Clinical Study Report

1 TITLE PAGE

An Open-label Study to Evaluate the Pharmacokinetics, Safety and Tolerability of a Single Dose of Brazikumab Administered by IV Infusion and SC Injection in Healthy Chinese and White Participants

Investigational Medicinal Products:	Test Product:	Brazikumab
	Reference Product:	None
Indication Studied:	Inflammatory bowel disease	
Parexel Study Number:	PXL254962	
Sponsor Study Number:	D5271C00004	
EudraCT Number:	111773	
Development Phase:	Phase I	
Sponsor:	AstraZeneca AB 151 85 Södertälje Sweden	
Investigator Name and Address:	Esther Yoon, MD Parexel Early Phase Clinical Unit Los Angeles 1560 E. Chevy Chase Drive, Suite 140 Glendale, CA 91206 USA	
Study Duration:	11 Oct 2021 (first participant first visit) to 13 Oct 2022 (last participant last visit)	
Version and Date of Report:	Final 1.0, 11 May 2023	

This study was conducted in compliance with International Council for Harmonisation Good Clinical Practice guidelines. The essential documentation related to this study has been retained by relevant parties.

2 SYNOPSIS

Title of Study:	An Open-label Study to Evaluate the Pharmacokinetics, Safety and Tolerability of a Single Dose of Brazikumab Administered by IV Infusion and SC Injection in Healthy Chinese and White Participants	
Study Numbers:	Parexel Study No.: PXL254962 Sponsor Study No.: D5271C00004	
Investigational Medicinal Products:	Test Product: Brazikumab Reference Product: None	
Indication Studied:	Inflammatory bowel disease	
Development Phase:	Phase 1	
Sponsor:	AstraZeneca AB 151 85 Södertälje Sweden	
Principal Investigator:	Esther Yoon, MD	
Study Centre:	Parexel Early Phase Clinical Unit – Los Angeles, USA	
Publication:	None	
Study Duration:	First participant first visit: 11 Oct 2021	Last participant last visit: 12 Oct 2022

Study Objectives:

Primary objective:

- To evaluate the pharmacokinetics (PK) of brazikumab in healthy Chinese and White participants.

Secondary objectives:

- To evaluate the safety and tolerability of brazikumab in healthy Chinese and White participants.
- To evaluate additional PK parameters of brazikumab in healthy Chinese and White participants.
- To evaluate the immunogenicity of brazikumab.

Study Design:

This was a Phase I, single-centre, open-label, parallel-group, single dose study in 32 healthy male and female Chinese participants and 16 healthy male and female White participants aged 18 to 55 years. The study consisted of a Screening period (Day -28 to Day -2), the study intervention period (including admission [Day -1], in-house phase [Days -1 to 4], outpatient visits from Day 8 through Day 133, and an End of Study (EOS) Visit (on or within 7 days after Day 133, or at Early Discontinuation [Termination] Visit).

Study Participants:

Planned for Inclusion:	**Enrolled:**	**Completed Study:**
48 participants	48 participants	47 participants

Main Inclusion Criteria:

This study was conducted in healthy Chinese participants (born in greater China with 2 Chinese biological parents and 4 Chinese grandparents, who were not living outside of greater China for more than 10 years) and White (of European or White Latin American descent) male and female participants aged 18 to 55 years (inclusive) who had a body mass index (BMI) ≥ 18 kg/m^2 and ≤ 30 kg/m^2.

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Investigational Medicinal Product(s):			
Formulation(s):	**Strength/Concentrations:**	**Batch/Manufacturing Lot Number(s):**	**Expiry Date(s):**
CCI mM acetate, CCI % Sorbitol, CCI % w/v polysorbate 80, pH CCI	Brazikumab Solution for injection CCI mg/mL	CCI	June 2022
CCI mM acetate, CCI % Sorbitol, CCI % w/v polysorbate 80, pH CCI	Brazikumab Solution for injection CCI mg/mL (CCI mg/vial)	CCI	August 2022

Duration of Treatment:

Each dose group received a single dose of brazikumab (CCI mg or CCI mg intravenous [IV]; or CCI mg or CCI mg subcutaneous [SC]) in parallel on Day 1.

Treatment Compliance:

When participants were dosed at the study centre, they received the investigational medicinal product (IMP) directly from the investigator or designee, under medical supervision. The date of the IMP administration, start and end time, dose and unit, total amount administered, route of administration, and any deviations in dosing were captured in the source documents and recorded in the electronic case report form (eCRF). The dose of the IMP and study participant identification were confirmed at the time of dosing by a member of the study centre staff other than the person administering the IMP. The IMP compliance was assumed to be 100% when dosing has been recorded in the eCRF. The study centre kept an accurate IMP disposition record.

Criteria for Evaluation:

Pharmacokinetic Parameters:

The following PK parameters were determined for brazikumab, using serum concentrations after IV administration and SC administration:

- Primary PK parameters (brazikumab): Cmax, AUCinf, AUC(0-28d) and AUClast
- Secondary PK parameters (brazikumab): Dose-normalised Cmax, dose-normalised AUCinf, dose-normalised AUC(0-28d), dose-normalised AUClast, tmax, λz, t½λz, CL/F, Vz/F, CL, Vz

Safety Variables:

- Adverse events (AEs)
- Clinical laboratory values
- Vital signs
- Electrocardiograms (ECGs)

Immunogenicity Parameters:

- Incidence of anti-drug antibodies (ADAs) to brazikumab in serum.

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Statistical Methods:

Determination of Sample Size:

The study was descriptive; thus, no power calculations were performed. A total of 48 participants, (32 healthy male and female Chinese participants and 16 healthy male and female White participants) were planned to be included in this study, allocating 8 participants per dose group. Groups 1, 2, 3, and 4 were planned to each consist of 8 healthy Chinese participants and Groups 5 and 6 to each consist of 8 healthy White participants. This number of participants was considered sufficient to provide reliable estimates of the PK parameters, and the relative comparison of the treatments.

Presentation and Analysis of Pharmacokinetic Data:

The serum concentrations and PK parameters of brazikumab were listed and presented in tabular and graphical form, as appropriate, according to the most recent version of the AstraZeneca Corporate Clinical Study Report High Level Document reporting standards. This includes applicable descriptive statistics, handling of individual concentrations below the lower limit of quantification for listings, descriptive statistics and figures, and precision and rounding rules for concentrations and PK parameter data.

The primary PK outcome variables, AUCinf, AUClast, AUC(0-28d) and Cmax of brazikumab, were analysed separately using linear-effects model using natural logarithm of AUCinf, AUClast, AUC(0-28d) and Cmax as the response variables and with race as a fixed effect. For each primary PK variable, results were transformed back from the logarithmic scale to present least-squares geometric mean (GM) together with 2-sided 95% confidence intervals (CI) for brazikumab in Chinese and White participants for IV administration and for SC administration, as well as ratios of the GM (Chinese to White), together with 2-sided 90% CI were estimated.

Presentation and Analysis of Safety Data:

The safety population was defined as all participants who received at least 1 dose of brazikumab and for whom any safety postdose data were available. All safety data (scheduled and unscheduled) were presented in the data listings. Continuous variables were summarised using descriptive statistics (n, mean, standard deviation [SD], minimum, median, and maximum) by treatment/dose group. Categorical variables were summarised in frequency tables (frequency and proportion) by treatment/dose group. The analysis of the safety variables was based on the Safety Analysis Set.

Adverse events were summarised by preferred term (PT) and System Organ Class (SOC) using Medical Dictionary for Regulatory Activities (MedDRA) vocabulary. Furthermore, listings of serious adverse events (SAEs) were provided. The number of participants who had any AEs, including SAEs, were summarised. Adverse events that occurred before dosing were reported separately.

Tabulations and listings of data for vital signs, clinical laboratory tests, and ECGs, were presented. Any new or aggravated clinically relevant abnormal medical physical examination finding compared to the baseline assessment was reported as an AE. Data was summarised for the observed values at each scheduled assessment, together with the corresponding changes (and/or percentage change) from the baseline when baseline was defined. Clinical laboratory data was reported in International System of Units (SI) units. Out of range values for safety laboratory and ECG were flagged in individual listings as well as summarised descriptively using agreed reference ranges (eg, laboratory ranges).

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Presentation and Analysis of Immunogenicity Data:

Serum samples to measure the presence of ADAs against brazikumab were collected according to the schedule of assessments. The prevalence and incidence of ADAs were reported by treatment group on the Safety Analysis Set. The ADA data was summarised using descriptive statistics at each timepoint by treatment group. Samples confirmed positive for ADA were to be further tested, including possible assessments of neutralising antibodies. The potential effects of immunogenicity on PK of brazikumab may have been evaluated, if appropriate.

Protocol Deviations:

There were no important protocol deviations reported for this study.

Pharmacokinetic Results:

Brazikumab PK after IV administration was characterised by median tmax of approximately 1.5 hours for White participants and 2 to 3 hours for Chinese participants, GM t½λz of approximately 560 hours (23 days) for Chinese participants and approximately 680 hours (28 days) for White participants, and quantifiable concentrations for all participants through 3168 hours (132 days) postdose. Exposure in terms of Cmax and AUCs (AUC(0-28d), AUClast and AUCinf) was in the same range for Chinese and White participants by comparison to dose-normalised parameters, with variability for all PK parameters less than 30%, except for Chinese participants that received CCI mg (IV) of brazikumab, where the Cmax variability was higher (approximately 50%). Cmax variability was low (below 30%) in the sensitivity analysis after the exclusion of the participant E0001036, whose PK profile showed slow absorption untypical of IV administration. Cmax is a parameter generally known to display high variability; this is regarded to be without clinical relevance for brazikumab. The GM ratios of brazikumab between Chinese and White participants following single dose IV administration were approximately 94%, 95%, 108% and 102% for AUCinf, AUClast, AUC(0-28d) and Cmax, respectively.

Brazikumab PK after SC administration was characterised by median tmax of approximately 120 hours (5 days) for White and Chinese participants, GM t½λz between approximately 640 and 720 hours (27 and 30 days) for Chinese participants and similar for White participants (approximately 730 hours [30 days]), and concentrations were quantifiable through 3168 hours (132 days) postdose for all Chinese and White participants that completed the schedule of collection (1 White participant had samples collected through 479.5 hours [20 days] only). Exposure in terms of Cmax and AUCs (AUC(0-28d), AUClast and AUCinf) was in the same range for Chinese and White participants by comparison to dose-normalised parameters, with variability for all PK parameters between 15% and 50%. The GM ratios of brazikumab between Chinese and White participants following single dose SC administration were approximately 76%, 89%, 88% and 97% for AUCinf, AUClast, AUC(0-28d) and Cmax, respectively.

Safety Results:

There were no SAEs, deaths or AEs leading to discontinuation for this study. Twenty-three (47.9%) participants reported AEs throughout the study. Of the 23, 12 (37.5%) participants were Chinese and 11 (68.8%) participants were White. A total of 8 (16.7%) participants reported AEs that were considered "possibly related" to the IMP (4 Chinese and 4 White participants).

There were no AEs of severe intensity recorded during this study. Most participants had AEs that were considered to be mild in intensity (20 out of 23 participants who reported AEs) and 3 participants had AEs that were considered to be moderate in intensity by the investigator. Overall, 2 participants from the White group and 1 participant from the Chinese group experienced AEs of moderate intensity. All 12 of the "possibly related" AEs were considered to be mild in severity by the investigator.

A total of 59 AEs were recorded for participants taking part in this study, of which 28 AEs were recorded for Chinese participants and 31 were recorded for White participants.

- Overall, by SOC the highest number of AEs (16) were recorded for "gastrointestinal disorders", followed by 10 AEs per SOC each for "nervous system disorders" and "general disorders and administration site conditions".
- Overall, by PT the highest number of AEs (5) were recorded for "headache", followed by 4 AEs for "abdominal pain", and 2 AEs each for "insomnia", "dizziness", "vision blurred", "abdominal pain upper", "constipation", "diarrhoea", "rash", "injection site pain", "weight increased" and "skin abrasion".

Twelve AEs were considered to be "possibly related" to the IMP, of which 6 AEs each were recorded for the Chinese and White participant groups.

- While the SC groups did not exceed CCI mg, there were more AEs reported for SC administration (overall 10 AEs) that were considered to be "possibly related" to the IMP, than the higher dose groups that received IV administration (overall 2 AEs). Furthermore, there were more AEs reported for the higher dose of CCI mg SC that were considered to be "possibly related" to the IMP, than the lower dose of CCI mg SC administration.
- Overall, by SOC "gastrointestinal disorders" had the highest number of participants (3 [6.3%] participants with 1 AE per PT) with recorded "possibly related" AEs which included 1 event of each PTs of abdominal discomfort, abdominal pain upper, constipation, and diarrhoea. This was followed by 2 (4.2%) participants per SOC each for "nervous system disorders" (which included 1 event each per PT for lethargy and somnolence) and "general disorders and administration site conditions" (which included 2 events for the PT of injection site pain).
- Overall, the highest number of participants with recorded "possibly related" AEs by SOC for Chinese participants were "gastrointestinal disorders" (3 [6.3%] participants) and for White participants were "general disorders and administration site conditions" (2 [4.2%] participants).
- The highest number of participants with recorded "possibly related" AEs by PT was for "injection site pain". This was recorded for 2 White (4.2%) participants overall. Both (12.5%) participants were from the CCI mg SC injection group.

There were no clinically relevant trends or significant values observed for any of the laboratory parameters.

No clinically relevant trends or differences were observed for vital signs overall or individually for the Chinese or White participant groups (blood pressure, respiratory rate, pulse, temperature, and weight).

While there were abnormalities for some ECG readings, none were considered clinically significant, and no ECG-related AEs were recorded during the study. No clinically relevant trends or differences were observed for ECGs overall or individually for the Chinese or White participant groups.

The Coronavirus Disease 2019 (COVID-19) pandemic did not impact the overall safety results of this.

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Immunogenicity Results:

- No participants had a positive ADA result at baseline.
- Throughout the study, at relevant visits (Days 29, 64, 106 and 133), there were no positive ADA results.
- Overall, 47 participants out of 48 had follow-up data for ADA results. One participant withdrew due to participant decision.
- The IMP was not found to elicit an immune response or reaction when given as a single dose (CCI, CCI, or CCI mg) under the described study conditions and observation time.

Discussion and Conclusion:

- Single doses of brazikumab, CCI and CCI mg administered SC and CCI and CCI mg administered IV, showed an acceptable safety profile and were well tolerated in the studied population. There was no indication that there was any difference in the safety and tolerability profile between Chinese and White participants.
- Throughout the study, at relevant visits (Days 29, 64, 106 and 133), there were no positive ADA results. The IMP was not found to elicit an immune response or reaction when given as a single dose (CCI, CCI or CCI mg) under the described study conditions and observation time.
- Following a single dose with IV administration, GM serum exposure (Cmax and AUC) was similar between Chinese and White participants.
- Following a single dose with SC administration, GM serum exposure (Cmax and AUC) was observed to be numerically lower in Chinese compared to White participants. The numerical differences for Cmax, AUClast and AUC(0-28d) between Chinese and White participants were found to be minimal (geometric mean ratio [GMR] range 88-97%). The lower GMR observed for AUCinf (GMR 76%, 90% CI 59%-98%) was not considered relevant when accounting for the variability.
- The COVID-19 pandemic was not judged to meaningfully impact the overall quality of the study, including the conduct, data, and interpretation of results.

Version and Date of Report: 1.0, dated 11 May 2023

This study was conducted in compliance with International Council for Harmonisation Good Clinical Practice guidelines.