

Draft Guidance on Linaclotide

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Capsule; Oral

Strength: 72 mcg, 145 mcg and 290 mcg

Overview:

This draft guidance provides recommendations for the development of generic drug product, Linaclotide Capsule, using synthetic linaclotide as the active pharmaceutical ingredient (API). First, FDA provides recommendations for characterizations to support a demonstration of API sameness. Second, FDA provides recommendations for demonstrating bioequivalence (BE) of this product. Third, FDA provides recommendations for in vitro nasogastric (NG) or gastrostomy (G) tube comparative studies.

Recommendations for Demonstrating API Sameness:

Sameness of synthetic linaclotide can be established based on comparative physico-chemical and biological characterizations. The characterizations should include the following categories in order to support API sameness:

1. Primary peptide sequence and related molecular properties such as molecular formula, specific optical rotation, and spectroscopic properties
2. Configuration of the three disulfide bonds
3. In vitro biological activity (e.g., binding, functional assays)

Recommendations for Demonstrating BE: Two options: In vitro and in vivo options

1. In vitro option

If the test product formulations are qualitatively (Q1) and quantitatively (Q2) the same as the reference listed drug (RLD)¹ in terms of inactive ingredients for the corresponding strength, then bioequivalence (BE) of that strength may be established based solely on comparative dissolution.

¹ Per drug labeling information, 72 mcg strength drug product uses different formulation compared to 145 mcg and 290 mcg strength drug products. Comparison on formulation of generic and RLD products should be made for each individual strength.

For each strength, when test product formulations are Q1 and Q2 the same as the RLD, dissolution data in each specified medium should be provided for 12 capsules each of test and RLD for 72 mcg, 145 mcg and 290 mcg strengths, as follows:

Apparatus: USP Apparatus 1 (basket)
Media: water, 0.1N HCl, pH 4.5 buffer and pH 6.8 buffer
Volume: 500 mL
Temperature: 37°C
Rotation speed: 50 rpm
Sampling time points: 10, 15, 20, 30 minutes

An f2 test should be performed using mean profiles to assure comparable test (T) and reference (R) product drug release under a range of pH conditions. The f2 test comparing T vs. R in each media should be 50 or greater. Note that the f2 test is not necessary when both T and R dissolve 85% or more in 15 minutes or less using all four media.

2. In vivo option

Type of study: BE Study with Clinical Endpoint
Design: Randomized, double blind, parallel, placebo controlled in vivo
Strength: 72 mcg and/or 145 mcg
Subjects: Male and nonpregnant female subjects with chronic idiopathic constipation
Additional comments: The clinical endpoint study below applies to linaclotide 72 mcg and 145 mcg. Applicants seeking approval of both strengths should conduct two separate studies, one for each strength. Specific recommendations on BE study with clinical endpoint are provided below after the section about NG/G tube studies.

Bioequivalence based on (90% CI): Clinical endpoint

Waiver request of in vivo testing: 290 mcg based on (i) acceptable bioequivalence studies on the 145mcg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro quantitative dissolution testing on all 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 all strengths of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application (ANDA).

In Vitro Comparative Nasogastric and Gastrostomy Tube Studies:

The approved labeling for the reference product states that the product may be administered by a nasogastric (NG) tube or gastrostomy (G) tube. Conduct the following in vitro comparative

testing to compare the performance of the test product (T) to that of the reference product (R) to support feeding tube administration. Both NG tube (8 Fr) and G tube (12 Fr) need to be evaluated.

Feeding tube preparation procedure: Prepare the feeding tube studies using 12 units each of the test and the reference products at the 72 mcg and 290 mcg strengths dispersed in bottled water for 0 and 15 minutes by the following procedure:

- a) Open the capsule and empty the beads into a clean container with 30 mL of room-temperature bottled water.
- b) Mix by gently swirling beads for at least 20 seconds.
- c) Draw-up the beads and water mixture into an appropriate sized catheter-tipped syringe and apply rapid and steady pressure (10 mL/10 seconds) to dispense the syringe contents into the tube.
- d) Add another 30 mL of water to any beads remaining in the container and repeat the process.
- e) After administering the bead-water mixture, flush NG/G tube with a minimum of 10 mL of water.
- f) Repeat the testing procedure described above with a fresh set of 12 units. However, after drawing the bead-water mixture, wait 15 minutes prior to injecting the contents into the feeding tube.

1. Comparative recovery testing:

Conduct comparative recovery studies to determine what percentage of the initial dose suspended in water passes through a combination of oral syringe and feeding tube. Follow the feeding tube preparation procedure outlined above. Determine the percentage of linaclotide recovered at the tube exit relative to the initial dose for both the test and the reference products using a validated analytical method. The T/R recovery ratio and the 90% confidence interval of the T/R recovery ratio should be calculated. If high variability is observed, you may increase the number of units used for this test. Visually examine the tube and the syringe for any aggregation, adherence, clogging, etc.

2. Risk assessment of administration conditions:

Feeding tubes (NG/G) may be made with different materials (e.g., PVC, silicone, and polyurethane) which can impact the inner tube diameter. Feeding tubes are also available with different designs (e.g. number of ports and/or eyes; retention balloons; open or closed distal end) which can impact the flow of material through the tube. The applicant should consider the design of the various feeding tubes that may be used for product administration and test a representative selection (a minimum of 3 for both NG and G tubes) of tube designs to ensure complete delivery of the drug product. Note that for G tubes, at least one tube should be tested with an inflated balloon configuration. Evaluation of testing conditions may be made on the basis of recovery study (testing procedure as above) and visual analysis and documented with photographs and videos.

3. Standard operating procedure submission:

Submit standard operating procedures for the above in vitro feeding tube testing. Include details about the tube and syringe used (e.g., material, brand, size, with or without balloon, etc.), the brand of the bottled water, the pH of water, flush volume used in the studies, holding positions of the tube, shaking method of the syringe, analytical site, testing dates, etc., for each of the studies. Submit individual data, mean values, standard deviations, and coefficient of variation (% CV) of the study in an Excel file. Visually examine the tubing and the syringe for any aggregation, adherence, clogging, etc., and report all observations and supporting photographs. Provide explanation if additional pressure is needed to be applied during the testing to ensure complete recovery. Provide the pre-study validation report and within-study assay validation report. Conduct the above testing on unexpired test and reference batches.

Specific recommendations on 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 chronic idiopathic constipation. After a 2-week baseline/washout period, subjects are to be randomized to receive the generic linaclotide capsule, the reference listed drug (RLD) capsule or placebo capsule once daily. The primary endpoint is the number of spontaneous bowel movements (SBM) during Week 1 (study Days 1-7) compared to baseline.
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 Applicant may add additional criteria)
 - a. Male or nonpregnant female aged ≥ 18 years with a clinical diagnosis of chronic idiopathic constipation defined as < 3 spontaneous bowel movements (SBMs) per week and confirmed by daily diary during baseline/pre-treatment period. An SBM is defined as any bowel movement that did not occur within 24 hours after rescue medication use.
 - b. Have 1 or more of the following symptoms related to bowel movements for at least 6 months before the baseline visit and confirmed by daily diary during the 2-week baseline/washout period:
 - lumpy or hard stools for more than 25% of the bowel movements (Bristol Stool Form Scale 1 to 2)
 - sensation of incomplete evacuation following more than 25% of the bowel movements
 - straining at defecation more than 25% of the time
 - c. Women of child-bearing potential have a negative pregnancy test prior to beginning therapy and agree to use effective contraceptive methods during the study.

- d. Meet the colonoscopy requirements defined by the American Gastroenterological Association (AGA) guidelines.
 - e. Willing to discontinue any laxatives used before the Pretreatment Visit in favor of the protocol-defined Rescue Medicine.
 - f. Agree to refrain from making any new major life-style changes that may have affected CIC symptoms (e.g., starting a new diet or changing his or her exercise pattern) from the time of screening to the last trial visit.
4. Exclusion Criteria (the Applicant may add additional criteria)
- a. Pregnant, breast feeding, or planning a pregnancy.
 - b. Subject of any age with evidence of weight loss, anemia, or rectal bleeding AND without documentation of the results of either a flexible sigmoidoscopy or colonoscopy performed during the 6 months prior to dosing.
 - c. Documented mechanical bowel obstruction (e.g., bowel obstruction due to tumor, hernia), megacolon/megarectum, or diagnosis of pseudo-obstruction.
 - d. Structural abnormality of the GI tract or a disease or condition that could affect GI motility
 - e. Known or suspected organic disorders of the large or small bowel (e.g., inflammatory bowel disease, ulcerative colitis, Crohn's Disease) or constipation secondary to a documented cause (e.g., surgery, bowel resection).
 - f. Fecal impaction that required hospitalization or emergency room treatment, or had a history of cathartic colon, laxative or enema abuse, ischemic colitis, or pelvic floor dysfunction (unless successful treatment had been documented by a normal balloon expulsion test)
 - g. Meet the Rome IV criteria for Irritable Bowel Syndrome or the Rome IV criteria for Opioid-Induced Constipation.
 - h. History of bowel resection.
 - i. Diagnosis or family history of familial adenomatous polyposis, hereditary nonpolyposis colorectal cancer, or any other form of familial colorectal cancer.
 - j. Unexplained and clinically significant alarm symptoms (lower GI bleeding [rectal bleeding or heme-positive stool], iron-deficiency anemia, weight loss) or systemic signs of infection or colitis.
 - k. Current active peptic ulcer disease
 - l. History of diverticulitis or any chronic condition (e.g., chronic pancreatitis, polycystic kidney disease, ovarian cysts, endometriosis) that could be associated with abdominal pain or discomfort and could confound the assessments in this trial, unless the patient was considered to have been cured of the condition.
 - m. Bariatric surgery for treatment of obesity, or surgery to remove a segment of the GI tract at any time before the Screening Visit, surgery of the abdomen, pelvis, or retroperitoneal structures during the 6 months before the Screening Visit, an appendectomy or cholecystectomy during the 60 days before the Screening Visit, other major surgery during the 30 days before the Screening Visit.
 - n. Potential central nervous system cause of constipation (e.g., Parkinson's disease, spinal cord injury, and multiple sclerosis)
 - o. History of diabetic neuropathy

- p. Untreated hypothyroidism or treated hypothyroidism for which the dose of thyroid hormone had not been stable for at least 6 weeks at the time of the Screening Visit
 - q. Hospitalized for any gastrointestinal or abdominal surgical procedure during the 3 months prior to dosing.
 - r. Clinically significant cardiovascular, liver, lung, neurologic, renal or psychiatric disorder, or clinically significant laboratory abnormalities.
 - s. Use within 4 weeks prior to baseline of systemic antibiotic. Used Rescue Medicine (bisacodyl tablet or suppository) or any other laxative, suppository, or enema, on the calendar day before or the calendar day of the start of the Treatment Period
 - t. Reported using a Prohibited Medicine (excluding laxatives, suppositories, and enemas) during the Pretreatment Period or was not willing or able to abide by the restrictions regarding use of Prohibited Medicines (Note: The use of fiber, bulk laxatives, or stool softeners [such as docusate] was acceptable provided the patient had been on a stable dose during the 30 days before the Screening Visit and planned to continue on a stable dose throughout the trial).
5. The protocol should include a list of the prescription and over-the-counter drug products, procedures, and activities that are prohibited during the study, such as:
 - a. Prescription and over-the-counter (OTC) laxatives other than those prescribed as a rescue medication during the baseline/washout period by the Investigator. Note: the use of fiber, bulk laxatives, stool softeners [surfactants such as docusate], and probiotics are acceptable, provided that the patient has been on a stable dose for 30 days before the Screening Visit and plans to continue stable dosing for the duration of the trial.
 - b. Significant change in diet.
 6. The study should include a 2-week screening and pretreatment period to assess study eligibility and baseline SBM frequency. Over-the-counter or prescription laxatives cannot be administered beginning the day prior to pre-treatment visit(s).
 7. The recommended primary endpoint is the number of spontaneous bowel movement (SBM) during Week 1 (study Days 1-7), compared to baseline. An SBM is defined as any bowel movement that did not occur within 24 hours after rescue medication use.
 8. Rescue medications (e.g. 5 mg bisacodyl tablets or 10 mg bisacodyl suppositories) should be available if ≥ 72 hours have passed since the previous bowel movement or when the patient's symptoms become intolerable. The Applicant should submit a data set that includes daily rescue medication use for each individual who used the rescue medication at any point during the study. The Applicant should pre-specify rescue medication use (amount, frequency), maximum daily rescue medication use, and any limitations on rescue medication use during the study.
 9. 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 meet all inclusion/exclusion criteria, dosed a pre-specified

- proportion of the scheduled doses (Generally At least 75% and no more than 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, 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 and safety populations include all randomized subjects who use at least one dose of product.
10. Subjects who are discontinued early 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, excluding pre-specified rescue therapies, for the treatment of constipation during the treatment phase of the study should be discontinued, included in the mITT and PP population analysis, and provided with effective treatment. Subjects discontinued early for other reasons should be excluded from the PP population but included in the mITT population. The protocol should clearly state how missing data will be handled in the statistical analyses and provide appropriate justification for the method chosen.
 11. The start and stop date calendar date (e.g. mm/dd/yyyy) and study day (e.g. Day X) of concomitant medication use should be provided in the data set in addition to the reason for the medication use. The Applicant should clearly explain whether the medication was used prior to baseline visit, during the study, or both.
 12. 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.
 13. All pregnancies should be reported, including outcome information
 14. If the inactive ingredients are different than those contained in the RLD or in significantly different amounts, then the Applicant 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.
 15. 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 Applicant 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 Applicant at any time.
18. It is the Applicant's responsibility to enroll sufficient subjects for the study to demonstrate bioequivalence between the products.
19. To establish bioequivalence for a continuous endpoint, it is recommended the following compound hypotheses be tested using the per protocol population:
- $$H_0: \mu_T / \mu_R < \theta_1 \quad \text{or} \quad \mu_T / \mu_R > \theta_2 \quad \text{versus} \quad H_A : \theta_1 \leq \mu_T / \mu_R \leq \theta_2$$
- 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_0 , 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.
20. To establish sensitivity within the study for a continuous primary endpoint, the test and reference products should both be statistically superior to the placebo. Conduct an appropriate two-sided inferential test with a type I error (α) of 0.05, using the mITT population and the primary endpoint.
21. The study data should be submitted in standardized format. Please refer study data standards published at [www.FDA.gov](http://www.fda.gov)².

² Study Data Standards for Submission to CDER, available at:
<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>.

22. The protocol should include a full detailed statistical analysis plan and describe how any missing data will be prevented and handled.
23. Please provide the Subject-Level Analysis Dataset (ADSL), one record per subject, using the following headings, if applicable:
 - a. Study identifier
 - b. Subject identifier
 - c. Study site identifier (if applicable)
 - d. Age
 - e. Age units (years)
 - f. Sex
 - g. Race
 - h. Name of planned treatment
 - i. Name of actual treatment
 - j. Safety population flag (yes/no)
 - k. Reason for exclusion from safety population
 - l. Modified Intent-to-Treat (mITT) population flag (yes/no)
 - m. Reason for exclusion from mITT population
 - n. Per-Protocol (PP) population flag (yes/no)
 - o. Reason for exclusion from PP population
 - p. Completers population flag (yes/no)
 - q. Randomized population flag (yes/no)
 - r. Datetime of first exposure to treatment
 - s. Datetime of last exposure to treatment
 - t. End of study date
 - u. End of study status
 - v. Subject required alternate or supplemental treatment due to unsatisfactory treatment response (yes/no)
 - w. Compliance rate (%)
 - x. Subject missed the scheduled dose for more than the pre-specified number of days (yes/no)
 - y. Number of spontaneous bowel movements at Baseline
 - z. Number of spontaneous bowel movements during Week 1 (study days 1-7)
 - aa. Adverse event reported (yes/no)
 - bb. Concomitant medication (yes/no)
24. Please provide the basic data structure (BDS) dataset with records per subject, per visit, per analysis time point, using the following heading, if applicable:
 - a. Study identifier
 - b. Unique subject identifier
 - c. Study site identifier
 - d. Name of planned treatment
 - e. Name of actual treatment
 - f. Safety population flag (yes/no)
 - g. mITT population flag (yes/no)
 - h. Per-Protocol (PP) population flag (yes/no)

- i. Completers population flag (yes/no)
- j. Analysis date
- k. Analysis visit
- l. Study visit within the designated window (yes/no)
- m. Number of SBMs on Baseline Day 1 (study day -14), Day 2 (study day -13), etc., to Baseline Day 14 (study day 0)
- n. Number of BMs with lumpy or hard stools on Baseline Day 1, Day 2, etc., to Baseline Day 14
- o. Number of BMs followed by sensation of incomplete evacuation on Baseline Day 1, Day 2, etc., to Baseline Day 14
- p. Number of BMs with straining at defecation on Baseline Day 1, Day 2, etc., to Baseline Day 14
- q. Number of SBMs on treatment Day 1 (study day 1), Day 2 (study day 2), etc., to treatment Day 7 (study day 7)
- r. Rescue medication/ laxative use reported (yes/no)
- s. If reported, provide name, dose, date(s), and time of rescue medication use
- t. Concomitant medication reported during this visit (yes/no)
- u. Adverse event reported during this visit (yes/no)
- v. Laboratory testing during this visit (yes/no)