Contains Nonbinding Recommendations

Draft Guidance on Clindamycin Phosphate

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

Active ingredient: Clindamycin Phosphate

Form/Route: Cream; Vaginal (NDA 050793)

Recommended study: 1 Study

Type of study: Bioequivalence (BE) study with clinical endpoint
Design: Randomized, double blind, 3-arm, parallel, placebo-controlled *in vivo*
Strength: EQ 2% base
Subjects: Healthy non-pregnant females with bacterial vaginosis
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 BE study with clinical endpoint:

1. The Office of Generic Drugs (OGD) recommends a bioequivalence study with a clinical endpoint in the treatment of bacterial vaginosis (BV) in non-pregnant female subjects. Subjects are to be randomized to receive the generic Clindamycin Phosphate vaginal cream, EQ 2% Base, the reference listed drug (RLD), or placebo as one applicator full (approximately 5 grams containing approximately 100 mg of clindamycin in the applicator to be provided with the test product or currently marketed applicator provided with the RLD) administered intravaginally as a single-dose. The primary endpoint is therapeutic cure rate, which includes both clinical cure (resolution of clinical signs and symptoms) AND bacteriological cure (Nugent Score <4, see Table 1), evaluated at the Test of Cure visit (study Day 22-30).

Table 1: Nugent Scoring System (0-10) for Gram-stained Vaginal Smears (a)

Score (b)	Lactobacillus morphotypes	*Gardnerella* and *Bacteroides* spp. morphotypes	Curved gram-variable rods
0	4+	0	0
1	3+	1+	1+ or 2+
2	2+	2+	3+ or 4 +
3	1+	3+	
4	0	4+	

Source: Nugent, R. P., M. A. Krohn, and S. L. Hillier. Reliability of diagnosing bacterial vaginosis is improved by a standardized method of Gram stain interpretation. *J. Clin. Microbiol*. 1991; 29: 297-301.

(a) Morphotypes are scored as the average number seen per oil immersion field. Note that less weight is given to curved gram-variable rods. Total score = lactobacilli + *G. vaginalis* and *Bacteroides* spp/ + curved rods.
(b) 0, No morphotypes present; 1, <1 morphotype present; 2, 1 to 4 morphotypes present; 3, 5 to 30 morphotypes present; 4, 30 or more morphotypes present.

2. Inclusion Criteria (the sponsor may add additional criteria):
    a. Healthy female aged ≥ 18 years.
    b. Diagnosis of bacterial vaginosis, defined as the presence of all of the following:
        i. Clinical diagnosis of bacterial vaginosis (e.g., thin, homogenous vaginal discharge associated with minimal or absent pruritus or inflammation AND
        ii. Saline wet mount of vaginal discharge demonstrating the proportion of clue cell to be ≥ 20% of the total epithelial cells AND
        iii. Vaginal pH > 4.5, using pH paper that measures from 4.0-6.0 AND
        iv. Positive "whiff test" after addition of a drop of 10% KOH to vaginal discharge) AND
        v. Gram stain Nugent score ≥ 4 on first day of dosing (study Day 1)
    c. Not pregnant and has a negative urine pregnancy test on the first day of dosing (study Day 1).
    d. Willing to refrain from using any vaginal product (e.g., spermicide, tampon, douche, diaphragm, or condom), other than study product, on study Days 1-6, for 48 hours prior to the first dose of study product, and for 48 hours prior to Test of Cure visit.
    e. Willing to refrain from sexual intercourse on study Day 1 and for 48 hours prior to Test of Cure visit.

3. Exclusion Criteria (the sponsor may add additional criteria):
    a. Pregnancy or breast feeding or planning to become pregnant during the study period.
    b. Menstruating when diagnosis of BV is determined at Baseline visit.
    c. Primary or secondary immunodeficiency.
    d. Severe liver disease.
    e. Regional enteritis, ulcerative colitis, or a history of *Clostridium difficile*-associated diarrhea.
    f. Evidence of any vulvovaginitis other than bacterial vaginosis. (e.g., candidiasis, *Trichomonas vaginalis*, *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, *Herpes simplex,* or human papilloma virus)
    g. Subject with another vaginal or vulvar condition, which would confound the interpretation of clinical response.
    h. Subject will be under treatment during the study period for cervical intraepithelial neoplasia (CIN) or cervical carcinoma.
    i. History of hypersensitivity to clindamycin or other lincosamides or allergic to any of the ingredients of the vaginal creams.
    j. Use within 2 weeks prior to baseline of 1) topical or systemic antibiotics or 2) topical or systemic antifungal.
    k. Use of spermicides, tampons, douches, diaphragms, condoms or other intra-vaginal product within 48 hours prior to dosing on study Day 1.

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:
    a. Systemic corticosteroid or immunosuppressive drugs.
    b. Systemic or topical antibiotics, other than study product.
    c. Neuromuscular blocking agents.
    d. Any product inserted into the vagina (e.g., spermicide, tampon, douche, condom or vaginal contraceptive diaphragms), other than study product, on study Days 1-6 and for 48 hours prior to Test of Cure visit.

e. Subjects should be instructed to not have vaginal intercourse during treatment (e.g., on study Day 1) and for 48 hours prior to Test of Cure visit, not use condoms or vaginal contraceptive diaphragms within 5 days following treatment (e.g., on study Days 1-6) and not put study product in eyes or mouth or on skin.

5. The primary endpoint of the study is the therapeutic cure rate, defined as both a clinical cure (resolution of clinical signs and symptoms, e.g., normal physiological vaginal discharge, whiff test is negative for any amine "fishy" odor, saline wet mount is negative for clue cells, and vaginal pH is < 4.7, using pH paper that measures pH from 4.0-6.0) AND a bacteriological cure (Nugent score <4), evaluated at the Test of Cure visit (study Day 22-30). Subjects who used any bacterial vaginosis therapy, other than study product, during the study or had a Nugent score >3 at the Test of Cure visit should be considered therapeutic failures.

6. The protocol should clearly define the per-protocol (PP), modified intent-to-treat (mITT) and safety populations.
   a. The PP population includes all randomized subjects who meet all inclusion/exclusion criteria, are compliant with the assigned study treatment, return to the study site for the primary endpoint visit within the specified window (on study Days 22-30) OR discontinue from the study as a treatment failure, and do not have any protocol violations. The PP population should be used for the bioequivalence evaluation of test vs. reference. The protocol should provide a definition of compliant subjects (e.g., use at least 75% and no more than 125% of study treatment doses) and specify how compliance will be verified (e.g., by the use of subject diaries).
   b. The mITT population includes all randomized subjects who meet all inclusion/exclusion criteria, receive study treatment, and return for at least one post-baseline visit. The mITT population should be used to compare both test and reference products to placebo.
   c. The safety population includes all randomized subjects who received study treatment.

7. Subjects who discontinue early from the study due to lack of treatment effect at least 3 days after completing treatment should be included in the mITT and PP population as treatment failures. Subjects discontinued early for other reasons, as well as those subjects who have a non-evaluable clinical outcome at the Test of Cure visit, should be excluded from the PP population, but included in the mITT population, using Last Observation Carried Forward (LOCF).

8. 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.

9. 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.

10. 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.

11. 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.

12. 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.

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

14. To establish bioequivalence, the 90% confidence interval for the primary endpoint (test-reference difference in cure rate) must be within [-0.20, +0.20] for dichotomous variables, using the PP population.

15. As a parameter for determining adequate study sensitivity at the lower end of the dose-response curve, the test product and RLD should both be statistically superior to placebo ($p<0.05$, two-sided) for the primary endpoint, using the mITT study population and LOCF.

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

    Equivalence Analysis for a Dichotomous Variable

    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

cn_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 = $(\hat{p}_T (1 - \hat{p}_T)/n_T + \hat{p}_R (1 - \hat{p}_R)/n_R)^{1/2}$

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

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

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

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.

17. 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.
    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 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, baseline admission criteria, adverse events, reasons for discontinuation of treatment, concomitant medications, medical history, compliance and comments, etc.

18. 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
    i. Duration of Treatment (total exposure in days)
    j. Per Protocol (PP) population inclusion (yes/no)
    k. Reason for exclusion from PP population

l. Modified Intent to Treat (mITT) population inclusion (yes/no)
m. Reason for exclusion from mITT population
n. Safety population inclusion (yes/no)
o. Reason for exclusion from safety population
p. Clinical cure(yes/no)
q. Bacteriological cure (yes/no)
r. Treatment success (therapeutic cure) (yes/no)
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 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 a summary dataset containing one line listing for each subject

STUDYID	SUBJID	SITEID	AGE	AGEU	SEX	RACE	EXTRT	EXDUR	pp	pp_rs	mitt	mitt_rs	safety	safe_rs	cure_cl	cure_ba	success	complian	CM	AE
101	1	01	22	YEARS	F	1	A	1	Y		Y		Y		Y	Y	Y	0	Y	Y
101	2	01	30	YEARS	F	1	B	1	Y		Y		Y		Y	N	N	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., F=Female
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
EXDUR: Duration of Treatment (total exposure in days)
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, B=negative baseline culture, 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.
cure_cl: Clinical cure, e.g., Y=Yes, N=No
cure_ba: Bacteriological cure, e.g., Y=Yes, N=No
success: Treatment success (therapeutic cure), 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

19. 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. Evaluator: identity of evaluator
    h. Abnormal vaginal discharge (yes/no)
    i. Clinical cure(yes/no)
    j. Bacteriological cure (yes/no)
    k. Treatment success (therapeutic cure) (yes/no)
    l. Concomitant medication reported during this visit (yes/no)
    m. Use of any vaginal products other than study product (yes/no)
    n. Compliant with protocol (yes/no)
    o. Adverse event reported during this visit (yes/no)
    p. Laboratory testing during this visit (yes/no)
    q. Clue cells on wet mount (≥20%, <20%, or none)
    r. Vaginal pH
    s. KOH "whiff test" (positive/negative)
    t. Nugent score (0, 1, 2, 3…10)
    u. Chlamydia trachomatis (positive/negative)
    v. Neisseria gonorrhoeae test, (positive/negative)
    w. Urine pregnancy test ((positive/negative)

    Please refer to Table 3 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 3: Example of dataset containing one line listing for each visit per subject

STUDYID	SUBJID	EXTRT	VISITNUM	SVSTDTC	ELTMBS	EVAL	abn_vagd	cure_cl	cure_ba	success	CMrpt	CMvag	complia	AErpt	LBtest	clue_c	ph_vag	koh	nugent	chlamydia	n_gonorr	preg_ur
101	1	A	1	2004-07-01	0	JB	N	Y	Y	Y	Y	N	Y	N	Y							

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)

abn_vagd:	Abnormal vaginal discharge, e.g., Y=Yes, N=No
cure_cl:	Clinical cure, e.g., Y=Yes, N=No
cure_ba:	Bacteriological cure, e.g., Y=Yes, N=No
success:	Treatment success (therapeutic cure), e.g., Y=Yes, N=No
CMrpt:	Concomitant Medication reported during this visit, e.g., Y=Yes, N=No
CMvag:	Use of any vaginal products other than study product, e.g., Y=Yes, N=No
complia:	Compliant with protocol, 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
clue_c:	Clue cells on wet mount, e.g., A= ≥ 20%, B= < 20%, C=none)
ph_vag:	Vaginal pH
koh:	KOH "whiff test", e.g., P=Positive; N=Negative
nugent:	Nugent score, e.g., 0, 1, 2, 3…10
chlamydia:	Chlamydia trachomatis test e.g., P=Positive; N=Negative
n_gonorr:	Neisseria gonorrhoeae test, e.g., P=Positive; N=Negative
preg_ur:	Urine pregnancy test, e.g., P=Positive; N=Negative

20. 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 clindamycin.