

A Phase 3b, Randomized, Open-label, Active-Controlled, Parallel-group, Multicenter Study to Evaluate the Efficacy and Safety of Icotrokinra Versus Vedolizumab in Participants with Moderately to Severely Active Ulcerative Colitis

Study Design

This is a Phase 3b, randomized, open-label, multicenter, active-comparator-controlled, parallel-group study to evaluate the efficacy and safety of icotrokinra compared with vedolizumab in adult participants with moderately to severely active UC (defined as a modified Mayo score of 5 to 9, inclusive, and an endoscopy subscore ≥ 2 obtained during the central review of the screening video endoscopy).

Participants must have demonstrated inadequate response or failure to tolerate conventional therapy but are naïve to advanced therapies (biologics or oral advanced therapies), or who have demonstrated an inadequate response (i.e. primary or secondary nonresponse) or failure to tolerate an approved advanced therapy. Participants who had an inadequate response or failure to tolerate biologics or oral advanced therapies (ie, ADT IR) will comprise a minimum of approximately 40% and a maximum of approximately 50% of the population randomized.

The key study inclusion and exclusion criteria for enrolling participants are described below:

Key Inclusion Criteria:

1. Participants ≥ 18 years of age or at least the legal age of consent in the jurisdiction in which the study is taking place.
2. Diagnosis of UC established at least 12 weeks before screening including both endoscopic evidence and histopathology report consistent with a diagnosis of UC. The participant must have a documented history of a complete colonoscopy during their disease course. Histopathology results supporting the diagnosis of UC, if unavailable, may be obtained during screening and should be interpreted locally.
3. Moderately to severely active UC, defined as a baseline (Week 0) modified Mayo score of 5 to 9, inclusive, using the endoscopy subscore obtained during the central review of the

screening video endoscopy. Participants with isolated proctitis (colonic involvement spanning <10 cm from the dentate line as determined during central review of the screening video endoscopy) at baseline who meet the other eligibility criteria for inclusion will be eligible. Participants with isolated proctitis will be capped at approximately 10% of the total participants enrolled.

4. An endoscopy subscore ≥ 2 as obtained during central review of the screening video endoscopy.

5. A participant who has had extensive UC for ≥ 8 years, or disease limited to the left side of the colon for ≥ 10 years before the first dose of study intervention must undergo the following:

- a. A complete colonoscopy to assess for the presence of dysplasia (recommended methods include nontargeted biopsies, narrow band imaging or chromoendoscopy with targeted biopsies) within 1 year before the first dose of study intervention. Completion of the colonoscopy with dysplasia assessment per local pathology interpretation should be completed during the screening period prior to the first dose of study intervention, if applicable.
- b. Participants with PSC must have a complete colonoscopy with extensive biopsies for dysplasia screening within 1 year before the first dose of study intervention regardless of the duration of UC disease history.

6. Screening laboratory test results in accordance with limits listed below, and if 1 or more of the laboratory parameters are out-of-range, a single re-test of the out-of-range laboratory value is permitted during the screening period:

- a. Hemoglobin ≥ 8.0 g/dL (SI: ≥ 80.0 g/L)
- b. WBCs $\geq 3.0 \times 10^3/\mu\text{L}$ (SI: $\geq 3.0 \times 10^9/\text{L}$)
- c. Neutrophils $\geq 1.5 \times 10^3/\mu\text{L}$ (SI: $\geq 1.5 \times 10^9/\text{L}$)
- d. Platelets $\geq 100 \times 10^3/\mu\text{L}$ (SI: $\geq 100 \times 10^9/\text{L}$)
- e. eGFR ≥ 45 mL/min/1.73 m² using the CKD-EPI formula
- f. AST $\leq 2 \times \text{ULN}$
- g. ALT $\leq 2 \times \text{ULN}$
- h. Total bilirubin (TBili) $\leq 1.5 \times \text{ULN}$ (Isolated total bilirubin $> 1.5 \times \text{ULN}$ is allowed for those participants with known Gilbert's syndrome. Gilbert's syndrome is suggested by direct bilirubin $< 30\%$ [Palmer 2020].)

7. Demonstrated an inadequate response, or failure to tolerate previous conventional therapy (ADT-naïve) or inadequate response (i.e., primary or secondary nonresponse) or failure to tolerate advanced therapy defined as biologics and/or advanced oral agents for the treatment of UC (ADT-IR):

Conventional therapies: in the absence of an approved label, conventional therapies used to qualify a participant as having had an inadequate response or intolerance must have been used in a manner consistent with the dose and regimens provided in Section 11.11.

- a. Oral or IV/IM corticosteroids (including budesonide and beclomethasone dipropionate)
- b. Thiopurines (i.e. AZA, 6-MP, 6-thioguanine)

Note: A history of oral corticosteroid dependence also satisfies the criterion of inadequate response.

Advanced therapies (biologics or oral advanced therapies): Advanced therapies used to qualify a participant as having had an inadequate response (i.e. primary or secondary nonresponse) or intolerance must be approved for the treatment of adult UC in the country of use.

- c. Anti - TNF α antibodies (i.e., infliximab, adalimumab, golimumab, or biosimilars)
- d. Anti-interleukin 12/23(p40) antibodies (i.e., ustekinumab or biosimilars)
- e. JAK inhibitors (i.e., tofacitinib, upadacitinib, filgotinib)
- f. S1P receptor modulators (i.e., ozanimod, etrasimod)

Note: The proportion of adult participants with inadequate response (i.e. primary or secondary nonresponse) or intolerance to ≥ 3 approved advanced therapies (agents, not number of classes) as listed above (in biologic or oral advanced therapies section) will be limited to 15% of the ADT-IR population.

Note: The number of adult participants with inadequate response (i.e. primary or secondary nonresponse) or intolerance to ustekinumab will be capped at 20% of the ADT-IR population.

8. A participant must adhere to all of the following requirements for medications for the treatment of UC. The following medications are permitted provided that doses meeting the requirements listed below are stable or have been discontinued prior to baseline (Week 0) within the timeframe specified below:

- a. Oral 5-ASA compounds on stable doses for at least 2 weeks; or if recently discontinued, must have been stopped for at least 2 weeks.

- b. Oral corticosteroids at a prednisone-equivalent dose at or below 20 mg/day, or up to 9 mg/day of budesonide, or 5 mg/day of beclomethasone dipropionate, and on a stable dose for at least 2 weeks; or if recently discontinued, must have been stopped for at least 2 weeks.
- c. Immunomodulators (i.e., AZA, 6-MP, or MTX) for at least 12 weeks and have been on a stable dose for at least 4 weeks; or if recently discontinued, must have been stopped for at least 4 weeks.

Key Exclusion Criteria:

1. Participants with current known complications of ulcerative colitis such as fulminant colitis, toxic megacolon, or any other manifestation that might require colonic surgery while enrolled in the study.
2. Presence of a stoma.
3. Presence or history of fistula.
4. Colonic resection within 24 weeks before baseline or any other intra-abdominal or other major surgery within 12 weeks before baseline.
5. Any planned major surgery through Week 46.
6. Presence of a symptomatic colonic or small bowel obstruction confirmed by objective radiographic (dilation of the intestine proximal to the stricture) or endoscopic (an inability to traverse the stricture with an endoscope) evidence of a stricture with resulting obstruction.
7. History of extensive colonic resection (i.e., <30 cm of colon remaining) or colonic resection that could impair the use of disease severity assessments (e.g. Mayo Score) to assess response to study intervention.
8. History or screening colonoscopy finding of high- or low-grade colonic mucosal dysplasia in an area of known colitis (active or historic). Participants will not be excluded for a pathology finding of indefinite dysplasia with reactive atypia.
9. Presence on screening endoscopy of adenomatous colon polyps outside of an area of known colitis not removed before randomization.
10. Diagnosis of indeterminate colitis, microscopic colitis, ischemic colitis, Crohn's colitis or clinical findings suggestive of Crohn's disease.

11. Stool culture or other examination positive for an enteric pathogen, including *Clostridioides difficile* (formerly known as *Clostridium difficile*) toxin, within 4 months before the first dose of study intervention unless a repeat examination is negative and there are no signs of ongoing infection with that pathogen.

Note: If time allows, treatment and repeat testing can occur in the current screening period prior to the first administration of study intervention.

12. History of severe, progressive, or uncontrolled renal, genitourinary, hepatic, biliary, hematologic, endocrine, cardiac, vascular, pulmonary, rheumatologic, neurologic, psychiatric, or metabolic disturbances, or signs and symptoms thereof.

13. A current malignancy or history of malignancy within 5 years before screening (with the exception of a nonmelanoma skin cancer that has been adequately treated with no evidence of recurrence for ≥ 12 months before the first dose of study intervention or cervical carcinoma in situ that has been treated with no evidence of recurrence for ≥ 12 months before the first dose of study intervention).

14. Have a history of active TB or show signs or symptoms suggestive of active TB upon medical history and/or physical examination at screening.

15. Transplanted organ (with exception of a corneal transplant >12 weeks before screening).

16. Received any of the following medications or therapies within a specified period from baseline (Week I-0):

a. Any prior exposure to compound targeting IL-23p19, including but not limited to, guselkumab, mirikizumab, or risankizumab, or the IL-23R (including but not limited to icotrokinra).

b. Any prior exposure to approved or investigational anti- integrins (e.g., vedolizumab, natalizumab, efalizumab, etrolizumab, AMG 181, carotegrast methyl), or anti-MAdCAM-1 antibodies.

b. Rectal 5-ASA compounds (5-ASAs administered rectally via foam, enema or suppository): 2 weeks.

c. Cyclosporine, tacrolimus, sirolimus or mycophenolate mofetil received: 4 weeks.

d. Thioguanine: 4 weeks.

e. Other immunomodulatory agents, including approved and investigational biologic and non-biologic agents: 12 weeks or 5 half-lives (whichever is longer).

f. Rectal corticosteroids (corticosteroids administered rectally via foam, enema, or suppository): 2 weeks.

g. IV/IM corticosteroids: 3 weeks.

h. Antibiotics for the primary treatment of UC (e.g., ciprofloxacin, metronidazole, or rifaximin): 2 weeks.

i. Parenteral nutrition: 2 weeks.

j. JAK inhibitors (e.g., tofacitinib, upadacitinib, or filgotinib): 2 weeks.

k. Ozanimod or other S1P receptor modulators: 4 weeks (must have lymphocyte count $>0.4 \times 10^3/\mu\text{L}$ at screening).

l. Biologic agents (including approved biosimilars of these therapies) (2 half-lives):

1) TNF α antagonist therapy, e.g.,

a) Infliximab: 3 weeks

b) Adalimumab: 4 weeks

c) Golimumab: 4 weeks

2) Ustekinumab: 5 weeks

A participant with undetectable levels of the above-mentioned biologics based on the results of an approved commercially available test would be eligible to receive their first dose of study drug without waiting for the specified periods.

17. A chest radiograph (posterior-anterior or per country regulation) must be obtained within 12 weeks before the first dose of study intervention and read by a qualified radiologist or pulmonologist. Findings suggestive of malignancy, infection, or previously unrecognized pulmonary pathology would be exclusionary. A chest CT scan obtained outside of the protocol instead of a chest radiograph is also acceptable.