BGB-16673, a Bruton Tyrosine Kinase Degrader, Has Low Risk of CYP3A-Mediated Drug-Drug Interaction: Phase 1 Absorption, Metabolism, and Excretion and Drug-Drug Interaction Study Results

PS1711

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CONCLUSIONS

- Human AME (study 106) results show that BGB-16673 is eliminated predominantly through intestinal or biliary excretion, with fecal recovery accounting for 88.5% of administered radioactivity and negligible renal or hepatic metabolism contribution
- Parent BGB-16673 is the predominant circulating component in plasma, supporting parent-dominant systemic exposure despite the presence of low-abundance metabolites
- The fecal-predominant recovery, negligible urinary elimination, and parent-dominant plasma profile from the AME study are consistent with the minimal effect of both strong CYP3A induction and strong CYP3A inhibition on BGB-16673 exposure in study 105
- The combined study 105 and study 106 findings indicate that human systemic disposition is not meaningfully driven by CYP3A-mediated oxidative clearance, despite an in vitro CYP3A metabolism signal
- These findings collectively indicate a low risk of clinically relevant CYP3A-mediated DDIs and support greater dosing flexibility for BGB-16673 than is typical for currently available BTK inhibitors

INTRODUCTION

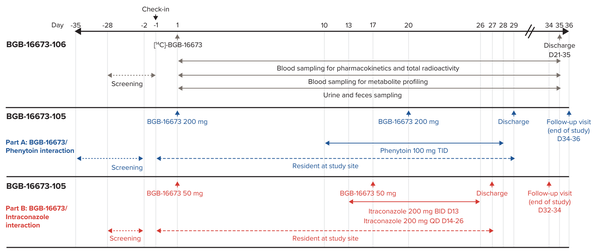
- BGB-16673 is a potential first-in-class oral Bruton tyrosine kinase (BTK) degrader that tags BTK for degradation through the cell's proteasome pathway, leading to tumor regression[1]
- Real-world data indicate that cytochrome P450 3A (CYP3A) inhibitors are frequently used in patients with B-cell malignancies, including chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), with reported use in patients with CLL/SLL ranging from 16.5% to 62.9%[2,3]
  - Many antifungal medications, particularly azoles, strongly inhibit CYP3A4, which can affect the metabolism of coadministered medications
- Currently available BTK inhibitors are primarily metabolized by CYP3A and often require dose modification or caution when coadministered with CYP3A modulators because of exposure changes[4,5]
- Nonclinical data suggested CYP3A4-mediated in vitro metabolism of BGB-16673, with low microsomal turnover, predominant fecal excretion in animals, and no CYP3A inhibition or induction[6]
- To assess whether BGB-16673 demonstrates a clinical CYP3A-mediated drug-drug interaction (DDI) profile comparable to that of currently available BTK inhibitors, two clinical studies were conducted:
  - A human absorption, metabolism, and excretion (AME) study (BGB-16673-106)
  - A fixed-sequence DDI study evaluating strong CYP3A induction with phenytoin and strong CYP3A inhibition with itraconazole (BGB-16673-105)

METHODS

Study Overview

- BGB-16673-106 (NCT06776679) is a phase 1, open-label radiolabeled AME study in healthy male participants who received a single oral dose of 200 mg [^{14}C]-BGB-16673 containing approximately 200 µCi (**Figure 1**)
- BGB-16673-105 (NCT06906809) is a phase 1, open-label, fixed-sequence crossover study in healthy participants designed to evaluate the effect of strong CYP3A induction and inhibition on the pharmacokinetics (PK) of BGB-16673 (**Figure 1**)
  - Part A evaluated phenytoin as a strong CYP3A inducer; participants received a single dose of BGB-16673 (200 mg) alone and in combination with phenytoin (100 mg) three times daily
  - Part B evaluated itraconazole as a strong CYP3A inhibitor; participants received a single dose of BGB-16673 (50 mg) alone and in combination with itraconazole (200 mg) administered orally twice on day 13 and once daily on days 14-26
- In both studies, BGB-16673 was administered in the fed state and included intensive serial PK sampling; study 106 also collected urine and feces for mass balance, excretion, and metabolite profiling

Figure 1. Study Design



Abbreviations: BID, twice daily; D, day; QD, once daily; TID, three times daily.

Participants, Endpoints, and Assessments

- The primary objectives of study 106 were to characterize routes and rates of elimination, mass balance, PK of parent drug and total radioactivity, and metabolite profiles in plasma and excreta
- The primary PK parameters of study 105 included area under the plasma concentration-time curve (AUC)$_{0\text{-last}}$, AUC$_{0\text{-}\infty}$, and maximum observed plasma concentration (C_{max}) in part A and AUC$_{0\text{-last}}$ plus C_{max} in part B
  - Secondary endpoints included time to maximum plasma concentration (T_{max}), terminal elimination half-life, apparent oral clearance, and apparent volume of distribution during terminal phase
- Safety assessments across both studies included treatment-emergent adverse events (TEAEs), laboratory tests, vital signs, electrocardiograms, and physical examinations

RESULTS

Study 106: Human Mass Balance

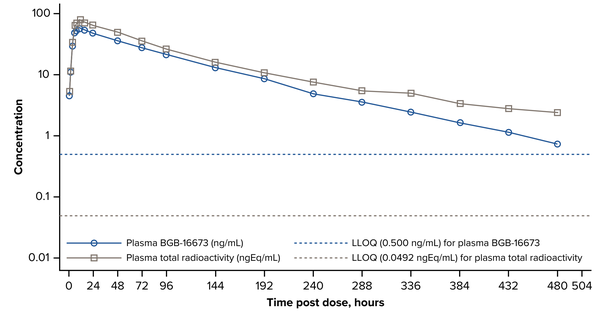
- Eight healthy male participants were dosed; baseline characteristics are shown in **Table 1** (age range, 26-47 years; mean body mass index, 25.5 kg/m^2)
- After a single 200-mg oral dose of [^{14}C]-BGB-16673, overall arithmetic mean recovery of total radioactivity in urine and feces combined was 88.6% through 816 hours post dose (**Figure 2**)
- Fecal excretion was the predominant route of elimination, with 88.5% of total radioactivity recovered in feces and only 0.07% recovered in urine (**Figure 3**)
  - Most of the administered radioactivity recovered in feces was observed between 0 and 72 hours post dose, and together with metabolic profiling, support rapid biliary and/or intestinal elimination of drug-related material into feces

Table 1. Baseline Patient Characteristics

Characteristic	Study 106 AME (N=8)	Study 105 Part A: Phenytoin (n=19)	Study 105 Part B: Itraconazole (n=18)
Age, mean (SD), years	33.8 (7.8)	41.4 (9.7)	38.9 (12.8)
Sex, n (%)			
Male	8 (100)	17 (89.5)	15 (83.3)
Female	0	2 (10.5)	3 (16.7)
Height, mean (SD), cm	176.7 (6.5)	173.72 (10.4)	174.6 (10.5)
Body weight, mean (SD), kg	79.4 (9.3)	84.8 (12.7)	83.9 (14.5)
BMI, mean (SD), kg/m^2	25.5 (2.9)	28.0 (2.4)	27.4 (3.2)

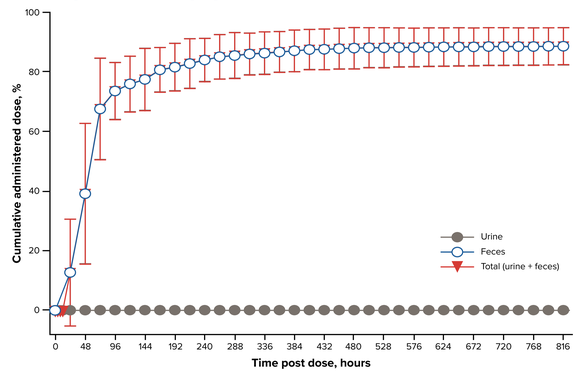
Data are presented as mean (SD) or n (%). Study 106 enrolled healthy male participants only. Study 105 part A evaluated phenytoin; part B evaluated itraconazole.
Abbreviations: AME, absorption, metabolism, and excretion; BMI, body mass index.

Figure 2. Arithmetic Mean Concentration-Time Profile After a Single Oral Dose of [^{14}C]-BGB-16673



Treatment: 200 mg [^{14}C]-BGB-16673; N=8. Axis scale (x-y): linear-logarithmic.
Abbreviation: LLOQ, lower limit of quantification.

Figure 3. Arithmetic Mean (SD) of Radioactive Dose Recovered in Urine and Feces After a Single Oral Dose of [^{14}C] BGB-16673



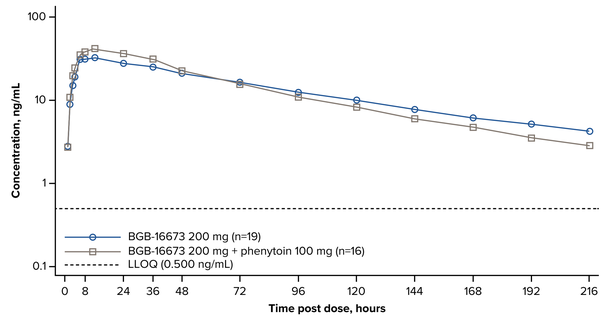
Study 106: Parent Drug and Metabolite Profile

- Median T_{max} for BGB-16673 and plasma total radioactivity was 12.0 hours post dose, indicating that parent and total circulating radioactivity reached peak levels at a similar time
- Geometric mean terminal half-life for parent BGB-16673 in plasma was approximately 82.4 hours, whereas geometric mean half-life for plasma total radioactivity was longer at approximately 135 hours
- The geometric mean BGB-16673 to plasma total radioactivity AUC ratio was approximately 0.705, indicating that parent drug was the dominant circulating component, in line with metabolite profiling in human plasma
- Parent BGB-16673 accounted for approximately 82.3% of total radioactivity in plasma
- Unchanged parent BGB-16673 was predominant in human feces and minor hepatic metabolites were observed, consistent with preclinical results demonstrating that the major elimination pathway was biliary and intestinal excretion of unchanged BGB-16673
- Overall, these findings support predominant elimination of unchanged parent through intestinal or biliary secretion, with limited contribution of oxidative hepatic metabolism and negligible renal contribution

Study 105: Effect of Strong CYP3A Inducer (Phenytoin)

- Healthy participants were enrolled in part A (n=19) and part B (n=18); mean age was 41.4 and 38.9 years, respectively, and mean body mass index was 28.0 and 27.4 kg/m^2, respectively (**Table 1**)
- In part A, maximum BGB-16673 concentrations were reached at the same time with and without phenytoin, with a median T_{max} of 12 hours in both treatment periods (**Figure 4**)
- Geometric mean half-life appeared shorter with phenytoin than without phenytoin (55.3 vs 74.6 hours), while the geometric mean PK estimates remained within the same overall range
- Relative to BGB-16673 alone, coadministration with phenytoin increased AUC$_{0\text{-last}}$ by approximately 9%, decreased AUC$_{0\text{-}\infty}$ by approximately 8%, and increased C_{max} by approximately 22% (**Table 2**)
  - The geometric least-squares mean (GLSM) ratios were 1.09 for AUC$_{0\text{-last}}$, 0.918 for AUC$_{0\text{-}\infty}$, and 1.22 for C_{max}. Although the 90% CIs were not fully contained within conventional 0.80 to 1.25 no-effect boundaries, all point estimates remained close to unity and support lack of clinically meaningful impact
  - Within-participant variability was high (44.7% for AUC$_{0\text{-last}}$, 49.9% for AUC$_{0\text{-}\infty}$, and 42.6% for C_{max}), and post hoc sensitivity analyses, in which participants with missing crossover data and outlier exposure were excluded, were directionally consistent with the primary analysis

Figure 4. Part A: BGB-16673/Phenytoin Interaction Arithmetic Mean Concentration-Time Profile



Matrix: plasma; analyte, BGB-16673. Axis scale (x-y): linear-logarithmic.
Abbreviation: LLOQ, lower limit of quantification.

Table 2. Pharmacokinetic Parameters From BGB-16673-105 Part A: BGB 16673/ Phenytoin Interaction

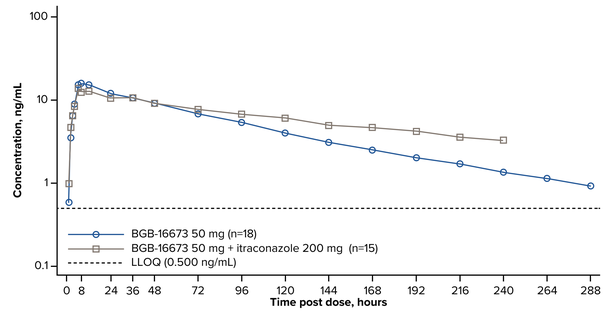
Parameter	Treatment	n	GLSM	Test vs reference: GLSM ratio (90% CI)	Test vs reference: Intrapatient CV, %
AUC$_{0\text{-last}}$, h × ng/mL	BGB-16673 200 mg (reference)	19	2640	–	–
	BGB-16673 200 mg + phenytoin 100 mg (test)	14	2880	1.09 (0.84-1.42)	44.7
AUC$_{0\text{-}\infty}$, h × ng/mL	BGB-16673 200 mg (reference)	17	3130	–	–
	BGB-16673 200 mg + phenytoin 100 mg (test)	16	2870	0.92 (0.70-1.21)	49.9
C_{max}, ng/mL	BGB-16673 200 mg (reference)	19	31.7	–	–
	BGB-16673 200 mg + phenytoin 100 mg (test)	16	38.6	1.22 (0.95-1.56)	42.6

Abbreviations: AUC$_{0\text{-}\infty}$, area under the plasma concentration-time curve from time 0 to infinity; AUC$_{0\text{-last}}$, area under the plasma concentration-time curve from time 0 to last quantifiable concentration; C_{max}, maximum observed plasma concentration; CV, coefficient of variation; GLSM, geometric least-squares mean.

Study 105: Effect of Strong CYP3A Inhibitor (Itraconazole)

- In part B, BGB-16673 reached maximum concentration at a similar time with and without itraconazole, with median T_{max} values of 8.01 and 6.99 hours, respectively (**Figure 5**)
- Geometric mean half-life appeared longer with itraconazole than without itraconazole (124 vs 77.6 hours, respectively)
- Relative to BGB-16673 alone, coadministration with itraconazole resulted in generally comparable AUC$_{0\text{-last}}$ and an approximately 23% lower C_{max} (**Table 3**)
  - The GLSM ratios were 1.05 for AUC$_{0\text{-last}}$ and 0.77 for C_{max}. AUC$_{0\text{-}\infty}$ was not included in the final analysis for part B due to AUC$_{0\text{-}\infty}$ extrapolation of >20% for most participants
  - Within-participant variability was high (37.5% for AUC$_{0\text{-last}}$ and 45.5% for C_{max}), and sensitivity analyses were consistent with the primary analysis

Figure 5. Part B: BGB-16673/Itraconazole Interaction Arithmetic Mean Concentration-Time Profiles



Matrix: plasma; analyte, BGB-16673. Axis scale (x-y): linear-logarithmic.
Abbreviation: LLOQ, lower limit of quantification.

Table 3. Pharmacokinetic Parameters From BGB-16673-105 Part B: BGB 16673/ Itraconazole Interaction

Parameter	Treatment	n	GLSM	Test vs reference: GLSM ratio (90% CI)	Test vs reference: Intrapatient CV, %
AUC$_{0\text{-last}}$, h × ng/mL	BGB-16673 50 mg (reference)	18	1270	–	–
	BGB-16673 50 mg + itraconazole 200 mg (test)	14[a]	1330	1.05 (0.84-1.33)	37.5
C_{max}, ng/mL	BGB-16673 50 mg (reference)	18	15.6	–	–
	BGB-16673 50 mg + itraconazole 200 mg (test)	14	12.0	0.77 (0.58-1.02)	45.5

[a]For part B, day 17, one participant had plasma concentrations of BGB-16673 below the limit of quantification for the whole profile. The participant was dosed and there were no AEs of vomiting. The day 17 profile for this participant was excluded from concentration summaries and no day 17 PK parameters were determined.
Abbreviations: AE, adverse event; AUC$_{0\text{-last}}$, area under the plasma concentration-time curve from time 0 to last quantifiable concentration; C_{max}, maximum observed plasma concentration; CV, coefficient of variation; GLSM, geometric least-squares mean.

Healthy Volunteer Safety

- In study 105 part A, 89.5% of participants experienced at least one TEAE overall; in part B, 94.4% participants experienced at least one TEAE. No grade ≥3 TEAEs, serious adverse events (AEs), or deaths were reported in either part A or part B
  - Most TEAEs in study 105 were grade 1, and petechiae was the most frequent event in both parts. In part A, one participant discontinued because of grade 1 hematuria considered related to study intervention; follow-up urinalysis after drug withdrawal showed normal result
- In study 106, only one TEAE was reported: grade 1 diarrhea that resolved and was not considered treatment-related. No serious AEs, deaths, or AE-related discontinuations occurred
- No clinically meaningful treatment-related trends or abnormalities were observed in laboratory tests, vital signs, electrocardiograms, or physical examinations across studies 105 and 106

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DISCLOSURES

BT, MT, PK, TZ, YZ, TC, FW, WDH, YCO: Employment and may own stock: BeOne Medicines, Ltd. **HZ:** Previous employment and may own stock: BeOne Medicines, Ltd; Employment, leadership, stock or other ownership: AusperBio. **SR:** Employment: BeOne Medicines, Ltd, BMS; Stock or other ownership: BeOne Medicines, Ltd, BMS, Celgene.

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