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

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Background: BGB-16673 is a BTK degrader that blocks signaling by tagging BTK for degradation through the cell's proteasome pathway, leading to tumor regression. Real-world data indicate that cytochrome P450 3A (CYP3A) inhibitors (eg, azole antifungals) are used by 15%-30% of patients with B-cell malignancies. Currently available covalent and noncovalent BTK inhibitors are primarily metabolized by CYP3A and require dose modification or caution when coadministered with CYP3A modulators due to exposure changes.

Aims: To characterize the human absorption, distribution, metabolism, and excretion (ADME) profile and to evaluate the impact of strong CYP3A modulators on BGB-16673 pharmacokinetics (PK).

Methods: BGB-16673-106 (NCT06776679) was a phase 1 human ADME study in healthy male participants (n=8) receiving a single oral dose of [^{14}C]-BGB-16673 (200 mg). Parent drug concentration and total radioactivity were measured in the plasma, urine, and feces; metabolite profiling was conducted using radiometric and mass spectrometric methods.

BGB-16673-105 (NCT06906809) was a phase 1, fixed-sequence, DDI study in healthy participants (n=37). Part A evaluated the strong CYP3A inducer phenytoin (100 mg three times daily) with a single-dose of BGB-16673 (200 mg). Part B evaluated the strong CYP3A inhibitor itraconazole (200 mg once or twice daily) with a single-dose of BGB-16673 (50 mg). Primary PK endpoints were area under the plasma concentration–time curve (AUC) and maximum observed plasma concentration (C_{max}), which were analyzed using mixed-effects models to derive geometric mean ratios (GMRs) and 90% CIs.

Both studies were conducted per the Declaration of Helsinki; all participants provided written informed consent.

Results: Following a single oral dose of [^{14}C]-BGB-16673, mean total radioactivity recovery was 88.5%, with the vast majority recovered in feces and minimal recovery in urine. Unchanged BGB-16673 was the predominant circulating drug-related component, with no significant plasma metabolites detected. Oxadiazole ring-cleaved metabolites generated by gut microbiota predominated in feces, whereas oxidative and amide hydrolysis pathways were minimal, indicating limited contribution of hepatic metabolism to systemic clearance. These findings are consistent with metabolic pathways observed in nonclinical species and support predominant elimination via intestinal or biliary

secretion of the unchanged parent drug, with negligible renal contribution. The median time to the maximum observed concentration was 12 hours, and the geometric mean terminal half-life of BGB-16673 was ≈82 hours.

In the DDI study, phenytoin coadministration resulted in no clinically meaningful exposure change in BGB-16673 (AUC GMR [coadministration vs alone], ≈0.9-1.0; C_{max} GMR, ≈1.2) (Table). Similarly, itraconazole did not meaningfully increase exposure (AUC GMR, ≈1.1), with a modest reduction in C_{max} (GMR, ≈0.77). Despite moderate variability, these changes were not clinically relevant.

Summary/Conclusion: BGB-16673 is primarily eliminated via intestinal or biliary excretion of the unchanged parent drug, with negligible renal clearance and minimal contribution of hepatic metabolism. Consistent with this profile, strong CYP3A induction and inhibition had no clinically meaningful impact on systemic exposure. These findings suggest a low risk of clinically relevant CYP3A-mediated DDIs and support greater dosing flexibility with BGB-16673.

Table. Statistical Analysis of Pharmacokinetic Parameters From BGB-16673-105

				Test vs reference	
Parameter	**Treatment**	**n**	**GLSM**	**GLSM ratio (90% CI)**	**Intrapatient CV (%)**
BGB-16673-105 part A: BGB-16673/phenytoin Interaction					
$AUC_{0\text{-}tlast}$, 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
BGB-16673-105 part B: BGB-16673/itraconazole Interaction					
$AUC_{0\text{-}tlast}$, h × ng/mL	BGB-16673 50 mg (reference)	18	1270	—	—
	BGB-16673 50 mg + itraconazole 200 mg (test)	14	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

$AUC_{0\text{-}\infty}$, area under the plasma concentration–time curve from time 0 to infinity; $AUC_{0\text{-}tlast}$, 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.