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

CT122

Nimita Dave[1], Marissa Devlin[1], Jill Rodstrom[1], Bei Yu[1], Megan Foley[1], Kevin He[1], Scott Rassmussen[2], Andrew Boral[1], Tuan Dong Si[1]

[1]Blueprint Medicines Corporation, Cambridge, Massachusetts, USA; [2]Celerion Inc, Lincoln, Nebraska, USA

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

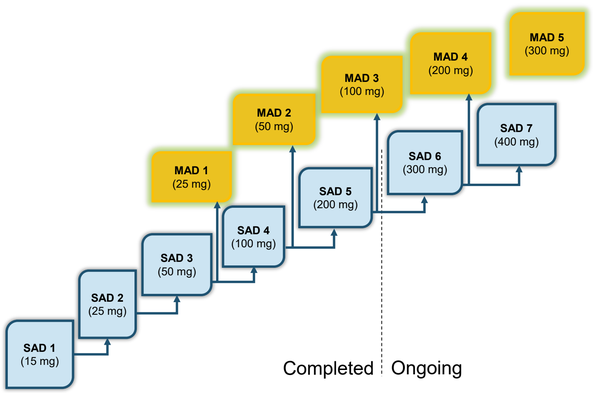
Compound	KIT D816V IC_{50} (nM)
BLU-263	0.20
Avapritinib	0.22
Imatinib	>10000

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)

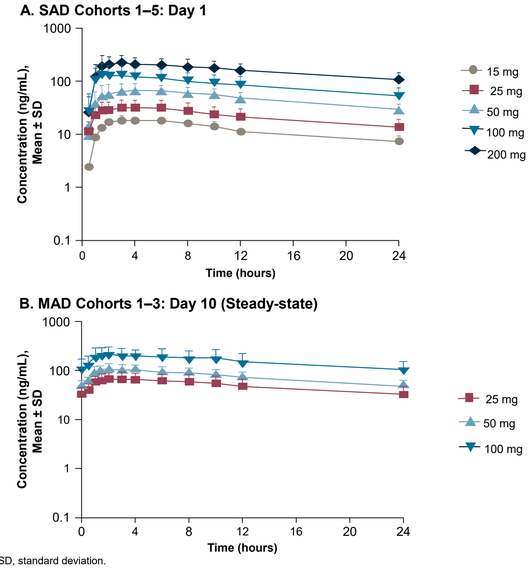
Table 3: BLU-263 does not prolong QTcF – ddQTcF changes and 90% CI by treatment, MAD Day 10

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

Acknowledgments

Medical writing support was provided by Gwendolyn Elphick, PhD, and editorial support was provided by Travis Taylor, BA all of Paragon, Knutsford, UK, supported by Blueprint Medicines Corporation, Cambridge, MA, according to Good Publication Practice guidelines

Disclosures

This research was funded by Blueprint Medicines Corporation. Blueprint Medicines reviewed and provided feedback on the poster. The authors had full editorial control of the poster and provided their final approval of all content.

ND, MD, JR, BY, MF, KH, AB, and TDS are employees of and hold equity interest in Blueprint Medicines.