Clinical Study Report Synopsis	
Drug Substance	Brazikumab
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A Phase 2 Open-label, Long-term Extension Safety Study of Brazikumab in Participants with Moderately to Severely Active Ulcerative Colitis

(EXPEDITION OLE)

Study dates: First subject enrolled: 03 March 2020
Last subject last visit: 10 October 2023
Date of early study termination: 01 June 2023

Phase of development: Phase 2

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This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

This submission /document contains trade secrets and confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object.

The study sponsor, AstraZeneca (AZ), decided not to pursue continued development of brazikumab for the indication of ulcerative colitis (UC). The study was therefore terminated on 01 June 2023 and the results are presented in the format of a synoptic clinical study report (CSR) per the AZ company standard process. Given the exploratory nature of efficacy and clinical pharmacology endpoints and the early termination of the study, the results presented in this report are focused on evaluation of participant safety.

Study centre(s)

A total of 36 study centres in 9 countries (Czech Republic, Germany, Israel, Italy, Japan, Poland, South Africa, Taiwan, and United States of America [USA]) consented at least 1 participant.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the safety of long-term treatment with brazikumab in UC participants who previously completed or discontinued participation due to lack of efficacy after Week 10 in the lead-in Study D5272C00001 (Legacy #3151-201-008)	• AEs • Clinical laboratory values • Vital signs • Physical exams • ECGs

Note: Results from the exploratory objectives are not reported in the CSR. No secondary objectives were included in the study.

AE = adverse event; CSR = clinical study report; ECG = electrocardiogram; UC = ulcerative colitis.

Study design

This was a Phase 2, global, multicentre, open-label, parallel group, long-term extension safety study. The purpose of the study was to evaluate long-term safety of brazikumab in participants ≥ 18 years of age with moderately to severely active UC disease who were previously enrolled in Study D5272C00001 (Legacy #3151-201-008; hereinafter referred to as the lead-in study). The study consisted of a 52-week open-label Treatment Period and an 18-week Safety Follow-up Period, for a total of up to 70 weeks.

It was anticipated that the enrolled population would consist of participants who had varying endoscopic and clinical symptom responses during the lead-in study, ranging from complete clinical remission to no response or worsening of their signs and symptoms of UC.

Participants who completed the lead-in study and met criteria for clinical response at Week 54, received CCI brazikumab dosing. Participants who did not meet criteria for clinical response at Week 54 or who met criteria for early termination (rescue treatment) prior to Week 54 in the lead-in study were administered CCI dosing with brazikumab.

After meeting all eligibility criteria, participants were assigned to 1 of 2 treatment groups based on their clinical response in the lead-in study. A summary of the 2 possible assigned treatment regimens is as follows:

- **Group A –** CCI **:** Participants who completed the lead-in study and met criteria for clinical response at Week 54 received CCI brazikumab CCI at Day 1 (Week 0) and every 4 weeks through Day 365 (Week 52).
- **Group B –** CCI **:** Participants who did not meet criteria for clinical response at Week 54 or who met criteria for early termination (rescue treatment) prior to Week 54 in the lead-in study received CCI brazikumab CCI at Day 1 (Week 0), Day 29 (Week 4), and Day 57 (Week 8), followed by CCI brazikumab CCI every 4 weeks beginning at Day 85 (Week 12) through Day 365 (Week 52).

There was an 18-week Safety Follow-up Period following the last dose of study intervention in this study. No study intervention was administered to participants during the safety follow-up.

Prior to Protocol Amendment 2, 3 treatment regimens were available:

- **Group A –** CCI **:** Participants who completed the lead-in study and met the criteria for clinical remission at Week 54 received CCI brazikumab CCI at Day 1 (Week 0) and every 4 weeks through Day 365 (Week 52).
- **Group B –** CCI Participants who completed the lead-in study and did not meet the criteria for clinical remission at Week 54 received CCI brazikumab CCI at Day 1 and every 4 weeks through Day 365 (Week 52).
- **Group C –** CCI For those participants in the lead-in study who did not meet the criteria for clinical response to treatment, CCI brazikumab CCI was administered at Baseline, Week 2, and Week 6 followed by CCI brazikumab CCI at Day 71 (Week 10) and every 4 weeks thereafter for the duration of the open-label Treatment Period (up to Week 50).

Target subject population and sample size

Number of participants (planned and enrolled): Up to a maximum of 255 participants were planned for enrolment, and 66 participants signed the informed consent form.

No separate sample size calculation was performed. This study was an extension study and the sample size was determined by the number of participants in the lead-in study who were eligible for and chose to participate in this study.

Eligible participants were 18 to 80 years of age inclusive with a diagnosis of UC who continued to meet eligibility criteria for the lead-in study and had not had AEs considered to be related to study medication that resulted in discontinuation of the initial lead-in study intervention, or that in the judgment of the investigator, would disqualify them from participating. Eligible participants did not need to complete the 18-week Safety Follow-up Period of the lead-in study if they rolled over into this study after they completed the final visit of the lead-in study. Refer to Appendix 16.1.1, Section 5.2 and Section 5.3 of the clinical study protocol (CSP) for exclusion criteria and lifestyle considerations, respectively.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

This was an open-label study in which the only study intervention planned was the administration of brazikumab. Administration was CCI for induction dosing and CCI for maintenance dosing.

Doses administered were brazikumab CCI and brazikumab CCI Prior to Protocol Amendment 2, doses also included CCI and CCI

Brazikumab for CCI was supplied as a CCI vial concentrate for solution for infusion. CCI The label claim volume was CCI

Brazikumab for CCI administration was supplied as a CCI solution for injection in a prefilled syringe. CCI The label-claim volume was CCI

CCI of brazikumab were used in this study.

Duration of treatment

The study consisted of a maximum 52-week open-label Treatment Period and an 18-week Safety Follow-up Period, for a total of up to 70 weeks.

Statistical methods

Due to the early termination of the study, a reduced set of tables and listings was defined for the reporting of the study. The reduced package includes descriptions of the study population

and safety analyses. No efficacy analyses are included due to the limited amount of data and the exploratory nature of the efficacy objectives.

All safety analyses for this study were summarised descriptively by the visit and the treatment sequences and overall, unless stated otherwise. The baseline as defined in the double-blind, lead-in study was used as the baseline for all data analyses in this study. Continuous variables were summarised by the number of participants and mean, standard deviation (SD), median, Q1, Q3, minimum, and maximum values. Categorical variables were summarised by number and percentage of participants. Visit time window for safety parameters and detailed statistical analyses for this study were defined in the Statistical Analysis Plan (SAP).

Due to the reduced scope of analysis and reporting, the Full Analysis Set was not implemented. The Safety Analysis Set was used for both the description of the study population and the safety analyses. The Safety Analysis Set comprised all participants who received 1 or more administration of study intervention in this extension study.

The treatment sequences in this open-label extension (OLE) study were presented as Brazikumab/Brazikumab for participants who received brazikumab study intervention in the double-blind, lead-in study, and Placebo/Brazikumab for participants who received placebo study intervention in the double-blind, lead-in study. Participants randomized to vedolizumab in the lead-in study are excluded from the safety summaries but included in the safety listings.

Study population

A total of 66 participants were screened and 60 participants were assigned to treatment. Of the 57 participants in Safety Analysis Set, 31 received brazikumab, 24 received placebo, and 2 received vedolizumab in the lead-in study. The 2 participants who received vedolizumab in the lead-in study were excluded from the safety summaries but included in the safety listings.

A total of 43 participants started Induction Period treatment (did not meet criteria for clinical response at Week 54 or met criteria for early termination [rescue treatment] prior to Week 54 in the lead-in Study) and 25 participants (58.1%) completed Induction Period treatment. A total of 39 participants (100%) started Maintenance Period treatment, including the 25 participants who completed the OLE Induction Period treatment.

Of the 39 participants who started the Maintenance Period, 15 participants (38.5%) completed the 52-week Treatment Period; 24 participants (61.5%) withdrew from the study prior to Week 52 due to study terminated by sponsor (21 participants [53.8%]), withdrawal by participant (2 participants [5.1%]), or lost to follow-up (1 participant [2.6%]).

Of the 57 participants who received treatment, 39 participants (68.4%) started the 18-week Safety Follow-up Period; 22 participants (38.6%) completed the Safety Follow-up Period and 17 participants (29.8%) prematurely discontinued during the Safety Follow-up Period. The

reasons for premature discontinuation were study terminated by sponsor (14 participants [24.6%]), withdrawal by participant (2 participants [3.5%]), and lost to follow-up (1 participant [1.8%]).

A total of 23 participants (41.8%) was aged < 40 years, 27 participants (49.1%) were between the ages of 40 to 65 years, and 5 participants (9.1%) were aged > 65 years; the mean (SD) age at screening was 42.9 (15.02) years. Overall, 26 participants (47.3%) were male and 29 (52.7%) were female. A total of 44 participants (80.0%) were white and 48 participants (87.3%) were not Hispanic or Latino.

At baseline, mean (SD) disease duration of UC was 8.6 (6.8) years, with the baseline disease location being descending colon in 38 participants (69.1%), pancolitis in 24 participants (43.6%), and other in 11 participants (20.0%). Forty-two participants (76.4%) had current aminosalicylate use. Three participants (5.5%) had prior JAK inhibitor use and 28 participants (50.9%) had prior biologic use. Many participants had inadequate response on prior biologics at baseline: 16 participants (29.1%) to anti-TNF therapies, 10 participants (18.2%) to integrin receptor antagonists, and 1 participant (1.8%) to IL-12/23 inhibitors. Mean (SD) C-reactive protein was 43.2 (62.5) mg/L and mean (SD) faecal calprotectin was 2411.0 (3722.3) µg/g.

At baseline, mean (SD) total score (0 to 9) for modified Mayo score (mMS) was 6.5 (1.2).

Summary of efficacy results

Efficacy assessments are not reported for this study.

Summary of anti-drug antibody results

Anti-drug antibodies analyses are not reported for this study.

Summary of pharmacokinetic results

Pharmacokinetic analyses are not reported for this study.

Summary of safety results

The following safety results were reported:

- A total of 26 participants (47.3%) reported adverse events (AEs), including 15 participants [48.4%] in the Brazikumab/Brazikumab group and 11 participants [45.8%] in the Placebo/Brazikumab group). One participant (1.8%) reported serious adverse events (SAEs); they received brazikumab in the lead-in study. No SAEs with the outcome of death were reported for this study. No participant reported an AE leading to discontinuation of the investigational product (IP). Adverse events considered as possibly related were reported by 8 participants (14.5%), including 4 participants [12.9%] in the Brazikumab/Brazikumab group and 4 participants [16.7%] in the Placebo/Brazikumab group. No participants (0%) experienced possibly related SAEs.

- The most commonly reported system organ class overall was Infections and infestations, with 15 participants (27.3%) total, including 9 participants (29.0%) in the Brazikumab/Brazikumab group and 6 participants (25.0%) in the Placebo/Brazikumab group.
- The most commonly reported AEs (> 5% total) were nasopharyngitis (5 participants [9.1%]: 2 participants [6.5%] in the Brazikumab/Brazikumab group and 3 participants [12.5%] in the Placebo/Brazikumab group), coronavirus disease 2019 (COVID-19) (4 participants [7.3%]; all 4 participants [12.9%] were in the Brazikumab/Brazikumab group), and injection site pruritus (3 participants [5.5%]; all 3 participants [9.7%] were in the Brazikumab/Brazikumab group).
- One participant (1.8%), in the Brazikumab/Brazikumab group, had an SAE of atrial fibrillation. No SAEs with an outcome of death were reported for this study.
- No participant reported an AE leading to treatment discontinuation.
- A total of 7 participants (12.7%) reported an adverse event of special interest (AESI) (6 participants [19.4%] in the Brazikumab/Brazikumab group and 1 participant [4.2%] in the Placebo/Brazikumab group). The most commonly reported AESIs (> 1 participant total) were injection site erythema (2 participants [3.6%]; both participants [6.5%] were in the Brazikumab/Brazikumab group) and injection site pruritus (2 participants [3.6%]; both participants [6.5%] were in the Brazikumab/Brazikumab group).
- No participants experienced AEs occurring in the lead-in study that resulted in discontinuation of IP in the OLE study.
- One participant, in the Placebo/Brazikumab group, experienced an AE (colitis ulcerative) occurring in the lead-in study that increased in severity in the OLE study and was considered not possibly related to IP.

Conclusion(s)

Safety findings in this study were consistent with the known profile of brazikumab, and no new safety concerns were observed.