Safety and pharmacokinetics of BLU-263, a next-generation KIT inhibitor, in healthy volunteers

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Background

- The *KIT* D816V mutation is the molecular driver in approximately 95% of systemic mastocytosis cases which have been shown to be vulnerable to KIT D816V inhibition[1–3]
- Avapritinib, a selective and potent KIT D816V inhibitor, is approved for certain molecularly defined forms of gastrointestinal stromal tumor (GIST) and is currently being investigated as a potential treatment for systemic mastocytosis
- BLU-263, equipotent to avapritinib *in vitro*, was designed to inhibit KIT D816V with minimal central nervous system (CNS) penetration (Table 1)
- Here we report on the safety, tolerability and pharmacokinetics (PK) of BLU-263 in an ongoing phase 1, randomized, double-blinded, placebo-controlled single ascending dose (SAD) and multiple ascending dose (MAD) study in healthy volunteers

Methods

- Primary objective of this first-in-human study was to assess the safety and tolerability of BLU-263 following administration of SAD and MAD in healthy adult subjects
- Secondary objective was to assess the plasma PK of SAD and MAD of BLU-263, as well as to assess the dose-effect and concentration-effect relationships of BLU-263 on electrocardiogram (ECG) intervals in healthy adult subjects. In addition, dose- and concentration-effects of BLU-263 on pharmacodynamic (PD) biomarkers were exploratory objectives
- In the SAD part of the study, cohorts of 8 healthy volunteers aged ≥18 years received either oral placebo (n=2/cohort) or single oral doses of BLU-263 (n=6/cohort) of 15, 25, 50, 100, or 200 mg (**Figure 1**)
- In the MAD part of the study, cohorts of 8 healthy volunteers aged ≥18 years received either oral placebo (n=2/cohort) or BLU-263 (n=6/cohort) at 25, 50, or 100 mg once daily (QD) for 10 consecutive days (**Figure 1**)
- Safety was assessed according to incidence and severity of adverse events in subjects who received BLU-263 as compared with placebo
- For the SAD PK analysis, blood plasma samples were collected at pre-dose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 48, and 72 hours post-dose. For the MAD PK analysis, blood plasma samples were collected at the same time intervals post-dose on days 1 and 10

Table 1: BLU-263 – A next-generation KIT inhibitor

EQUIVALENT POTENCY

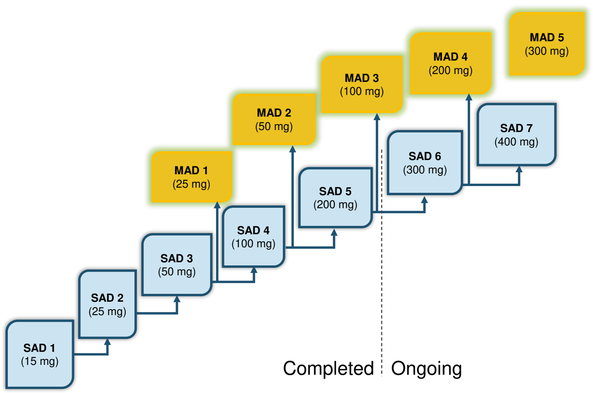
Compound	KIT D816V IC_{50} (nM)
BLU-263	0.20
Avapritinib	0.22
Imatinib	>10000

SELECTIVITY AND CNS PROFILES

Measure	Avapritinib	BLU-263
Nav1.2 sodium channel IC_{50}	280 nM	>10 µM
Rat $K_{pu,u}$ homogenate	0.40	0.024

IC_{50}, half-maximal inhibitory concentration; $Kp_{u,u}$, unbound brain-to-plasma AUC ratio.

Figure 1: Ongoing phase 1 study of BLU-263 in healthy volunteers



Results

Table 2A and 2B: Treatment-related adverse events (TRAEs) in SAD and MAD cohorts

TRAEs, N of subjects	Table 2A: SAD cohorts		
	All other doses N=24	200 mg N=6	Placebo N=10
Any TRAE	0	1	2
Upper abdominal pain	0	1[a]	0
Decreased appetite	0	1[a]	0
Somnolence	0	0	1[b]
Headache	0	0	1

[a]Same subject. [b]Two occurrences.

TRAEs, N of subjects	Table 2B: MAD cohorts			
	25 mg N=6	50 mg N=6	100 mg N=6	Placebo N=6
Any TRAE	1	0	0	0
Upper abdominal pain	1[a,b]	0	0	0
Fatigue	1[a]	0	0	0
Chapped lips	1[a]	0	0	0
Nausea	1[a,c]	0	0	0
Headache	1[a]	0	0	0

[a]Same subject. [b]Two occurrences. [c]Three occurrences.

- All AEs were reported as Grade 1 (mild) in severity and resolved
- Regardless of causality, 21 AEs in 11 subjects were reported across all subjects treated with BLU-263
- No serious AEs or discontinuations due to AEs were reported
- No laboratory AEs were reported: mean serum chemistry, hematology, coagulation, and urinalysis parameters were within normal limits
- No abnormal vital sign findings were noted (pulse rates & blood pressure)

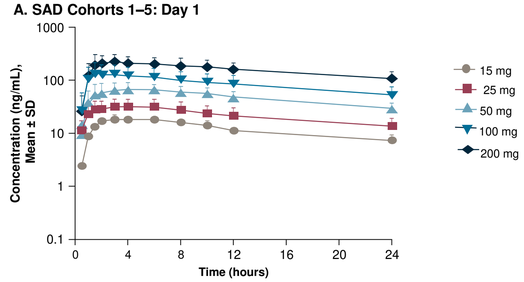
Table 3: BLU-263 does not prolong QTcF – ddQTcF changes and 90% CI by treatment, MAD Day 10

Treatment BLU-263 QD	Geometric mean C_{max} (ng/mL)	Predicted maximum ddQTcF (msec)	90% CI (msec)
25mg	64.54	-2.69	-3.92 to -1.45
50mg	98.73	-2.37	-3.45 to -1.27
100mg	204.60	-1.38	-3.39 to 0.65

QD, once per day; C_{max}, maximum plasma concentration; ddQTcF, time-matched, placebo-corrected, baseline-adjusted QT interval corrected by Fridericia's formula (QTcF); CI, confidence interval.

- The potential relationship between BLU-263 plasma concentrations and ddQTcF was explored using linear mixed-effect model regressing ddQTcF on time-matched BLU-263 concentrations with data across all treatments
- There were no treatment related trends noted in the mean observed ECG parameters or change from baseline assessed in this study
- There were no subjects that met the specifications for cardiac outlier of QTcF or ddQTcF based on ECG actual values (**Table 3**)
- There was no increase of concern in heart rate due to BLU-263, indicating Fridericia's correction (QTcF) was adequate

Figure 3: PK Results – Rapid absorption, linear PK, and half-life support BLU-263 QD dosing



SD, standard deviation.

Pharmacokinetics

- After single-dose administration of BLU-263 15 mg to 200 mg QD (**Table 4**):
  - T_{max} ranged from 1.5 to 6 h post-dose indicating rapid absorption
  - $t_{1/2}$ ranged from 20 h to 28 h supporting QD dosing
  - Vz/F ranged from 794 L to 1117 L indicating wide tissue distribution
- After 10 days QD, the geometric mean accumulation ratio for AUC_{0-24} ranged from 1.6 to 1.8 (**Table 5**)
- Following single 15 to 200 mg doses and multiple oral 25 to 100 mg doses of BLU-263 for 10 days, a statistical linear relationship with dose was established for plasma BLU-263 C_{max} and area under the curve parameters

Table 4: SAD PK: Plasma BLU-263 PK following single oral dose administered under fasted conditions

Pharmacokinetic parameters	15 mg (N=6)	25 mg (N=6)	50 mg (N=6)	100 mg (N=6)	200 mg (N=6)
C_{max} (ng/mL)	19.0 (18.5)	32.8 (41.8)	68.4 (29.1)	130.0 (60.3)	236.5 (33.0)
T_{max} (h)	4.0 (2.0, 6.0)	4.5 (1.5, 6.0)	5.0 (1.6, 6.0)	3.0 (1.5, 6.1)	2.50 (1.5, 6.0)
AUC_{0-24} (h*ng/mL)	286.9 (17.8)	491.3 (45.4)	1087 (26.4)	1858 (54.8)	3688 (26.3)
C_{24} (ng/mL)	7.32 (22.6)	12.72 (48.3)	28.45 (26.2)	48.80 (47.4)	106.10 (24.5)
AUC_{0-inf} (h*ng/mL)	500 (24.0)	874 (47.0)	1980 (28.7)	3741 (52.1)	8103 (32.7)
$t_{1/2}$ (h)	19.8 ± 2.9	21.4 ± 1.4	21.6 ± 4.2	26.4 ± 4.7	28.4 ± 4.9
CL/F (L/h)	30.7 ± 7.0	31.3 ± 16.2	26.1 ± 7.5	29.6 ± 15.1	25.7± 7.2
Vz/F (L)	856.7 ± 116.3	965.3 ± 517.8	794.0 ± 203.9	1117.0 ± 617.2	1019.0 ± 213.0

C_{max}, AUC, C_{24} are geometric mean (% CV), T_{max} is median (range), $t_{1/2}$, CL/F, Vz/F are arithmetic mean ± SD. AUC_{0-24}, area under the curve through 24 hours; AUC_{0-inf}, area under the curve through t=infinity; C_{24}, plasma concentration at 24 hours; CL/F, oral clearance; C_{max}, maximum plasma concentration; CV, coefficient of variation; SD, standard deviation; $t_{1/2}$, elimination half-life; T_{max}, time to maximum plasma concentration; VzF, volume of distribution.

Table 5: MAD PK: plasma BLU-263 PK on Day 10 following multiple oral dose

Pharmacokinetic parameters	25 mg (N=6)	50 mg (N=6)	100 mg (N=6)
C_{max} (ng/mL)	64.5 (31.4)	98.7 (31.4)	204.6 (36.1)
T_{max} (h)	2.5 (1.5, 3.0)	2.5 (1.5, 4.0)	2.1 (1.5, 4.0)
AUC_{0-24} (h*ng/mL)	1084 (37.7)	1685 (29.6)	3396 (41.0)
C_{24} (ng/mL)	29.28 (45.2)	46.48 (30.5)	94.16 (45.1)
RA.AUC	1.76	1.60	1.66

C_{max}, AUC, C_{24} are geometric mean (% CV), T_{max} is median (range). AUC_{0-24}, area under the curve through 24 hours; C_{24}, plasma concentration at 24 hours; C_{max}, maximum plasma concentration; CV, coefficient of variation; RA.AUC, accumulation ratio for AUC_{0-24} T_{max}, time to maximum plasma concentration.

Conclusions

- In healthy volunteers, BLU-263, a next-generation investigational KIT D816V inhibitor, was safe at all doses tested
- The pharmacokinetics of BLU-263 were linear across the dose ranges in SAD and MAD cohorts and the half-life supports once-daily dosing
- These results support continued development of BLU-263 for patients with systemic mastocytosis
- The phase 2/3 HARBOR study will evaluate BLU-263 doses ranging from 25 to100 mg QD in patients with non-advanced systemic mastocytosis, with an anticipated start in mid-2021

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