In Vitro, *In Silico*, and Clinical Investigations of BLU-5937 as Perpetrator of Drug-Drug Interactions

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Introduction

- BLU-5937 (INN camlipixant) is a potent, non-competitive antagonist of P2X3 receptors, ATP-gated ion channels found at the surface of sensory afferent neurons[1].
- BLU-5937 did not display antagonist activities on human P2X1, P2X2b, P2X4, P2X5 and P2X7 receptors (IC50 > 30 µM), or P2X2/3 (IC50 > 21 µM)[1,2].
- Clinical development of BLU-5937 for the treatment of Refractory Chronic Cough is ongoing, with predicted therapeutic doses of 25 mg and 50 mg BID[3].
- *In vitro* studies with BLU-5937 (up to 400 µM) identified BLU-5937 as a weak CYP3A4 inducer (EC_{50}=60 µM), BCRP inhibitor (IC_{50} =5.6 µM) and a weak inhibitor of P-gp (IC_{50} =30 µM) and OATP1B1 (IC_{50} =27 µM)[2].
- Clinical and *in silico* investigations were conducted to examine the relevance of these findings.

Methodology

- The clinical significance of in-vitro data was explored in a Phase 1, single center, open-label sequential drug-drug interaction (DDI) study in 28 healthy subjects.
- The impact of repeated doses (for 11 days) of BLU-5937 200 mg on the pharmacokinetics of single doses of index substrates[4] of CYP3A4 (midazolam, 5 mg), OATP1B1 (pravastatin, 40 mg), and BCRP (sulfasalazine, 500 mg) was investigated.
- Plasma PK parameters for midazolam, pravastatin, and sulfasalazine were estimated.
- The 90% confidence intervals for the ratio of geometric means for the probe drug administered alone or in presence of BLU-5937 were calculated for AUC and C_{max}.

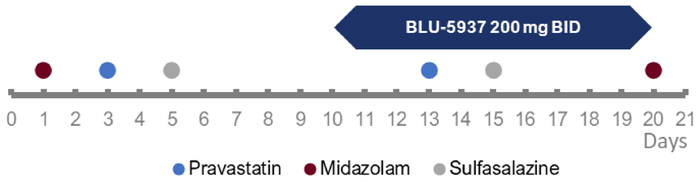
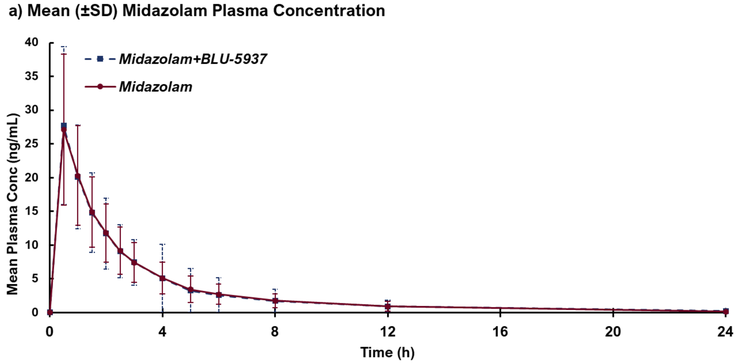


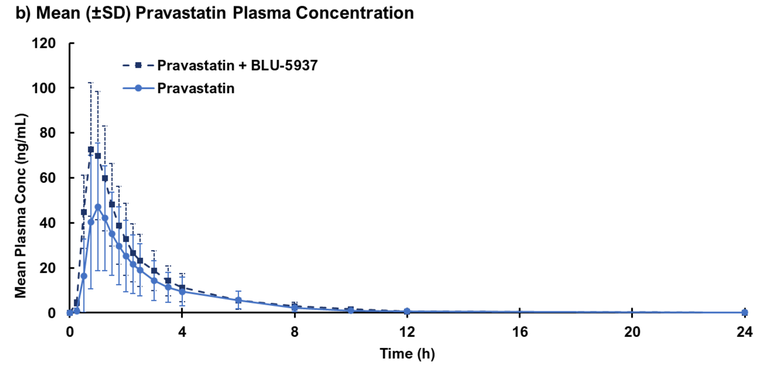
Figure 1. Clinical DDI Study Design

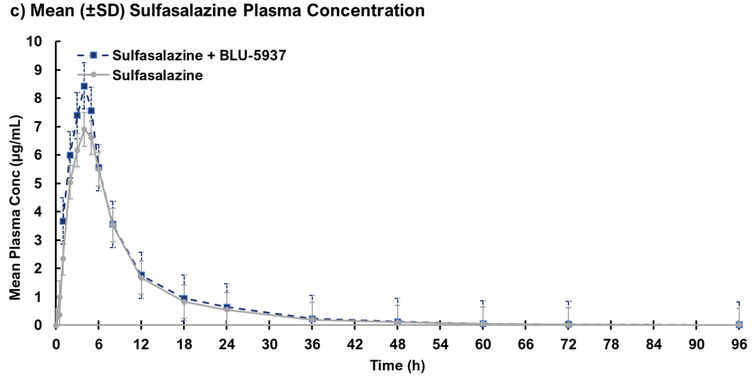
- A PBPK model that included a mechanistic absorption model (Simcyp Advanced Dissolution, Absorption and Metabolism (ADAM) model) was employed to explore DDI potential with P-gp substrates.
- The *in vitro* P-gp competitive inhibition constant for (Ki,u) was incorporated into the model. DDI simulations were repeated after reducing the Ki,u values by 15-fold to evaluate the impact of Ki,u on the estimated DDI magnitude.
- The model was then used to simulate the extent of the DDI between BLU-5937 and P-gp probe substrates digoxin and dabigatran etexilate.

Results

- BLU-5937 200 BID did not impact midazolam exposure, with LSM ratios and 90% CI for AUC and C_{max} within 80-125% (Fig 2a).
- A weak interaction was observed with pravastatin, with LSM ratio of 140% for AUC (Fig 2b).
- No clinically significant interaction was observed between BLU-5937 and sulfasalazine (LSM ratio of 116 and 117% for AUC and C_{max}) (Fig 2c).
- Simulations using the Ki for P-gp inhibition showed no significant interactions with digoxin and dabigatran (GMRs for AUC and C_{max} between 101-107%).
- Using a 15-x reduced P-gp Ki, a minor increase in C_{max} and no significant increase in AUC was predicted for digoxin and 56% and 44% increase in C_{max} and AUC was predicted for dabigatran at the 50 mg BID dose of BLU-5937.







PK Parameter	Geometric LSM (BLU-5937 +Substrate)	Geometric LSM (Substrate)	Ratio (%)[a]	90% Lower CI (%)[b]	90% Upper CI (%)[b]
	Midazolam				
Ln(AUC_{0-inf})	67.00	67.96	98.58	89.11	109.06
Ln(C_{max})	25.88	25.77	100.41	90.29	111.66
	Pravastatin				
Ln(AUC_{0-inf})	142.66	101.51	140.53	123.45	159.99
Ln(C_{max})	68.56	42.47	161.43	139.12	187.32
	Sulfasalazine				
Ln(AUC_{0-inf})	71.04	607.33	116.96	103.49	132.19
Ln(C_{max})	8.29	7.06	117.56	102.40	134.98

*a. Calculated using least-square means according to the formula: exp (DIFFERENCE) * 100*
b. 90% Geometric Confidence Interval (CI) calculated according to the formula: exp(DIFFERENCE ± t(dfResidual) SEDIFFERENCE)*100*

Figure 2. Mean Plasma Concentrations of Midazolam, Pravastatin, and Sulfasalazine

Conclusions

- BLU-5937 (200 mg BID dose) did not cause drug-drug interactions via CYP3A4 induction or BCRP inhibition, and a weak interaction was observed via OATP1B1 inhibition.
- No significant interactions are predicted through Pgp inhibition, which will be confirmed in a future DDI study.
- Overall, results to date indicate that BLU-5937 is unlikely to perpetrate clinically meaningful DDIs at therapeutically relevant doses.

References

1. Garceau D, Chauret N. (2019) *Pulm Pharmacol Ther*. 56:56-62.
2. *Bellus Health, Data On File*
3. *NCT05599191, A 52-Week Study of the Efficacy and Safety of BLU-5937 in Adults With Refractory Chronic Cough (CALM-1) & NCT05600777, A 24-Week Study of the Efficacy and Safety of BLU-5937 in Adults With Refractory Chronic Cough (CALM-2)*
4. *FDA's Web site for Drug Development and Drug Interactions. https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers*