

**Pharmacology Studies presented at the  
51<sup>st</sup> Interscience Conference on Antimicrobial Agents and Chemotherapy  
(ICAAC), Chicago, 17-20 September 2011.**

*This report summarises pharmacology studies presented at the recent meeting in Chicago.*

*Abstracts (excluding late breakers) are available **for a limited time** on the [conference website](#) or via the links in this report.*

## Contents

<b>Drug Interactions .....</b>	<b>2</b>
FPV/r and dolutegravir (Abstract A1-1727).....	2
RAL and telaprevir (Late Breaker A1-1738a).....	2
Switching from EFV to rilpivirine (Late Breaker H2-794c).....	2
<b>Renal Excretion Studies .....</b>	<b>3</b>
Cobicistat (Abstract H2-804) .....	3
Cobicistat and RTV (Abstract A1-1724) .....	3
Dolutegravir (Abstract A1-1728) .....	3
<b>Other Studies .....</b>	<b>4</b>
Plasma and intracellular pharmacokinetics of 3TC at two doses (Abstract A1-1720) .....	4
Pharmacokinetics of extended release NVP (Abstract A1-1721) .....	4
CYP2B6 polymorphisms with EFV and rifampicin (Abstract A1-1723).....	4
New integrase inhibitor (Abstract H2-801) .....	5

## Drug Interactions

### **FPV/r and dolutegravir (Abstract A1-1727)**

#### **Effect of fosamprenavir/ritonavir on the pharmacokinetics of the integrase inhibitor, dolutegravir, in healthy subjects.**

*Song I, et al. A1-1727.*

Dolutegravir (S/GSK1349572) is a once daily, unboosted, next generation integrase inhibitor with activity against viruses resistant to raltegravir. As DTG is primarily metabolized by UGT1A1 with CYP3A as the minor route and fosamprenavir/ritonavir (FPV/r) are inducers/inhibitors of these enzymes, the effect of FPV/r on DTG pharmacokinetics was evaluated in a single-centre, open-label, single-sequence study in 12 healthy adult subjects. Subjects received DTG (50 mg once daily for 5 days followed by DTG (50 mg once daily) in combination with FPV/r (700/100 mg twice daily) for 10 days. Co-administration of FPV/r decreased DTG AUC, C<sub>max</sub> and C<sub>trough</sub> by 35%, 24%, and 49%, respectively. Amprenavir pharmacokinetic parameters were similar to historical values. Despite these reductions, DTG concentrations remained well above the protein adjusted-IC<sub>90</sub> for wild type HIV viruses and no dose adjustment is needed when DTG is co-administered with FPV/r in integrase inhibitor-naïve subjects.

### **RAL and telaprevir (Late Breaker A1-1738a)**

#### **The pharmacokinetic interaction between telaprevir and raltegravir in healthy volunteers.**

*Van Heeswijk R, et al. A1-1738a.*

The interaction between telaprevir (a novel HCV protease inhibitor) and raltegravir (an HIV integrase inhibitor) was investigated in 20 HIV/HCV-negative subjects who received telaprevir (750 mg every 8 hours) and RAL (400 mg twice daily) alone and in combination. There was no significant effect of RAL on telaprevir pharmacokinetics – AUC, C<sub>max</sub> and C<sub>min</sub> increased by 7%, 7% and 14%, respectively. In the presence of telaprevir, RAL AUC, C<sub>max</sub> and C<sub>min</sub> increased by 31%, 26% and 78%, respectively. Exposure to RAL-glucuronide was similarly increased. The increase in RAL exposure may possibly be due to inhibition of intestinal P-gp by telaprevir. The similar ratio of RAL-glucuronide to RAL suggests that telaprevir did not influence UGT1A1 activity. The effect of telaprevir on RAL was not considered to be clinically relevant.

### **Switching from EFV to rilpivirine (Late Breaker H2-794c)**

#### **Switching from efavirenz/emtricitabine/tenofovir disoproxil fumarate (EFV/FTC/TDF) single tablet regimen (STR) to emtricitabine/rilpivirine/tenofovir disoproxil fumarate (FTC/RPV/TDF) STR in virologically suppressed, HIV-1 infected subjects.**

*Mills A, et al. H2-794c.*

A previous pharmacokinetic study in HIV-negative subjects showed that switching from EFV decreased rilpivirine C<sub>min</sub> by up to 25% for approximately 4 weeks due to EFV-mediated CYP3A induction. This study in 49 virologically suppressed HIV-infected subjects evaluated the effect of switching from EFV to rilpivirine. All subjects maintained HIV RNA <50 copies/ml through the 12 weeks of study. Rilpivirine mean trough concentrations at 2 weeks post switch (55 ng/ml) and 4-12 weeks post switch (68-85 ng/ml) were similar to those observed in phase 3 studies (~50-80 ng/ml). No subject had rilpivirine concentrations below the limit of quantification at any visit. Mean EFV baseline trough concentration was 2.2 µg/ml and 50% of subjects had measurable EFV concentrations at 4 weeks post switch. These results suggest that the brief EFV inductive effects on rilpivirine metabolism may not be clinically relevant in virologically suppressed patients.

## Renal Excretion Studies

### **Cobicistat (Abstract H2-804)**

#### **Effect of cobicistat on glomerular filtration rate (GFR) in subjects with normal and impaired renal function.**

*German P, et al. H2-804.*

Cobicistat is a potent CYP3A inhibitor (pharmacoenhancer) currently in Phase 3 testing in combination with the HIV integrase inhibitor elvitegravir and with atazanavir. Decreases in estimated creatinine clearance (eGFR) were observed in subjects in Phase 1 and 2 clinical studies, which occurred within the first few days of dosing and reversed upon discontinuation of study drugs. This study evaluated the potential effect of cobicistat (150 mg once daily) on renal function in two cohorts of non-HIV infected subjects with normal renal function (eGFR >80 ml/min, n=12) and mild-moderate impairment (eGFR 50-79 ml/min, n=18) using iohexol, a probe drug excreted almost exclusively by glomerular filtration. Actual GFR was measured on Days 0, 7 and 14 (7 days post-dosing) while eGFR was assessed daily. Cobicistat did not affect actual GFR, but eGFR determination based on serum creatinine. Onset was within days of initiation and quickly reversed upon stopping cobicistat. The time to onset, magnitude and time to resolution of changes in eGFR are consistent with altered proximal tubular secretion of creatinine through inhibition of transporters in the kidney tubules.

### **Cobicistat and RTV (Abstract A1-1724)**

#### **Effect of cobicistat and ritonavir on proximal renal tubular cell uptake and efflux transporters.**

*Lepist EI, et al. A1-1724.*

Increases in serum creatinine and a corresponding reduction in estimated glomerular filtration rate (eGFR) without changes in actual GFR (aGFR) have been reported with a number of approved drugs. Since eGFR is commonly used to monitor renal function, further understanding of the mechanism for decreased creatinine elimination is important. In this study, inhibition of OCT2, OCTN1, MATE1, MATE2-K, Pgp, MRP2 and BCRP transporters was investigated in transfected cell-lines with drugs known to reduce eGFR including cimetidine, trimethoprim, dolutegravir, cobicistat and ritonavir. Dolutegravir was shown to inhibit active tubular secretion of creatinine facilitated by uptake from plasma into the proximal tubule by OCT2, whereas cobicistat and ritonavir inhibited the efflux into the urine by MATE1. These results may explain the effects of these agents on creatinine and eGFR.

### **Dolutegravir (Abstract A1-1728)**

#### **An open label, placebo-controlled study to evaluate the effect of dolutegravir (S/GSK1349572) on iohexol and para-aminohippurate clearance in healthy subjects.**

*Koteff J, et al. A1-1728*

Small, reversible increases in serum creatinine have been observed in clinical trials with DTG; these changes are consistent with in-vitro data indicating that DTG is an inhibitor of the organic cation transporter 2 (OCT2), responsible for tubular secretion of creatinine. This study evaluated the effect of DTG on glomerular filtration rate (GFR), renal plasma flow, and serum creatinine clearance (CrCl) in 34 healthy subjects. Subjects received DTG 50 mg (once or twice daily) or placebo for 14 days. The primary endpoint was GFR measured by iohexol plasma clearance on day 14. Secondary endpoints were effective renal plasma flow, assessed by para-aminohippurate and CrCl measured by 24-hour urine collection. A modest decrease (10-14%) in CrCl was observed with DTG compared to placebo, consistent with observations from clinical studies, but DTG had no significant effect on GFR or renal plasma flow. These data support the hypothesis that DTG increases serum creatinine by inhibition of OCT2.

## Other Studies

### Plasma and intracellular pharmacokinetics of 3TC at two doses ([Abstract A1-1720](#))

#### Pharmacokinetics of lamivudine, and 3TC-triphosphate following administration of 3TC 300 mg and 150 mg once daily to HIV-negative volunteers-in the ENCORE2 study.

*Else LJ, et al, A1-1720.*

The bioequivalence of plasma 3TC and intracellular 3TC-TP concentrations after administration of 3TC (150 or 300 mg once daily) was determined in a randomized crossover study in 24 subjects (13 female). Regimens were bioequivalent if the 90% CI fell within the range of 0.8-1.25. All 24 subjects completed the study, but bioequivalence was not demonstrated. Geometric mean ratios (90% CI) for plasma 3TC AUC, C<sub>max</sub> and C<sub>trough</sub> were 0.57 (0.55-0.60), 0.56 (0.53-0.60) and 0.63 (0.59-0.67), respectively. For the intracellular 3TC-TP, geometric mean ratios (90% CI) for AUC, C<sub>max</sub> and C<sub>trough</sub> were 0.73 (0.64-0.83), 0.70 (0.61-0.82) and 0.82 (0.68-0.99), respectively. No gender-related differences in 3TC-TP pharmacokinetics were observed. 3TC at 150 mg is not bioequivalent to the standard regimen of 300 mg, indicating that saturation of cytosine phosphorylation pathways is not achieved at a dose of 150 mg.

### Pharmacokinetics of extended release NVP ([Abstract A1-1721](#))

#### Pharmacokinetic analysis of nevirapine extended release 400 mg qd vs immediate release 200 mg bid in patients with HIV-1 infection.

*Yong CL et al. A1-1721.*

Non-inferiority in virological efficacy has been shown for nevirapine extended release (NVP XR, 400 mg once daily) compared with nevirapine immediate release (NVP IR, 200 mg twice daily). Steady state pharmacokinetics were determined in treatment-naïve, HIV-1-infected subjects at week 4 (AUC over 24 h) and week 48 (trough concentrations). Forty nine subjects completed the study; 24 received NVP XR, and 25 NVP IR. Trough levels over 48 weeks were stable for both formulations, but NVP XR exhibited lower AUC (23% decrease), C<sub>max</sub> (31% decrease) and C<sub>min</sub> (17% decrease) than NVP IR. Subjects on the extended release formulation had less peak-to-trough fluctuation (34.5%) than those on the immediate release formulation (55.2%). These data (with efficacy results) suggest NVP XR compared with NVP IR achieved lower but effective NVP exposure.

### CYP2B6 polymorphisms with EFV and rifampicin ([Abstract A1-1723](#))

#### Cytochrome P450 2B6\*6 as well as \*11 polymorphism play a major role in rifampicin enzyme induction effect on efavirenz clearance.

*Mukonzok J, et al. A1-1723.*

This study examined the influence of CYP450 polymorphisms on efavirenz clearance over the initial twelve weeks of efavirenz in 107 Ugandan HIV patients receiving efavirenz (600 mg daily), lamivudine and zidovudine, 47 of which received rifampicin for TB co-infection. Overall mean efavirenz clearance in L/h was  $11.99 \pm 5.41$ ,  $11.34 \pm 5.50$  and  $10.68 \pm 5.55$  on days 14, 56 and 84, respectively. Efavirenz clearance was higher for efavirenz plus rifampicin ( $13.57 \pm 5.67$ ) than efavirenz only ( $10.38 \pm 4.96$ ), ( $p=0.02$ ) on day 14, but no significant difference was observed between groups on days 56 and 84. Significantly lower efavirenz clearance for CYP2B6\*6 genotypes were observed on all the three occasions: days 14 ( $p=0.005$ ), days 56 and 84 ( $p<0.0001$ ). CYP2B6\*11 was also associated with lower efavirenz clearance particularly on day 14 ( $p=0.007$ ) and 84 ( $p=0.014$ ). CYP2B6\*6 and \*11 genetic polymorphisms influence efavirenz clearance in patients co-treated with rifampicin and might be a more important predictor for long-term efavirenz treatment outcomes than rifampicin co-treatment in HIV-TB patients.

### **New integrase inhibitor (Abstract H2-801)**

**An integrase inhibitor with a new recognition motif that shows notable anti-HIV activity and a superior drug-drug interaction profile.**

*Nair V, et al. H2-801.*

Resistance, toxicity and drug-drug interaction profiles are recurring issues with anti-HIV/AIDS drugs and so the discovery of novel anti-HIV active integrase inhibitors with promising drug interaction profiles remains an important scientific challenge. This abstract described in vitro antiviral, drug-drug interaction and stability studies for a new, as yet unnamed, integrase inhibitor. Antiviral assays of the compound against HIV-1 isolate 91US004 (subtype B) showed an EC<sub>50</sub> of 6.89 nM and CC<sub>50</sub> of 96,200 nM (therapeutic index 13,962). The compound also exhibited significant antiviral activity against other HIV-1 isolates, HIV-2 and SIV. Drug-drug interaction experiments revealed that it was not an inhibitor of key CYP isozymes (IC<sub>50</sub> for CYP 3A4, 2D6, 2C8, 2C9, 2C19 were >200 micromolar), nor was induction observed. The compound was not a substrate, inhibitor or inducer of key UGT isoforms, 1A1, 1A4, 1A6, 1A9 and 2B7. Studies showed relative stability in microsomes, cytosol and blood plasma and metabolites were identified.