2. SYNOPSIS

Name of Sponsor/Company: BeiGene, Ltd. c/o BeiGene USA, Inc.	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: BGB-23339		
Name of Active Ingredient: BGB-23339		
Title of Study: A First-in-Human, Single- and Multiple-Ascending Dose and Food-Effect Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of BGB-23339 in Healthy Subjects		
Principal Investigators: [redacted] **Investigators:** A list of investigators is presented in Appendix 16.1.4.		
Study center(s): The study was conducted at 3 study centers in Australia and China.		
Publications (reference): None at the time of writing this report		
Studied period (years): Date first subject dosed: 15 November 2021 Date last subject completed: 26 December 2022		**Phase of development:** I

Objectives:

Primary:

- To investigate the safety and tolerability of BGB-23339 administered orally as a single dose and as multiple doses in healthy subjects

Secondary:

- To evaluate the pharmacokinetics (PK) of BGB-23339 and its metabolite BGB-25808 when BGB-23339 is administered orally as a single dose and as multiple doses in healthy subjects
- To evaluate the effect of food on the PK of BGB-23339 and its metabolite BGB-25808 when BGB-23339 is administered orally as a single dose in healthy subjects

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

Methodology:

This was a Phase 1, first-in-human (FIH), randomized, double-blind, placebo-controlled study to investigate the safety, tolerability, and PK of BGB-23339 as a single dose and multiple doses and to assess the food effect of BGB-23339 after a single dose, in healthy subjects. This study comprised 4 parts: Part A was a single ascending dose (SAD) study to evaluate the safety, tolerability, and PK profile of BGB-23339 after a single dose; Part B was a multiple ascending dose (MAD) study to assess the safety, tolerability, and PK and pharmacodynamic profile of BGB-23339 after multiple doses; Part C was a MAD study to evaluate the safety, tolerability, and PK and pharmacodynamic profile of BGB-23339 in healthy Chinese adults; and Part D was an open-label, randomized, three-period, crossover design study to evaluate the effect of food on BGB-23339 after a single dose. The study planned to enroll up to 115 healthy subjects and be conducted at approximately 2 centers in Australia and China.

After being confirmed as eligible, subjects were sequentially enrolled to the 4 parts.

Part A

On the morning of Day 1, a single dose of BGB-23339 or matching placebo was administered after an overnight fasting (≥ 8 hours). Subjects were asked to remain at the study site for safety monitoring until the completion of study evaluations. Then they were discharged on Day 8 if there were no safety concerns as determined by the investigator. The subjects were contacted by phone for a safety follow-up on Day 31 (30 days after the last dose of the study drug). The duration of subject participation in Part A was approximately 9 weeks.

Part B and C

Subjects were asked to remain at the study site until the 72-hour postdose PK samples of the last dose were collected, and then they were discharged. They were required to return to the site for a Safety Follow-up Visit 7 days after the last dose of the study drug. They were also contacted for a safety follow-up 30 days after the last dose by phone. The duration of subject participation in Part B was approximately 11 weeks.

Part D

Each subject received 3 single doses of BGB-23339, and there was a 7-day washout period between the treatments. Each dose was administered after the subject had fasted for ≥ 8 hours, followed by a high-fat or low-fat meal, or no breakfast. The subjects were asked to stay at the site until 72-hour postdose PK samples of the last dose were collected. The duration of subject participation in Part D was approximately 11 weeks.

Number of subjects (planned and analyzed):

Part A single ascending dose study: 40 subjects planned; 40 subjects analyzed

Part B multiple ascending dose study: 32 subjects planned; 25 subjects analyzed

Part C Chinese substudy: 24 subjects planned 12 subjects analyzed

Part D food-effect study: 15 subject plann d; 15 subjects analyzed

Diagnosis and main criteria for inclusion:

Subjects included in this study were adults between 18 and 55 years of age for Parts A, B, and D, and between 18 and 45 years of age for Part C at the time of informed consent and in good general health

Test product, dose and mode of administration, batch number:

BGB-23339: oral administration

Part A: 10 mg, 30 mg, 100 mg, 300 mg, or 750 mg

Part B: 30 mg, 100 mg, or 300 mg, once daily for 10 days

Part C: 300 mg once daily for 10 days

Part D: 3 single doses of 100 mg

Refer to Appendix 16.1.6 for batch numbers.

Duration of treatment:

Part A: A single dose. The duration of subject participation was approximately 9 weeks.

Part B and C: One single dose daily for continued 10 days. The duration of subject participation was approximately 11 weeks.

Part D: One single dose daily at 3 days with two 7-day washout periods. The duration of subject participation was approximately 11 weeks.

Reference therapy, dose and mode of administration, batch number:

Matching placebo.

The numbers of the batches used for this study are provided in Appendix 16.1.6.

Criteria for evaluation:

Study-specific assessments and procedures were performed as outlined in the Schedule of Assessments in the BGB-23339-101 Protocol.

Pharmacokinetics:

The Pharmacokinetics endpoints were as follows:

- Area under the plasma concentration-time curve from time zero to last quantifiable time (AUC_{last}) for Parts A, B, C, and D
- Area under the plasma concentration-time curve from time zero to 24 hours postdose (AUC_{0-24}) for Part D only
- Area under the plasma concentration-time curve from time zero to end of dosing interval (AUC_{tau}) for Parts A, B, C, and D
- Area under the plasma concentration-time curve from time zero to infinity (AUC_{inf}) for Parts A, B, C, and D
- Maximum observed plasma concentration (C_{max}) for Parts A, B, C, and D
- Time to maximum plasma concentration (T_{max}) for Parts A, B, C, and D
- Trough plasma concentration (C_{trough}) for Parts A, B, and C
- Apparent terminal elimination half-life ($t_{½}$) for Parts A, B, C, and D (in fed and fasted states for BGB-23339)
- Apparent systemic clearance (CL/F) for Parts A, B, and C
- Apparent volume of distribution (Vz/F) for Parts A, B, and C
- Accumulation ratios, and metabolite to parent ratio for BGB-23339 and its metabolite BGB-25808 as appropriate for Parts A, B, C, and D

Safety:

The Safety endpoints were as follows:

- Number of Participants Experiencing Adverse Events
- Number of participants with clinically significant changes from baseline in vital signs (blood pressure and pulse rate)
- Number of participants with clinically significant changes from baseline in clinical laboratory values (hematology, clinical chemistry, coagulation, and urinalysis)

Statistical methods:

Analysis Sets

The Safety Analysis Set included all subjects who received ≥ 1 dose of study drug.

The PK Analysis Set included all subjects who received ≥ 1 dose of study drug and had any measurable concentration of study drug. Where subjects experienced issues that affected exposure to the study drug (emesis, dosing errors, etc), data were reviewed by the study pharmacokineticist and evaluated for exclusion from the PK Analysis Set on a case-by-case basis. All subjects excluded from the PK Analysis Set will be documented in the data listings.

The Pharmacodynamic Analysis Set included subjects in Part B and Part C who received ≥ 1 dose of study drug and had any estimable pharmacodynamics parameter.

Safety Analysis

All safety analyses were performed based on the Safety Analysis Set. Descriptive statistics were used to analyze all safety data. Detailed methods of calculation of Safety Analysis could be found be in statistical analysis plan (SAP) provided in Appendix 16.1.9.

Pharmacokinetic Analysis

PK parameters will be determined where possible from the plasma and/or [redacted] concentrations of BGB-23339 and its metabolite BGB-25808 with noncompartmental methods using Phoenix™ WinNonlin® (Version 7.0 or higher). [redacted] provided in Appendix 16.1.9.

[redacted]

SUMMARY – CONCLUSIONS

PHARMACOKINETICS RESULTS:

The PK profile of BGB-23339 after single oral administration in healthy subjects was found to be rapidly absorbed and eliminated in plasma with a geometric mean terminal half-life ($T_{1/2}$) ranging from 7.1 to 18.1 hours. The longer half-life observed from 30 mg to 750 mg could be due to better characterization of the terminal phase. However, the less-than-dose-proportional increase in the C_{max} and AUC_{inf} between 10 mg and 750 mg could be due to the poor water solubility of BGB-23339 (Section 11.4.4.1.1).

A similar profile was seen from 30 mg to 300 mg once daily dosing on Day 1, with low accumulation ratios at steady state (eg, 0.8 to 1.6 for C_{max} and 1.1 to 1.5 for AUC_{tau} in Part B). The exposure in

healthy Chinese subjects appeared to be trending higher but should be interpreted with caution due to the limited number of subjects and moderate-to-high inter-subject variability (Section 11.4.4.1.2).

Co-administration of BGB-23339 with a low-fat meal or a high-fat meal resulted in 2.1 to 2.8-fold increase in AUC_{inf} and 4.2 to 4.7-fold increases in C_{max}, respectively, compared to the fasted status. Peak BGB-23339 concentrations were delayed by approximately 3 hours under high-fat fed status compared to the observed t_{max} under fasted or low-fat fed status (Section 11.4.4.1.3).

[redacted]

The metabolite-to-parent ratio indicated that the proportion of BGB-23339 converted to metabolite BGB-25808 was broadly similar at the dose range studied, with a geometric mean metabolite to parent ratios (MPR) of 0.1 to 0.2. The exposure to metabolite BGB-25808 under fed status increased relative to the fasted status, which is consistent with the food effect on parent compound, BGB-23339 (Section 11.4.4.1.5).

PHARMACODYNAMICS RESULTS

[redacted]

SAFETY RESULTS:

Across the single and multiple dose levels, BGB-23339 demonstrated a favorable safety and tolerability profile in subjects during dose escalation. No subjects who received BGB-23339 or placebo experienced ≥ Grade 3, serious treatment-emergent adverse events, or treatment-emergent adverse events leading to death or dose interruption. No subjects were reported to have treatment-related adverse events of ≥ Grade 3, serious. Additionally, no treatment-related adverse events leading to death, treatment discontinuation, or dose interruption were observed among the enrolled subjects (Section 12.2.1). Only 1 subject in Part B who received BGB-23339 experienced a treatment-emergent adverse event that led to treatment discontinuation due to the acquisition of COVID-19.

The number of subjects who received BGB-23339 or placebo experiencing any treatment-emergent adverse events was 17 subjects (42.5%) in Part A, 14 subjects (56.0%) in Part B, and 6 subjects (50.0%) in Part C. Combining Part A, Part B, and Part C of this study, the percentages of treatment-emergent adverse events reported in placebo and BGB-23339 were comparable. The most commonly reported treatment-emergent adverse events (by Preferred Term in ≥ 2 subjects) in subjects receiving BGB-23339 included headache, nausea, abdominal pain, dermatitis contact, musculoskeletal chest pain, and oropharyngeal pain (Section 12.2.2.1).

In Part D, 3 subjects (20.0%) experienced a treatment-emergent adverse event. No subjects experienced ≥ Grade 3 or serious treatment-emergent adverse events, or treatment-emergent adverse events led to death, treatment discontinuation, or dose interruption. Only 1 subject (6.7%) experienced a treatment-related treatment-emergent adverse event (Section 12.2.1.1.4 and Section 12.2.2.1.4).

CONCLUSION:

- This was the first-in-human study of BGB-23339, the dose range selected for investigation in this trial was expected to provide a broad range of exposures and target engagement.
- In healthy subjects, oral administration of BGB-23339 demonstrates a favorable safety profile and well-tolerated treatment during the study. The adverse events are often mild, self-limiting, or manageable with supportive therapy.
- No serious treatment-emergent adverse event was observed at the highest dose level of single dose at 750 mg or multiple doses at 300 mg once daily for 10 days.
- [redacted]
- The PK and pharmacodynamic profiles BGB-23339 support further clinical development of BGB-23339 and suggest the potential for once-daily administration.
- No major differences in the PK profiles of BGB-23339 were observed between healthy Chinese and healthy Non-Chinese subjects following 300 mg QD dosing, given the high inter-subject variability and limited sample size.
- Co-administration of either a low-fat meal or a high-fat meal with BGB-23339 at 100 mg could increase the PK exposure, as compared to the fasted state in healthy subjects.

Date of the report:

30 May 2023