

## Draft Guidance on Rifaximin

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

**Dosage Form; Route:** Tablet; oral

**Recommended Studies:** Two options

### Option 1:

If the test product formulations are qualitatively and quantitatively (Q1/Q2) the same as the Reference Listed Drug (RLD) with respect to inactive ingredients, bioequivalence (BE) may be established by conducting both in vivo BE studies with pharmacokinetic (PK) endpoints and in vitro comparative dissolution studies.

#### In vivo BE study with PK endpoints:

1. Type of study: Fasting

Design: Single-dose, two-treatment, two-period crossover in vivo

Strength: 200 mg

Subjects: Healthy males and nonpregnant/nonlactating females, general population.

Additional Comments: Applicants may consider using a reference-scaled average bioequivalence approach for this drug product. Please refer to the Progesterone Capsule Guidance for additional information regarding the reference-scaled average bioequivalence approach.

2. Type of study: Fed

Design: Single-dose, two-treatment, two-period crossover in vivo

Strength: 200 mg

Subjects: Healthy males and nonpregnant/nonlactating females, general population.

Additional Comments: Same as comments above

#### In vitro dissolution study:

3. Type of study: Comparative dissolution study

Strength: 200 mg

Apparatus: U.S. Pharmacopeia (USP) Apparatus 2 (paddle)

Media: pH 4.5, 0.125% and 0.375% SDS

pH 6.8, 0.125% and 0.375% SDS

Volume: 1000 mL

Temperature: 37°C

Rotation speed: 75 rpm

Sampling times: 10, 20, 30, 45, 60, 90, and 120 minutes

4. Type of study: Comparative dissolution study

Strength: 550 mg

Apparatus: U.S. Pharmacopeia (USP) Apparatus 2 (paddle)  
Media: pH 4.5, 0.25% and 0.5% SDS  
pH 6.8, 0.25% and 0.5% SDS  
Volume: 1000 mL  
Temperature: 37°C  
Rotation speed: 75 rpm  
Sampling times: 10, 20, 30, 45, 60, 90, and 120 minutes

**Analytes to measure (in appropriate biological fluid):** Rifaximin in plasma

**Bioequivalence based on (90% CI):** Rifaximin

**Waiver request of in vivo testing:** 550 mg strength based on (i) acceptable bioequivalence studies on the 200 mg strength, (ii) proportional similarity of the formulations between both strengths, and (iii) acceptable in vitro dissolution testing of both strengths.

**Dissolution test method and sampling times:** The dissolution information for this drug product can be found on the FDA-Recommended Dissolution Methods web site, available to the public at the following location: <http://www.accessdata.fda.gov/scripts/cder/dissolution/>. Conduct comparative dissolution testing on 12 dosage units each of both strengths of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application (ANDA).

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**Option 2:**

If the test product formulations are not Q1/Q2 the same as the RLD with respect to inactive ingredients, BE should be established by conducting an in vivo study with clinical endpoints, in vivo study with PK endpoints, and in vitro comparative dissolution testing.

In vivo BE study with PK endpoints:

The same studies as recommended under Option 1.

In vitro dissolution study:

The same studies as recommended under Option 1.

In vivo BE study with clinical endpoints:

Type of study: BE Study with Clinical Endpoints

Design: Three-arm, randomized, double blind, parallel, placebo controlled in vivo

Strength: 200 mg (dosed: three times daily for 3 days)

Subjects: Male and nonpregnant/nonlactating female subjects with travelers' diarrhea

Additional comments: Specific recommendations are provided below.

## **Additional comments regarding the BE study with clinical endpoints (200 mg):**

1. The Office of Generic Drugs (OGD) recommends conducting a BE study with clinical endpoints 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 and non-lactating female aged  $\geq 18$  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 with a negative pregnancy test prior to beginning therapy and who 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 ( $\geq 100$  °F or  $\geq 37.8$  °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  $\leq 3$  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, were dosed a pre-specified proportion of the scheduled administrations (e.g., 75% to 125%) of the assigned product for the specified duration of the study, do not miss a pre-specified number of scheduled doses for more than pre-specified number of days (e.g. 1 consecutive day), and complete 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 dose at least one dose of assigned product.
  - c. The safety population includes all randomized subjects who receive 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 Last Observation Carried Forward (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 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. The method of randomization should be described in the protocol and the randomization schedule should be provided. 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.
16. 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.
17. 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.

18. It is the sponsor's responsibility to enroll sufficient subjects for the study to demonstrate bioequivalence between the products.
19. To establish bioequivalence for a dichotomous endpoint, it is recommended the following compound hypotheses be tested using the per protocol population:

$$H_0: \pi_T - \pi_R \leq \Delta_1 \text{ or } \pi_T - \pi_R \geq \Delta_2 \text{ versus } H_A: \Delta_1 < \pi_T - \pi_R < \Delta_2$$

where  $\pi_T$  = the success rate of the primary endpoint for the treatment group, and  
 $\pi_R$  = the success rate of the primary endpoint for the reference group.

The null hypothesis,  $H_0$ , is rejected with a type I error ( $\alpha$ ) 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.

20. To establish sensitivity within the study for either a dichotomous or continuous primary endpoint, the test and reference product should both be statistically superior to the placebo. Conduct an appropriate inferential test with a type I error ( $\alpha$ ) of 0.05, using the mITT population and the primary endpoint.
21. Study data should be submitted to the OGD in electronic format.
- 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).
  - 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).
  - 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.
22. Please provide a summary dataset containing a separate line listing for each subject (if data exist) using the following headings, if applicable:
- Study identifier
  - Subject identifier
  - Site identifier: study center
  - Age
  - Age units (years)
  - Sex
  - Race
  - Name of Actual Treatment (exposure): test product, RLD, placebo control
  - Duration of Treatment (total exposure in days)
  - 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  $\leq 3$  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	complan	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)
complan:	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

23. 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)  
ELTMBS: 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

24. The study data should be submitted in standardized format. Please refer to more details at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>.
  25. These recommendations are specific to this product and may not be appropriate for bioequivalence studies of any other product, including any other dosage forms or strengths of rifaximin.
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Type of study: BE Study with Clinical Endpoints

Design: Three–arm, randomized, double blind, parallel, placebo-controlled in vivo

Strength: 550 mg (dosed: three times a day for 14 days)

Subjects: Male and nonpregnant/non-lactating female subjects with irritable bowel syndrome with diarrhea (IBS-D)

**Additional comments regarding the BE study with clinical endpoints (550 mg):**

1. The Office of Generic Drugs (OGD) recommends conducting a BE study with clinical endpoints in the treatment of irritable bowel syndrome with diarrhea (IBS-D). After a 1-2-week screening period, subjects are to be randomized to receive the generic rifaximin 550 mg tablet, the reference listed drug (RLD) 550 mg tablet or placebo tablet three times a day for 14 days. Subjects are then to be followed for an additional 4 weeks. Rifaximin may be taken with or without food.
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. Male or nonpregnant/non-lactating female aged  $\geq 18$  years with a clinical diagnosis of irritable bowel syndrome with diarrhea (IBS-D) confirmed by the Rome III diagnostic criteria. At least 12 weeks, which need not be consecutive, in the preceding 12 months of abdominal discomfort or pain associated with 2 or more of the following:
    - i. Relieved with defecation
    - ii. Onset associated with a change in frequency of stool
    - iii. Onset associated with a change in form(appearance) of stool
  - b. **Abdominal Pain Intensity:** weekly average of *worst daily (in past 24 hours) abdominal pain* score of  $> 3.0$  on a 0 to 10 point scale  
and  
**Stool Consistency:** at least one stool with a consistency of Type 6 or Type 7 Bristol stool score (BSS) on at least 2 days per week
  - c. Subject has undergone a colonoscopy within the last 2 years as part of an evaluation for IBS or IBS symptoms (which excluded inflammatory or neoplastic disease). The subject has a colonoscopy scheduled and completed within 30 days of signing the informed consent.

- d. Subject required to maintain a stable diet for the duration of the study.
  - e. Subjects on stable treatment with a daily dietary fiber supplementation or bulking agents may be enrolled provided that the administration schedule is intended to be maintained throughout the study and the subject has been on therapy for at least 30 days prior to signing the informed consent.
  - f. 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)
- a. Subjects presenting with the following symptoms of constipation IBS (during the diary eligibility phase of  $\geq 7$  days immediately prior to the first dose of study drug):
    - i. Less than 3 bowel movements a week
    - ii. Hard or lumpy stools
    - iii. Straining during a bowel movement
  - b. Subject fails to record at least 7 days of daily diary assessments during the screening phase.
  - c. Subject had current evidence of duodenal ulcer, gastric ulcer, diverticulitis, gastroesophageal reflux disease (GERD), or infectious gastroenteritis. **Note:** Subjects with GERD controlled by stable doses of medication or diet are eligible to participate in the study.
  - d. Subject has a history of inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis, and celiac disease), GI malignancy, GI obstruction, gastroparesis, carcinoid syndrome, pancreatitis, amyloidosis, ileus, or cholelithiasis. Subjects may participate if they have a cholecystectomy.
  - e. Subject has diabetes (Type 1 or Type 2).
  - f. Subject is a candidate for GI surgery or has a history of GI surgery (exceptions appendectomy, cholecystectomy, benign polypectomy, and inguinal hernia).
  - g. Subject has lactose intolerance not controlled by a lactose-free diet.
  - h. Subject had a positive stool test for *Yersinia enterocolitica*, *Campylobacter jejuni*, *Salmonella*, *Shigella*, ovum and parasites, and/or *Clostridium difficile*. (Note: Stool sample was not required if a negative test was obtained within 14 days of randomization).
  - i. Subject has psychiatric disorder not controlled with current therapy.
  - j. Subject has current or recent (within 12 months) history of drug or alcohol abuse.
  - k. Subject is pregnant, breast feeding, or planning a pregnancy.
  - l. Subject has a history of HIV, Hepatitis (B or C), abnormal thyroid function not controlled by medication, hepatic disease manifested by twice the ULN for AST, ALT, alkaline phosphatase or total bilirubin (except an isolated elevation of unconjugated bilirubin).
  - m. Subject has renal disease manifested by 1.5 times the ULN of serum creatinine or blood urea nitrogen levels.
  - n. Subject has unstable cardiovascular or pulmonary disease, categorized by a worsening in the disease condition that requires a change in treatment or medical care within one month of randomization.
  - o. Subject has any condition or circumstance that could cause noncompliance with treatment or visits.
  - p. Subject has known allergy to rifaximin or rifampin or excipients.
  - q. Subject has had an active malignancy except for basal cell carcinoma or in situ cervical carcinoma that has been excised within the last 5 years.
  - r. Subject has participated in an investigational drug or device study within the 30 days prior to signing the informed consent.

- s. Subject has taken rifaximin within 60 days of signing the ICF.
  - t. Subject has taken any experimental drugs within 30 days of signing the ICF and subjects who have taken probiotics after initiation of the diary eligibility phase (yogurt and standard food products are allowed).
  - u. Subject has taken any antibiotics within 14 days prior to signing the ICF.
  - v. Subject has taken antipsychotic drugs, antispasmodics, antidiarrheals (e.g. loperamide, lubiprostone, and bismuth subsalicylate), narcotics, prokinetic drugs, drugs indicated for IBS (e.g. Alosetron), or warfarin after the initiation of the diary eligibility phase.
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. This may include over-the-counter anti-diarrheals or a significant change in diet.
  6. The study should include a 1- to 2- week screening period. The 1- to 2-week screening period can be used to establish the presence and persistence of trial entry criteria and train patients in the mode of data collection selected for the trial. The screening period can also be used to select patients with specified levels of severity of signs and symptoms.<sup>1</sup> Baseline should be defined from the diary data collected during seven days immediately preceding the beginning of the treatment period.
  7. The recommended primary endpoint is responder rate at week 6 and should measure the effect of treatment on two major IBS signs and symptoms (i.e. abnormal defecation and abdominal pain). A patient should be categorized as an overall responder if the patient is weekly responder for at least two weeks during the four-week follow-up period. A patient is categorized as a weekly responder if the patient achieves the following improvement in both pain intensity and stool consistency for a week as described below:
    - $\geq 30\%$  improvement from the baseline in the weekly average abdominal pain score based on the daily question: “In regards to your specific IBS symptoms of abdominal pain, on a scale of 0-10, what was your worst IBS-related abdominal pain over the last 24 hours? ‘Zero’ means you have no pain at all; ‘ten’ means the worst possible pain you can imagine”
    - At least a 50% reduction in the number of days in a week with a daily stool consistency of Bristol Stool Scale type 6 or 7 compared with the baseline where 6=fluffy pieces with ragged edges, a mushy stool; 7=watery stool, no solid pieces; entirely liquid.
  8. Sponsors should choose a format for daily sign or symptom assessment (e.g., interactive voice response or personal digital assistant) so that patients can evaluate IBS signs or symptoms on a daily basis throughout the trial. Daily questionnaire should be answered at approximately same time each day. Appropriate questions to evaluate IBS signs and symptoms include (sponsor may add additional):
    - a. How many bowel movements did you have in the last 24 hours?
    - b. On a scale of 1-7, what was the score of your least formed bowel movement in the last 24 hours (Bristol Stool Scale)?
      - 1 = Separate hard lumps, like nuts (hard to pass)
      - 2 = Sausage-shaped but lumpy
      - 3 = Like a sausage but with cracks on its surface
      - 4 = Like a sausage or snake, smooth and soft

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<sup>1</sup> Guidance for Industry Irritable Bowel Syndrome-Clinical Evaluation of Drugs for Treatment, May 2012.

- 5 = Soft blobs with clear cut edges (passed easily)
- 6 = Fluffy pieces with ragged edges, a mushy stool
- 7 = Watery stool, no solid pieces; entirely liquid.

- c. Have you felt or experienced a sense of urgency in the last 24 hours with any of your bowel movements? (Yes/No)
  - d. In regards to your specific IBS symptom of abdominal pain, on a scale of 0-10, what was your worst IBS-related abdominal pain over the last 24 hours? 'Zero' means you have no pain at all; 'Ten' means the worst possible pain you can imagine.
  - e. In regards to your specific IBS symptom of bloating, on a scale of 0-6, how bothersome was your IBS-related bloating in the last 24 hours?
    - 0 = not at all
    - 1 = hardly
    - 2 = somewhat
    - 3 = moderately
    - 4 = a good deal
    - 5 = a great deal
    - 6 = a very great deal
  - f. In regards to all your symptoms of IBS, on a scale of 0-6, how bothersome were your symptoms of IBS in the last 24 hours?
    - 0 = not at all
    - 1 = hardly
    - 2 = somewhat
    - 3 = moderately
    - 4 = a good deal
    - 5 = a great deal
    - 6 = a very great deal
9. The protocol should clearly define the PP, mITT and safety populations.
- a. The accepted PP population used for bioequivalence evaluation includes all randomized subjects who meet all inclusion/exclusion criteria, dose a pre-specified proportion of the scheduled doses (e.g., 75% to 125%) of the assigned product for the specified duration of the study, do not miss a pre-specified number of scheduled doses for more than pre-specified number of days (e.g. 1 consecutive day), and complete the evaluation within the designated visit window 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 dose at least one dose of assigned product.
  - c. The safety population includes all randomized subjects who receive study product.
10. Subjects who are discontinued early (any time before end of week 6) from the study due to lack of treatment effect should be included in the PP population. Subjects whose condition worsens and who require alternate or supplemental therapy for the treatment of diarrhea during the treatment phase of the study 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.
11. 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.

12. All 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.
13. The method of randomization should be described in the protocol and the randomization schedule should be provided. 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 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.
15. 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.
16. It is the sponsor's responsibility to enroll sufficient subjects for the study to demonstrate bioequivalence between the products.
17. To establish bioequivalence for a dichotomous endpoint, it is recommended the following compound hypotheses be tested using the per protocol population:
 
$$H_0: \pi_T - \pi_R \leq \Delta_1 \text{ or } \pi_T - \pi_R \geq \Delta_2 \text{ versus } H_A: \Delta_1 \leq \pi_T - \pi_R \leq \Delta_2$$
 where  $\pi_T$  = the success rate of the primary endpoint for the treatment group, and  
 $\pi_R$  = the success rate of the primary endpoint for the reference group.
 

The null hypothesis,  $H_0$ , is rejected with a type I error rate ( $\alpha$ ) 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.
18. To establish sensitivity within the study for either a dichotomous or continuous primary endpoint, the test and reference product should both be statistically superior to the placebo. Conduct an appropriate inferential test with a type I error rate ( $\alpha$ ) of 0.05, using the mITT population and the primary endpoint.

19. Study data should be submitted to the OGD in electronic format.
  - 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, B = RLD, C = placebo).
  - b. Provide two summary data sets, one without missing data imputation (pure data set) and one with missing data imputation (modified data set).
  - c. Provide daily diary data of each subject in a separate dataset.
  - 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. 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 planned treatment based on randomization
  - i. Name of Actual Treatment (exposure): test product, RLD, placebo control
  - j. Duration of Treatment (total exposure in days)
  - k. Completed the study (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. Mean abdominal pain score at baseline
  - u. Number of days with daily stool consistency of Bristol Stool Scale type 6 or 7 at baseline
  - v. Mean abdominal pain score at Week 1
  - w. Number of days with daily stool consistency of Bristol Stool Scale type 6 or 7 during Week 1
  - x. Mean abdominal pain score at Week 2
  - y. Number of days with daily stool consistency of Bristol Stool Scale type 6 or 7 during Week 2
  - z. Mean abdominal pain score at Week 3
  - aa. Number of days with daily stool consistency of Bristol Stool Scale type 6 or 7 during Week 3
  - bb. Mean abdominal pain score at Week 4
  - cc. Number of days with daily stool consistency of Bristol Stool Scale type 6 or 7 during Week 4
  - dd. Mean abdominal pain score at Week 5
  - ee. Number of days with daily stool consistency of Bristol Stool Scale type 6 or 7 during Week 5
  - ff. Mean abdominal pain score at week 6
  - gg. Number of days with daily stool consistency of Bristol Stool Scale type 6 or 7 during Week 6
  - hh. Weekly responder in abdominal pain intensity for Week 3 (yes/no)
  - ii. Weekly responder in stool consistency for Week 3 (yes/no)
  - jj. Weekly responder for Week 3 (yes/no)
  - kk. Weekly responder in abdominal pain intensity for Week 4 (yes/no)

- ll. Weekly responder in stool consistency for Week 4 (yes/no)
- mm. Weekly responder for Week 4 (yes/no)
- nn. Weekly responder in abdominal pain intensity for Week 5 (yes/no)
- oo. Weekly responder in stool consistency for Week 5 (yes/no)
- pp. Weekly responder for Week 5 (yes/no)
- qq. Weekly responder in abdominal pain intensity for Week 6 (yes/no)
- rr. Weekly responder in stool consistency for Week 6 (yes/no)
- ss. Weekly responder for Week 6 (yes/no)
- tt. Overall responder (yes/no)
- uu. Treatment compliance: number of missed doses per subject
- vv. Concomitant medication (yes/no)
- ww. 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	ARM	EXTRT	EXDUR	completd	disc_rs	add_trt	pp	pp_rs	mitt	mitt_rs	safety	safe_rs
101	1	01	21	YEARS	F	1	A	A	14	Y		N	Y		Y		Y	
101	2	01	30	YEARS	F	1	B	B	14	Y		N	Y		Y		Y	

pain_0	stool_0	pain_1	stool_1	pain_2	stool_2	pain_3	stool_3	pain_4	stool_4	pain_5	stool_5	pain_6	stool_6
5.4286	4	4.5714	4	3.8571	3	3.1429	3	2.4286	2	1.5714	1	0.8571	1
3.5714	3	3.1429	3	2.7143	2	2.1429	2	1.7143	2	1.2857	1	0.4286	0

presp_3	sresp_3	resp_3	presp_4	sresp_4	resp_4	presp_5	sresp_5	resp_5	presp_6	sresp_6	resp_6	resp	complan	CM	AE
Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	0	Y	Y
Y	N	N	Y	N	N	Y	Y	Y	Y	Y	Y	Y	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

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
ARM:	Name of planned treatment based on randomization
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
add_trt:	Subject required additional treatment for constipation 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.
pain_0:	Mean abdominal pain score at baseline
stool_0:	Number of days with daily stool consistency of Bristol Stool Scale type 6 or 7 at baseline
pain_1:	Mean abdominal pain score during Week 1
stool_1:	Number of days with daily stool consistency of Bristol Stool Scale type 6 or 7 during Week 1
pain_2:	Mean abdominal pain score at during Week 2
stool_2:	Number of days with daily stool consistency of Bristol Stool Scale type 6 or 7 during Week 2
pain_3:	Mean abdominal pain score during Week 3
stool_3:	Number of days with daily stool consistency of Bristol Stool Scale type 6 or 7 during Week 3
pain_4:	Mean abdominal pain score during Week 4
stool_4:	Number of days with daily stool consistency of Bristol Stool Scale type 6 or 7 during Week 4
pain_5:	Mean abdominal pain score during Week 5

stool_5:	Number of days with daily stool consistency of Bristol Stool Scale type 6 or 7 during Week 5
pain_6:	Mean abdominal pain score during Week 6
stool_6:	Number of days with daily stool consistency of Bristol Stool Scale type 6 or 7 during Week 6
presp_3:	Weekly responder in abdominal pain intensity for Week 3
sresp_3:	Weekly responder in stool consistency for Week 3
resp_3:	Weekly responder for Week 3
presp_4:	Weekly responder in abdominal pain intensity for Week 4
sresp_4:	Weekly responder in stool consistency for Week 4
resp_4:	Weekly responder for Week 4
presp_5:	Weekly responder in abdominal pain intensity for Week 5
sresp_5:	Weekly responder in stool consistency for Week 5
resp_5:	Weekly responder for Week 5
presp_6:	Weekly responder in abdominal pain intensity for Week 6
sresp_6:	Weekly responder in stool consistency for Week 6
resp_6:	Weekly responder for Week 6
resp:	Overall responder
complan:	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. Please provide a dataset containing a separate line listing of diary data for each study day (including the screening, treatment and follow-up periods) per subject (if data exist) using the following headers, if applicable:
- Study identifier
  - Subject identifier
  - Study Site Identifier
  - Name of Actual Treatment (exposure): test product, RLD, placebo control
  - Date/time of answer to daily IBS sign and symptom questionnaire
  - Number of days since treatment start date
  - Worst abdominal pain score on a scale of 0-10 in the past 24 hours
  - Bristol Stool Scale score of the least formed bowel movement in the past 24 hours
  - Rescue medication (e.g. anti-diarrheal) use reported during the past 24 hours (yes/no)
  - Concomitant medication reported during this visit (yes/no)
  - Adverse event reported during this visit (yes/no)
  - 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 study day per subject**

STUDYID	SUBJID	SITEID	EXTRT	QSDTC	QSDY	pain	bss	RSCrpt	CMrpt	Aerpt	LBtest
101	1	01	A	2004-07-01	1	3	6	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.

STUDYID:	Study Identifier
SUBJID:	Subject Identifier for the Study
SITEID:	Study Site Identifier
EXTRT:	Name of Actual Treatment (exposure), e.g., A=test product, B=RLD, C= placebo control
QSDTC:	Date/time of answer to daily IBS sign and symptom questionnaire
QSDY:	Actual study day of answer to IBS sign and symptom questionnaire expressed in integer days relative to RFSTDTC (date/time of first exposure to study treatment)
pain:	Worst abdominal pain score on a scale of 0-10 in the past 24 hours
bss:	Bristol Stool Scale score of the least formed bowel movement in the past 24 hours
RSCrpt:	Rescue medication (e.g. anti-diarrheal) use reported during the past 24 hours, 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

22. The study data should be submitted in standardized format. Consider the implementation and use of data standards as early as possible in the product development lifecycle, so that standards are accounted for in the design, conduct, and analysis of clinical studies. For more details, please refer to <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>.
23. The protocol should include a complete and detailed statistical analysis plan and describe how missing data (both daily missing data and weekly missing data), if present, will be handled.
24. 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.

**Waiver request of in vivo testing:** clinical endpoint BE studies on the 200 mg strength and PK studies on the 550 mg strength based on (i) proportional similarity of the formulations between both strengths, (ii) acceptable BE studies with clinical endpoints on the 550 mg strength, (iii) acceptable BE studies with PK endpoints on the 200 mg strength, and (iv) acceptable comparative in vitro dissolution tests on both 200 mg and 550 mg strengths.

**Dissolution test method and sampling times:** The dissolution information for this drug product can be found on the FDA-Recommended Dissolution Methods web site, available to the public at the following location: <http://www.accessdata.fda.gov/scripts/cder/dissolution/>. Conduct comparative dissolution testing on 12 dosage units each of both strengths of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application (ANDA).