Contains Nonbinding Recommendations

Draft Guidance on Rifaximin

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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

Form/Route: Tablet/Oral

Recommended studies 1 study

Type of study: BE Study with Clinical Endpoint
Design: Randomized, double blind, parallel, placebo controlled in vivo
Strength: 200 mg (dosed: three times daily for 3 days)
Subjects: Male and nonpregnant female subjects with travelers' diarrhea
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: Please note that a **Dissolution Methods Database** is available to the public at the OGD website at http://www.accessdata.fda.gov/scripts/cder/dissolution/. Please find the dissolution information for this product at this website. Please 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.

Additional comments regarding the BE study with clinical endpoint:

1. The Office of Generic Drugs (OGD) recommends conducting a BE study with a clinical endpoint in the treatment of travelers' diarrhea. After three unformed stools are recorded within the 24 hours immediately preceding randomization, subjects are to be randomized to receive the generic rifaximin 200 mg oral tablet, the reference listed drug (RLD) 200 mg oral tablet or placebo three times daily for 3 days (i.e., on study Days 1, 2, and 3). The primary endpoint is clinical cure at the test of cure (TOC) visit on study Day 5.

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. Adult male or nonpregnant female aged ≥ 18 years non-indigenous travelers (e.g., visiting students/faculty or international tourists) affected by naturally acquired acute diarrhea. Diarrhea is defined as the passage of at least three unformed stools in a 24-hour period. Stools are classified as formed (retains shape), soft (assumes shape of container), or watery (can be

poured). When using this classification, both soft and watery stools are unformed and abnormal.

b. At least three unformed stools recorded within the 24 hours immediately preceding randomization.
c. At least one of the following signs and symptoms of enteric infection:
   - abdominal pain or cramps
   - nausea
   - vomiting
   - fecal urgency
   - excessive gas/flatulence
   - tenesmus
d. Women of child-bearing potential have a negative pregnancy test prior to beginning therapy and agree to use effective contraceptive methods during the study.

4. Exclusion Criteria (the sponsor may add additional criteria)
   a. Pregnant, breast feeding, or planning a pregnancy.
   b. Immediately prior to randomization, acute diarrhea for > 72 hours.
   c. Presence of:
      - fever (≥ 100 °F or ≥ 37.8 °C), or
      - hematochezia (blood in stool), or
      - clinical findings suggesting moderate or severe dehydration.
   d. Active, uncontrolled, or clinically significant diseases or disorders of the heart, lung, kidney, GI tract (other than infectious diarrhea in travelers), or central nervous system.
   e. Administration of any of the following:
      - any antimicrobial agents with an expected activity against enteric bacterial pathogens within 7 days preceding randomization
      - more than two doses of a symptomatic antidiarrheal compound such as antimotility agents, absorbent agents, and antisecretory agents within 8 hours preceding randomization
   f. Use of any drug such as aspirin or ibuprofen (Advil), which can cause GI bleeding. Acetaminophen (Tylenol) or paracetamol is acceptable.
   g. If required during the study antimalarial prophylactic treatment, including doxycycline, is permitted prior to and during the study

5. Stools at subject screening (Day 0) and end of study (Day 5) should be cultured for pathogenic organisms, but microbiological cure rates will be considered as supportive of the similarity of populations in each arm of the study and not considered as evidence of bioequivalence.

6. Possible patient subgroups with travelers' diarrhea that should be considered in planning for the populations size required for this study include:
   - inflammatory/invasive pathogens,
   - diarrheagenic *E. coli* without evidence of inflammatory/invasive pathogens,
   - other agents without evidence of inflammatory/invasive pathogens.

7. 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. Prescription and over-the-counter (OTC) anti-diarrheal drug product other than study product.
   b. Opioid analgesics.

8. The recommended primary endpoint is clinical cure at the TOC visit (study Day 5). Clinical cure is defined as either:
    a. No stools or only formed stools within a 48 hour period and no fever, with or without other enteric symptoms, OR
    b. No watery stools or no more than two soft stools passed within a 24 hour period with no fever and no other enteric symptoms except for mild excess gas/flatulence.

9. In addition, clinical deterioration by study Day 5 or failure to achieve formed stool in ≤ 3 days is a clinical failure.

10. The recommended secondary endpoint is Time to Last Unformed Stool (TLUS) defined as the interval beginning with the first dose of study drug and ending with the last unformed stool passed.

11. The protocol should clearly define the per-protocol (PP), modified intent-to-treat (mITT) and safety populations:
    a. The accepted PP population used for bioequivalence evaluation includes all randomized subjects who met all inclusion/exclusion criteria, dosed a prespecified proportion of the scheduled administrations (e.g., 75% to 125%) of the assigned product for the specified duration of the study and completed the evaluation within the designated visit window (+/- 1 day) 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 met all inclusion/exclusion criteria, administered at least one dose of assigned product and returned for at least one post-baseline evaluation visit.
    c. The safety population includes all randomized subjects who received at least one dose of study product.

12. Subjects who are discontinued early from the study due to lack of treatment effect after completing 3 days of treatment should be included in the PP population using LOCF. Subjects whose condition worsens and who require alternate or supplemental therapy for the treatment of travelers' diarrhea should be discontinued, included in the PP population analysis using LOCF, and provided with effective treatment. 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).

13. 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.

14. 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.

15. 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.

16. 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.

17. 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.

18. 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.

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

20. To establish bioequivalence, the 90% confidence interval of the test - reference difference between products for the primary endpoint (clinical cure evaluated on study Day 5) must be contained within [-0.20, +0.20] for dichotomous variables (success versus failure), using the PP population.

21. 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 using the mITT study population and LOCF.

22. 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 = success rate of test treatment and p_R = success rate of reference treatment.

Let

n_T = sample size of test treatment group

cn_T = number of successes in test treatment group

n_R = sample size of reference treatment group

cn_R = number of successes in reference treatment group

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

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

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.

23. 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.

24. 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. Protocol Violations (yes/no)
l. Reason for premature discontinuation of subject
m. Subject required additional treatment for diarrhea due to unsatisfactory treatment response (yes/no)
n. Per Protocol (PP) population inclusion (yes/no)
o. Reason for exclusion from PP population
p. Modified Intent to Treat (mITT) population inclusion (yes/no)
q. Reason for exclusion from mITT population
r. Safety population inclusion (yes/no)
s. Reason for exclusion from Safety population
t. Number of unformed bowel movements during 24 hours immediately prior to randomization
u. Number of formed bowel movements during 24 hours immediately prior to randomization
v. Number of unformed bowel movements during study Day 1
w. Number of formed bowel movements during study Day 1
x. Number of unformed bowel movements during study Day 2
y. Number of formed bowel movements during study Day 2
z. Number of unformed bowel movements during study Day 3
aa. Number of formed bowel movements during study Day 3
bb. Number of unformed bowel movements during study Day 4
cc. Number of formed bowel movements during study Day 4
dd. Number of unformed bowel movements during study Day 5
ee. Number of formed bowel movements during 2 study Day 5
ff. After randomization, no stools or only formed stools within a 48 hour period (yes/no)
gg. After randomization, no watery stools or no more than two soft stools passed within a 24 hour period (yes/no)
hh. After randomization, clinical deterioration (yes/no)
ii. Achieved formed stool in ≤ 3 days after randomization (yes/no)
jj. At TOC visit, any enteric symptom except for mild excess gas/flatulence (yes/no)
kk. Clinical cure at TOC visit (yes/no)
ll. Time to Last Unformed Stool (hours)
mm. Treatment compliance: number of missed doses per subject
nn. Concomitant medication (yes/no)
oo. 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	prot_vio	disc_rs	add_trt	pp	pp_rs	mitt	mitt_rs	safety	safe_rs
101	1	01	21	YEARS	F	1	A	14	Y	N		N	Y		Y		Y	
101	2	01	30	YEARS	F	1	B	14	Y	N		N	Y		Y		Y	

bas_ubm	bas_fbm	day1_ubm	day1_fbm	day2_ubm	day2_fbm	day3_ubm	day3_fbm	day4_ubm	day4_fbm	day5_ubm	day5_fbm	48hrcure	24hrcure	cl_deter	fstool	ent_sx	cl_cure	tlus	complian	CM	AE
6	0											Y	Y	N	Y	N	Y	70	0	Y	Y
7	0											N	Y	N	Y	N	Y	48	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
prot_vio:	Protocol Violations, 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
add_trt:	Subject required additional treatment for diarrhea due 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.
bas_ubm:	Number of unformed bowel movements during 24 hours immediately prior to randomization
bas_fbm:	Number of formed bowel movements during 24 hours immediately prior to

	randomization
day1_ubm:	Number of unformed bowel movements during study Day 1
day1_fbm:	Number of formed bowel movements during study Day 1
day2_ubm:	Number of unformed bowel movements during study Day 2
day2_fbm:	Number of formed bowel movements during study Day 2
day3_ubm:	Number of unformed bowel movements during study Day 3
day3_fbm:	Number of formed bowel movements during study Day 3
day4_ubm:	Number of unformed bowel movements during study Day 4
day4_fbm:	Number of formed bowel movements during study Day 4
day5_ubm:	Number of unformed bowel movements during study Day 5
day5_fbm:	Number of formed bowel movements during study Day 5
48hrcure:	After randomization, no stools or only formed stools within a 48 hour period, e.g., Y=Yes, N=No
24hrcure:	After randomization, no watery stools or no more than two soft stools passed within a 24 hour period, e.g., Y=Yes, N=No
cl_deter:	After randomization, clinical deterioration, e.g., Y=Yes, N=No
fstool:	Achieved formed stool in $\leq$ 3 days after randomization, e.g., Y=Yes, N=No
ent_sx:	At TOC visit, any enteric symptom except for mild excess gas/flatulence, e.g., Y=Yes, N=No
cl_cure:	Clinical cure at TOC visit, e.g., Y=Yes, N=No
tlus:	Time to Last Unformed Stool (hours)
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

25. 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. Study day; i.e., day of randomization is study day 1
    g. Fever (yes/no)
    h. Moderate or severe dehydration (yes/no)
    i. Hematochezia (blood in stool) (yes/no)
    j. Abdominal pain or cramps (yes/no)
    k. Nausea (yes/no)
    l. Vomiting (yes/no)
    m. Fecal urgency (yes/no)
    n. Excessive gas/flatulence (yes/no)
    o. Tenesmus (yes/no)
    p. Use of anti-diarrheal drug product, other than study product, or opioid analgesic reported during this visit (yes/no)
    q. If reported during this visit, provide date(s) of use of anti-diarrheal drug product, other than study product, or opioid analgesic.
    r. Concomitant medication reported during this visit (yes/no)
    s. Adverse event reported during this visit (yes/no)
    t. 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	fever	dehydrat	hematoc	abd_pain	nausea
101	1	A	1	2004-07-01	1					

vomiting	fec_urg	ex_gas	tenesmus	proh_med	proh_m_d	CMrpt	AErpt	LBtest
				N		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)
fever:	Fever , e.g., Y=Yes, N=No
dehydrate:	Moderate or severe dehydration, e.g., Y=Yes, N=No
hematoc:	Hematochezia (blood in stool), e.g., Y=Yes, N=No
abd_pain:	Abdominal pain or cramps e.g., Y=Yes, N=No
nausea:	Nausea, e.g., Y=Yes, N=No
vomiting:	Vomiting, e.g., Y=Yes, N=No
fec_urg:	Fecal urgency, e.g., Y=Yes, N=No
ex_gas:	Excessive gas/flatulence, e.g., Y=Yes, N=No
tenesmus:	Tenesmus, e.g., Y=Yes, N=No
proh_med:	Use of anti-diarrheal drug product, other than study product, or opioid analgesic reported during this visit, e.g., Y=Yes, N=No
proh_m_d:	If reported during this visit, provide date(s) of use of anti-diarrheal drug product, other than study product, or opioid analgesic.
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

26. 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 rifaximin.