

**Title:** Accelerator Mass Spectrometry (AMS) Enables Pediatric PK/PD Analysis in a Neonate Clinical Trial

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**Objectives:** Clinical drug testing is often not done in newborns, significantly due to a lack of non-invasive and sensitive assays and tools. This often results in needed medicines being prescribed off-label, with doses scaled from adult data using techniques based on body mass and surface-area. Ursodiol (Actigal®) (UDCA) is an example of a drug neither clinically tested nor approved by the FDA for use in pediatric patients. However, UDCA has been used to treat pediatric cholestasis. This poster describes the first clinical trial of UDCA in neonates, and the determination of neonate UDCA PK. In addition, UDCA pharmacodynamics were investigated using physiological models based upon the PK analysis.

**Methods:** Measurement of UDCA pharmacokinetics (PK) requires differentiating between the endogenous and exogenous forms of the compound, using a labeled tracer. Accelerator Mass Spectrometry (AMS) is an analytical method with very high sensitivity and specificity[1,2,3]. AMS enables clinical trials to be carried out in neonates as it yields accurate UDCA concentrations with remarkably low (10 microlitres) sample volumes and negligible radiological exposure. Lower sample volume allows more frequent sampling, with fewer subjects required. In this trial, five subjects in the NICU were given 3 escalating doses of radiolabeled UDCA (8, 26, 80 ng) at 48 hr intervals. Subjects did not have cholestasis and all caloric intake was parenteral. Three subjects completed 2 doses, 1 subject completed 2 doses, and 1 subject completed 1 dose.

**Results:** Noncompartmental analysis of the UDCA concentration data, fitted to account for multiple doses, showed that UDCA concentrations were dose-proportional. A mixed-effect compartmental modeling approach indicated that a 2-compartment model best described UDCA pharmacokinetics, with typical CL and V<sub>ss</sub> values of 22mL/hr and 2.145 L, respectively. The model was extended to represent UDCA effect on cholestasis, and to predict changes in bile release to allow for dose determination.

**Conclusions:** AMS provided accurate concentration data with advantages being minimal sample volume and very low radiological exposure. The very high sensitivity of AMS allows a significant lower-than-standard tracer dose (0.33nCi versus 1nCi). Using measurements from this technique, we found UDCA to have low intrasubject variability. This supports AMS as a useful tool for modeling and insight into UDCA PK. There was significant inter-subject variability in the five neonate subjects. AMS sensitivity was sufficient to measure UDCA over the wide range of concentrations. Modeling suggested experiments to understand variability between subjects, and methods to set dosing to reduce it. The PK model constructed from AMS data has been extended to a PD model to study and understand bile flux in cholestatic patients. AMS coupled with PK/PD modeling is a useful pharmacological tools for pediatric clinical trial design and analysis.

#### **References:**

1. Vogel JS, Love AH. Quantitating Isotopic Molecular Labels with Accelerator Mass Spectrometry. *Methods in Enzymology*. 2005; 402: 402-422.
2. L. Vuong, P. Lohstroh, A. Blood, H. Vasquez, J. Vogel, Applying 14C-AMS in Neonatal Research and Care, *Journal of Labeled Compounds and Radiopharmaceuticals*, 2010, v3:346.
3. Applications of Accelerator Mass Spectrometry (AMS) in Pediatric Drug Evaluation, Vuong, L.T., Blood A., Vogel J.S., Anderson M.E., Goldstein B, in *Microdosing in Investigational Clinical Trials: Challenges And Perspectives*, editors: H. Mucke & G. Lappin, Publisher: John Wiley & Sons, In Press.