Contains Nonbinding Recommendations

Draft Guidance on Mupirocin Calcium

Active ingredient: Mupirocin Calcium

Form/Route: Ointment/Nasal

Recommended studies: 1 study

Type of study: Clinical Endpoint Bioequivalence (BE) Study
Design: Randomized, double blind, parallel, placebo controlled, in vivo
Strength: EQ 2% Base
Subjects: Healthy males and nonpregnant females with nasal colonization of *Staphylococcus aureus*.
Additional comments: Specific recommendations are provided below.

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

Bioequivalence based on (90% CI): Clinical endpoint

Waiver request of in vivo testing: Not Applicable

Dissolution test method and sampling times: Not Applicable

Additional comments regarding the clinical endpoint BE study:

1. The Office of Generic Drugs (OGD) recommends conducting a clinical endpoint bioequivalence study in the eradication of nasal colonization with *Staphylococcus aureus*. Subjects are to be randomized to receive the generic mupirocin nasal ointment, 2%, the reference listed drug (RLD) or placebo vehicle. The study treatment is to be administered as approximately one-half of the ointment from the single-use tube applied into one nostril and the other half into the other nostril twice daily (morning and evening) for 5 days. After application, the nostrils should be closed by pressing together and releasing the sides of the nose repetitively for approximately one minute. This will spread the ointment throughout the nares. The empty tubes should be returned to the study site. The primary endpoint is to be evaluated 48 to 96 hours after the end of treatment (study Day 7, 8, or 9).

2. A placebo 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 female aged ≥ 12 years with nasal colonization with *Staphylococcus aureus*, including methicillin-resistant strains (MRSA).

b. Two or more positive baseline nasal cultures (at least 24 hours apart) for *S. aureus* within 5 days before starting treatment, including an adequate number with methicillin-resistant strains to provide assurance of activity against these organisms.
c. Healthy adult health care workers who are colonized with *S. aureus* would be an appropriate study population. Patients are more likely to be colonized with methicillin-resistant *S. aureus* (MRSA) and could be included if they can be screened and followed up adequately.

4. Exclusion Criteria (the sponsor may add additional criteria)
   a. Pregnant, breast feeding, or planning a pregnancy.
   b. Use within 1 week prior to baseline of systemic antibiotic or systemic corticosteroid.
   c. Use within 48 hours prior to baseline of topical corticosteroid or topical antibiotic.
   d. Signs and symptoms of a concurrent infection requiring additional antibiotic therapy.
   e. Primary or secondary immunodeficiency.
   f. Diabetes.
   g. Presence of any other medical condition that might adversely impact the safety of the study participants or confound the study results.
   h. History of hypersensitivity or allergy to mupirocin and/or any of the study medication ingredients.

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. Systemic (e.g., oral or injectable) antibiotics.
   b. Systemic steroid or immunosuppressive drugs.

6. Nasal culture should be obtained 48 to 96 hours after the last application of study treatment.

7. The recommended primary endpoint of the study is the proportion of subjects with treatment success at 48 to 96 hours after the end of treatment. Treatment success is defined as complete eradication of *S. aureus*. Treatment failures include those with persistent colonization of the baseline strain of *S. aureus* or with colonization of the anterior nares with a different strain of *S. aureus* than that found at baseline.

8. The protocol should clearly define the per-protocol (PP), modified intent-to-treat (mITT) and safety populations in the protocol.

9. The accepted PP population used for bioequivalence evaluation includes all randomized subjects who met all inclusion/exclusion criteria, had at least two positive baseline bacteriological cultures, applied a prespecified proportion of the scheduled applications (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 3 consecutive days, and completed the evaluation within the designated visit window (+/- 4 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.

10. The mITT population includes all randomized subjects who met all inclusion/exclusion criteria, including at least two positive baseline bacteriological cultures, applied at least one dose of assigned product and returned for at least one post-baseline evaluation visit.

11. The safety population includes all randomized subjects who received study product.

12. Subjects discontinued early from the study for any reasons should be excluded from the PP population, but included in the mITT population, using LOCF.

13. Subjects with less than two positive nasal cultures for *S. aureus* within 5 days before starting treatment should be discontinued from the study and excluded from the mITT and PP populations, but included in the safety population for the safety analysis if they received study product.

14. The start and stop date of concomitant medication use during the study should be provided in the dataset in addition to the reason for the medication use.

15. 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.

16. If the inactive ingredients are different than those contained in the RLD or in significantly different amounts, then the sponsor is to 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.

17. The method of randomization should be described in the protocol. 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.

18. 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.

19. 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 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.

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

21. To establish bioequivalence, the 90% confidence interval of the difference between products for the primary endpoint (success proportion) must be contained within [-0.20, +0.20] for dichotomous variables (cure versus failure), using the PP study population.

22. As a parameter for determining adequate study sensitivity, the test product and RLD should be statistically superior to placebo ($p<0.05$, two-sided) for the primary endpoint (cure versus failure) using the mITT study population and Last Observation Carried Forward (LOCF).

23. The following Statistical Analysis Method is recommended for equivalence testing for a dichotomous variable (success/failure):

    Equivalence Analysis

    Based on the usual method used in OGD for binary outcomes, the 90% confidence interval for the difference in success proportions between test and reference treatment must be contained within [-0.20, +0.20] in order to establish equivalence.

    The compound hypothesis to be tested is:

    H_0: $p_T - p_R < -0.20$ or $p_T - p_R > 0.20$

    versus

    H_A: $-0.20 \leq p_T - p_R \leq 0.20$

    where p_T = cure rate of test treatment and p_R = cure rate of reference treatment.

    Let

    n_T = sample size of test treatment group

    $c n_T$ = number of cured subjects in test treatment group

    n_R = sample size of reference treatment group

    $c n_R$ = number of cured subjects in reference treatment group

    $\hat{p}_T = c n_T / n_T$, $\hat{p}_R = c n_R / n_R$,

    and $se = (\hat{p}_T(1 - \hat{p}_T)/n_T + \hat{p}_R(1 - \hat{p}_R)/n_R)^{½}$.

    The 90% confidence interval for the difference in proportions between test and reference was calculated as follows, using Yates' correction:

    $L = (\hat{p}_T - \hat{p}_R) - 1.645\ se - (1/n_T + 1/n_R)/2$

    $U = (\hat{p}_T - \hat{p}_R) + 1.645\ se + (1/n_T + 1/n_R)/2$

    We reject H_0 if $L \geq -0.20$ and $U \leq 0.20$

    Rejection of the null hypothesis H_0 supports the conclusion of equivalence of the two products.

24. Study data should be submitted to the OGD in electronic format.
    a. A list of file names, with a simple description of the content of each file, should be included. Such a list should include an explanation of the variables included in each of the data sets.
    b. Please provide a "pdf" document with a detailed description of the codes that are used for each variable in each of the SAS datasets (for example, Y=yes, N=no for analysis population).
    c. All SAS transport files, covering all variables collected in the Case Report Forms (CRFs) per subject, should include .xpt as the file extension and should not be compressed. A simple SAS program to open the data transport files and SAS files should be included.
    d. Primary data sets should consist of two data sets: No Last Observation Carried Forward (NO-LOCF-pure data set) and Last Observation Carried Forward (LOCF-modified data set).
    e. Please provide a separate dataset for variables such as demographics, vital signs, adverse events, disposition (including reason for discontinuation of treatment), concomitant medications, medical history, compliance and comments, etc.

25. Please provide a summary dataset containing a separate line listing for each subject (if data exist) using the following headings, if applicable:
    a. Study identifier
    b. Subject identifier
    c. Site identifier: study center
    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. Per Protocol (PP) population inclusion (yes/no)
    m. Reason for exclusion from PP population
    n. Modified Intent to Treat (mITT) population inclusion (yes/no)
    o. Reason for exclusion from mITT population
    p. Safety population inclusion (yes/no)
    q. Reason for exclusion from Safety population
    r. Treatment outcome (cure/failure)
    s. Treatment compliance: number of missed doses per subject
    t. Concomitant medication (yes/no)
    u. Adverse event(s) reported (yes/no)

    Please refer to Table 1 as an example. This sample table may contain additional information not applicable to your study and/or it may not contain all information applicable to your study.

Table 1: Example of a summary dataset containing one line listing for each subject

STUDYID	SUBJID	SITEID	AGE	AGEU	SEX	RACE	EXTRT	EXDUR	completd	disc_rs	pp	pp_rs	mitt	mitt_rs
101	1	01	21	YEARS	F	1	A	14	Y		Y		Y	
101	2	01	30	YEARS	F	1	B	14	Y		Y		Y	

safety	safe_rs	outcome	complian	CM	AE
Y		S	0	Y	Y
Y		F	0	N	N

Note: Capitalized headings are from 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
SUBJID:	Subject Identifier for the Study
SITEID:	Study Site Identifier
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, C=placebo control
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 unblinded, F=subject moved out of area, G=unsatisfactory treatment response, H=withdrew consent, I=protocol violation, K=other event
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.
outcome:	Primary Endpoint outcome, e.g., S=success (cure); F=Failure
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

26. Please provide a dataset containing a separate line listing for each visit per subject (if data exist) using the following headers, if applicable:
    a. Study identifier
    b. Subject identifier
    c. Name of Actual Treatment (exposure): test product, RLD, placebo control
    d. Visit number
    e. Visit date
    f. Number of days since baseline visit
    g. Culture result
    h. MRSA (yes/no)
    i. Bacterial cure (yes/no)
    j. Concomitant medication reported during this visit (yes/no)
    k. Adverse event reported during this visit (yes/no)
    l. Laboratory testing during this visit (yes/no)

    Please refer to Table 2 as an example. This sample table may contain additional information not applicable to your study and/or it may not contain all information applicable to your study.

Table 2: Example of dataset containing one line listing for each visit per subject

STUDYID	SUBJID	EXTRT	VISITNUM	SVSTDTC	ELTMBS	culture	mrsa	bactcure	CMrpt	AErpt	LBtest
101	1	A	1	2004-07-01	1				Y	Y	N

Note: Capitalized headings are from 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
SUBJID:	Subject Identifier for the Study
EXTRT:	Name of Actual Treatment (exposure), e.g., A=test product, B=RLD, C= placebo control
VISITNUM:	Visit Sequence Number
SVSTDTC:	Visit date: (SVSTDTC=Subject Visit Start Date Time-Character)
ELTMBL:	Elapsed Time since Baseline (days)
culture:	Culture result
mrsa:	Methicillin-resistent *S. aureus* (MRSA), e.g., Y=Yes, N=No
bactcure:	Bacterial cure, e.g., Y=Yes, N=No
CMrpt:	Concomitant Medication reported during this visit, e.g., Y=Yes, N=No
AErpt:	Adverse Event reported during this visit, e.g., Y=Yes, N=No
LBtest:	Laboratory Testing performed during this visit, e.g., Y=Yes, N=No

27. These recommendations are specific to this product and may not be appropriate for bioequivalence studies of any other product, including any other dosage form or strength of mupirocin calcium.