Safety and Pharmacokinetics (PK) of BLU-808 Following Oral Dosing in Healthy Volunteers

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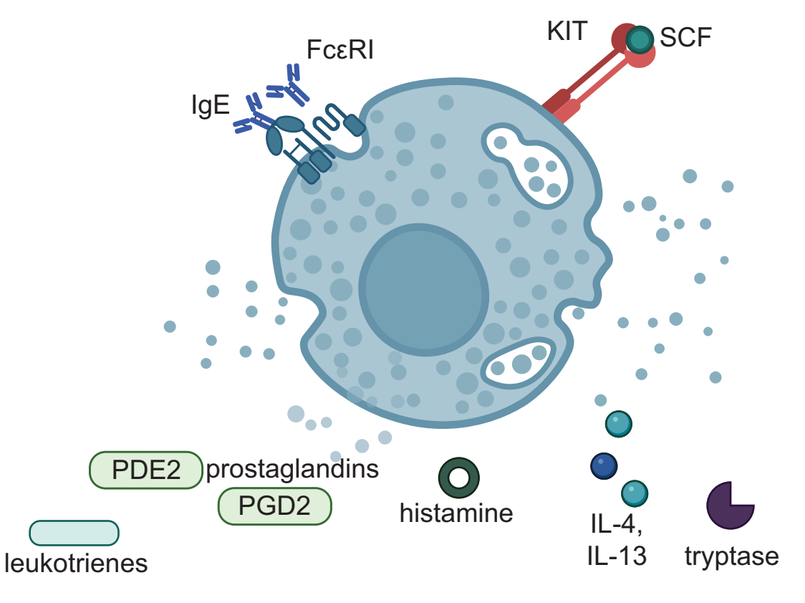
Introduction

- Mast cells (MCs) serve an important role in inflammatory and allergic reactions[1]
- Activated MCs release mediators including histamines, proteases (such as tryptase), cytokines, and chemokines[2]
  - Activation and/or proliferation of MCs through wild-type (WT) KIT signaling is involved in Type 2 inflammation, including inflammatory diseases such as chronic urticaria and asthma[3–5]
- BLU-808 is an investigational, potent, selective, and orally bioavailable WT KIT inhibitor, with low brain penetration and high selectivity for WT KIT that has shown preclinical activity (**see poster #535 at AAAAI 2025**)[6,7]

Mast cells play a known role in Type 2 inflammation

- MCs release mediators that further **activate inflammation**
- Inflammatory responses can lead to **long-term effects** including tissue remodeling
- Targeting **KIT, the regulator of MC survival and differentiation**, is a promising approach to improve disease outcomes

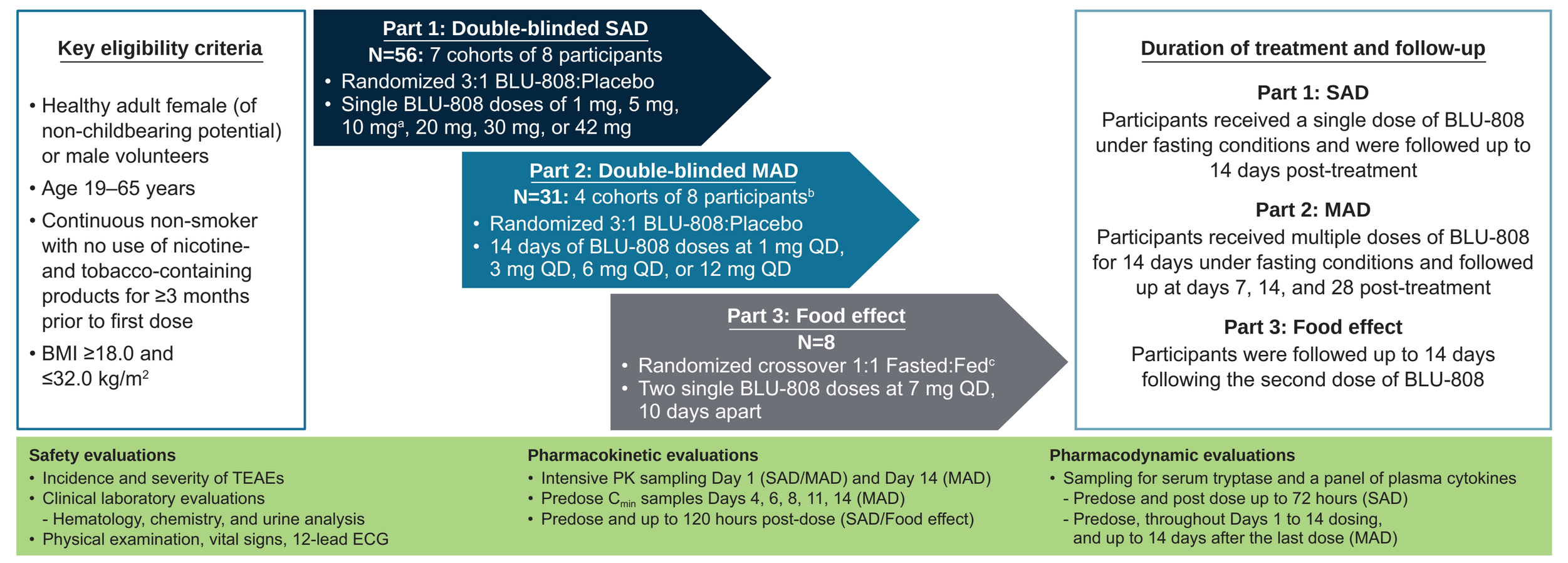


FcεRI, high-affinity immunoglobulin E receptor; KIT, tyrosine protein kinase; IgE, immunoglobulin E; IL, interleukin; MC, mast cell; PDE, phosphodiesterase; PGD, prostaglandin; SCF, stem cell factor. Image generated using BioRender illustration software.

Methods

- BLU-808-0101 is a first-in-human randomized, double-blind, placebo-controlled study in the USA (**Figure 1**)
  - Part 1 evaluated single ascending doses (SAD); BLU-808 was administered orally as either 1 mg or 10 mg tablets, fasted
  - Part 2 evaluated multiple ascending doses (MAD) for 14 days; BLU-808 was administered orally as 1 mg tablets, fasted
  - Part 3 evaluated the effects of food on the pharmacokinetics (PK) of BLU-808; BLU-808 was administered orally as 7 x 1 mg tablets, fasted or fed

Figure 1. Study design


Key eligibility criteria
• Healthy adult female (of non-childbearing potential) or male volunteers
• Age 19–65 years
• Continuous non-smoker with no use of nicotine- and tobacco-containing products for ≥3 months prior to first dose
• BMI ≥18.0 and ≤32.0 kg/m²
Part 1: Double-blinded SAD
N=56: 7 cohorts of 8 participants
• Randomized 3:1 BLU-808:Placebo
• Single BLU-808 doses of 1 mg, 5 mg, 10 mg^a, 20 mg, 30 mg, or 42 mg
Part 2: Double-blinded MAD
N=31: 4 cohorts of 8 participants^b
• Randomized 3:1 BLU-808:Placebo
• 14 days of BLU-808 doses at 1 mg QD, 3 mg QD, 6 mg QD, or 12 mg QD
Part 3: Food effect
N=8
• Randomized crossover 1:1 Fasted:Fed^c
• Two single BLU-808 doses at 7 mg QD, 10 days apart
Duration of treatment and follow-up
Part 1: SAD
Participants received a single dose of BLU-808 under fasting conditions and were followed up to 14 days post-treatment
Part 2: MAD
Participants received multiple doses of BLU-808 for 14 days under fasting conditions and followed up at days 7, 14, and 28 post-treatment
Part 3: Food effect
Participants were followed up to 14 days following the second dose of BLU-808
Safety evaluations
• Incidence and severity of TEAEs
• Clinical laboratory evaluations
- Hematology, chemistry, and urine analysis
• Physical examination, vital signs, 12-lead ECG
Pharmacokinetic evaluations
• Intensive PK sampling Day 1 (SAD/MAD) and Day 14 (MAD)
• Predose C_min samples Days 4, 6, 8, 11, 14 (MAD)
• Predose and up to 120 hours post-dose (SAD/Food effect)
Pharmacodynamic evaluations
• Sampling for serum tryptase and a panel of plasma cytokines
- Predose and post dose up to 72 hours (SAD)
- Predose, throughout Days 1 to 14 dosing, and up to 14 days after the last dose (MAD)

[a]The 10 mg dose was tested using 2 formulations (10 mg x 1 and 1 mg x 10); PK/pharmacodynamics results from the 1 mg tablet x 10 cohort are presented. [b]MAD 12 mg cohort had only 7 participants (5 BLU-808, 2 placebo). [c]High-fat/high-calorie meal.
BMI, body-mass index; C_{min}, minimum plasma concentration; ECG, electrocardiogram; MAD, multiple ascending doses; PK, pharmacokinetic; QD, once daily; SAD, single ascending dose; TEAE, treatment-emergent adverse event.

Study demographics

- As of January 11, 2025, 87 participants received either a single dose (N=56) of placebo (n=14) or BLU-808 (n=42), or multiple doses (N=31) of placebo (n=8) or BLU-808 (n=23)
- Baseline serum tryptase levels were balanced across the BLU-808-treated and placebo cohorts

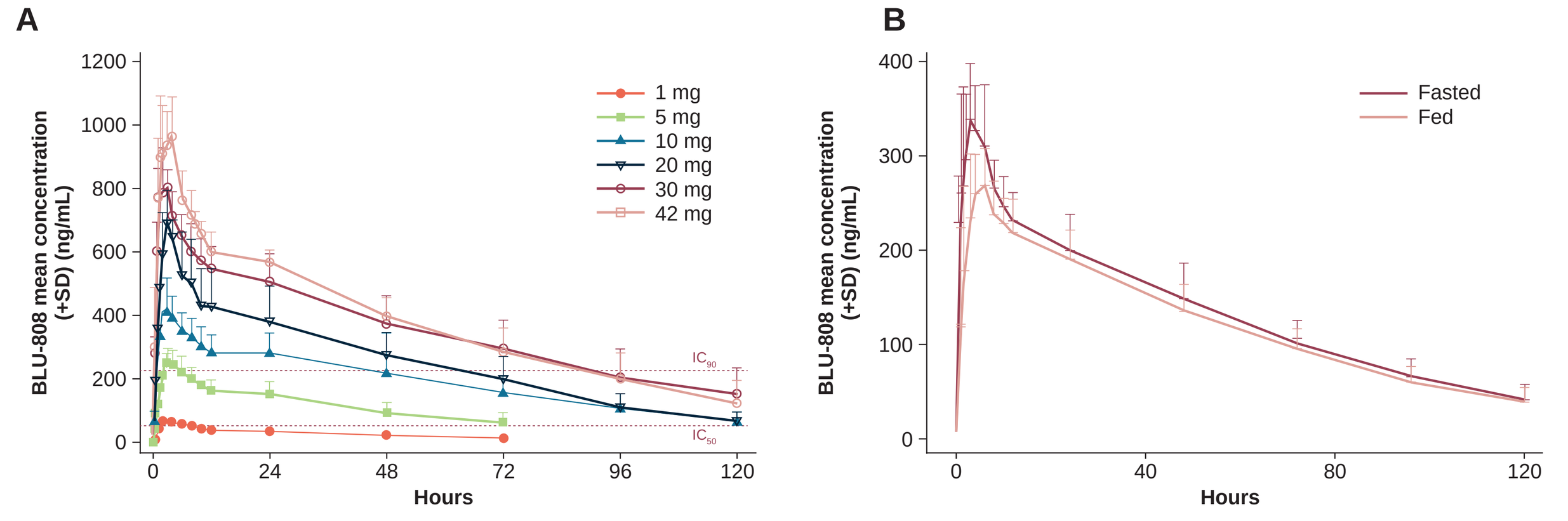
Table 1. Baseline demographics

Characteristic	SAD (N=56) Placebo (n=14)	SAD (N=56) BLU-808 (n=42)	MAD (N=31[a]) Placebo (n=8)	MAD (N=31[a]) BLU-808 (n=23)	Food effect (N=8)
Age (years), median (range)	44 (23–63)	47 (21–63)	49 (28–62)	42 (24–60)	46 (26–61)
Female, n (%)	5 (36)	13 (31)	2 (25)	4 (17)	1 (13)
Baseline BMI (kg/m²), median (range)	27.3 (20.7–31.3)	27.5 (20.6–31.8)	28.0 (22.2–31.1)	28.4 (21.1–31.1)	28.7 (19.4–31.2)
Race, n (%)					
White	9 (64)	31 (74)	5 (63)	11 (48)	4 (50)
Black or African American	5 (36)	6 (14)	2 (25)	10 (44)	3 (38)
Multiple[b]	0 (0)	4 (10)	1 (13)	1 (4)	1 (13)
Asian	0 (0)	1 (2)	0 (0)	1 (4)	0 (0)

[a]All except for two participants completed the study; 1 participant (placebo cohort) was removed at Day 12 due to violation of site policy unrelated to study drug, 1 participant (MAD 6 mg cohort) was found to be ineligible at Day 8 due to medical history of benign ethnic neutropenia.
[b]Includes participants with >1 race selected.

Results

Figure 2. SAD: Mean (+SD) BLU-808 plasma concentrations following (A) BLU-808 administered to healthy adults, fasted (preliminary PK results), (B) fasted *versus* fed conditions, and (C) plasma PK parameters



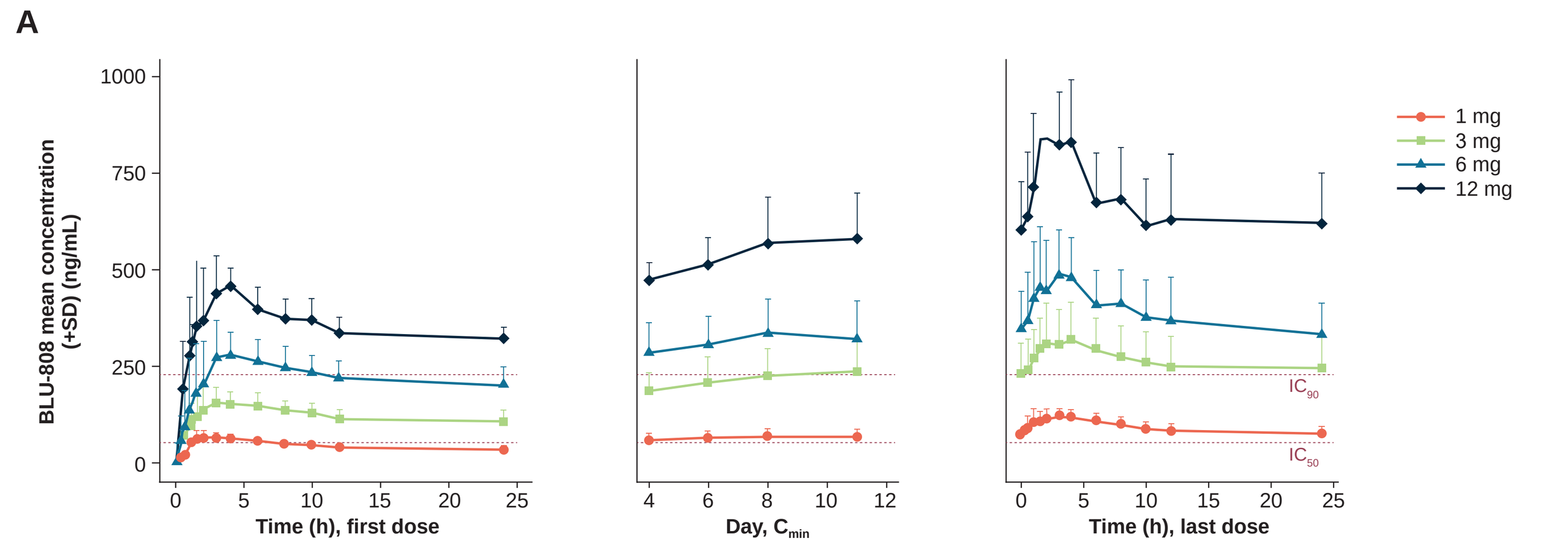
C

PK parameter	1 mg (n=6)	5 mg (n=6)	10 mg (n=6)	20 mg (n=6)	30 mg (n=6)	42 mg (n=6)	7 mg fasted (n=8)	7 mg fed (n=8)
C_{max} (ng/mL) GM (%CV)	69 (22)	252 (20)	427 (19)	681 (20)	838 (10)	1011 (10)	350 (15)	280 (16)
T_{max} (h) median (range)	3.0 (1–4)	3 (1.5–3)	2.5 (1–3)	3 (2–4)	2.5 (1–6)	3.5 (1–4)	2.5 (1–6)	5 (1.5–8)
$AUC_{0–last}$ (h*ng/mL) GM (%CV)	2257 (21)	8716 (28)	13421 (53)	29031 (28)	41554 (22)	44578 (17)	15828 (20)	14422 (19)
Half-life (h) mean (SD)	39 (11)	37 (14)	44 (26)	30 (4)	53 (25)	42 (18)	41 (8)	38 (8)

$AUC_{0–last}$, area under the plasma concentration curve from time 0 to the last measurable non-zero concentration; C_{max}, maximum plasma concentration; GM, geometric mean; h, hour; IC_{50}, half-maximal inhibitory concentration; IC_{90}; 90% of the maximum inhibition; SD, standard deviation; T_{max}, time to maximum concentration; %CV, coefficient of variation

- BLU-808 demonstrated a half-life of ~40 hours, supporting once-daily (QD) dosing (**Figure 2C**)
- PK was generally dose proportional through 30 mg, with minimal further increase between 30 and 42 mg
- Low PK variability was observed
- No food effect was observed; geometric mean ratio (GMR) indicated a 9% decrease in area under the plasma concentration curve from time zero to infinity under fed conditions compared to fasted (GMR 0.91; 90% confidence interval [IC_{90}] 0.83–0.99; **Figure 2B**)

Figure 3. MAD: (A) Mean (+SD) BLU-808 plasma concentrations following oral doses of BLU-808 administered to healthy adults, fasted, for 14 Days (preliminary PK results) and (B) plasma PK parameters



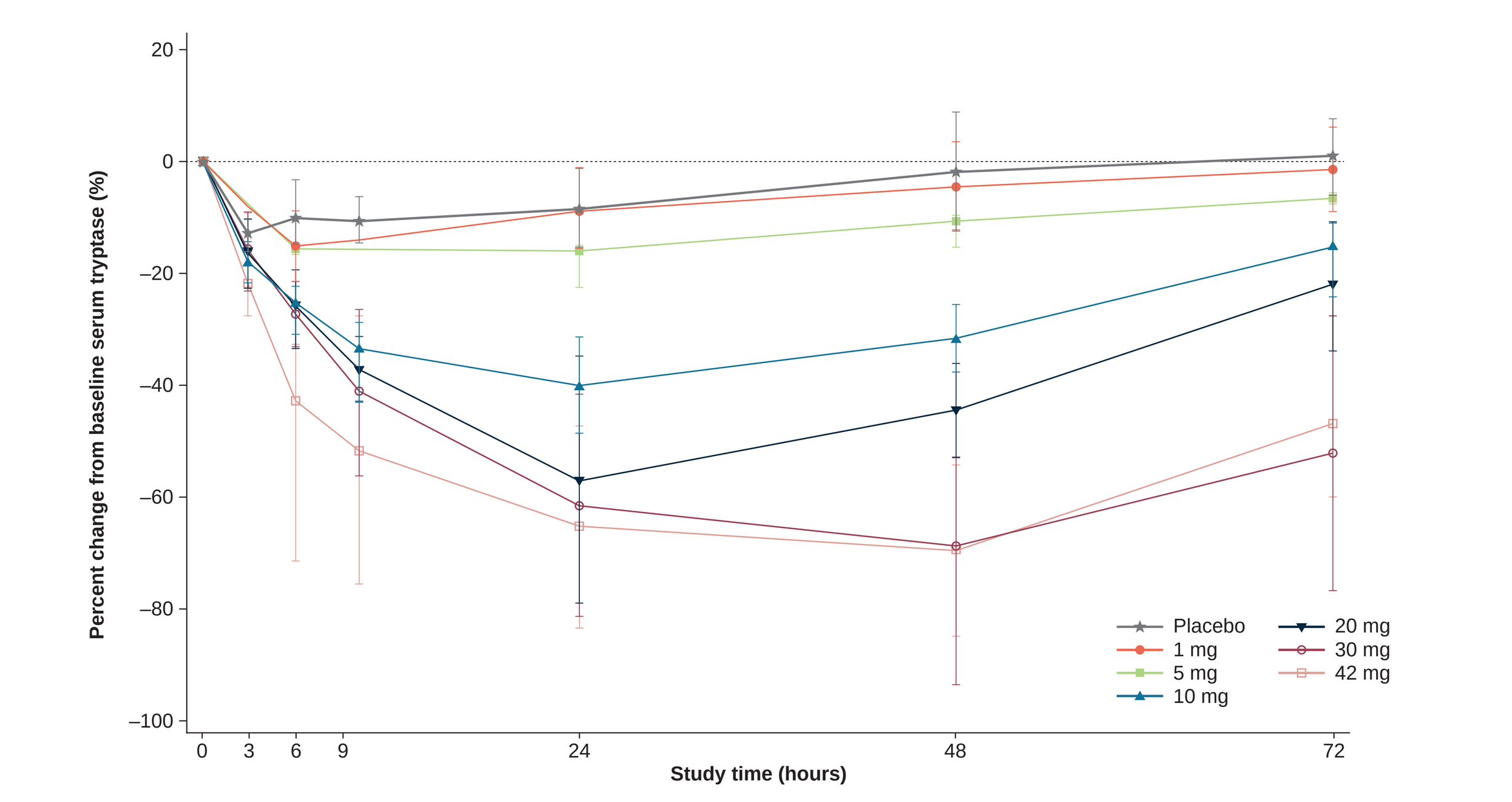
B

PK parameter	1 mg QD (n=6)	3 mg QD (n=6)	6 mg QD (n=6)	12 mg QD (n=5)
$C_{max,ss}$ (ng/mL) GM (%CV)	122 (17)	316 (31)	491 (23)	878 (25)
$T_{max,ss}$ (h) median (range)	2.5 (1–4)	3.5 (2–4)	3 (1.5–4)	2 (1.5–4)
$AUC_{(0–24),ss}$ (h*ng/mL) GM (%CV)	2133 (21)	6080 (31)	8987 (26)	15733 (21)
$C_{min,ss}$ (ng/mL) GM (%CV)	70 (25)	211 (37)	312 (30)	566 (22)
Day 14 half-life (h) mean (SD)	34 (8)	60 (38)	43 (12)	56 (17)

$AUC_{(0–24),ss}$, area under the plasma concentration curve from time zero to 24 hrs at steady-state; $C_{max,ss}$, maximum plasma concentration at steady-state; C_{min}, minimum plasma concentration; $C_{min,ss}$, minimum plasma concentration at steady-state; QD, once daily; T_{max}, time to maximum concentration at steady-state.

- PK increased approximately dose proportionally from 1 to 12 mg of BLU-808
- Steady-state was achieved after ~8 days of QD dosing (**Figure 3**) and approximately 2-fold accumulation of BLU-808 at steady-state
- Low PK variability was observed

Figure 4. SAD: Mean (±SD) percent change from baseline serum tryptase following BLU-808 or placebo

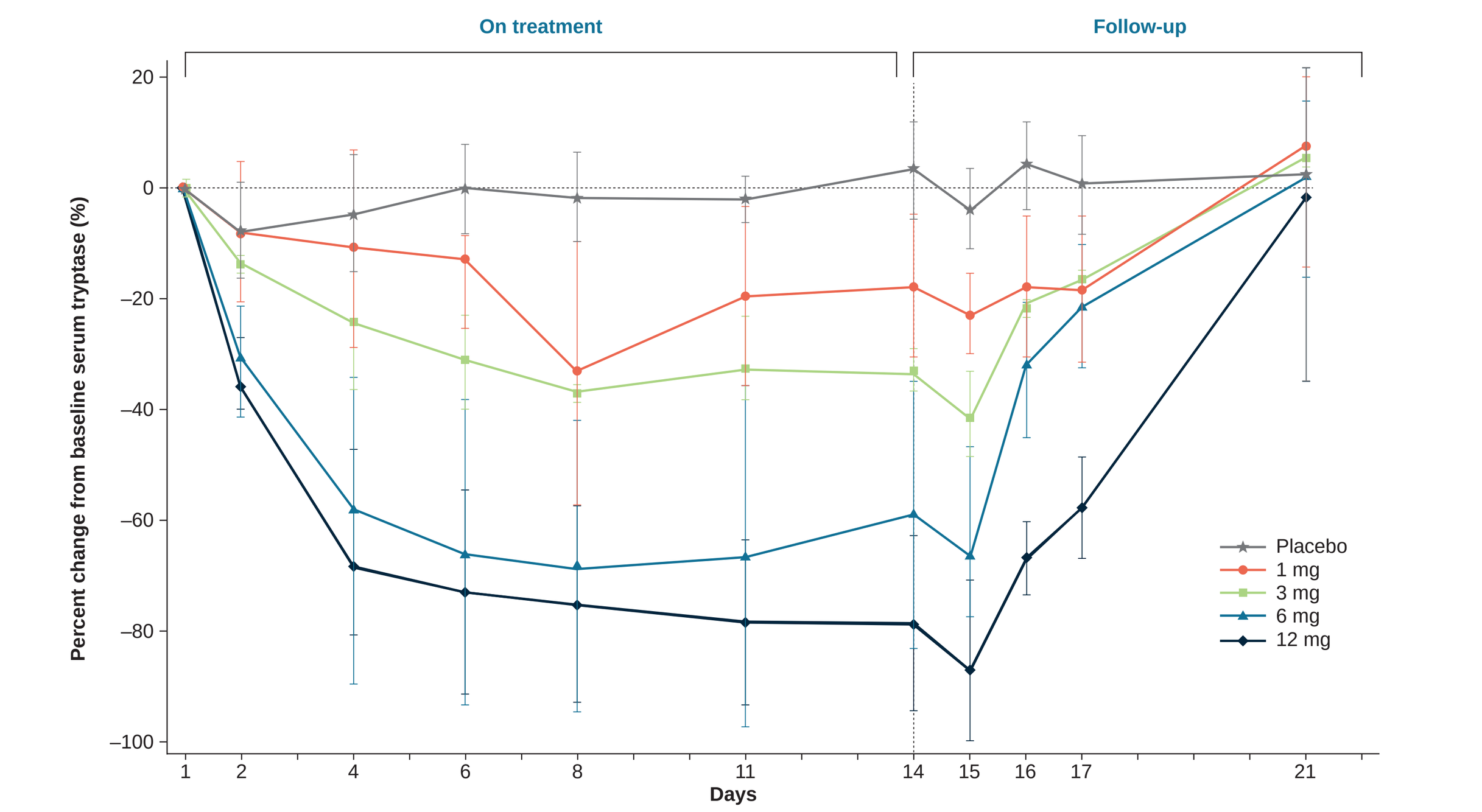


SAD Dose	Change from baseline serum tryptase Maximum (%)	Change from baseline serum tryptase 24hr (%)
Placebo (n=14)	–12	–8
1 mg (n=6)	–15	–9
5 mg (n=6)	–16	–16
10 mg (n=6)	–40	–40
20 mg (n=6)	–57	–57
30 mg (n=6)	–69	–61
42 mg (n=6)	–70	–65

Tryptase values below lower limit of quantification (LLOQ; 1 ng/mL) were imputed at 0 ng/mL.

- Maximum decreases of >60% were observed at 30 and 42 mg BLU-808 (**Figure 4**)
- Similar change in tryptase at the 30 and 42 mg doses reflect similar PK at those doses

Figure 5. MAD: Mean (±SD) percent change from baseline serum tryptase following BLU-808 or placebo



MAD Dose	Change from baseline serum tryptase: Percentage reduction at Day 15 (%)	Change from baseline serum tryptase: Participants reaching LLOQ
Placebo (n=8)	–4	0
1 mg (n=6)	–23	1/6
3 mg (n=6)	–41	1/6
6 mg (n=6)	–66	3/6
12 mg (n=4)[a]	–87	3/4

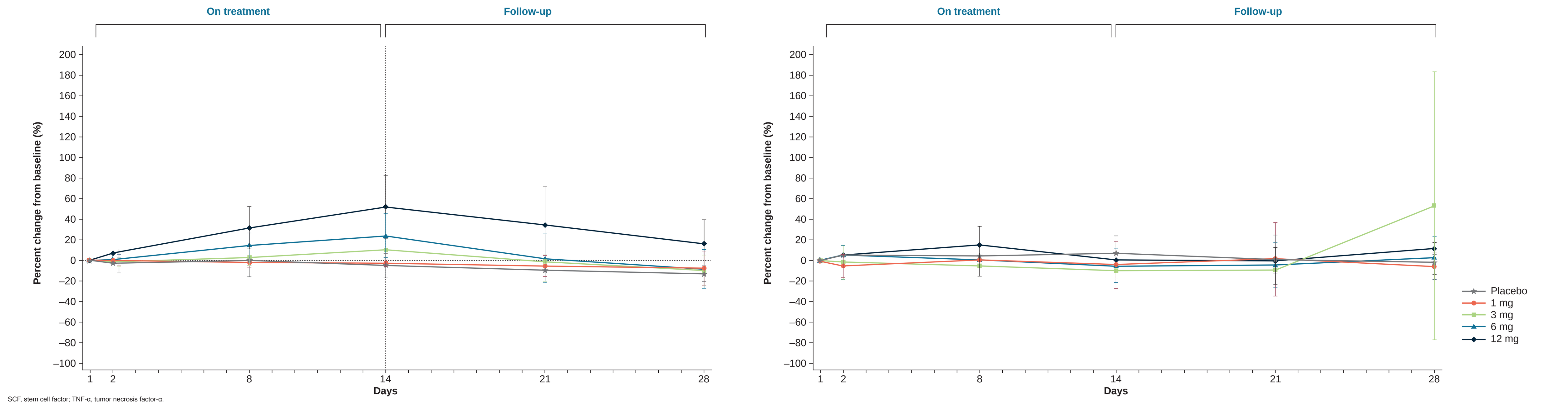
Tryptase values below lower limit of quantification (LLOQ; 1 ng/mL) were imputed at 0 ng/mL. [a]One participant had undetectable tryptase levels at baseline and was not included in the tryptase analysis.

- Maximum mean tryptase reduction in the 12 mg cohort was 87% (at 24 hours after last dose; **Figure 5**)

Figure 6. MAD: Trends in biomarkers (A) SCF and (B) TNF-α over time in BLU-808 treated MAD cohorts, over time with BLU-808 or placebo

A. Mean (±SD) percentage change from baseline in SCF over time with BLU-808 or placebo

B. Mean (±SD) percentage change from baseline in TNF-α over time with BLU-808 or placebo



SCF, stem cell factor; TNF-α, tumor necrosis factor-α.

- Cytokine analysis assessing a panel of 21 cytokines in MAD cohorts:
  - Dose-dependent trends were only observed in the KIT ligand, SCF, (**Figure 6A**) consistent with the high selectivity of BLU-808 for KIT
  - No other dose-dependent cytokine trends were observed with 2 weeks of treatment; as a representative example, TNF-α, a classic pro-inflammatory cytokine, that would not be expected to be directly modulated in response to selective KIT inhibition, is shown (**Figure 6B**)

Safety

SAD/Food Effect

- TEAEs observed in ≥2 participants in the SAD cohort:
  - **Placebo arm:** headache (n=2), fatigue (n=2), and rhinorrhea (n=2)
  - **BLU-808-treated arm:** headache (n=4); two in the 30 mg cohort, and one each in the 20 mg and 42 mg cohorts
  - No serious adverse events (SAEs), all TEAEs were Grade 1 except for one Grade 2 headache (30 mg cohort); all AEs resolved
- No clinically significant changes in laboratory measures

MAD

- No SAEs were reported in the MAD cohort, and all AEs were Grade 1 except for a Grade 2 constipation (in placebo cohort)
- All AEs resolved
- No treatment discontinuations due to AEs and no dose modifications
- No significant changes in electrocardiograms (ECGs), vital signs, or laboratory measures (including aspartate transaminase [AST] and alanine transaminase [ALT])

Table 2. MAD: TEAEs by dosing group (reported in ≥2 participant)[a]

Characteristic	Placebo (n=8)	MAD (N=31) 1 mg (n=6)	MAD (N=31) 3 mg (n=6)	MAD (N=31) 6 mg (n=6)	MAD (N=31) 12 mg (n=5)
Most common TEAEs,[b] n					
Hair color changes	0	0	0	4	3
Constipation	2	0	2	0	2
Headache	1	2	0	0	1
Pruritus	1	0	0	1	1
Fatigue	1	1	0	0	0
Rash	0	0	0	2	0

[a]AEs presented are based on TEAEs present in ≥2 participants in the overall population (N=31). [b]Three participants in the 12 mg cohort experienced Grade 1 adverse events with blood draw, consisting of vessel puncture site pain, 2 of them with lightheadedness.
AE, adverse event.

Table 3. MAD: Mean absolute (A) neutrophils and (B) hemoglobin following BLU-808 or placebo for 14 days

A. Neutrophils

Dose	Mean (SD) neutrophils, 10^9/L Baseline	Day 14	Day 28
Placebo	3.3 (0.99)	3.3 (1.18)	3.4 (1.05)
1 mg	2.7 (1.31)	2.3 (1.37)	3.3 (1.21)
3 mg	3.3 (0.58)	2.5 (0.48)	2.9 (1.15)
6 mg	2.5 (1.18)	2.7 (1.34)	2.1 (0.51)
12 mg	3.4 (0.89)	2.5 (0.61)	2.4 (0.78)

B. Hemoglobin

Dose	Mean (SD) hemoglobin, g/dL Baseline	Day 14	Day 28
Placebo	15.1 (0.88)	14.6 (0.98)	14.1 (1.13)
1 mg	16.1 (1.09)	15.5 (0.74)	15.2 (0.96)
3 mg	15.1 (0.61)	14.8 (0.75)	14.0 (0.66)
6 mg	15.3 (1.38)	14.7 (1.98)	13.4 (1.31)
12 mg	14.6 (0.94)	13.3 (0.93)	12.6 (1.12)

- No TEAEs were reported for any hematologic parameters
- Neutrophil counts were generally stable across all BLU-808 dose levels
- Hemoglobin decreased slightly over time in all dose groups, including placebo, consistent with the effects of phlebotomy; however, there were no significant decreases relative to placebo at any dose level

Conclusions

- BLU-808 had a favorable safety profile up to the maximum dose tested in SAD (42 mg QD) and MAD (12 mg QD) cohorts
  - In the MAD cohort, all TEAEs in participants treated with BLU-808 were Grade 1; no serious TEAEs and no discontinuations or dose modifications due to AEs were reported
  - No significant changes in laboratory assessments, ECGs, or vital signs were reported
- The PK and pharmacodynamics properties of BLU-808 enable tunable dosing to either fully deplete MCs or fully/partially inhibit their activity to maximize benefit-risk
  - BLU-808 demonstrated dose-dependent PK, low PK variability, and a long half-life, supporting QD dosing; BLU-808 C_{min} covered *in vitro* WT KIT IC_{50} at 1 mg QD and reached IC_{90} at doses of ≥3 mg QD
  - Food did not affect the PK of BLU-808
  - BLU-808 resulted in dose-dependent decreases in serum tryptase, reaching a maximum decrease of 87% at 12 mg QD
  - Dose-dependent SCF changes were observed in BLU-808-treated cohorts
- These results support continued development of BLU-808 for patients with MC-driven allergic diseases

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Disclosures

Dr Suram is an employee and equity holder of Blueprint Medicines Corporation. Full disclosures for all authors are available upon request at medinfo@blueprintmedicines.com

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