Crohn's Disease: Developing Drugs for Treatment

Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
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I. INTRODUCTION

The purpose of this guidance is to help sponsors in the clinical development of drugs to treat adults with Crohn's disease (CD).[2] This draft guidance addresses the Food and Drug Administration's (FDA's) current recommendations on clinical trials for drugs being developed under section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355), section 351 of the Public Health Service Act (42 U.S.C. 262) and 21 CFR parts 312, 314, and 601for treating CD. Specifically, this guidance addresses FDA's current thinking about the necessary attributes of clinical trials for drugs being developed for treating CD, including trial population, trial design, efficacy considerations, and safety assessments.[3]

This guidance does not address extraintestinal manifestations of CD, stricturing or fistulizing disease, pediatric drug development, or the treatment or prevention of long-term complications of CD.

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[1] This guidance has been prepared by the Division of Gastroenterology (the Division) in the Center for Drug Evaluation and Research at the Food and Drug Administration and the Center for Biologics Evaluation and Research (CBER).

[2] For the purposes of this guidance, all references to *drugs* include both human drugs and biological products unless otherwise specified.

[3] In addition to consulting guidances, sponsors are encouraged to contact the appropriate review division to discuss specific issues that arise during the development of drugs to treat CD.

II. BACKGROUND

CD is a chronic, relapsing, and remitting inflammatory bowel disease characterized by transmural inflammation that may affect any area or areas of the gastrointestinal tract from the mouth to the anus. Clinical manifestations of active CD include abdominal pain, weight loss, diarrhea, fever, gastrointestinal bleeding, and anemia; some patients may also develop fistulae, fissures, and abscesses. The transmural inflammatory nature of CD may lead to fibrosis and strictures of the bowel, which are not typically seen in ulcerative colitis.

The treatment goals of CD include resolution or reduction of the signs and symptoms of active disease to provide relief to the patient and healing or control of the underlying mucosal inflammation and its complications.

Traditionally, the Crohn's Disease Activity Index (CDAI),[4] a weighted index comprising eight clinical and laboratory variables that estimate disease activity in CD, has been the most commonly used tool in trials intended to support approval of CD treatments. However, the CDAI has been shown to be poorly associated with intestinal inflammation (Levesque 2015; Peyrin-Biroulet 2014).

Given the limitations of the CDAI, FDA's thinking on clinical endpoints for CD has evolved, and the recommended approach is to use coprimary endpoints to ensure that, in addition to relieving signs and symptoms, treatments have a meaningful impact on the underlying inflammation. Thus, coprimary endpoint assessment should include CDAI to evaluate signs and symptoms and an ileocolonoscopy to evaluate the impact of the drug on mucosal inflammatory changes. Although we currently recommend assessing signs and symptoms using the CDAI in the coprimary endpoint definition, sponsors are also encouraged to explore other methods for assessing clinically relevant signs and symptoms.

For general recommendations about patient-reported outcome (PRO) assessments (as well as information relevant for other clinical outcome assessments) and the documents to be provided to FDA for review, see the guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims* (December 2009).[5]

III. DEVELOPMENT PROGRAM

A. Trial Population

Sponsors developing drugs to treat CD should consider the following:

- Subjects should have a confirmed diagnosis of CD based on documented findings on endoscopy and histopathology.

[4] See Appendix, Table 1.

[5] We update guidances periodically. 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.

- For clinical trials for drugs intended to treat moderately to severely active CD:
  - Subjects should have a CDAI score of at least 220 *and* a simple endoscopic score for Crohn's disease (SES-CD) of at least 6 (or at least 4 if isolated ileal disease) at baseline.
  - Sponsors should enroll subjects across the whole range of both moderately and severely active disease categories.
  - We recommend a balanced representation of subjects who have never received treatment with a biologic and subjects who have failed prior therapy with one or more biologics or other advanced therapies.
- For drugs intended to support an indication of mildly to moderately active CD, sponsors should discuss eligibility criteria with the appropriate review division.
- Sponsors should enroll subjects who reflect the characteristics of clinically relevant populations, including with regard to race and ethnicity, and should consider clinical trial sites that include higher proportions of racial and ethnic minorities to recruit a diverse study population.[6]

B. Trial Design

Sponsors developing drugs to treat CD should consider the following:

- We recommend a randomized, double-blind, placebo-controlled trial design that would be able to demonstrate that beneficial effects observed initially with treatment are continued long term to support chronic administration. This goal may be achieved through various study designs, and the overall design of a program should be agreed upon with the appropriate review division before trial initiation.
  - One approach (*induction followed by randomized withdrawal maintenance)* is to conduct a randomized, placebo-controlled induction trial to assess clinical benefit in the short term, followed by a maintenance trial in which all subjects who achieve initial response (i.e., clinical or endoscopic response[7]) to active drug at the end of induction are re-randomized to receive either active treatment or placebo, and efficacy is evaluated again at the end of the maintenance phase (e.g., 52 weeks).[8]

[6] For additional recommendations, see the guidance for industry *Enhancing the Diversity of Clinical Trial Populations - Eligibility Criteria, Enrollment Practices, and Trial Designs* (November 2020).

[7] As defined in section C, Efficacy Considerations.

[8] Placebo responders at the end of induction should continue to receive blinded placebo in maintenance. Early escape criteria should be incorporated to ensure that subjects who are worsening or not improving after a reasonable time frame are discontinued from blinded study treatment and offered either rescue dosing or an alternative active treatment.

- Another approach (*treat-through design*) is to randomize subjects once at the start of the trial to one of the treatment arms (i.e., a dosing regimen or placebo), and subjects are then treated continuously without rerandomization through 52 weeks. Sponsors should assess the coprimary endpoints at the end of treatment (e.g., 52 weeks). Earlier periodic assessments throughout the trial are useful to characterize the time to onset of initial clinical improvement. Early escape criteria should be incorporated to ensure that subjects who are worsening or not improving after a reasonable time frame have the opportunity to receive active treatment.

- For drugs intended to be administered chronically, we recommend a total controlled treatment period of at least 1 year in duration to adequately assess both early efficacy and durability of response over time and to adequately characterize the safety profile. Sponsors should discuss with the appropriate review division the number of subjects exposed to the to-be-marketed dosing regimen for a minimum of 1 year that should be available at the time of application submission.

- We encourage active controlled trials designed to demonstrate superiority to an approved therapy.

C. Efficacy Considerations

1. Efficacy Assessments

Sponsors developing drugs to treat CD should consider the following:

- We recommend the following coprimary endpoints[9] that evaluate a drug's effect on signs and symptoms *and* on underlying mucosal inflammation:

  - **Clinical remission:** Defined as a CDAI score of less than 150.

    - To calculate the CDAI stool frequency and abdominal pain subscores, we recommend defining a 7-day period during which the daily scores are collected before the specified study visit in which the CDAI is calculated. The scores should be calculated by averaging the daily scores from within this 7-day period then multiplied by 7, excluding the day of bowel preparation and day of endoscopy (for visits that include an endoscopy). A minimum of 3 consecutive days of completed diary entries or 4 nonconsecutive days are necessary (otherwise the score should be considered *missing* and the subject's result imputed as nonresponder).

[9] Demonstrating treatment effects on both distinct endpoints is necessary to establish clinical benefit for this indication. See the draft guidance for industry *Multiple Endpoints in Clinical Trials* (January 2017). When final, this guidance will represent the FDA's current thinking on this topic. 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.

- **Endoscopic remission**: Defined as SES-CD[10] of 0 to 2 (Vuitton 2016). An alternative definition of SES-CD score of 0 to 4, with no individual subscore greater than 1, may also be acceptable.[11]

    - We recommend using centralized reading of endoscopies as the primary approach to scoring the endoscopic component of the primary and secondary endpoint assessments. Both the endoscopist performing the procedure and the central readers reviewing high-definition video recordings of the procedure should be blinded to treatment assignment and should document the endoscopic findings. The protocol should specify clearly how discrepancies between the findings by the endoscopist and the central reader will be handled in the efficacy analyses (e.g., adjudication by a third reader). Efforts should be made to minimize bias and standardize reading of endoscopy across trial sites and among investigators through training and education on the definition of each item described in the scale. Sponsors should draft charters that standardize procedures, video recordings/equipment, and endoscopy assessment early in drug development and share them with FDA for comment.

- We recommend the following secondary endpoints:

    - **Clinical response:**[12] Defined as a decrease from baseline of at least 100 points on the CDAI.

    - **Endoscopic response:**[11,12] **Error! Bookmark not defined.**Defined as a 50 percent reduction from baseline on the SES-CD.

    - **Corticosteroid-free remission**: Defined as subjects who are in clinical remission at the conclusion of the controlled trial (e.g., 52 weeks) and having no corticosteroid exposure during a prespecified period (e.g., at least 8 to 12 weeks) before that assessment.

      The proportion of subjects achieving corticosteroid-free remission, of those who were using corticosteroids at enrollment, is of interest and should be reported.

[10] See Appendix, Table 2.

[11] We acknowledge that not all drugs may be able to achieve endoscopic remission within the duration of the clinical trial, and that there are currently limited data on the ability of available approved drugs to induce endoscopic remission. As a result, it may be acceptable to assess endoscopic response as the endoscopic component of the coprimary endpoint. If endoscopic response is included in the coprimary endpoints, then endoscopic remission should be assessed as a secondary endpoint.

[12] Although clinical or endoscopic response is not the final treatment goal, this definition may also be used as a criterion at the end of induction to rerandomize subjects who are demonstrating improvement to continue into a maintenance phase in the induction/maintenance design.

- **Maintenance of remission:** We recommend the following to demonstrate the durability of benefit:

  - For trial designs in which subjects who achieve clinical response at the end of the induction phase are rerandomized in the maintenance phase, we recommend that sponsors assess remission within the subset of subjects who enter the maintenance phase in remission to support the ability of the therapy to maintain a durable state of remission.

  - For trial designs in which subjects are treated continuously without rerandomization (treat-through design), sponsors should assess the proportion of subjects who individually achieve clinical remission (i.e., defined by CDAI) at both early (e.g., 8 weeks) and late (e.g., 52 week) time points to demonstrate that a clinical benefit was attained and was durable. A similar analysis should be performed for the SES-CD.

- **Composite endpoint of clinical remission and endoscopic remission**:[11] A secondary endpoint should assess the proportion of subjects who achieved both clinical remission and endoscopic remission. This endpoint should be assessed at the conclusion of the controlled trial (e.g., 52 weeks).

- We recommend the following exploratory endpoints, each of which should be discussed with FDA before trial initiation:

  - **Histologic response/remission**: At this time, there is no scientific consensus on a definition of, or scoring system for, histologic resolution of mucosal inflammation in subjects who have achieved endoscopic remission in CD. Sponsors should provide adequate justification for the proposed endpoint definitions, grading scales, and scoring techniques.

  - **Interim clinical assessments based on noninvasive measures:** Sponsors should incorporate interim assessments of clinical remission (without endoscopic assessment) at prespecified time points during the trial, up until and including the last visit (e.g., 52 weeks), to support maintenance of remission.

  - **Change from Baseline in the SES-CD Score**: We recommend that sponsors evaluate the absolute change in the SES-CD score from baseline to the last visit (e.g., 52 weeks).

  - **Additional Endpoints:** We encourage sponsors to explore the effect of an investigational drug on additional symptoms of CD identified by subjects as important but that are not captured within the CDAI (e.g., urgency) using fit-for-purpose patient-reported outcome (PRO) instruments (see Section III. C. 3. Future Patient-Reported Outcome Instrument Development).

2. Statistical Considerations

Sponsors developing drugs to treat CD should consider the following:

- To support efficacy, the trial results should demonstrate statistical significance on both coprimary analyses (clinical endpoint and endoscopic endpoint).

- To gain precision in evaluating overall treatment effects (e.g., the overall difference in remission rates), we recommend statistical analyses adjust for subject characteristics at baseline that may affect efficacy outcomes (e.g., duration of disease, disease severity, concurrent use of corticosteroids, prior biologic use).

- Sponsors should conduct efficacy analyses in all randomized subjects.

- Sponsors should prespecify methods to handle intermittent missing data (e.g., lack of at least 3 consecutive diary days, or 4 nonconsecutive diary days, during the 7 days before a visit).

- Subjects who drop out before the end of treatment should be considered treatment failures.

- Sponsors should prespecify a primary estimand of interest for each endpoint and justify that it is meaningful and that it can be estimated with minimal and plausible assumptions with the proposed analysis. The estimand is a precise description of the treatment effect, reflecting the clinical question posed by a given clinical trial objective. See the International Council for Harmonisation harmonized guideline *E9 R1 Addendum on Estimands and Sensitivity Analysis in Clinical Trials* to the guideline on *Statistical Principles for Clinical Trials*.[13] The following considerations apply:

  - The important intercurrent events that should be considered when defining the estimand include treatment discontinuation attributable to lack of efficacy or adverse events, use of rescue medication, and CD-related surgery.

  - Potential strategies for defining and handling intercurrent events include the following:

    - A treatment policy strategy in which outcomes are collected after the intercurrent event and used in analyses.

    - A composite strategy in which subjects who experience the intercurrent event are considered to have an unfavorable outcome (e.g., to have not achieved remission).

  - Sponsors should continue to follow subjects after the occurrence of all intercurrent events, regardless of the strategy used in the primary analysis, to facilitate important

[13] Available at https://database.ich.org/sites/default/files/E9-R1_Step4_Guideline_2019_1203.pdf.

analyses using a treatment policy strategy. The protocol should distinguish between reasons for treatment discontinuation and reasons for study withdrawal and should include plans to follow subjects for collection of relevant data after treatment discontinuation and use of rescue therapies.

- Sponsors should prespecify sensitivity analyses to evaluate whether the results from the primary and secondary analyses are robust to the missing data assumptions. These sensitivity analyses should comprehensively explore the space of plausible assumptions.

3. Future Patient-Reported Outcome Instrument Development[14,15]

- Sponsors wishing to develop additional novel PRO instruments (or adapt existing instruments for use in CD patients) to assess concepts that are relevant to CD patients but not captured within the CDAI can submit a PRO instrument development proposal for FDA review.

  - Sponsors pursuing PRO instrument development may need to collect additional qualitative information from patients to support the relevance of the selected symptom(s), and document that patients understand and can use the instrument's proposed items.

  - To support potential labeling claims, an adequate number of patients should demonstrate the presence of the additional symptom(s) at baseline, with sufficient degree of severity in order to be able to measure a clinically meaningful improvement over the course of treatment.

  - Additionally, sponsors may need to collect evidence that captures clinically important improvement at the individual patient level to inform the definition of response using the PRO instrument, preferably by including anchor-based analyses but also by other methods.

D. Safety Considerations

Sponsors developing drugs to treat CD should consider the following:

- In general, FDA has recommended a washout period of 5 half-lives for prior therapies or undetectable serum levels (when available) for trial subjects. To promote timely enrollment of subjects with active disease and reduce the potential need for escalation of

[14] For general recommendations regarding PRO assessments (as well as information relevant for other clinical outcome assessments), see the guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*.

[15] For general recommendations regarding PRO assessments (as well as information relevant for other clinical outcome assessments), see the FDA Patient-Focused Drug Development Guidance Series for Enhancing the Incorporation of the Patient's Voice in Medical Product Development and Regulatory Decision Making web page at https://www.fda.gov/drugs/development-approval-process-drugs/fda-patient-focused-drug-development-guidance-series-enhancing-incorporation-patients-voice-medical.

corticosteroids as *bridging* therapy, sponsors may propose shorter washout periods with appropriate justification.

  - Sponsors proposing a shorter washout period should acknowledge within the protocol and informed consent the potential increased risk of adverse events (e.g., serious infections) in the early portion of the trial, and sponsors should include appropriate close monitoring and risk mitigation plans.

- For drugs intended for long-term treatment, such as for CD, a sufficient number of subjects should be exposed to the to-be-marketed dosing regimen (selected induction dose, followed by selected maintenance dose, when applicable) for at least 52 weeks to characterize the safety profile of the drug.[16]

- Drug-specific considerations may alter the minimum acceptable size of the safety database, including whether the drug in question is a new molecular entity or has relevant supportive safety data from other populations, the known and anticipated adverse events of the drug and drug class, and nonclinical findings.

- For trials of therapeutic protein products, such as monoclonal antibodies, sponsors should consider recommendations in the guidance for industry *Immunogenicity Assessment for Therapeutic Protein Products* (August 2014). Sponsors should evaluate neutralizing capabilities of antidrug antibodies and their impact on clinical efficacy and safety.

- Sponsors should prospectively plan for safety analyses to compare treatment groups with respect to risk (e.g., with a risk difference, relative risk, rate ratio, or hazard ratio) along with a confidence interval for the chosen metric to help quantify the uncertainty in the treatment comparison. Sponsors should stratify by study any analyses of integrated data from multiple studies.

[16] For recommendations about duration of exposure and number of patients to be included in the safety database, see the guidance for industry *Premarketing Risk Assessment* (March 2005).

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Guidances[1]

Draft guidance for industry *Multiple Endpoints in Clinical Trials* (January 2017)[2]

Guidance for industry and FDA staff *Qualification Process for Drug Development Tools* (November 2020)

Guidance for industry, FDA staff, and other stakeholders *Patient-Focused Drug Development: Collecting Comprehensive and Representative Input* (June 2020)

Guidance for industry *Immunogenicity Assessment for Therapeutic Protein Products* (August 2014)

Guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims* (December 2009)

Guidance for industry *Premarketing Risk Assessment* (March 2005)

[1] We update guidances periodically. 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.

[2] When final, this guidance will represent the FDA's current thinking on this topic. 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.

International Council for Harmonisation harmonized guideline *E9 R1 Addendum on Estimands and Sensitivity Analysis in Clinical Trials* to the guideline on *Statistical Principles for Clinical Trials* (November 2019)[3]

[3] Available at https://database.ich.org/sites/default/files/E9-R1_Step4_Guideline_2019_1203.pdf.

APPENDIX

The Crohn's Disease Activity Index (CDAI) (see Table 1), a weighted index comprising eight clinical and laboratory variables that estimate disease activity in Crohn's disease (CD), has been the most commonly used tool in trials intended to support approval of CD treatments. Table 2 outlines the components of the Simple Endoscopic Score for Crohn's Disease (SES-CD), a scoring algorithm that can be used to measure endoscopic features of CD.

Table 1. Crohn's Disease Activity Index (CDAI)*

Variable Description	Multiplier
Number of liquid or soft stools (each day for 7 days)	X 2
Abdominal pain, sum of 7 daily ratings (0=none, 1=mild, 2 = moderate, 3=severe)	X 5
General well-being, sum of 7 daily rating (0=generally well, 1=slightly under par, 2=poor, 3=very poor, 4=terrible)	X 7
Number of listed complications (arthritis or arthralgia, iritis or uveitis, erythema nodosum or pyoderma gangrenosum or aphthous stomatitis, anal fissure or fistula or abscess, other fistula, fever over 37.8ºC [100ºF])	X 20
Use of diphenoxylate or loperamide for diarrhea (0=no, 1=yes)	X 30
Abdominal mass (0=no, 2=questionable, 5=definite)	X 10
Hematocrit (males, 47-Hct [%], females, 42-Hct [%])	X 6
Body weight 1-weight/standard weight) x 100 (add or subtract according to sign)	X 1

*The total CDAI score is calculated using the sum of each variable times the multiplier. Best WR, Becktel JM, Singleton JW, Kern F Jr. "Development of a Crohn's disease activity index. National Cooperative Crohn's Disease Study". Gastroenterology 1976. 70 (3): 439–444.

Table 2. Simple Endoscopic Score for Crohn's Disease (SES-CD)

Variable	SES-CD Values			
	0	1	2	3
Size of ulcers	None	Aphthous ulcers (diameter 0.1-0.5 cm)	Large ulcers (diameter 0.5-2 cm)	Very large ulcers (diameter>2 cm)
Ulcerated surface	None	<10%	10-30%	>30%
Affected surface	Unaffected segment	<50%	50-75%	>75%
Presence of narrowing	None	Single, can be passed	Multiple, can be passed	Cannot be passed

Adapted from M Daperno, D'Haens G, Van Assche G, Baert F, Bulois P, Maunoury V, Sostegni R, Rocca R, Pera A, Gevers A, Mary J-Y, Colombel J-F, and Rutgeerts P, 2004, Development and Validation of a New, Simplified Endoscopic Activity Score for Crohn's Disease: the SES-CD, Gastrointest Endosc, 60(4):505–512.