Contains Nonbinding Recommendations

Draft Guidance on Minocycline Hydrochloride

This draft guidance once finalized will represent the Food and Drug Administration's (FDA's, or the Agency's) current thinking on this topic.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 the 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 (OGD).

Active Ingredient: Minocycline hydrochloride (HCl)

Dosage Form; Route: Powder, extended-release (ER); dental

Recommended Studies: One study

Type of study: Bioequivalence (BE) study with clinical endpoint
Design: Randomized, double-blind, parallel, three-arm, vehicle-controlled in vivo
Strength: Equivalent (EQ) 1 mg base (administered to all initial and new periodontal pockets with mean pocket depth (PD) of ≥ 5 mm)
Subjects: Male and nonpregnant female adults with generalized, moderate-to-advanced periodontitis
Additional comments: Specific recommendations are provided below

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

Bioequivalence based on (90% CI): Clinical endpoint

Waiver request of in vivo testing: N/A

Dissolution test method and sampling times: A Dissolution Methods Database is available to the public at the OGD website at http://www.accessdata.fda.gov/scripts/cder/dissolution/. The dissolution information for this product is available at this website. 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 application. For the dissolution test, we recommend that the dissolution testing be conducted at multiple pH conditions including pH 4.2, 6.8, and 8.1.

Additional comments regarding the BE study with clinical endpoint:

1. OGD recommends conducting a BE study with clinical endpoint in the treatment of moderate-to-advanced adult periodontitis comparing the following treatments:
   - Scaling and root planing (S/RP) followed by subgingival application of generic minocycline HCl dental ER powder (M) at the Baseline (Day 1) visit and subgingival application of M at the Month 3 (Day 90 ± 7) visit

- S/RP followed by subgingival application of reference listed drug (RLD) at the Baseline (Day 1) visit and subgingival application of RLD at the Month 3 (Day 90 ± 7) visit
- S/RP followed by subgingival application of vehicle (V) at the Baseline (Day 1) visit and subgingival application of V at the Month 3 (Day 90 ± 7) visit

Evaluate the primary endpoint at the Month 6 (Day 180 ± 14) visit.

2. The S/RP and placebo (vehicle) control arm are 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 at the lower end of the dose/response curve.

3. Inclusion criteria (the sponsor may add additional criteria):
   a. Male or female aged ≥ 18 years
   b. Generalized, moderate-to-advanced adult periodontitis—American Dental Association Class 3 or 4—as determined by the investigator or designee during the screening periodontal examination
   c. Have at least 10 teeth in the functional dentition, excluding third molars.
   d. Have at least four teeth with periodontal pocketing [pocket depth (PD) = 6-9 mm] and bleeding on probing (BOP) on the majority of qualifying teeth, as determined by single-pass probing depth measurements

4. Exclusion criteria (the sponsor may add additional criteria):
   a. Female who is pregnant, breast feeding, or planning a pregnancy
   b. Female of childbearing potential who does not agree to utilize an adequate form of contraception throughout the study
   c. Clinically significant or unstable organic disease or compromised healing potential [e.g., diabetes (Type I) or connective tissue disorders]. Subjects with Type II diabetes (non-insulin-dependent diabetes) can be included if they are considered stable and had no medication changes during the three months prior to baseline.
   d. Need for antibiotic prophylaxis, e.g., for heart murmur(s), prosthetic joint replacement, valvular disease or history of rheumatic fever
   e. Known allergy or hypersensitivity reaction to tetracycline, minocycline, or any of the study treatment excipients
   f. Within six months prior to baseline, any quadrant or maintenance S/RP, and/or periodontal surgical therapy
   g. Use within three months prior to baseline of any systemic or topical antibiotic.
   h. Within two months prior to baseline, initiation of any new medication for a chronic medical condition
   i. Use within one month prior to baseline of systemic or inhaled steroid medication. Short term use of topical steroid is permitted
   j. Use for at least two weeks within one month prior to baseline of any medication known to affect periodontal status (e.g., phenytoin, calcium antagonists, cyclosporine, warfarin, and nonsteroidal anti-inflammatory drugs) examination. Prophylactic use of aspirin (≤ 325 mg daily) for cardiovascular indications is permitted.

5. The protocol should include a list of the prescription and over-the-counter drug products that are prohibited during the study, such as:
    a. Antibacterial oral rinses (e.g., chlorhexidine, Listerine®, Plax®, sanguinarine or hydrogen peroxide products) or dentifrices (e.g., triclosan or 0.454% stannous fluoride products)
    b. Systemic penicillin, amoxicillin (without clavulanate) or erythromycin for more than 14 consecutive days per treatment
    c. Acute medical use of the following antibiotics: amoxicillin with clavulanate (e.g., Augmentin), cephalosporins, tetracyclines (including minocycline and doxycycline), clindamycin, metronidazole, tinidazole, ornidazole, ciprofloxacin, ofloxacin, and temafoxacin
    d. Non-steroidal anti-inflammatory drugs (NSAIDs) (except prophylactic doses of ≤ 325 mg/day aspirin) for more than 14 consecutive days or more than 30 total days
    e. Systemic or inhaled steroids

6. S/RP should be performed only at the Baseline (Day 1) visit. After a full mouth S/RP, the assigned study treatment should be applied to all sites with PD ≥ 5 mm. Retreatment with the study treatment should be performed at the Month 3 (Day 90 ±7) visit to all sites that were treated at baseline, as well as all new sites with PD ≥ 5 mm.

7. The recommended primary endpoint is the change of within-subject average PD from the Baseline (Day 1) visit to the Month 6 (study Day 180 ± 14) visit.

8. 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 meet all inclusion/exclusion criteria, received the assigned study treatment at the Baseline (Day 1) and Month 3 (Day 90 ± 7) visits, returned to the study site for the primary endpoint Month 6 (Day 180 ± 14) visit within the specified window (± 14 days) or discontinued from the study as a treatment failure, and did not have any protocol violations that would affect the treatment evaluation.
    b. The mITT population includes all randomized subjects who meet all inclusion/exclusion criteria, received at least one assigned study treatment, and returned for at least one post-baseline visit.
    c. The safety population includes all randomized subjects who received study treatment.

9. Subjects who discontinued early from the study due to lack of treatment effect after receiving only one treatment should be included in the PP population as treatment failures. Subjects whose condition worsen and require alternate or supplemental therapy for the treatment of their periodontal disease during the study should be discontinued, included in the PP population analysis, and provided with effective treatment. Subjects discontinued early for reasons other than lack of treatment effect should be excluded from the PP population, but included in the mITT population, using Last Observation Carried Forward (LOCF).

10. 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.

11. 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.

12. If the inactive ingredients of the test product are different than those contained in the RLD or in significantly different amounts, then 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.

13. 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.

14. A detailed description of the blinding procedure is to be provided in the protocol. The packaging of the test, reference and vehicle-control products should be similar in appearance to make differences in treatment less obvious to the subjects and dental examiners, and to maintain adequate blinding of evaluators. Neither the subject nor the investigator should be able to identify the treatment.

15. 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 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 (GLPs) and good clinical practices (GCPs). 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.

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

17. To establish BE for a continuous endpoint, it is recommended the following compound hypotheses be tested using the per protocol population:

H_O: $\mu_T/\mu_R \leq \theta_1$ or $\mu_T/\mu_R \geq \theta_2$ versus H_A: $\theta_1 < \mu_T/\mu_R < \theta_2$

where μ_T = mean of the primary endpoint for the test group, and
μ_R = mean of the primary endpoint of 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 ratio of the means between test and reference products (μ_T/μ_R) is contained within the interval $[\theta_1, \theta_2]$, where $\theta_1 = 0.80$ and $\theta_2 = 1.25$. Rejection of the null hypothesis supports the conclusion of equivalence of the two products.

18. 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.

19. Study data should be submitted to the 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 = RLD and B = TEST).
    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.

20. Provide a summary data set 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, vehicle control
    i. Number of Treatments (none, one, two)
    j. Completed the study (yes.no))
    k. Reason for premature discontinuation of subject
    l. Subject required additional treatment for periodontal disease 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. Total number of teeth treated at Baseline (Day 1) visit
t. Total number of teeth treated on Month 3 (Day 90) visit
u. Average pocket depth (PD) per subject at Baseline (Day 1) visit
v. Average PD per subject at Month 3 (Day 90) visit
w. Average PD per subject at Month 6 (Day 180) visit
x. Concomitant medication (yes/no)
y. 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 Data Set Containing One Line Listing for Each Subject

STUDYID	SUBJID	SITEID	AGE	AGEU	SEX	RACE	EXTRT	num_trt	completed	disc_rr	add_trt	pp	pp_rs	mitt	mitt_rs	safety	safe_rs	tt_b	tt_3	pd_b	pd_3	pd_6	CM	AE
101	1	01	52	YEARS	F	1	A	2	Y			Y		Y		Y		4	6	8	2		Y	Y
101	2	01	55	YEARS	F	1	B	2	Y			Y		Y		Y		5	2	7	1		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=vehicle control
num_trt:	Number of Treatments, e.g., 0=none, 1=one , 2=two
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.
pd_b: Average PD at Baseline (Day 1) visit
pd_3: Average PD at Month 3 (Day 90) visit
pd_6: Average PD at Month 6 (Day 180) visit
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

21. Provide a data set 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, vehicle control
    d. Visit number
    e. Visit date
    f. Number of days since baseline visit
    g. Evaluator: identity of evaluator
    h. Number of teeth treated
    i. PD for each tooth treated
    j. Average PD per visit
    k. Concomitant medication reported during this visit (yes/no)
    l. Adverse event reported during this visit (yes/no)
    m. Laboratory testing during this visit (yes/no)

    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 Data Set Containing One Line Listing for Each Visit Per Subject

STUDYID	SUBJID	EXTRT	VISITNUM	SVSTDTC	ELTMBS	EVAL	tt	pd_1	pd_2	pd_3	pd_4	pd_5	pd_6	pd_7	ave_pd	CMrpt	AErpt	LBtest
101	1	A	1	2004-07-01	0	JB	7	4	2	3	8	5	5	3	4.3	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= vehicle control

VISITNUM:	Visit Sequence Number
SVSTDTC:	Visit date: (SVSTDTC=Subject Visit Start Date Time-Character)
ELTMBL:	Elapsed Time since Baseline (days)
EVAL:	Evaluator: identity of the evaluator, e.g., initials
tt:	Number of teeth treated
pd_1:	Pocket depth of treated tooth #1
pd_2:	Pocket depth of treated tooth #2
pd_3:	Pocket depth of treated tooth #3
pd_4:	Pocket depth of treated tooth #4
pd_5:	Pocket depth of treated tooth #5
pd_6:	Pocket depth of treated tooth #6
pd_7:	Pocket depth of treated tooth #7
aver_pd:	Average pocket depth at this visit of all treated teeth
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

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 minocycline.

23. Any sponsor who has data or references from the scientific literature that would support an in vitro option for this drug product or has proposals for valid in vitro studies or other methods for evaluating BE for this drug product to submit them to the OGD for review.