Population Pharmacokinetics ofAzithromycin in Preterm Neonates

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Purpose
To characterize the PK/PD parameters and microbiological efficacy of Azithromycin (AZI) 20 mg/kg IV x3 in infants 240-286 wk gestation receiving positive pressure ventilation within 72h of birth who are at high risk of *Ureaplasma* respiratory tract colonization and development of Bronchopulmonary Dysplasia (BPD).

Methods
Fifteen subjects (*Ureaplasma*-positive=7) enrolled at 6 sites received AZI 20 mg/kg IV over 60 min every 24h x 3. AZI concentrations were determined in plasma samples, obtained up to 168h post first dose, by a validated LC/MS/MS method. Respiratory samples for *Ureaplasma* culture, PCR, antibiotic susceptibility testing, and cytokine concentrations were obtained pre-dose and 2d, 4d post last dose and 21d of age. Population Pharmacokinetic modeling was conducted using non-linear mixed-effect modeling (NONMEM) approach. BPD was confirmed by a timed-oxygen reduction test at 36 wk post-menstrual age (PMA).

Results
The best model to describe the AZI PK in preterm neonates was a 2-compartment model with all parameters scaled on body weight. The final model was based on data obtained from 40 subjects (10 mg/kg single dose (N=12); 20 mg/kg single dose (N=13) and 20 mg/kg multiple dose (N=15)). The population PK parameters’ estimates (%RSE) for Cl, V1, Q1 and V2 were 0.15 x WT(kg) 0.75 (10), 1.88 x WT (kg)(11), 1.79 x WT (kg) 0.75 (10) and 13 x WT (kg)(12). The AUC24 (u) /MIC90 for the multiple dose was 5.69h. All cultures were negative post 3 doses and the drug was well tolerated with no drug-related AE. There was a shorter duration of supplemental oxygen and shorter duration of mechanical ventilation in the 20 mg/kg AZI multidose treated infants compared to the single dose groups.

Conclusion
A Population PK model for AZI in preterm neonates was developed and AZI 20 mg/kg x3 dosage regimen appears to be safe and effective for eradication of *Ureaplasma* in infected neonates. A randomized placebo-controlled trial of AZI to demonstrate efficacy to eradicate *Ureaplasma* and to prevent BPD is needed. This is an "Encore Presentation" previously presented at the annual meeting of the Pediatric Academic Societies, May 2013.