Title: Clinical Trial Simulations and Pharmacometrics Analysis in Pediatrics: Application to Inhaled Loxapine in Children and Adolescents

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Problem Statement: Loxapine for inhalation is a drug-device combination product that has been approved in adults for the acute treatment of agitation associated with schizophrenia or bipolar I disorder. This case study intends to illustrate how to utilize adult information to inform trial design including dosage selection in children and adolescent patients.

Description: A nonlinear mixed-effects population PK model was developed using adult loxapine PK data and was adjusted for the targeted pediatric age groups by applying allometric scaling to account for body size effects. Based on this pediatric model, age-appropriate regimens to achieve loxapine exposures (area under the concentration-time curve and peak concentration) similar to the ones associated with therapeutic effect in the adult studies were identified via trial simulation. D-optimal design and power analysis were conducted to identify optimal PK sampling times and sample size, respectively.

Applications & Learnings: The developed clinical trial design was considered appropriate and feasible and formed the basis of a phase I study to assess the safety and pharmacokinetics of loxapine for inhalation in children and adolescents (ClinicalTrials.gov ID: NCT02184767). The results of the phase I study showed that overall loxapine exposures in the pediatric patients were consistent with what had been predicted by the trial simulations. The presented example illustrates how population PK modeling and simulation can assist in the design of informative clinical trials as part of the process of identifying safe and effective doses and dose ranges in children and adolescents.

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