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Supplementary information

Interpreting modern randomized controlled trials of medical therapy in inflammatory bowel disease

In the format provided by the authors and unedited

Supplementary Table 1. Regulatory guidance recommendations for eligible trial populations for developing drugs for the treatment of Crohn's disease and ulcerative colitis

Disease State	Trial Population
Crohn's disease	**2022 US FDA Draft Guidance[1]** • Confirmed diagnosis of CD based on documented findings on endoscopy and histopathology • CDAI score of at least 220 and SES-CD ≥6 (or ≥4 if isolated ileal disease) at baseline • Patients across the whole range of moderately and severely active disease • Balanced representation of advanced treatment naïve and failure individuals **2019 EMA Guidance[2]** • Active CD: clinical signs and symptoms, and evidence of mucosal inflammation • Enrolment of patients with active mucosal inflammation documented by recent (within 3 months) endoscopy for ileocolonic disease and/or imaging of the small intestine (e.g., capsule endoscopy) for small intestinal disease • Refractory CD: active inflammation despite adequate course of treatment • Intolerance to treatment: serious side effects precluding continued treatment • Treatment dependence: respond to treatment but flare upon discontinuation • Distinguish refractoriness due to primary non-response or loss of response (secondary non-response) • CD in remission: mucosal healing (defined as absence of macroscopic signs of inflammation as judged by endoscopy) who have no or very mild symptoms and signs
Ulcerative colitis	**2022 US FDA Draft Guidance[3]** • Confirmed diagnosis of UC based on documented findings on endoscopy and histopathology • Score of 5 to 9 on the mMS including an endoscopy subscore ≥2 • Patients across the whole range of moderately and severely active disease • Balanced representation of advanced treatment naïve and failure patients • For mildly-to-moderately active UC, mMS ≥4 and endoscopy subscore ≥2 and rectal bleeding subscore ≥1 **2019 EMA Guidance[4]** • Diagnosis of UC based on symptoms, endoscopic, and histologic findings • Rule out infectious causes of colitis • Classify patients by extent of disease (proctitis, left-sided, extensive) and severity (mild, moderate, severe) • Refractory UC: active inflammation despite adequate course of treatment • Intolerance to treatment: serious side effects precluding continued treatment • Treatment dependence: respond to treatment but flare upon discontinuation • Distinguish refractoriness due to primary non-response or loss of response (secondary non-response) • UC in remission: mucosal healing (defined as absence of macroscopic signs of active inflammation as judged by endoscopy) who have no or very mild symptoms and signs

Abbreviations: CD Crohn's disease, CDAI Crohn's disease activity index, EMA European Medicines Agency, FDA Food and Drug Administration, mMS modified Mayo Score, SES-CD Simple Endoscopic Score for Crohn's Disease, UC ulcerative colitis

Adapted from:
[1] Crohn's Disease: Developing Drugs for Treatment. Guidance for Industry (Draft Guidance). US Department of Health and Human Services Food and Drug Administration. April 2022.
[2] Guideline on the development of new medicinal products for the treatment of Crohn's Disease. European Medicines Agency. 2019.
[3] Ulcerative Colitis: Developing Drugs for Treatment. Guidance for Industry (Draft Guidance). US Department of Health and Human Services Food and Drug Administration. April 2022.
[4] Guideline on the development of new medicinal products for the treatment of ulcerative colitis. European Medicines Agency. 2019.

Supplementary Table 2. Regulatory guidance on efficacy considerations for developing drugs for the treatment of Crohn's disease and ulcerative colitis

Disease State	Trial Population

Crohn's disease	**2022 US FDA Draft Guidance[1]**
	• Coprimary endpoints for evaluating a drug's effect on signs and symptoms and on underlying mucosal inflammation:
	  o Clinical remission defined as a CDAI score of less than 150
	  o Endoscopic remission defined as SES-CD of 0-2 (or alternative definition of SES-CD 0-4 with no individual subscore greater than 1)
	• Secondary endpoints:
	  o Clinical response defined as CDAI decrease from baseline of at least 100 points
	  o Endoscopic response defined as 50% reduction from baseline on SES-CD
	  o Corticosteroid-free remission
	  o Maintenance of remission
	  o Composite endpoint of clinical remission and endoscopic remission
	• Exploratory endpoints:
	  o Histologic response/remission
	  o Interim clinical assessments based on non-invasive measures
	  o Change from baseline in SES-CD score
	  o Additional endpoints based on fit-for-purpose PRO instruments
	
	2019 EMA Guidance[2]
	• Coprimary endpoints of symptomatic remission and endoscopic remission
	  o Symptomatic remission by PRO2 <8
	  o Mucosal healing evaluated by CDEIS 0-2
	• Secondary endpoints:
	  o Both mucosal healing and symptomatic remission
	  o Response (according to instruments used for evaluating symptoms and endoscopic appearance)
	  o Remission
	  o Symptomatic and endoscopic remission without concomitant steroids
	  o Individual components of the symptom and mucosal healing scores
	  o Histologic evaluation of mucosal inflammation, histologic normalization
	  o Combined symptomatic, biomarker, and histologic normalization
	  o Change in stool frequency
	  o Laboratory measures of inflammation (e.g., fecal calprotectin)
	  o Time to remission and responses
	  o Validated QoL measures

Ulcerative colitis	**2022 US FDA Draft Guidance[3]**
	• Primary endpoint: clinical remission, defined by mMS 0-2, with stool frequency subscore 0 or 1, rectal bleeding subscore 0, and centrally read endoscopy subscore 0 or 1 without friability
	• Secondary endpoints:
	  o Clinical response (decrease in mMS ≥2 points or at least 30%, and a decrease in rectal bleeding ≥1 or absolute rectal bleeding subscore 0 or 1)
	  o Corticosteroid-free remission
	  o Endoscopic improvement (centrally read endoscopy subscore 0 or 1)
	  o Endoscopic remission (centrally read endoscopy subscore 0)
	  o Maintenance of remission
	• Exploratory endpoints:
	  o Histologic response/remission
	  o Interim clinical assessments based on non-invasive measures
	  o Additional endpoints based on fit-for-purpose PRO instruments
	
	2019 EMA Guidance[4]
	• Coprimary endpoints of symptomatic remission and endoscopic remission
	  o If using the Mayo score, symptom scores of 0 or 1 to define symptomatic remission, remission should include cessation of rectal bleeding

○ If using the Mayo endoscopy subscore, 0 or 1 may be used to define endoscopic healing (stringent definition preferred) • Secondary endpoints: ○ Both mucosal healing and symptomatic remission ○ Response (according to the instruments used for evaluating symptoms and endoscopic appearance) ○ Remission ○ Symptomatic and endoscopic remission without concomitant steroids ○ Individual components of the symptom and mucosal healing scores ○ Histologic evaluation of mucosal inflammation, histologic normalization ○ Combined symptomatic, biomarker, and histologic normalization ○ Change in stool frequency ○ Laboratory measures of inflammation (e.g., fecal calprotectin) ○ Time to remission and responses ○ Validated QoL measures

Abbreviations: CD Crohn's disease, CDAI Crohn's disease activity index, EMA European Medicines Agency, FDA Food and Drug Administration, mMS modified Mayo Score, QoL quality of life; SES-CD Simple Endoscopic Score for Crohn's Disease, UC ulcerative colitis

Adapted from:

[1] Crohn's Disease: Developing Drugs for Treatment. Guidance for Industry (Draft Guidance). US Department of Health and Human Services Food and Drug Administration. April 2022.

[2] Guideline on the development of new medicinal products for the treatment of Crohn's Disease. European Medicines Agency. 2019.

[3] Ulcerative Colitis: Developing Drugs for Treatment. Guidance for Industry (Draft Guidance). US Department of Health and Human Services Food and Drug Administration. April 2022.

[4] Guideline on the development of new medicinal products for the treatment of ulcerative colitis. European Medicines Agency. 2019.