

Safety, Tolerability, Immunogenicity, and Pharmacokinetics of BCX17725: Single and Multiple Ascending Dose

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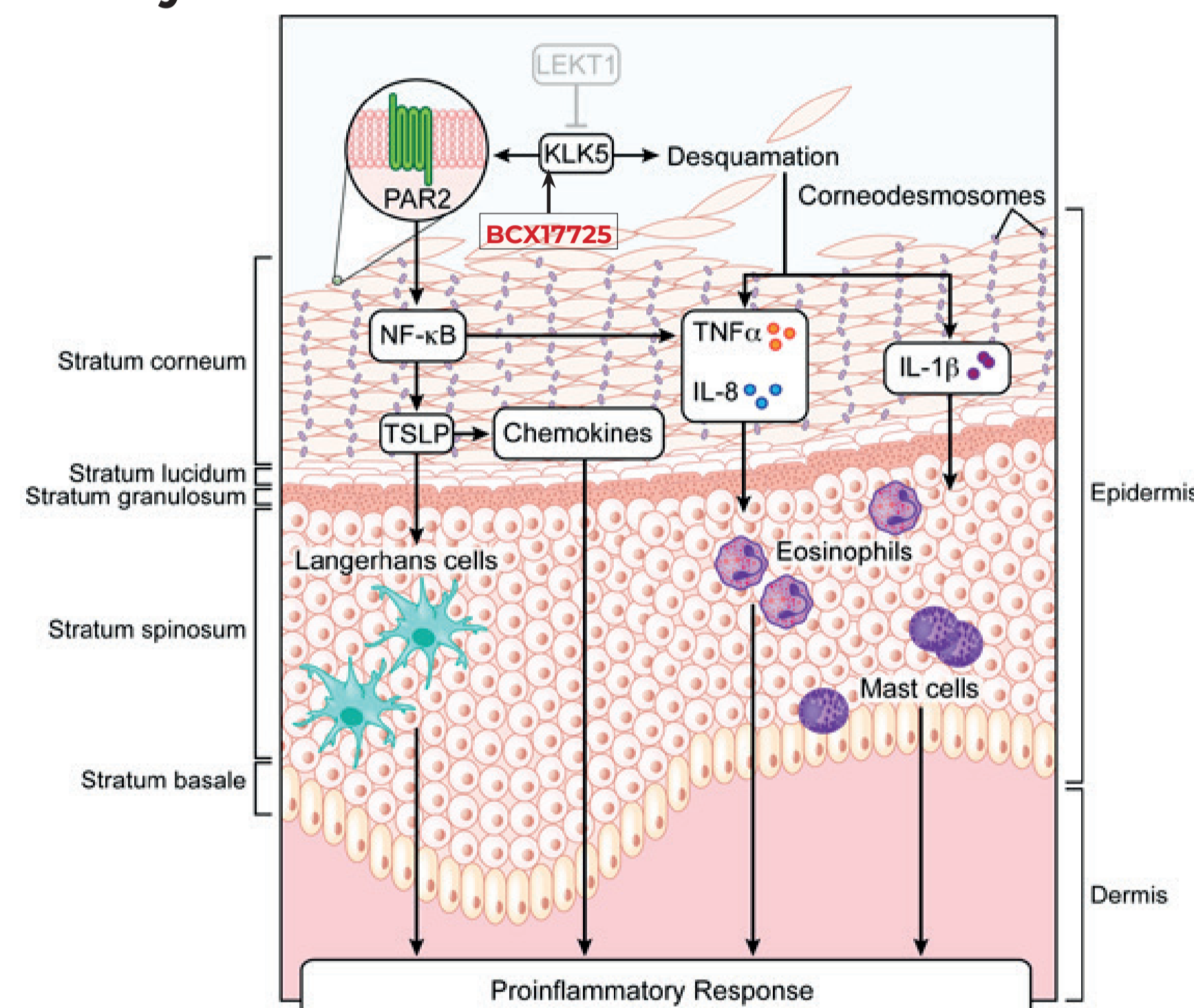
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INTRODUCTION

- SPINK5-syndromic epidermal differentiation disorder (SPINK5-sEDD) or Netherton syndrome (NS) is a rare, severe, genetic disorder caused by pathogenic variations in the *SPINK5* gene, characterized by skin barrier dysfunction, chronic inflammation, and atopy, driven by unregulated epidermal kallikrein (KLK) activity.
- The KLK cascade, initiated by KLK-related peptidase 5 (KLK5), with key downstream effector proteins including KLK-related peptidase 7 (KLK7) and KLK-related peptidase 14 (KLK14), becomes overactive in patients with NS owing to lympho-epithelial Kazal-type-related inhibitor (LEKTI) deficiency.
- BCX17725, a novel recombinant fusion protein, is a potent inhibitor of KLK5 and KLK14 designed to help to restore epidermal protease balance and improve skin barrier function in patients with NS.

Figure 1. Proposed Mechanism of BCX17725 for Treatment of Netherton Syndrome



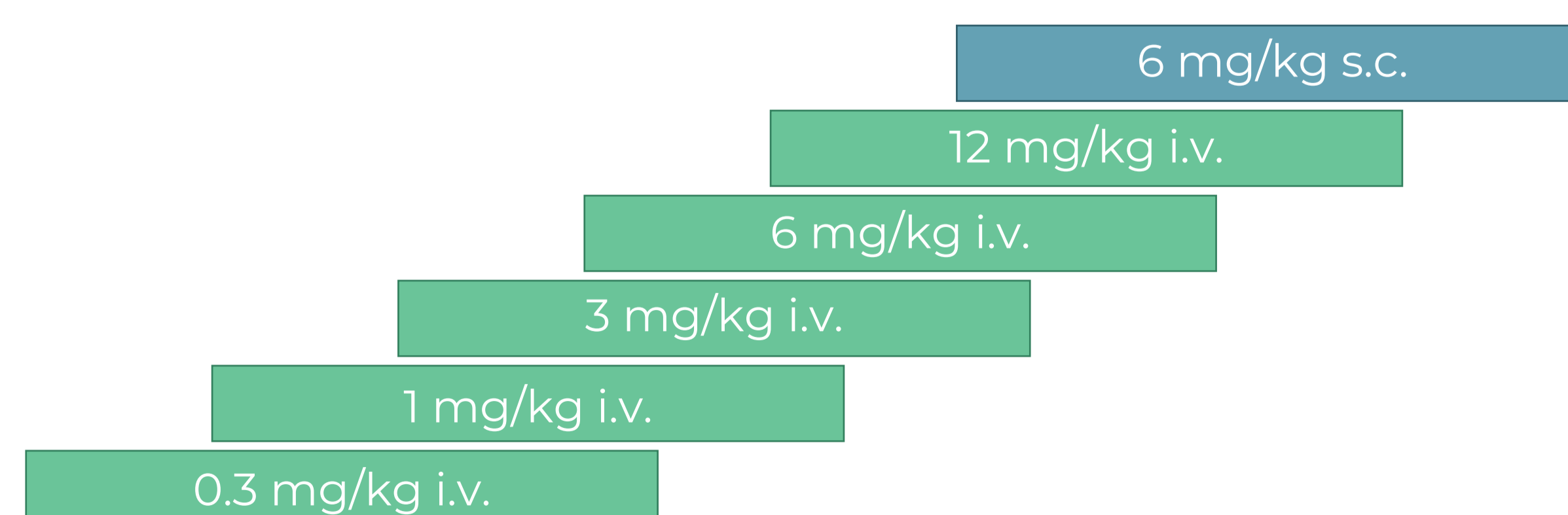
Adapted from Beutler B et al. Phenotypic mutation 'crusty2'. UT Southwestern Medical Center Mutagenetix. 2024. https://mutagenetix.utsouthwestern.edu/phenotypic/phenotypic_rec.cf.m?pk=695.

IL, interleukin; NF-κB, nuclear factor kappa B; PAR2, protease-activated receptor 2; TNF, tumor necrosis factor; TSLP, thymic stromal lymphopoietin.

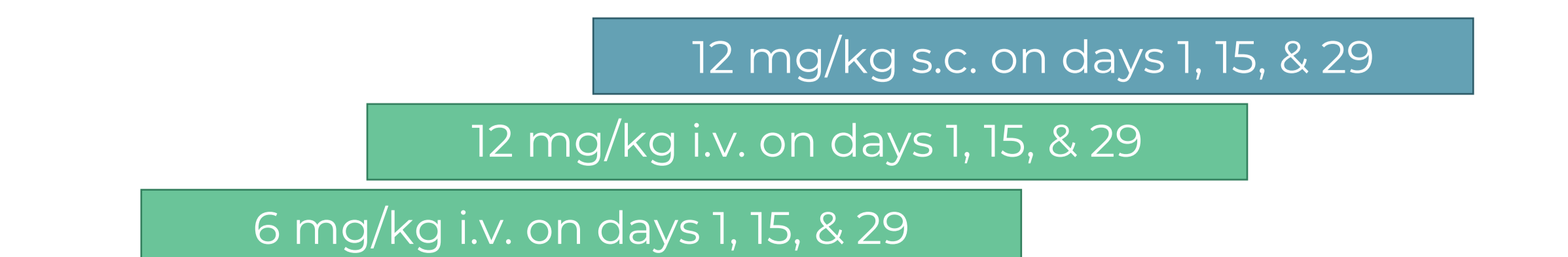
METHODS

- This was a randomized, double-blind, placebo-controlled first-in-human study in healthy adult participants (NCT06539507).
- Single and multiple ascending doses of BCX17725 were administered by intravenous and subcutaneous injections to evaluate safety, tolerability, pharmacokinetics (PK), and immunogenicity.
- Both study parts were placebo-controlled, with 6 and 8 healthy volunteers receiving each dose in part 1 (4 active; 2 placebo) and part 2 (6 active; 2 placebo), respectively.

Part 1: Single ascending doses (SAD)



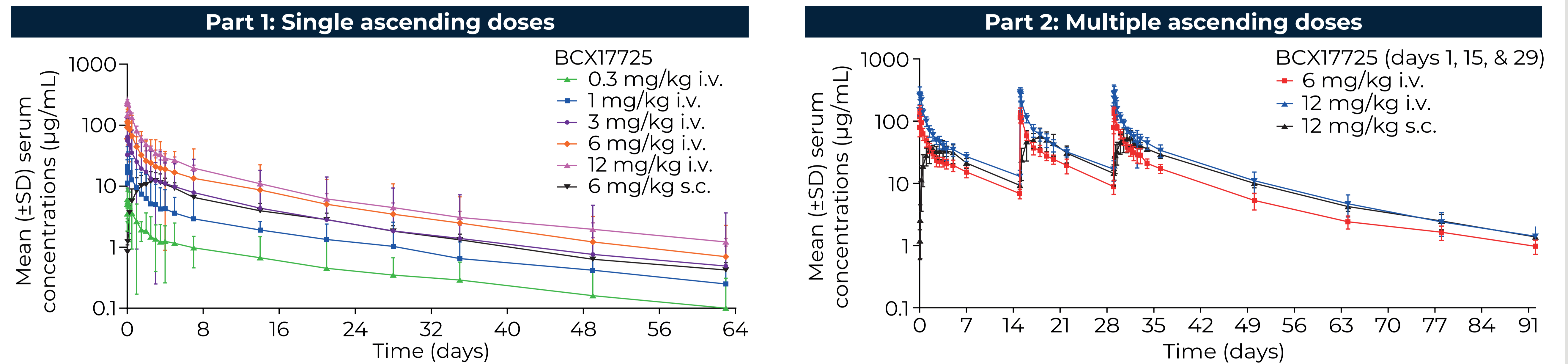
Part 2: Multiple ascending doses (MAD)



i.v., intravenous; s.c., subcutaneous.

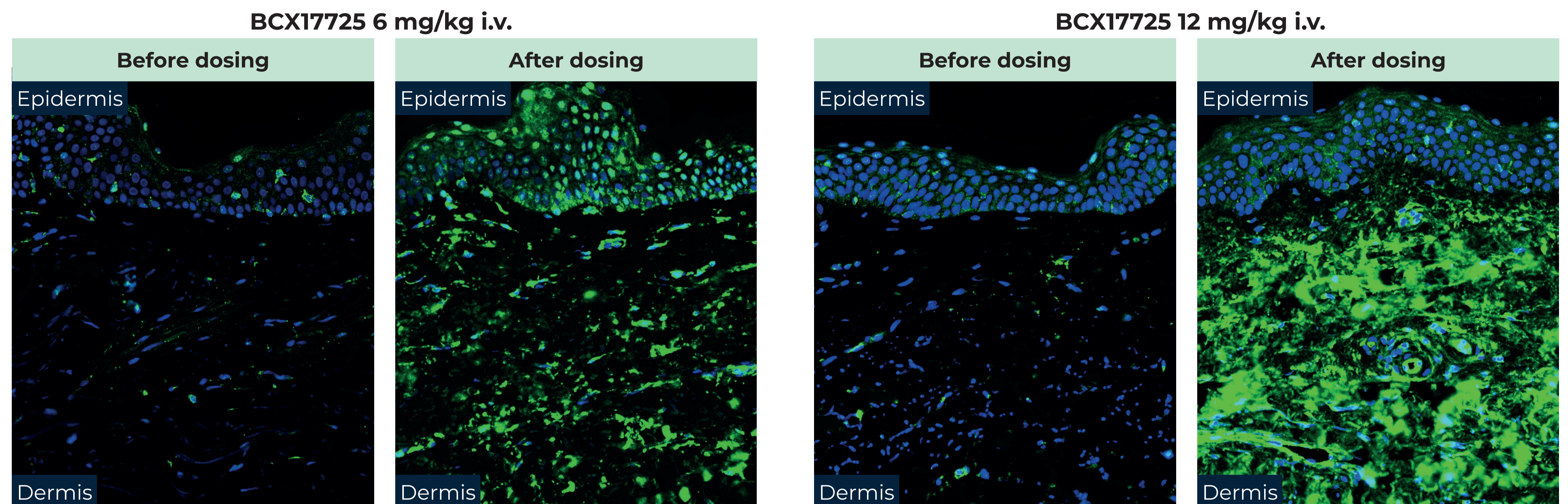
RESULTS

Figure 2. Serum Concentration–Time Profiles of BCX17725 in Healthy Volunteers Following Single or Multiple Doses of BCX17725 for Parts 1 and 2 on a Semi-Log Scale



- No exposure-related adverse events (AEs) were observed across tested doses.
- PK profiles were predictable, with low to moderate variability and consistent concentration–time profiles. Concentrations approximated steady state by the second dose.
- Area under the curve (AUC) and maximum plasma concentration (C_{max}) were approximately dose-proportional.
- Geometric mean terminal half-life ($t_{1/2}$) ranged from 15 to 19 days.
- There was no evidence of time-dependent PK.
- No PK effects were attributable to anti-drug antibody formation.

Figure 3. BCX17725 Distributes to Dermis and Epidermis After Intravenous Dosing in Healthy Volunteers



Samples taken from part 2 participants before and after multiple ascending doses of BCX17725, with biopsy performed on day 1 prior to the first dose of BCX17725 and on day 29, 5 hours after the end of infusion after the third dose of BCX17725. Skin biopsies represent a single sample from one participant at each dose level. Immunofluorescence using an antibody specific to BCX17725, followed by a fluorescence-tagged secondary antibody (green). Cell nuclei: 4',6-diamidino-2-phenylindole (DAPI) fluorescence (DNA, blue).

SAFETY

- All treatment-emergent adverse events (TEAEs) were either mild or moderate and consisted mainly of injection-site reactions (e.g., injection-site pain, erythema, swelling, pruritus), dermatologic events (e.g., contact dermatitis, rash, urticaria, dry skin), and other events such as headache, fatigue, and mild infections, with no drug-related serious AEs and no discontinuations due to AEs.
- No clinically meaningful immunogenic responses were observed or attributed to anti-drug antibody formation.

Table 1. Summary of TEAEs by Study Part

Category, number of participants, n (%)	Part 1: SAD (n=37)	Part 2: MAD (n=24)
Participants with ≥1 TEAE	28 (75.7)	17 (70.8)
Participants with treatment-related TEAEs	9 (24.3)	10 (41.7)
Grade ≥3 TEAEs	0 (0)	0 (0)
Serious TEAEs	0 (0)	1 (4.2) ^a
TEAEs leading to withdrawal or death	0 (0)	0 (0)
Injection-site reactions ^b	3 (42.9) ^b	8 (100) ^b

Data shown represent each study part as combined cohorts with BCX17725 and placebo patients pooled.

TEAEs were defined as AEs occurring on or after initiation of study drug. Treatment-related TEAEs assessed by investigator as 'related'. AEs were coded using Medical Dictionary for Regulatory Activities version 27.0.

^aNot treatment related. ^bFor subcutaneous cohorts only (part 1: 6 mg/kg s.c., n = 7; part 2: 12 mg/kg s.c., n = 8).

CONCLUSIONS

- BCX17725 demonstrated a favorable safety profile in healthy adult participants across single and multiple dose administrations.
- BCX17725 demonstrated predictable PK with consistent profiles across both single and multiple intravenous and subcutaneous dosing.
- BCX17725 achieved substantial distribution into the dermis, with epidermal penetration.
- These data support further clinical evaluation of BCX17725 for the treatment of NS.