Population PK Analysis of Relebactam Lung Penetration Profile in Healthy Subjects

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Objectives: Relebactam (REL) is a novel dual class A/C β-lactamase inhibitor co-administered with imipenem/cilastatin (IMI), and has shown efficacy in pulmonary infection models with imipenem-resistant *Pseudomonas aeruginosa*. However, REL penetration into the lung had not been studied in humans. Thus, we aimed to develop a REL population PK model that describes the plasma and intrapulmonary PK of multiple IV doses of REL in combination with IMI in healthy volunteers and estimate the degree of REL intrapulmonary penetration.

Methods: Data from 65 PK observations (n = 17) from a phase I study were used to develop the REL population PK model. A naïve pooled data approach was taken due to the sparse nature of lung sampling. To elucidate the relationship between plasma and epithelial lining fluid (ELF) concentrations, three approaches were tested: (1) as a third compartment (Figure 1a), (2) as a constant partition coefficient (Figure 1b), and (3) as an effect compartment (Figure 1c). Modeling was performed in NONMEM 7, with data processing and graphic in R (version 3.3).

Results: A two compartment model with first-order elimination sufficiently described REL plasma PK, consistent with previous approaches. A constant partition coefficient of 0.55 based on unbound plasma levels best described REL penetration into the ELF.

Conclusions: These results suggest that under the current dosing regimen, REL exhibited satisfactory penetration into lung (55% of unbound levels in plasma). REL plasma and ELF concentration-time profiles exhibited similar kinetics, and thus a time-invariant partition coefficient approach was optimal. Our proposed dosing regimen is targeted to achieve the goals of maintaining and/or restoring imipenem efficacy in patients with pneumonia.