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

Poster Number 698

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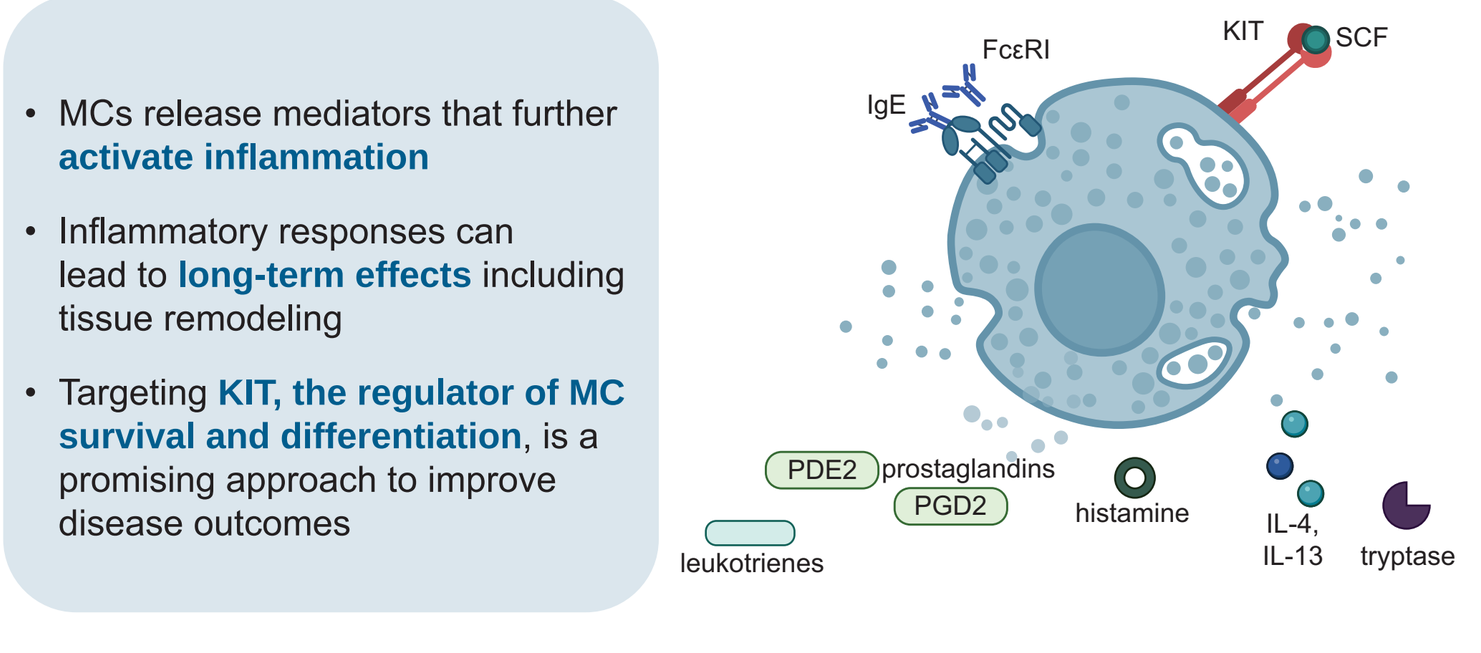
Introduction

- 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

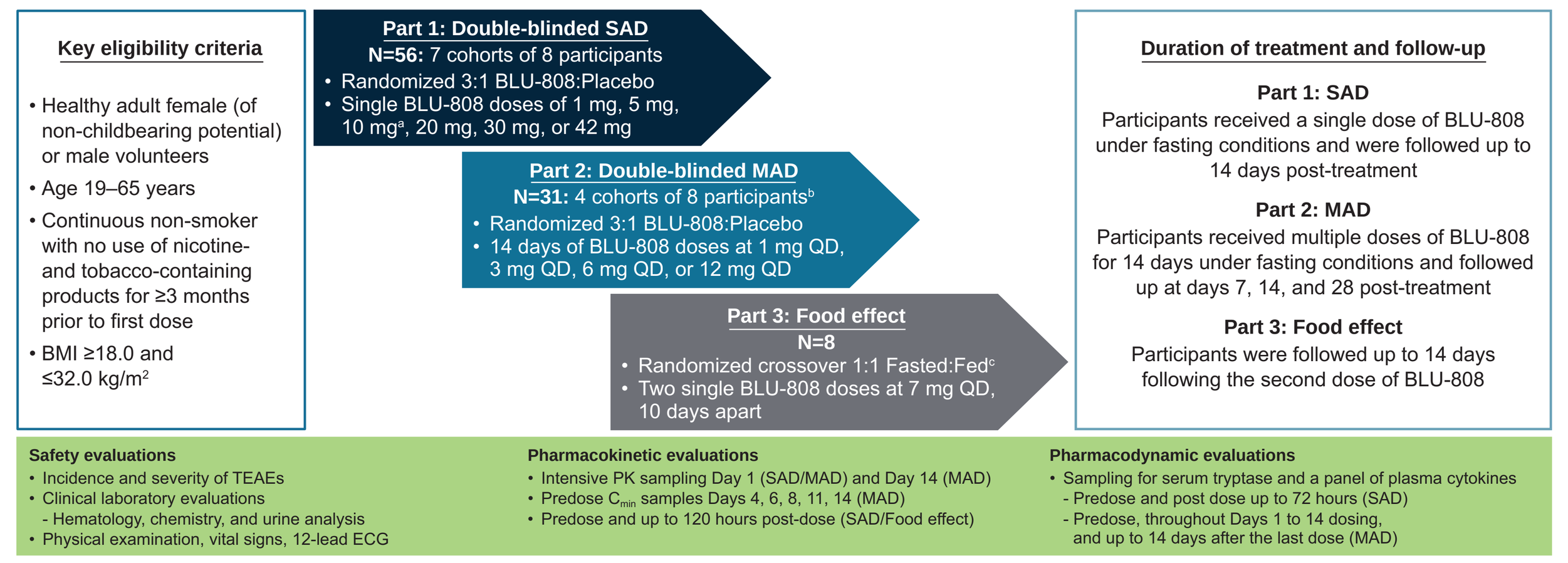

MCs release mediators that further activate inflammation
Inflammatory responses can lead to long-term effects including tissue remodeling
Targeting KIT, the regulator of MC survival and differentiation, is a promising approach to improve disease outcomes
FcεRI
KIT
SCF
IgE
PDE2
prostaglandins
PGD2
leukotrienes
histamine
IL-4
IL-13
tryptase

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 Cmin 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

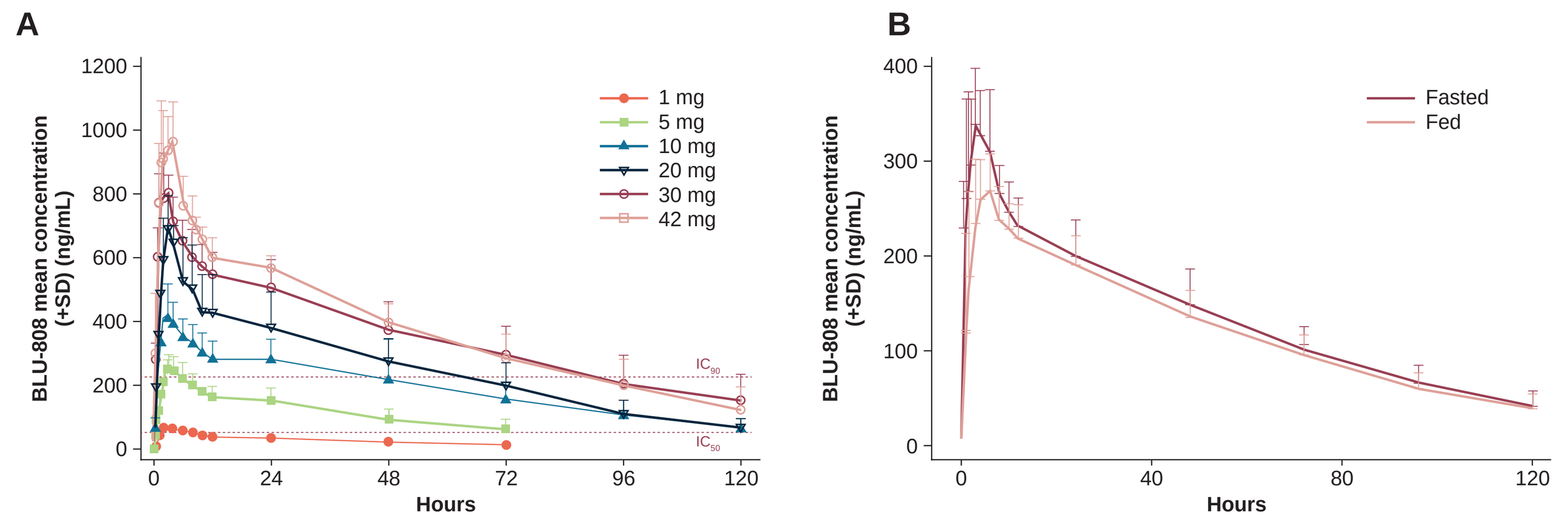
Table 1. Baseline demographics

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



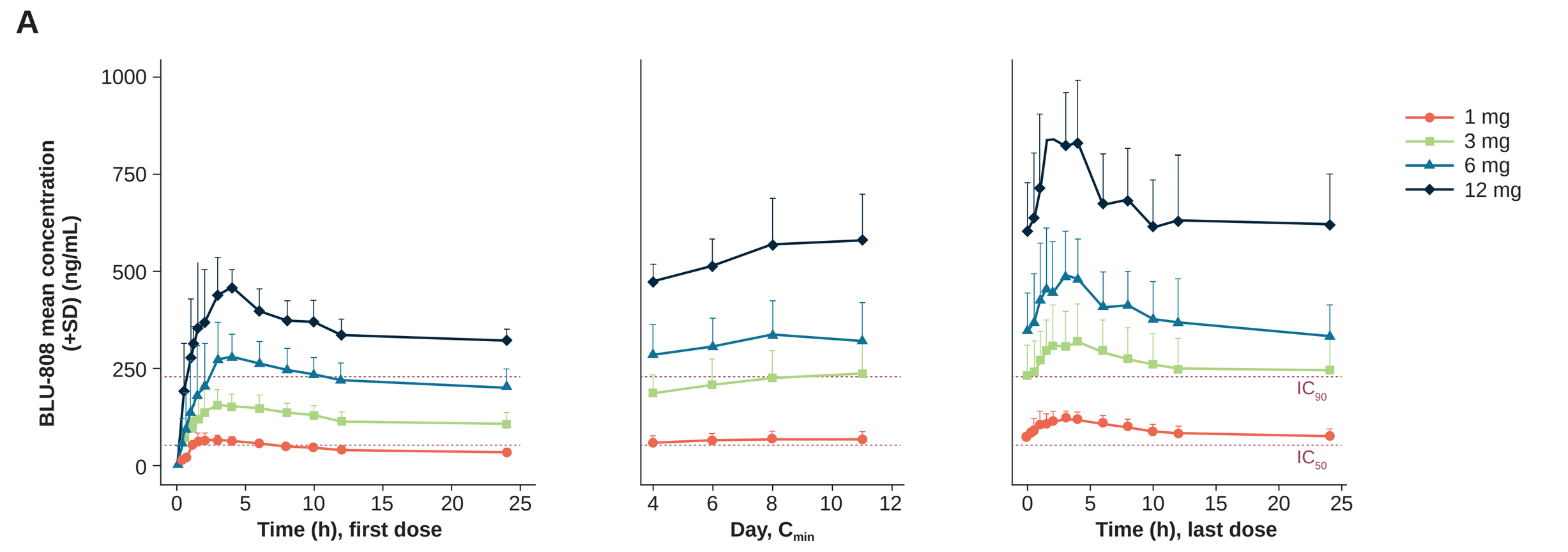
C

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



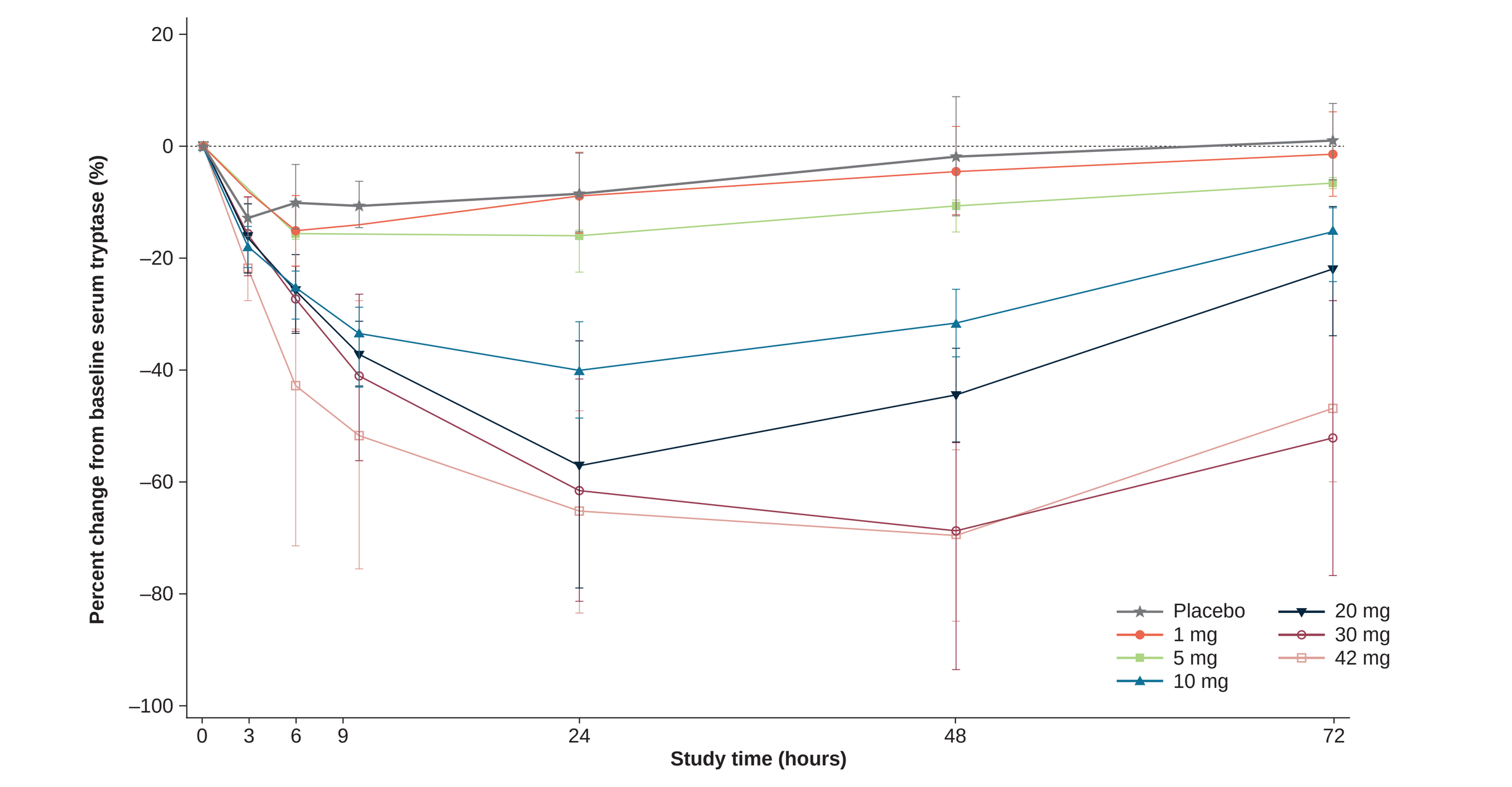
B

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

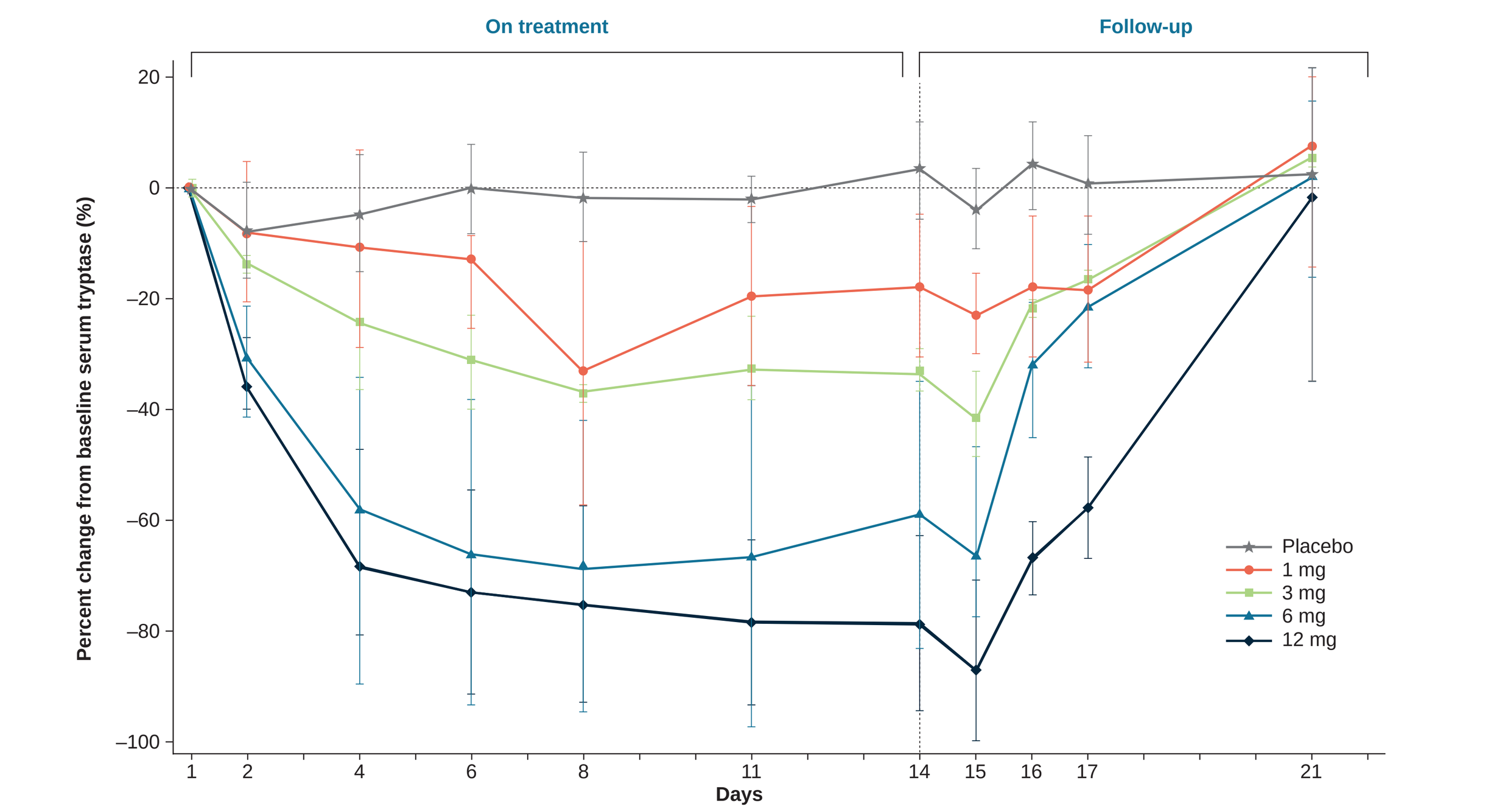


SAD Dose	Change from baseline serum tryptase Maximum (%)	Change from baseline serum tryptase 24hr (%)
Placebo (n=14)	–12	–8
1 mg (n=6)	–15	–9
5 mg (n=6)	–16	–16
10 mg (n=6)	–40	–40
20 mg (n=6)	–57	–57
30 mg (n=6)	–69	–61
42 mg (n=6)	–70	–65

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



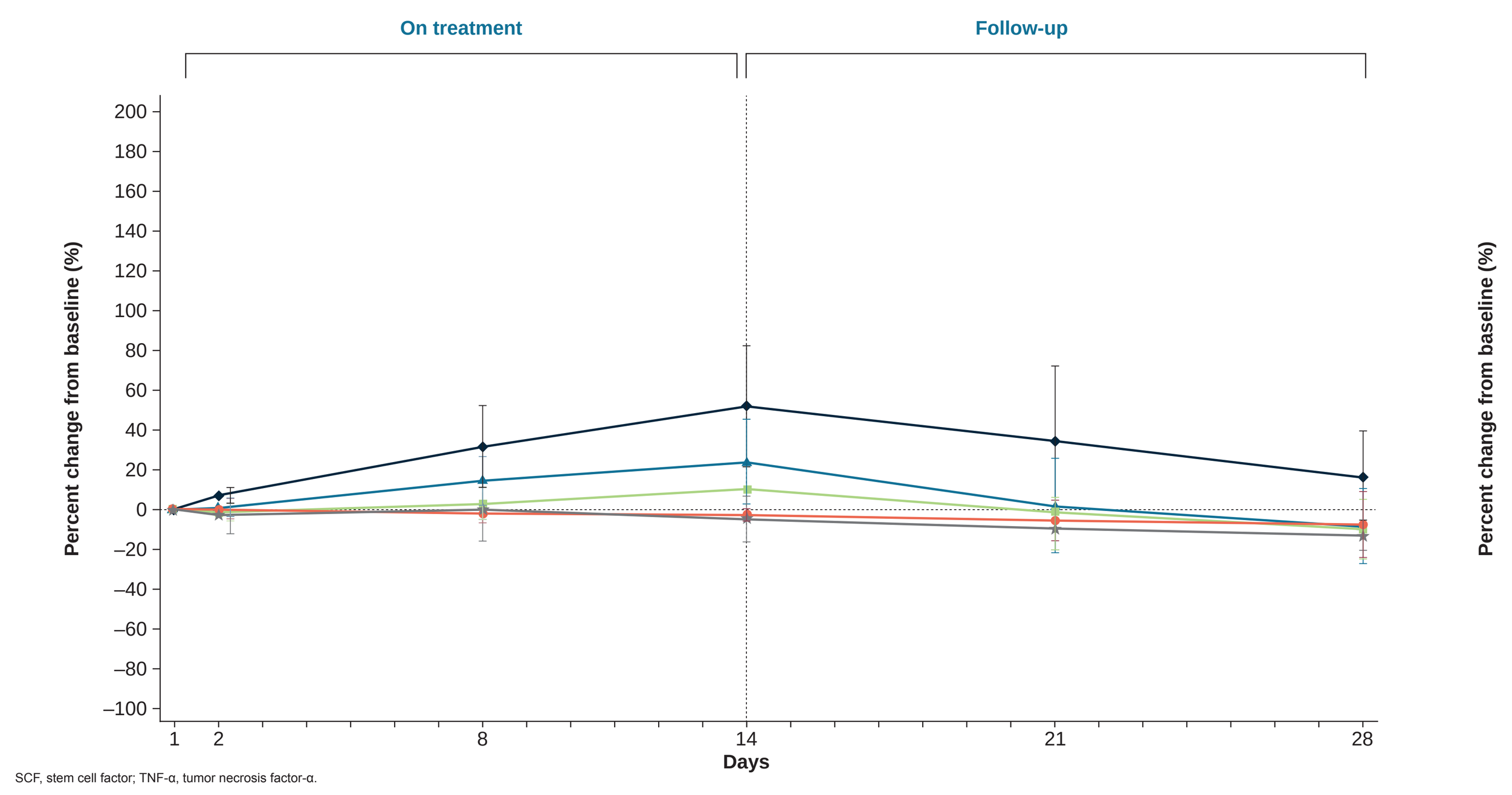
MAD Dose	Change from baseline serum tryptase Percentage reduction at Day 15 (%)	Change from baseline serum tryptase Participants reaching LLOQ
Placebo (n=8)	–4	0
1 mg (n=6)	–23	1/6
3 mg (n=6)	–41	1/6
6 mg (n=6)	–66	3/6
12 mg (n=4)[a]	–87	3/4

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.

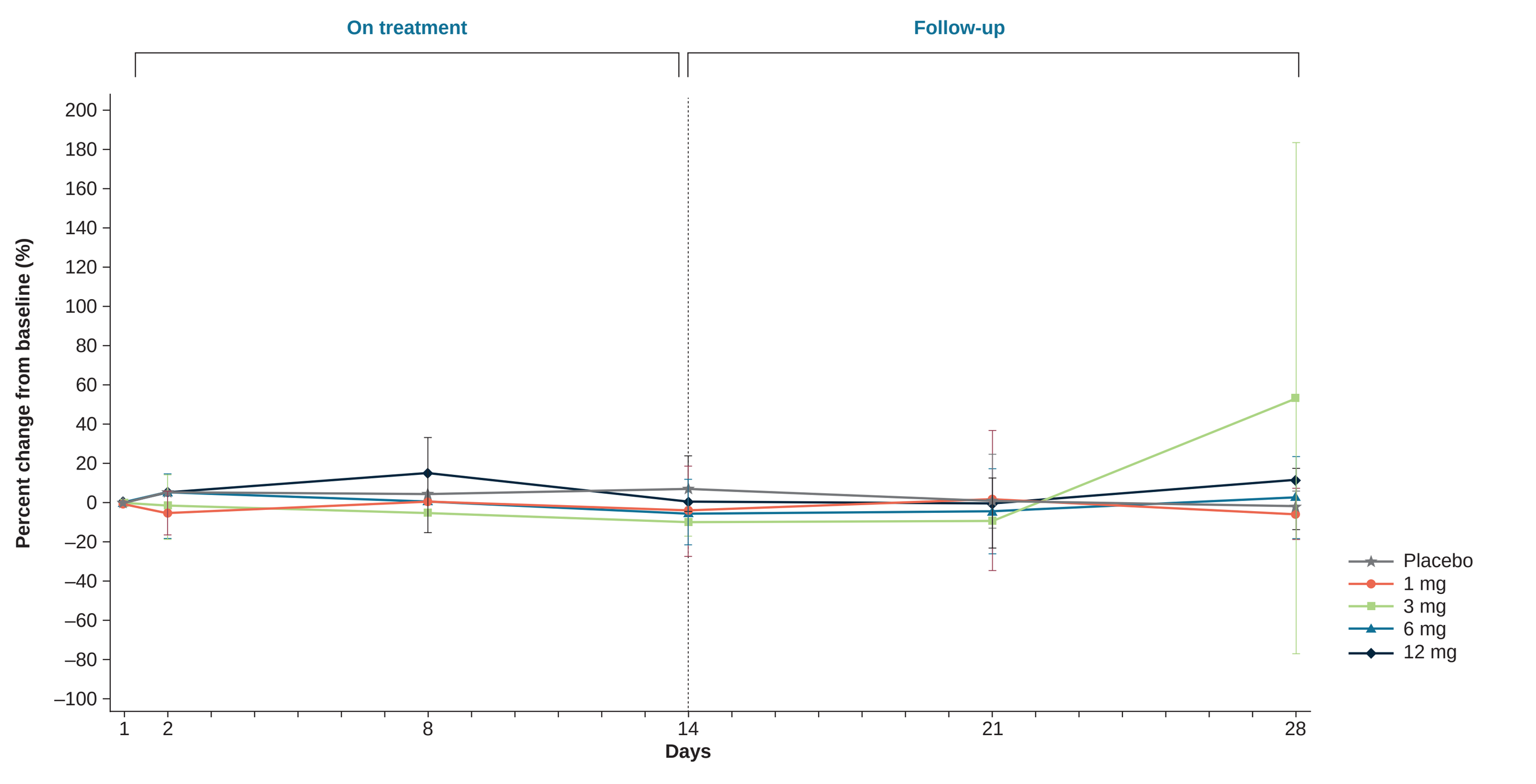
- Maximum mean tryptase reduction in the 12 mg cohort was 87% (at 24 hours after last dose; **Figure 5**)

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

References

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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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Acknowledgements

The authors thank the participants, their families, all other investigators and all investigational site members involved in this study. The authors would like to acknowledge the substantial contributions to analysis in this poster provided by Phaneendhar Gondesi, Chimnonso Onuoha, and Jenkaa Dzekashu.
Medical writing and editorial support was provided by Akanksha Srivastava, MSc and Travis Taylor, BA, all of Paragon (a division of Prime, Knutsford), funded by Blueprint Medicines Corporation. Responsibility for all opinions, conclusions, and data interpretation lies with the authors

Funding

This poster was funded by Blueprint Medicines Corporation.