Clinical Study Report Synopsis	
Drug Substance	Brazikumab
Study Code	D5272C00001 (Legacy #3151-201-008)
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A 54-Week, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group Phase 2 Study to Assess the Efficacy and Safety of Brazikumab in Participants with Moderately to Severely Active Ulcerative Colitis

(EXPEDITION Lead-in)

Study dates: First subject enrolled: Allergan 07 August 2018, AstraZeneca 08 October 2021
Last subject last visit: 23 October 2023
Date of early study termination: 01 June 2023
The analyses presented in this report are based on a clinical data lock date of 24 January 2024

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.

Study centre(s)

A total of 126 study centres in 18 countries (Canada, Czech Republic, Germany, Hungary, India, Israel, Italy, Japan, Poland, Russia, Slovakia, South Africa, South Korea, Spain, Taiwan, Ukraine, United Kingdom, 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

Objective	Endpoint	Population	Intercurrent event strategy	Population-level summary (analysis)
Primary				
To compare the efficacy of brazikumab with that of placebo to achieve clinical remission	Clinical remission defined as: • mMS at Week 10: – Endoscopy subscore = 0 or 1, AND – Rectal bleeding subscore = 0, AND – Stool frequency subscore = 0 or 1, AND at least a 1-point decrease from baseline	Participants with moderately to severely active UC	NRI will be used for the following intercurrent events before Week 10: • Discontinues treatment prematurely for any reason • Takes rescue treatment • Uses prohibited treatment	Percentage of participants achieving the endpoint

Objective	Endpoint	Population	Intercurrent event strategy	Population-level summary (analysis)
Secondary				
To compare the efficacy of brazikumab with that of placebo to achieve sustained clinical remission	Sustained clinical remission defined as: • mMS at both Week 10 and Week 54: – Endoscopy subscore = 0 or 1, AND – Rectal bleeding subscore = 0, AND – Stool frequency subscore = 0 or 1, AND at least a 1-point decrease from baseline	Participants with moderately to severely active UC	NRI will be used for the following intercurrent events before Week 10: • Discontinues treatment prematurely for any reason • Takes rescue treatment • Uses prohibited treatment	Same as primary
To compare the efficacy of brazikumab with that of placebo to achieve CS-free clinical remission	CS-free clinical remission defined as: • mMS at Week 54 for participants who are CS-free for at least the last 12 weeks before the assessment at Week 54: – Endoscopy subscore = 0 or 1, AND – Rectal bleeding subscore = 0, AND – Stool frequency subscore = 0 or 1, AND at least a 1-point decrease from baseline	Participants with moderately to severely active UC	NRI will be used for the following intercurrent events before Week 54: • Discontinues treatment prematurely for any reason • Takes rescue treatment • Uses prohibited treatment	Same as primary

Objective	Endpoint	Population	Intercurrent event strategy	Population-level summary (analysis)
To compare the efficacy of brazikumab with that of placebo to achieve clinical response	Clinical response is defined as • Reduction in mMS ≥ 2 points from baseline AND ≥ 30% from baseline AND a decrease in the rectal bleeding score ≥ 1 point from baseline or a score of 0 or 1 at Week 10	Participants with moderately to severely active UC	NRI will be used for the following intercurrent events before Week 10: • Discontinues treatment prematurely for any reason • Takes rescue treatment • Uses prohibited treatment	Same as primary
To compare the efficacy of brazikumab with that of placebo to achieve endoscopic improvement	Endoscopic improvement is defined as • Endoscopy subscore ≤ 1 at Week 10	Participants with moderately to severely active UC	NRI will be used for the following intercurrent events before Week 10: • Discontinues treatment prematurely for any reason • Takes rescue treatment • Uses prohibited treatment	Same as primary
To evaluate the PK and immunogenicity of brazikumab	Population PK model of serum concentrations of brazikumab and analysis for serum anti-brazikumab antibodies	Participants with moderately to severely active UC		
To characterize the exposure-response relationships of brazikumab	Exposure-response model linking primary endpoints to metrics of model-predicted individual brazikumab exposures	Participants with moderately to severely active UC		

Note: Pharmacokinetic and immunogenicity analyses, and results from exploratory objectives are not reported in the CSR.
CS = corticosteroid; mMS = modified Mayo score; NRI = non-responder imputation; PK = pharmacokinetic(s);
UC = ulcerative colitis.

Study design

This was a Phase 2, global, multicenter, randomized, double-blind, placebo-controlled, parallel-group, 54-week study. The purpose of this study was to assess efficacy and safety of brazikumab in participants with moderately to severely active UC.

In 2020, AZ resumed full ownership of brazikumab clinical development. AstraZeneca re-evaluated the development plan, and the Clinical Study Protocol (CSP) D5272C00001 (Legacy #3151-201-008) was consequently reviewed and amended. The major components of the amendments were: removal of the active comparator group (vedolizumab), removal of the brazikumab high dose group CCI , change in dose levels in remaining groups CCI CCI , and change in Clinical Remission definition (stool frequency: change from 0 to 0 or 1, with at least a 1-point reduction from baseline).

After meeting all eligibility criteria, participants were randomized in a 1:1:1 ratio to receive study intervention CCI during the Induction Period (up to Week 10). Participants were stratified according to prior treatment experience, biological-naïve or prior biological use (failed or were intolerant to prior biological treatment). Following Induction, participants who received brazikumab were re-randomized 1:1 (stratified according to the same stratification factors listed for the Induction Period and by induction dose) at Week 10 to receive either CCI CCI ; participants randomized into the Induction Period placebo treatment group received CCI in the Maintenance Period. The study was terminated early on 01 June 2023. All participants who were in the study at that point in time went into the Safety Follow-up Period. Participants who completed the study or discontinued participation due to lack of efficacy after Week 10 may have been eligible to enroll into an open-label extension study.

Target subject population and sample size

Number of participants (planned and randomized): Approximately 255 participants were planned for randomization; 240 participants were randomized; 237 participants were in the Safety Analysis Set; and 195 participants were in the Efficacy Analysis Set.

Brazikumab and placebo responder rates were assumed to be 22.4% and 5.4%, respectively, considering previous study results and available external data, along with the expected ratio of biologic naïve to biologic intolerant of refractory participants. Based on these assumptions, a continuity-corrected Cochran-Mantel-Haenszel (CMH) test of odds ratio = 1 for 2 × 2 tables in 2 strata had 81% power to detect an odds ratio of 5.3 using a 2-sided 5% test level.

The sample size of 225 participants accounted for the 4 treatment groups, brazikumab CCI CCI , brazikumab CCI brazikumab CCI , and CCI . Participants

previously randomized to the brazikumab CCI and CCI groups under Protocol Amendment 4 and earlier were not included in the sample size of 225 participants.

Eligible participants were 18 to 80 years of age inclusive and had a diagnosis of UC with an onset of symptoms for a minimum of 3 months prior to screening as determined by the investigator based on clinical history, exclusion of infectious causes, and characteristic endoscopic and histologic findings.

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

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

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

Treatment groups were as follows:

- Brazikumab CCI: CCI brazikumab CCI on Week 0 (Day 1), Week 2, and Week 6 followed by CCI brazikumab CCI, or CCI every 4 weeks beginning at Week 10
- Brazikumab CCI CCI brazikumab CCI, or CCI at Week 0 (Day 1), Week 2, and Week 6 followed by CCI brazikumab CCI or CCI, or CCI CCI every 4 weeks beginning at Week 10
- Active comparator group: CCI
- CCI: CCI at Week 0 (Day 1), Week 2, and Week 6 followed by CCI every 4 weeks beginning at Week 10

Thirty-one batches of brazikumab and 6 batches of vedolizumab were used in this study.

Duration of treatment

Following a Screening Period of up to 5 weeks, the study duration was up to 68 weeks, consisting of a 54-week Treatment Period (Induction Period up to Week 10 and Maintenance Period up to Week 54 with the last dose of study intervention at Week 50) and an 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, efficacy, and safety analyses.

Due to the early termination of the study, the analysis set used for efficacy analysis was updated. The Full Analysis set, including all participants who were randomized (excluding participants randomized to the CCI brazikumab), was modified to the Efficacy Analysis Set to avoid bias in the efficacy analysis. The Efficacy Analysis Set included all randomized participants who completed the Induction Period at the time of study termination, or who had had the opportunity to complete the Induction Period at the time of study termination if not prematurely discontinuing treatment, ie, all participants randomized at least 10 weeks prior to study termination.

The efficacy endpoints reported are the primary endpoint, clinical remission at Week 10, and the secondary endpoints, clinical response at Week 10 and endoscopic improvement at Week 10. The following study intercurrent events were captured in the definition of the efficacy endpoints:

- Discontinuation of study intervention prematurely before Week 10
- Intake of rescue treatment before Week 10
- Use of prohibited medication before Week 10

Participants who had any of these intercurrent events were considered as being unsuccessfully treated and were imputed as non-responders. Efficacy endpoints were analysed using a continuity-corrected CMH test controlling for the randomization stratification factor (status of prior biologic use [yes or no] at randomization). All statistical tests were 2-sided hypothesis tests, and all confidence intervals (CIs) were 2-sided 95% CIs.

For all responder endpoints, participants who did not meet responder criteria, either due to missing assessments or early discontinuation, were considered non-responders for analysis purposes. This method was applied to both primary and secondary efficacy endpoints. Considering that this was not a confirmatory study, no multiplicity adjustments were planned.

Safety data were summarized descriptively using the Safety Analysis Set, which included all participants who received at least 1 dose of study intervention. The Safety Population included participants who enrolled prior to and after the initiation of Amendment 5. Only pre-Amendment 5 participants randomized to the vedolizumab group are listed. Participants in the pre-Amendment 5 CCI brazikumab group CCI were included in the overall (grouped) brazikumab summaries but were not summarized separately. The other pre-Amendment 5 participants were grouped with their corresponding post-Amendment 5 dose group and are included in safety summary tables.

Study population

A total of 545 participants were screened and 240 participants were randomised from 126 study centres in 18 countries. A total of 237 participants (100%) started the Induction Period treatment, 172 participants (72.6%) completed the Induction Period treatment, 151 participants (100%) entered the Maintenance Period treatment, and 46 participants (30.5%) completed the Maintenance Period treatment.

A total of 49 participants (32.5%) completed the Week 54 Visit. Overall, 102 participants (67.5%) were withdrawn from the study prior to Week 54 due to the following: study terminated by sponsor (78 participants [51.7%]); withdrawal by participant (8 participants [5.3%]); lack of efficacy (6 participants [4.0%]); physician decision (3 participants [2.0%]); lost to follow-up, coronavirus disease 2019 (COVID-19), or other (2 participants [1.3%] each); or pregnancy (1 participant [0.7%]). A total of 133 participants (56.1% of the participants who started the Induction Period) started the 18-week Safety Follow-up Period and 54 participants (22.8%) completed the Safety Follow-up Period. Overall, 73 participants (30.8%) withdrew from the study during the Safety Follow-up Period due to the following: study terminated by the sponsor (63 participants [26.6%]); withdrawal by participant or other (4 participants [1.7%] each); or physician decision or AE (1 participant [0.4%] each). There were 6 participants where safety follow-up was indicated but no safety data was collected.

A total of 92 participants (47.2%) were aged < 40 years, 91 participants (46.7%) were between the ages of 40 to 65 years, and 12 participants (6.2%) were aged > 65 years; the mean (standard deviation [SD]) age at Screening was 41.4 (14.09) years. Ninety-five participants (48.7%) were female and 100 participants (51.3%) were male. Overall, 138 participants (70.8%) were white, and 181 participants (92.8%) were not Hispanic or Latino.

The mean (SD) duration of UC was 8.5 (7.6) years. Forty-eight participants (24.6%) had current immunomodulator use and 156 participants (80.0%) had current aminosalicylate use. Ten participants (5.1%) had prior JAK inhibitor use and 71 participants (36.4%) had prior biologic use. Ninety-three participants (47.7%) had current corticosteroid use and the mean dose was CCI . The number of different mechanisms of action of biologics were the following: 124 participants (63.6%) for 0, 54 participants (27.7%) for 1, and 17 participants (8.7%) for 2. The following participants had an inadequate response on prior biologics at baseline: 40 participants (20.5%) to anti-TNF therapies, 22 participants (11.3%) to integrin receptor antagonists, and 4 participants (2.1%) to IL-12/23 inhibitors. Mean (SD) C-reactive protein at baseline was 69.0 (148.7) mg/L, and mean (SD) fecal calprotectin at baseline was 2845.0 (4266.5) µg/g.

Summary of efficacy results

For the primary efficacy endpoint, the proportion of participants with clinical remission at Week 10 was 20.0% (13 participants) in the brazikumab CCI group, 24.6% (16 participants) in the brazikumab CCI, and 6.2% (4 participants) in the placebo group. The difference in proportion of responders between active treatment and placebo was 12.3% for the brazikumab CCI (95% CI: -0.6, 25.2; p = 0.061), and 18.4% for the brazikumab CCI (95% CI: 5.0, 31.7; p = 0.007). The number and percent of participants who were non-responder imputation in the primary analysis at Week 10 are presented in a summary table.

For the secondary efficacy endpoints, clinical response and endoscopic improvement at Week 10 were investigated and are presented in a summary table.

Summary of pharmacokinetic results

Pharmacokinetic analyses are not reported for this study.

Summary of safety results

Induction Safety Reporting Period:

In the brazikumab total group (N = 156), 71 participants (45.5%) had adverse events (AEs) and 6 participants (3.8%) had serious adverse events (SAEs). No participants had an SAE with an outcome of death. Adverse events leading to discontinuation of the investigational product (IP) were reported for 2 participants (1.3%). Fifteen participants (9.6%) had possibly related AEs, and no participants had possibly related SAEs. In the placebo group (N=71), 24 participants (33.8%) had AEs, and 4 participants (5.6%) had SAEs. No participants had an SAE with an outcome of death. An AE leading to discontinuation of the IP was reported for 1 participant (1.4%). Five participants (7.0%) had possibly related AEs, and no participants had possibly related SAEs.

In the brazikumab total group (N=156), the most commonly reported AEs (> 2 participants) were COVID-19 (10 participants [6.4%]), upper respiratory tract infection and fatigue (6 participants [3.8%], each); nasopharyngitis, headache, and constipation (4 participants [2.6%], each); and colitis ulcerative, haemorrhoids, alopecia, and arthralgia (3 participants [1.9%], each). In the placebo group (N=71), the most commonly reported AEs (> 2 participants) were upper respiratory tract infection, anaemia, headache, and colitis ulcerative (3 participants [4.2%], each).

Three participants had events entered as medical history that should have been reported as AEs. Investigations of the data indicated that these events occurred prior to exposure of IP. For more detailed information refer to the Note to File.

In the brazikumab total group (N=156), the SAEs reported were perirectal abscess, anaemia, microcytic anaemia, cerebral artery stenosis, cerebrovascular accident, acute myocardial infarction, and colitis ulcerative. All SAEs were reported for 1 participant (0.6%). In the placebo group (N=71), the SAEs colitis ulcerative (3 participants [4.2%]) and pancreatitis acute (1 participant [1.4%]) were reported.

In the brazikumab total group (N=156), the most commonly reported AESI (> 1 participant) was infusion related reaction (2 participants [1.3%]). All other AESIs were reported for 1 participant. In the placebo group (N=71), the AESI was infusion site swelling (1 participant [1.4%]).

In the brazikumab total group (N=156), AEs leading to treatment discontinuation were reported for 2 participants (1.3%); 1 participant (0.6%) had an AE of basal cell carcinoma and 1 participant (0.6%) had an AE of cerebrovascular accident. In the placebo group (N=71), 1 participant (1.4%) had an AE of colitis ulcerative that led to treatment discontinuation.

Maintenance Safety Reporting Period:

In the brazikumab total group (N=131), 60 participants (45.8%) had AEs and 3 participants (2.3%) had SAEs. No participants had an SAE with an outcome of death. An AE leading to discontinuation of the IP was reported for 1 participant (0.8%). Eleven participants (8.4%) had possibly related AEs and no participants had possibly related SAEs. In the placebo group (N=58), 23 participants (39.7%) had AEs, and 2 participants (3.4%) had SAEs. No participants had an SAE with an outcome of death. No participants had an AE leading to discontinuation of the IP. Three participants (5.2%) had possibly related AEs, and no participants had possibly related SAEs.

In the brazikumab total group (N=131), the most commonly reported AEs (> 2 participants) were COVID-19 (7 participants [5.3%]); nasopharyngitis (5 participants [3.8%]); and upper respiratory tract infection, headache, hypertension, injection site pruritus, injection site swelling, weight increased, contusion, and fall (3 participants [2.3%], each). In the placebo group (N=58), the most commonly reported AEs (> 2 participants) were COVID-19, colitis ulcerative, and arthralgia (3 participants [5.2%], each).

In the brazikumab total group (N=131), the SAEs were COVID-19, haemorrhoids, acetabulum fracture, fall, pelvic fracture, and skull fracture. All SAEs were reported by 1 participant (0.8%). In the placebo group (N=58), the SAEs were colitis ulcerative and haemorrhoids (1 participant [1.7%], each).

In the brazikumab total group (N=131), the most commonly reported AESI (> 1 participant) were injection site swelling, clostridium difficile infection, CCI [redacted], and

CCI (2 participants [1.5%] each). In the placebo group (N=58), no participants had AESIs.

In both the brazikumab total (N=131) and placebo groups (N=58), no participants had AEs leading to treatment discontinuation.

Conclusion(s)

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