OMICS Group Conferences
Accelerating Scientific Discovery

2nd International Conference and Exhibition on
Pharmacovigilance & Clinical Trials
November 18-19, 2013 Hilton San Antonio Airport, TX, USA

Renal excretion of apricitabine: *Ex vivo* and *In vivo* studies

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Apricitabine (ATC) is a novel nucleoside reverse transcriptase inhibitor undergoing phase 2/3 clinical development for the treatment of HIV infection. In this investigation, the renal handling of ATC was evaluated in isolated perfused rat kidney (IPK) model with follow-up *in vivo* studies. IPK experiments were performed to characterize the renal excretion of ATC, to probe mechanisms of ATC excretion using known inhibitors of organic cation (cimetidine) and organic anion (probenecid) transport systems, and to screen for potential drug-drug interactions between ATC and clinically relevant medications (dapsone, metformin, pentamidine, stavudine, tenofovir and ritonavir). ATC demonstrated net tubular secretion in the IPK with average excretion ratio (XR) of 2.1. ATC XR decreased 3.6-fold in the presence of cimetidine and 2-fold in the presence of probenecid. Among the clinically relevant medications, metformin produced the greatest inhibitory effect on ATC excretion. *In vivo* studies were conducted in rats to evaluate ATC disposition upon co-administration with compounds that showed a significant effect on ATC clearance in the IPK model. Co-administration of cimetidine and trimethoprim significantly reduced ATC renal clearance, but resulted in only a moderate increase in plasma exposure. Metformin had no apparent effect on ATC clearance. These findings indicate that the IPK model is more sensitive to secretory inhibition as compared to *in vivo*. The medications screened showed minimal effects on ATC renal excretion in the IPK, and should thus be excluded as potential *In vivo* interactants. Overall, this study generated important information on renal handling of ATC to support its development and commercialization.

Biography

Mariana Babayeva is an Associate Professor at Touro College of Pharmacy, New York City. In addition to her role at Touro, she is also a Visiting Scientist at Arnold and Marie Schwartz School of Pharmacy of LIU, an Adjunct Professor at Rockefeller University, and Instructor at UNC, Eshelman School of Pharmacy. She has over 10 years of experience in clinical practice. She is recognized for her expertise in the pharmacokinetics of renal excretion and the use of animal and organ models to explore mechanism and kinetics of renal clearance. She has conducted several international research projects. She has published in peer-reviewed journals focusing on pharmocokinetics of interaction.

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