 0, 1, 2 or 3
cea15_3:	CEA score at Day 15 visit at 3 hours post-application, e.g., 0, 1, 2 or 3
cea15_6:	CEA score at Day 15 visit at 6 hours post-application, e.g., 0, 1, 2 or 3
cea15_9:	CEA score at Day 15 visit at 9 hours post-application, e.g., 0, 1, 2 or 3
cea15_12:	CEA score at Day 15 visit at 12 hours post-application, e.g., 0, 1, 2 or 3
psa_s:	PSA score at screening visit, e.g., 3 or 4
psa1_p:	PSA score at Day 1 visit at pre-dose, e.g., 3 or 4
psa1_3:	PSA score at Day 1 visit at 3 hours post-application, e.g., 0, 1, 2 or 3
psa1_6:	PSA score at Day 1 visit at 6 hours post-application, e.g., 0, 1, 2 or 3
psa1_9:	PSA score at Day 1 visit at 9 hours post-application, e.g., 0, 1, 2 or 3
psa1_12:	PSA score at Day 1 visit at 12 hours post-application, e.g., 0, 1, 2 or 3
psa15_p:	PSA score at Day 15 visit at pre-dose, e.g., 0, 1, 2 or 3
psa15_3:	PSA score at Day 15 visit at 3 hours post-application, e.g., 0, 1, 2 or 3
psa15_6:	PSA score at Day 15 visit at 6 hours post-application, e.g., 0, 1, 2 or 3
psa15_9:	PSA score at Day 15 visit at 9 hours post-application, e.g., 0, 1, 2 or 3
psa15_12:	PSA score at Day 15 visit at 12 hours post-application, e.g., 0, 1, 2 or 3

success:	Treatment success, e.g., Y=Yes, N=No
complian:	Treatment compliance, e.g., number of missed doses per subject
CM:	Concomitant medication, e.g., Y=Yes, N=No
AE:	Adverse event(s) reported, e.g., Y=Yes, N=No

22. These recommendations are specific to this product and may not be appropriate for BE studies of any other product, including any other dosage form or strength of brimonidine.