Clinical Study Report Synopsis	
Drug Substance	Brazikumab
Study Code	D5271C00002 (Legacy #3150-303-008)
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An Open-label, Long-term Extension Study of Brazikumab in Participants With Moderately to Severely Active Crohn's Disease (INTREPID OLE)

Study dates: First subject enrolled: 06 January 2020
Last subject last visit: 19 September 2023
Date of early study termination: 01 June 2023

Phase of development: Phase 3

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

The study sponsor, AstraZeneca (AZ), decided not to pursue continued development of brazikumab for the indication of Crohn's disease. The study was therefore terminated on 01 June 2023, and the results are presented in the format of a synoptic clinical study report 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 15 study centres in 5 countries (Germany, Poland, South Africa, Taiwan, and United States) consented to 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 participants who previously completed Study D5271C00001 (Legacy #3150-301-008) or discontinued from the study at or after Week 12 due to lack of efficacy	• AEs • Clinical laboratory values • Vital signs • Physical exams • ECGs
Exploratory	
• To assess efficacy of long-term treatment with brazikumab in participants who previously completed Study D5271C00001 (Legacy #3150-301-008) or discontinued from the study at or after Week 12 due to lack of efficacy	• SES-CD • CDAI • PRO
• To evaluate the PK and immunogenicity of brazikumab	• Serum concentration of brazikumab • Serum ADAs
• To explore transcriptional, histological, protein, microbiome, and clinical biomarkers in participants who previously completed Study D5271C00001 (Legacy #3150-301-008) or discontinued from the study at or after Week 12 due to lack of efficacy, and the effect of long-term brazikumab treatment on these biomarkers	• Serum, plasma, faecal, or gut tissue proteins; whole blood or gut transcriptional changes; histological, microbiome, and clinical lab assessments

ADA = anti-drug antibody; AE = adverse event; CDAI = Crohn's Disease Activity Index; ECG = electrocardiogram; PK = pharmacokinetic(s); PRO = patient-reported outcome; SES-CD = Simple Endoscopic Score for Crohn's Disease.

Study design

This was a Phase 3, multicentre, 2-arm, parallel-group, open-label, 52-week extension 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 Crohn's disease who were previously enrolled in Study D5271C00001 (Legacy #3150-301-008) (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.

Target subject population and sample size

Number of participants (planned and enrolled): Up to a maximum of 240 participants were planned for enrolment, and 20 participants signed informed consent.

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 and chose to participate in this study.

Eligible participants were 18 to 80 years of age inclusive with a diagnosis of ileal, ileocolonic, or colonic Crohn's disease who completed the lead-in study or completed 12 weeks of treatment in the lead-in study but were subsequently discontinued due to lack of efficacy; continued to meet eligibility criteria; and did not have adverse events (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.

See Appendix 16.1.1, Section 5.2 and Section 5.3 of Study D5271C00001 of the clinical study protocol for the exclusion criteria and the 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. CCI [redacted]

Brazikumab for CCI [redacted] was supplied as a CCI [redacted] vial concentrate for solution for infusion. The solution contained CCI [redacted] brazikumab, CCI [redacted], CCI [redacted] The label-claim CCI [redacted].

Brazikumab for CCI was suppled as a CCI solution for injection in a prefilled syringe. The solution contained CCI brazikumab, CCI , CCI . The label-claim volume was CCI.

A participant's treatment regimen depended on whether the participant was considered a completer with Crohn's Disease Activity Index (CDAI) response or an inadequate responder/non-responder in the lead-in study. A completer with CDAI response completed lead-in study requirements through Week 52 and met CDAI response (CDAI score of < 150 points or CDAI reduction from Baseline of ≥ 100 points) without having met the criteria for rescue therapy during the lead-in study. An inadequate responder/non-responder met criteria for early termination due to lack of efficacy (rescue treatment criteria) or did not meet CDAI response at Week 52 in the lead-in study.

- Completer with CDAI response:
  - Maintenance dose: CCI brazikumab every 4 weeks through Week 52
- Inadequate responder/non-responder:
  - Induction dose: CCI brazikumab at Week 0, Week 4, and Week 8
  - Maintenance dose: CCI brazikumab every 4 weeks thereafter through Week 52

Fourteen batches of brazikumab were used in this study.

Duration of treatment

The study consisted of the following consecutive periods:

- 52-week Treatment Period
- 18-week Safety Follow-up Period

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 from the lead-in study was used for the analyses. Continuous variables were summarised by the number of participants and mean, standard deviation (SD), median, first quartile, third quartile, minimum, and maximum values. Categorical variables were summarised by number and percentage of participants.

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 administration of study intervention in this extension study.

Participants are summarised according to the actual study treatment received in the lead-in 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 randomised to adalimumab in the lead-in study are excluded from the safety summaries but are included in the safety listings.

Study population

A total of 20 participants were screened and assigned to treatment, and 18 participants received at least 1 dose of study drug (Safety Analysis Set). Of these 18 participants, 12 received brazikumab, 4 received placebo, and 2 received adalimumab in the lead-in study. Nine participants started Induction Period treatment, and 17 participants started Maintenance Period treatment (including 8 participants who completed Induction Period treatment).

Of the 17 participants who started the Maintenance Period, 8 participants (47.1%) completed the 52-week Treatment Period; 9 participants (52.9%) withdrew from the study prior to Week 52 because of study terminated by sponsor (5 participants [29.4%]), lost to follow-up (2 participants [11.8%]), an AE (1 participant [5.9%]), or other (1 participant [5.9%]; withdrawal from the study was due to site closure in 2021. Thirteen participants started the 18-week Safety Follow-up Period; 10 participants (76.9%) completed the Safety Follow-up Period, and 3 participants (23.1%) prematurely discontinued during the Safety Follow-up Period because of withdrawal by study participant (2 participants [15.4%]) or site terminated by sponsor (1 participant [7.7%]).

Note that the results below do not include the 2 participants who received adalimumab in the lead-in study; information on these 2 participants are provided in the listings only.

A total of 5 participants (31.3%) were aged < 40 years, 9 participants (56.3%) were between the ages of 40 to 65 years, and 2 participants (12.5%) were aged > 65 years; the mean (SD) age at study entry was 44.7 (15.70) years. Six participants (37.5%) were male, and 10 participants (62.5%) were female. Twelve participants (75.0%) were white and 11 participants (68.8%) were not Hispanic or Latino.

The mean (SD) duration of Crohn's disease was 11.229 (8.416) years, with the baseline disease location being ileocolonic in 8 participants (50.0%), the ileum only in 5 participants (31.3%), and the colon only in 3 participants (18.8%). No participants had current

immunomodulator use, and 6 participants (37.5%) had current corticosteroid use. No participants had prior JAK inhibitor use, and 5 participants (31.3%) had prior biologic use. Some participants had an inadequate response on prior biologics at baseline: 2 participants (12.5%) to anti-TNF therapies, 2 participants (12.5%) to IL-12/23 inhibitors, and 1 participant (6.3%) to integrin receptor antagonists. Mean (SD) C-reactive protein was 10.024 (11.918) mg/L, and mean (SD) faecal calprotectin was 621.3 (575.47) µg/g.

At baseline, 7 participants (43.8%) had CDAI scores between 220 and 450 (moderate to severe disease), and no participants had CDAI scores more than 450 (very severe disease); CDAI scores were missing for 9 participants (56.3%). Mean (SD) total Simple Endoscopic Score for Crohn's Disease at baseline was 12.6 (8.10).

Summary of efficacy results

Efficacy assessments are not reported for this study.

Summary of anti-drug antibody (ADA) results

ADA 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:

- Twelve of 16 participants (75.0%) reported AEs (11 of 12 participants [91.7%] in the Brazikumab/Brazikumab group and 1 of 4 participants [25.0%] in the Placebo/Brazikumab group), and 3 of 16 participants (18.8%) reported serious adverse events (SAEs) (2 of 12 participants [16.7%] in the Brazikumab/Brazikumab group and 1 of 4 participants [25.0%] in the Placebo/Brazikumab group). No participants had an SAE with an outcome of death. AEs leading to discontinuation of the investigational product (IP) were reported for 1 of 16 participants (6.3%); this participant was in the Brazikumab/Brazikumab group. No participants experienced AEs or SAEs assessed by the investigator as possibly related to IP.
- Most AEs were singular in nature. The most commonly reported system organ classes were Gastrointestinal Disorders (6 of 16 participants [37.5%]; 5 of 12 participants [41.7%] in the Brazikumab/Brazikumab group and 1 of 4 participants [25.0%] in the Placebo/Brazikumab group), Infections and Infestations (5 of 16 participants [31.3%]; all 5 participants were in the Brazikumab/Brazikumab group), and Injury, Poisoning, and Procedural Complications (4 of 16 participants [25.0%]; all 4 participants were in the Brazikumab/Brazikumab group).
- Three of 16 participants (18.8%) reported 6 SAEs: 1 participant in the Brazikumab/Brazikumab group had an SAE of ileal stenosis; 1 participant in the Brazikumab/Brazikumab group had SAEs of intestinal perforation, sepsis, and peritonitis;

and 1 participant in the Placebo/Brazikumab group had SAEs of renal impairment and anaemia. There were no SAEs with an outcome of death.

- One of 16 participants (6.3%) reported an AE (intestinal perforation) leading to discontinuation of IP; this participant was in the Brazikumab/Brazikumab group.
- One of 16 participants (6.3%) reported an AE of special interest (peritonitis); this participant was 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 or increased in severity in the OLE study.

Conclusion(s)

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