Clinical Study Report Synopsis	
Drug Substance	Brazikumab
Study Code	D5271C00001 (Legacy #3150-301-008)
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A 52-Week, Multicenter, Randomized, Double-blind, Placebo and Active-controlled, Operationally Seamless Phase 2b/3, Parallel Group Study to Assess the Efficacy and Safety of Brazikumab in Participants With Moderately to Severely Active Crohn's Disease

(INTREPID Lead-In)

Study dates: First subject enrolled: Allergan_07 December 2018; AZ_25 Aug 2021
Last subject last visit: 18 October 2023
Date of early study termination: 01 June

Phase of development: Phase 2b/3

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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 102 study centres in 17 countries (Canada, Czech Republic, Germany, Hungary, India, Israel, Italy, Poland, Russia, Slovakia, South Africa, South Korea, Spain, Taiwan, Ukraine, United Kingdom, United States) consented at least 1 participant.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Objectives and Endpoints of Participants with Moderately to Severely Active Crohn's Disease: Stage 1

Stage 1 Objectives	Stage 1 Endpoints	Intercurrent Event Strategy	Population Level Summary (analysis)
Primary			
To compare the efficacy of brazikumab with that of placebo to achieve CDAI remission at Week 12	• CDAI remission at Week 12: ° CDAI score < 150	NRI will be used for the following intercurrent events before Week 12: • discontinues treatment prematurely for any reason • takes rescue treatment or meet the rescue criteria • uses prohibited treatment	Percentage of participants achieving the endpoint
Secondary			
To compare the efficacy of brazikumab with that of placebo to achieve endoscopic response, CDAI response, and clinical remission at Week 12	• **Key Secondary**: Endoscopic response at Week 12: ° Minimum of 50% decrease from Baseline in SES-CD total score • Clinical remission at Week 12: ° Average daily LSF subscore of ≤ 3 as assessed on the CDAI LSF item AND average daily AP subscore of ≤ 1 as assessed on the CDAI AP item • CDAI response at Week 12: ° CDAI score of < 150 points or CDAI reduction from Baseline of ≥ 100 points	NRI will be used for the following intercurrent events before Week 12: • discontinues treatment prematurely for any reason • takes rescue treatment or meet the rescue criteria • uses prohibited treatment	Same as primary
To compare the efficacy of brazikumab with that of placebo to achieve sustained CDAI remission, CDAI response, endoscopic response, and clinical remission at both Week 12 and Week 52	• CDAI remission at both Week 12 and Week 52 • CDAI response at both Week 12 and Week 52 • Endoscopic response at both Week 12 and Week 52 • Clinical remission at both Week 12 and Week 52	NRI will be used for the following intercurrent events before Week 12: • discontinues treatment prematurely for any reason • takes rescue treatment or meet the rescue criteria • uses prohibited treatment	Same as primary

Stage 1 Objectives	**Stage 1 Endpoints**	**Intercurrent Event Strategy**	**Population Level Summary (analysis)**
To compare the efficacy of brazikumab with that of placebo in achieving CDAI remission, CDAI response, endoscopic response, SES-CD total score of 0-2, endoscopic remission, and clinical remission at Week 52	• Endoscopic remission at Week 52: ◦ SES-CD total score of 0-2, OR ◦ SES-CD total score of ≤ 4 and at least 2-point reduction from Baseline with no subscore > 1 • Clinical remission at Week 52 • CDAI response at Week 52 • CDAI remission at Week 52 • Endoscopic response at Week 52 • SES-CD total score of 0-2 at Week 52	NRI will be used for the following intercurrent events before Week 12: • discontinues treatment prematurely for any reason • takes rescue treatment or meet the rescue criteria • uses prohibited treatment	Same as primary
To compare the efficacy of brazikumab with that of placebo to achieve endoscopic response at Week 12 and endoscopic remission at Week 52	Endoscopic response at Week 12 and endoscopic remission at Week 52	NRI will be used for the following intercurrent events before Week 12: • discontinues treatment prematurely for any reason • takes rescue treatment or meet the rescue criteria • uses prohibited treatment	Same as primary
To evaluate the PK and immunogenicity of brazikumab in participants with CD	Population PK model of serum concentrations of brazikumab and analysis for serum anti-brazikumab antibodies		
To characterize the exposure-response relationships of brazikumab	Exposure-response model linking primary endpoint to metrics of model-predicted individual brazikumab exposures		
To establish the serum IL-22 concentration Baseline clinical cutoff for its value in predicting the efficacy of brazikumab	Exploration of relationship of Baseline serum IL-22 concentration with efficacy of brazikumab at Week 12, and establishment of the serum IL-22 concentration clinical cutoff to stratify participants in Stage 2 through CDAI remission and endoscopic response at Week 12.	NRI will be used for the following intercurrent events before Week 12: • discontinues treatment prematurely for any reason • takes rescue treatment or meet the rescue criteria • uses prohibited treatment	Differential approach method.
To evaluate the safety and tolerability of brazikumab in participants with CD	AEs, clinical laboratory values, vital signs, physical exams, ECGs		

All secondary and exploratory endpoints were not analysed for this study.

AE, adverse event; AP = abdominal pain; CD = Crohn's disease; CDAI = Crohn's Disease Activity Index; ECG = electrocardiogram; IL-22 = interleukin-22; LSF = loose stool frequency; NRI = non-responder imputation; PK = pharmacokinetics; SES-CD = Simple Endoscopic Score for Crohn's Disease.

Due to the study termination by the sponsor, Stage 2 was never initiated. Refer to the D5271C00001 clinical study protocol (CSP) (Amendment 5 version 6) for Stage 2 objectives and endpoints.

Study design

This was a Phase 2b/3, multicentre, randomised, double-blind, placebo- or active-controlled, parallel-group, operationally seamless, 52-week study. The study evaluated the efficacy and safety of brazikumab versus placebo in participants aged 18 to 80 years inclusive with moderately to severely active Crohn's disease (CD).

In 2020, AZ resumed full ownership of brazikumab clinical development. AstraZeneca re-evaluated the development plan, and the CSP D5271C00001 (Legacy #3150-301-008) was consequently reviewed and amended (Amendment 4 version 5). The major components of the amendment are provided below:

- **Removal of adalimumab (HUMIRA®, Abbvie, Inc) group from Stage 1**:
  - In the original protocol, adalimumab was selected as an active control for Stage 1 to provide internal evidence for assay sensitivity in preparation for Stage 2. In addition, the previous sponsor had elected to determine the biomarker (BM) cutoff for serum interleukin-22 (IL-22), for brazikumab enhanced response versus adalimumab. On review, it was deemed that the BM cutoff should be brazikumab versus placebo to ascertain a BM cut-point for optimum risk-benefit for treatment with brazikumab. Therefore, from a scientific perspective of determining the BM cutoff, the adalimumab group was not required. Given that adalimumab was not necessary for Stage 1, removing the adalimumab group also decreased participant burden by removing the double-dummy design and reducing the number of visits.
- **Replaced co-primary endpoints of endoscopic response and clinical remission at Week 12 with a single primary endpoint of Crohn's Disease Activity Index (CDAI) remission at Week 12**:
  - Endpoints and objectives were updated to reflect and align appropriately with changes to the study design and primary endpoint. The change in the primary endpoint from endoscopic response and clinical remission to CDAI remission was based on the sponsor's prior experience with the endpoint in a Phase 2a study and limited available data for patient-reported outcomes (PRO) remission. Therefore, there was a reasonable rationale for the sample size calculation with CDAI as a primary endpoint. Endoscopic response and PRO remission data were to be evaluated as secondary endpoints in this study to facilitate planning for Phase 3. Additional endpoints related to CDAI were added as a result of the change in primary endpoint.
- **Reduction of sample size:** The basis of the sample size calculation was changed:
  - From: The sample size for Stage 1 was based on the probability to choose the correct serum IL-22 concentration clinical cutoff value within a certain range, the overall

probability that Stage 2 would be triggered at the end of Stage 1, and the probability that Stage 2 would be triggered and successful (D5271C00001 CSP version 1)
- To: The sample size for Stage 1 was chosen to provide at least 80% power to detect a difference between brazikumab and placebo in the CDAI remission rate after a 12-week induction treatment period, assuming the response rates are 37% and 13%, respectively. This sample size also provided at least 80% power to detect a difference in brazikumab and placebo endoscopic response rates, assuming the response rates are 37% and 13%, respectively.

– CCI Reduced from 125 participants per brazikumab dose group to 85 participants per brazikumab dose group.
– CCI: Reduced from 125 participants to 0 participants (note: this group was removed from Stage 1 of the protocol as noted above).
– CCI Reduced from 75 to 51 participants.

This study was planned to be conducted in 2 stages: Stage 1 design allowed for the confirmatory study (Stage 2) to proceed after Stage 1, but the data from the 2 studies were to be kept distinct. The sponsor was to commence Stage 2 after all participants were randomised into Stage 1 and completed the Week 12 Treatment Period and the data from the Stage 1 primary analysis were fully evaluated.

Stage 1 was a Phase 2b study to evaluate the dose-response relationship to select intravenous (IV) brazikumab induction doses for continued development and to establish the serum IL-22 concentration clinical cutoff to stratify enrolment into Stage 2. Participants were randomised in a 5:5:3 ratio for brazikumab CCI, brazikumab CCI, and CCI and stratified by prior history of biologic use and current corticosteroid (CS) use. Stage 1 objectives and endpoints at Week 12 were to inform Stage 2 design features:

- Determine the BM cutoff value of serum IL-22 concentration.
- Confirm the number of brazikumab treatment groups for Stage 2.
- Confirm the sample size for Stage 2 (to achieve endoscopic response and clinical remission at Week 12).
- Confirm selection of PROs for Stage 2.

After Week 12, Stage 1 participants continued with their assigned study group treatments through Week 52. Participants in Stage 1 were not eligible for enrolment in Stage 2. The study was to be unblinded, and the primary analysis for the study was to be conducted after the last participant completed the Week 12 visit. AstraZeneca personnel who were directly involved with the conduct of the study, study site personnel, as well as participants remained blinded to the treatment assignment for individual participants until the completion of the study.

Stage 2 was to be a Phase 3 study to evaluate the safety and efficacy of brazikumab compared with adalimumab in participants who were BM+ (serum IL-22 concentrations at or above a pre-established cutoff) and to validate the clinical utility of serum IL-22 concentration as a predictive BM for efficacy of brazikumab in a subset of participants with CD. However, no participants were enrolled in Stage 2.

All participants in Stage 1 were centrally assigned to randomised study intervention using an interactive response technology/randomization and trial supply management.

Target subject population and sample size

Number of participants (planned and actually randomized):

Stage 1: Approximately 240 participants were planned for randomisation. This sample size included participants randomized before Amendment 4 version 5. However, given the change of the primary endpoint and that the final primary endpoint was not assessed before Amendment 4 version 5, these participants were not included in the sample size for the primary analysis (brazikumab = 170; placebo = 51). A total of 88 participants (legacy and AZ) were randomized before the study was terminated on 01 June 2023.

Stage 2: No participants were enrolled in Stage 2.

A sample size of 85 participants per brazikumab dose and 51 in the placebo group provided at least 80% power to detect a 25% difference versus placebo in the CDAI remission rate (assuming a 38% and 13% remission rate for the Brazikumab and placebo groups respectively) using continuity-corrected Mantel-Haenszel (Cochran) test of odds ratio = 1 with 2 strata using a 2-sided 0.05 level test.

Inclusion/exclusion criteria

Eligible participants capable of giving informed consent aged 18 to 80 years inclusive were to have the following disease characteristics:

- Diagnosis of ileal, ileocolonic, or colonic CD 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 other aetiologies including infectious causes, and characteristic endoscopic and/or histologic findings.
- Moderately to severely active CD, defined by a CDAI score of 220 to 450 points with an average daily CDAI LSF score ≥ 5 or average daily CDAI AP score ≥ 2.
- Evidence of active intestinal mucosal inflammation with a Simple Endoscopic Score for Crohn's Disease (SES-CD) score of at least 6 or isolated ileal disease with an SES-CD score greater than 4.
- Inadequate response or intolerance to intervention with conventional treatment (oral aminosalicylates, oral CS, azathioprine, methotrexate, or 6-mercaptopurine), or prior

biological treatment, or demonstrated CS dependence for the treatment of CD were also eligible for enrolment. For participants who had previously used biological treatment, a participant could fail up to 3 biologics that included up to 2 different mechanisms of action.

- No known history of active or latent tuberculosis (TB) without completion of an appropriate course of intervention.
- Participants with a history of using an anti-tumour necrosis factor alpha (anti-TNFα) agent for a treatment course of 1 year or longer who have discontinued a TNFα agent within 6 months prior to Screening must have obtained a chest x-ray showing no evidence of active TB within 8 weeks prior to Screening or during Screening.

Refer to the D5271C00001 CSP (Amendment 5 version 6) for additional inclusion criteria, exclusion criteria, and lifestyle considerations.

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

Brazikumab for IV administration was supplied as a CCI vial concentrate for solution for infusion. The solution contains CCI brazikumab, CCI The label-claim volume was CCI

Brazikumab for subcutaneous (SC) administration was supplied as a CCI solution for injection in a prefilled syringe. The solution contains CCI brazikumab, CCI sodium acetate, CCI sorbitol, and 0.01% (w/v) polysorbate 80; it has a pH of 5.1. The label-claim volume was CCI

Stage 1 Treatment Groups:

- Brazikumab high dose: CCI on Days 1, 29, and 57, followed by CCI CCI on Day 85 and every 4 weeks through Week 48.
- Brazikumab low dose: CCI on Days 1, 29, and 57, followed by CCI brazikumab CCI on Day 85 and every 4 weeks through Week 48.
- Adalimumab: CCI on Day 1, CCI on Day 15, and CCI beginning on Day 29 and every 2 weeks through Week 50. Note: The adalimumab group was removed in Amendment 4 version 5. Refer to the D5271C00001 CSP (Amendment 4 version 5).
- Placebo: CCI on Days 1, 29, and 57, followed by SC placebo on Day 85 and every 4 weeks through Week 48.

Stage 2 Treatment Groups: No participants were enrolled in Stage 2.

Thirty-one batches of brazikumab and 8 batches of adalimumab were used in this study

Duration of treatment

Stage 1 Study Duration: Following a Screening Period of up to 5 weeks (Screening visit 1, Screening visit 2, and Screening ileocolonoscopy), the study duration was up to 66 weeks, consisting of a 52-week Treatment Period (Induction Period up to Week 12 and Maintenance Period up to Week 52 with the last dose of study intervention at Week 48) and an 18-week post-last brazikumab/placebo dose Safety Follow-up Period. For participants who qualified and enrolled into an open label extension (OLE) study of brazikumab, the Safety Follow-up Period was not applicable.

Stage 2 Study Duration: No participants were enrolled in Stage 2.

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 analysis. No efficacy data are included due to the limited amount of data.

Due to the early termination and hence the reduced scope of analysis and reporting, the Full Analysis Set was not implemented. The Safety Analysis Set was used both for the description of the study population and the safety analysis. The Safety Analysis Set comprises all participants who received at least 1 administration of study intervention, including all participants enrolled prior to Amendment 4. Refer to the D5271C00001 CSP (Amendment 4 version 5).

The analysis of safety endpoints was summarised descriptively for the Safety Analysis Set, which includes participants who enrolled prior to and after the initiation of Amendment 4. Pre-Amendment 4 participants randomized to the adalimumab group are listed only. The other pre-Amendment 4 participants are grouped with their corresponding post-Amendment 4 dose group and included in the safety summary tables. Continuous variables were summarized by the number of participants and mean, standard deviation (SD), median, minimum, and maximum values. Categorical variables were summarized by number and percentage of participants.

Refer to the D5271C00001 CSP (Amendment 5 version 6) for definitions of analysis sets.

The final analysis was performed once all final follow-up visits were completed and included updated safety data presentations; no efficacy analyses were performed at the final analysis

Study population

A total of 322 participants were screened, 88 participants were randomised, of which 2 participants were marked as randomized prior to Amendment 4 but had no randomization

record and were not treated, and 86 participants were treated with either brazikumab CCI CCI adalimumab (CCI or placebo. Note: Stage 2 was not opened.

In the Screened Analysis Set (participants who signed the informed consent form), 86 participants (100%) started the Induction Period treatment, 57 participants (66.3%) completed the Induction Period treatment, and 2 participants (2.3%) entered the OLE study in the Induction Period. A total of 19 participants (22.1%) discontinued study CCI prior to Week 12, with 13 participants (15.1%) discontinuing due to other reason. A total of 10 participants (11.6%) discontinued study SC treatment on Week 12, with the primary reason due to other in 7 participants (8.1%). A total of 26 participants (30.2%) were withdrawn from the study prior to Week 12, with the primary reason due to the sponsor terminating the study in 18 participants (20.9%). At Week 12, 69 participants (80.2%) had an ileocolonoscopy.

A total of 56 participants started the Maintenance Period treatment, 16 participants (28.6%) completed the Maintenance Period treatment, and 18 participants (32.1%) entered the OLE study in the Maintenance Period. A total of 40 participants (71.4%) discontinued Maintenance Period treatment, with the primary reason due to other in 35 participants (62.5%). A total of 16 participants (28.6%) completed Week 52 and 46 participants (82.1%) were withdrawn from the study prior to Week 52, with the primary reason due to the sponsor terminating the study in 39 participants (69.9%). Note: A total of 6 participants entered the Maintenance Period treatment, but study drug was discontinued during the Induction Period, leading to a difference in the number of participants who discontinued study drug (40 participants) and withdrew from the study in the Maintenance period (46 participants).

A total of 35 participants started the safety follow-up period, 14 participants (40.0%) completed the safety follow-up period, and 20 participants (57.1%) prematurely discontinued during the safety follow-up period, with the primary reason due to the sponsor terminating the study in 17 participants (48.6%). One participant had a disposition record indicating that he entered the safety follow-up period, but no records in the safety follow-up data.

In the Safety Analysis set (N=84; not including the 2 participants in the adalimumab group), a total of 46 participants (54.8%) were aged < 40 years, 32 participants (38.1%) were between the ages of 40 to 65 years, and 6 participants (7.1%) were aged > 65 years; the mean (SD) age at screening was 38.7 (16.64) years. Overall, 53 participants (63.1%) were male, 64 participants (76.2%) were white, and 76 participants (90.5%) were not Hispanic or Latino. The majority of participants (79.8%) were from non-US regions.

The mean (SD) duration of Crohn's disease was 9.063 (7.893) years; 20 participants (23.8%) currently used immunomodulators, with 18 participants (21.4%) using azathioprine, and 2 participants (2.4%) using methotrexate. A total of 51, participants (60.7%) had no extraintestinal manifestations, and 38 participants (45.2%) had a baseline disease location in the ileocolonic region. All (98.8%) but 1 participant had no prior treatment of JAK inhibitors,

44 participants (52.4%) had no prior biologic treatment, and 53 participants (63.1%) had no current use of corticosteroids. The mean (SD) C-reactive protein level was 15.049 mg/L (18.457), and the mean (SD) faecal calprotectin level was 1799.6 µg/g (3378.47).

The baseline CDAI score was 220 to 450 (moderate to severe disease) in 69 participants (82.1%) and > 450 (very severe disease) in 2 participants (2.4%). The total mean (SD) SES-CD score was 13.3 (6.66): rectum only 2.2 (2.71), left colon only 2.4 (2.76), transverse colon only 1.8 (2.34), right colon only 3.2 (2.41), and ileum only 4.5 (3.20).

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

Of the 66 participants in the brazikumab total group and the 18 participants in the placebo group, 37 participants (56.1%) and 13 participants (72.2%), respectively, reported adverse events (AEs). Serious adverse events (SAEs) were reported for 6 participants (9.1%) in the brazikumab total group and 2 participants (11.1%) in the placebo group; no SAEs were reported with an outcome of death, and there were no AEs leading to discontinuation of the investigational product. Four participants (6.1%) in the brazikumab total group and 1 participant (5.6%) in the placebo group reported a possibly related AE. No participants reported a possibly related SAE.

Of the 66 participants in the brazikumab total group and the 18 participants in the placebo group, the most commonly reported AEs by preferred term (> 10% in any group) were bronchitis (brazikumab total: no participants; placebo: 2 participants [11.1%]), COVID-19 (brazikumab total: 1 participant [1.5%]; placebo: 3 participants [16.7%]); nasopharyngitis (brazikumab total: 7 participants [10.6%]; placebo: 2 participants [11.1%]) anaemia (brazikumab total: no participants; placebo: 2 participants [11.1%]), and aphthous ulcer (brazikumab total: 1 participant [1.5%]; placebo: 2 participants [11.1%].

A total of 6 participants (9.1%) in the brazikumab total group reported SAEs of herpes zoster, pneumonia, atrial fibrillation, anal fistula, Crohn’s disease, oesophageal ulcer, and small intestine obstruction (1 participant each). A total of 2 participants (11.1%) in the placebo group reported SAEs of anaemia, functional gastrointestinal disorder, gastritis, gastrointestinal haemorrhage, and intestinal obstruction (1 participant each).

A total of 2 participants (3.0%) in the brazikumab total group reported AESIs of herpes zoster, hordeolum, injection site erythema, and injection site pruritus (1 participant each). Note: The AESI of hordeolum was initially categorized as an AESI pre-Amendment 4, but not an AESI per Amendment 4 and later. No AESIs were reported in the placebo group.

Conclusion(s)

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