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Draft – Not for Implementation

Draft Guidance on Linaclotide

May 2022

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This guidance, which interprets the Agency's regulations on bioequivalence at 21 CFR part 320, provides product-specific recommendations on, among other things, the design of bioequivalence studies to support abbreviated new drug applications (ANDAs) for the referenced drug product. FDA is publishing this guidance to further facilitate generic drug product availability and to assist the generic pharmaceutical industry with identifying the most appropriate methodology for developing drugs and generating evidence needed to support ANDA approval for generic versions of this product.

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In December 2018, FDA issued a draft product-specific guidance for industry on generic linaclotide. We are now issuing revised draft guidance for industry that replaces the previously issued guidance.

Active Ingredient:	Linaclotide
Dosage Form; Route:	Capsule; oral
Recommended Studies:	Demonstrate active pharmaceutical ingredient (API) sameness and two options: (1) one in vitro bioequivalence comparative dissolution study or (2) one in vivo bioequivalence study with clinical endpoint

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 to support API sameness:

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

Recommendations for demonstrating bioequivalence

I. Option 1: One in vitro bioequivalence comparative dissolution study

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

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: U.S. Pharmacopeia (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, and 30 minutes

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

II. Option 2: One in vivo bioequivalence study with clinical endpoint

Type of study: Bioequivalence study with clinical endpoint
Design: Randomized, double blind, parallel, placebo controlled in vivo
Strength(s): 72 mcg and/or 145 mcg
Subjects: Males and non-pregnant, non-lactating females 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 bioequivalence study with clinical endpoint are provided below after the section of product-specific testing conditions for in vitro feeding tube studies.

[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.

Bioequivalence based on (90% CI): Clinical endpoint

Waiver request of in vivo testing: 290 mcg strength based on (i) acceptable bioequivalence study on the 145 mcg strength, (ii) acceptable in vitro dissolution testing of both strengths, and (iii) proportional similarity of the formulations between both strengths

Dissolution test method and sampling times: The dissolution information for this drug product can be found in the FDA's Dissolution Methods database, http://www.accessdata.fda.gov/scripts/cder/dissolution/. Conduct comparative dissolution testing on 12 dosage units for each of all strengths of the test and reference products. Specifications will be determined upon evaluation of the abbreviated new drug application.

Product-specific testing conditions for in vitro feeding tube studies: The approved labeling for the reference product states that the product may be administered via a nasogastric (NG) tube or gastrostomy (G) tube. Conduct the in vitro feeding tube studies including comparative recovery testing, and sedimentation volume and redispersibility testing. For general procedures of in vitro feeding tube studies, refer to the most recent version of the FDA guidance for industry on *Oral Drug Products Administered Via Enteral Feeding Tube: In Vitro Testing and Labeling Recommendations*.[a]

Testing tubes: NG tube (8 French) and G tube (12 French)

Testing strengths: 72 mcg and 290 mcg

Dispersion medium: Disperse the capsule contents in 30 mL of room temperature bottled water. Add another 30 mL of water to any beads remaining in the container and repeat the process followed by flushing with a minimum of 10 mL of water.

Incubation times: 0 and 15 minutes

Specific recommendations on bioequivalence study with clinical endpoint:

1. FDA recommends conducting a bioequivalence study with clinical endpoint in the treatment of chronic idiopathic constipation. After a 2-week baseline/washout period, patients should be randomized to receive a test product of linaclotide capsule, reference product 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. Inclusion Criteria (the applicant may add additional criteria as needed):
    a. Males or non-pregnant females aged ≥18 years with a clinical diagnosis of chronic idiopathic constipation defined as <3 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 one 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. Meet the colonoscopy requirements defined by the American Gastroenterological Association guidelines
d. Willing to discontinue any laxatives used before the Pretreatment Visit in favor of the protocol-defined Rescue Medicine
e. Agree to refrain from making any new major life-style changes that may have affected chronic idiopathic constipation symptoms (e.g., starting a new diet or changing his or her exercise pattern) from the time of screening to the last trial visit

3. Exclusion Criteria (the applicant may add additional criteria as needed):
    a. Pregnant, breast feeding, or planning a pregnancy
    b. Patient 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 gastrointestinal (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 study, 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 GI 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] is 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.)

4. The protocol should include a list of the prescription and over-the-counter (OTC) drug products, procedures, and activities that are prohibited during the study, such as:
    a. Prescription and 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.

5. The study should include a 2-week screening and pretreatment period to assess study eligibility and baseline SBM frequency. OTC or prescription laxatives cannot be administered beginning the day prior to pre-treatment visit(s).

6. The recommended primary endpoint is the number of 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.

7. 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.

8. Provide the Subject-Level Analysis Dataset, one record per patient, using the following headings, if applicable:
    a. Study identifier
    b. Unique patient identifier
    c. Patient identifier for the study
    d. Study site identifier
    e. Age
    f. Age units (years)
    g. Sex
    h. Race
    i. Name of planned treatment
    j. Name of actual treatment
    k. Safety population flag (yes/no)
    l. Reason for exclusion from safety population
    m. mITT population flag (yes/no)
    n. Reason for exclusion from mITT population
    o. PP population flag (yes/no)
    p. Reason for exclusion from PP population
    q. Completers population flag (yes/no)
    r. Randomized population flag (yes/no)
    s. Date of randomization
    t. Date of enrollment
    u. Date/time of first exposure to treatment
    v. Date/time of last exposure to treatment
    w. End of study date
    x. End of study status
    y. Reason for premature discontinuation of patient
    z. Patient required additional treatment due to unsatisfactory response (yes/no)
    aa. Date/time of additional treatment
    bb. Patient missed the scheduled dose for more than the pre-specified number of days (yes/no)
    cc. Number of SBM at Baseline
    dd. Number of SBM during Week 1 (study days 1-7)
    ee. Compliance rate (%)
    ff. Concomitant medication (yes/no)
    gg. Adverse event(s) reported (yes/no)

9. Provide the basic data structure dataset with records per patient, per visit, per analysis timepoint, using the following heading, if applicable:
    a. Study identifier

b. Unique patient identifier
c. Patient identifier for the study
d. Study site identifier (if applicable)
e. Name of planned treatment
f. Name of actual treatment
g. Safety population flag (yes/no)
h. mITT population flag (yes/no)
i. PP population flag (yes/no)
j. Completers population flag (yes/no)
k. Analysis date
l. Analysis visit
m. Study visit within the designated window (yes/no)
n. Number of SBMs on Baseline Day 1 (study day -14), Day 2 (study day -13), etc., to Baseline Day 14 (study day 0)
o. Number of bowel movements with lumpy or hard stools on Baseline Day 1, Day 2, etc., to Baseline Day 14
p. Number of bowel movements followed by sensation of incomplete evacuation on Baseline Day 1, Day 2, etc., to Baseline Day 14
q. Number of bowel movements with straining at defecation on Baseline Day 1, Day 2, etc., to Baseline Day 14
r. Number of SBMs on treatment Day 1 (study day 1), Day 2 (study day 2), etc., to treatment Day 7 (study day 7)
s. Rescue medication/ laxative use reported (yes/no)
t. If reported, provide name, dose, date(s), and time of rescue medication use
u. Concomitant medication reported during this visit (yes/no)
v. Adverse event reported during this visit (yes/no)
w. Laboratory testing during this visit (yes/no)

10. Refer to the most recent version of the FDA product-specific guidance on *Adapalene; Benzoyl Peroxide Topical Gel* (NDA 207917)[b] or a recommended approach to statistical analysis and study design for in vivo bioequivalence studies with clinical endpoints.

11. Refer to the study data standards resources, https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources.

Revision History: Recommended December 2018; Revised May 2022

Unique Agency Identifier: PSG_202811

[a] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.
[b] For the most recent version of a product-specific guidance, check the FDA product-specific guidance web page at https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm