Brilacidin is a synthetic molecule that represents a novel class of antimicrobial agents that mimic the structure and function of host defense proteins. Brilacidin (BRI), which acts by disrupting bacterial cell membrane integrity, has potent antimicrobial activity against a wide range of Gram-positive, Gram-negative, and Gram-variable bacteria. Phase 1 studies (Studies PMX63-101, PMX63-102, and PMX63-103) and patients with ABSSSI were included in this analysis. A PPK model, developed using all BRI PK data collected to date, allowed for identification of significant covariate effects.

Study Data
A total of 2,960 plasma brilacidin concentrations collected from 391 individuals were used to develop and evaluate the final population PK model. The study population included 179 healthy subjects and 212 patients with ABSSSI enrolled in three Phase 1 studies (Studies PMX63-203 and CTIX-BRI-204) where IV brilacidin was infused over 1 hour as a single dose or as repeated doses either every 24 (q24h) or 48 hours (q48h). The study design included a placebo arm and a brilacidin group with two different dose levels.

RESULTS
The final population PK model, including all statistically significant covariate effects, was qualified and validated. Model fit was assessed using standard statistical and graphical goodness-of-fit (GOF) criteria and was found to be consistent with the observed data. Individual post-hoc parameters were used to calculate the alpha-, beta-, and gamma-phase half-lives, which were 1.4, 10.7, and 73.2 h, respectively. A prediction-corrected visual predictive check was performed, demonstrating excellent agreement between the observed data and both the population predictions and the individual post-hoc predictions. The model was also validated in a separate dataset from Study PMX63-203.

The most statistically significant parameter-covariate relationship identified was the impact of body weight on BRI clearance. Males had a 21.5% faster brilacidin CL relative to females throughout the entire range of each body weight. The coefficient (Vp1 at a median weight of 78 kg) for Vc was 0.140 (37.4% CV) while as expected, body size was predictive of the overall Vc.

The total population PK model parameter estimates and associated precision (%SEM) are presented in Table 1. The parameter estimates were qualitatively consistent with those from previous studies.

CONCLUSIONS
A three-compartment model with zero-order input and first-order elimination best described the plasma brilacidin concentration-time profile in both healthy subjects and patients with ABSSSI. The most statistically significant parameter-covariate relationship identified was the impact of body weight on BRI clearance. Males had a 21.5% faster clearance relative to females. The model was validated in a separate dataset from Study PMX63-203, demonstrating excellent agreement between the observed data and both the population predictions and the individual post-hoc predictions. The model was also validated in a separate dataset from Study PMX63-203.

REFERENCES