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Abstract Book

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15th International Workshop on Clinical Pharmacology of HIV & Hepatitis Therapy

Abstracts
Oral presentations

Abstract: O_01

PK-PD of Drug Efficacy and Toxicity

Population PK-PD analysis of 400mg vs. 600mg efavirenz (EFV) once daily in treatment-naïve HIV patients at 48 weeks: results of the ENCORE1 study

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Background: Dose reduction strategies that maintain therapeutic success may decrease costs and reduce drug-related toxicities. Reduction of EFV to 400mg once daily showed non-inferior viral suppression (<200copies/mL) with the standard 600mg dose at 48 weeks in treatment-naïve patients in the ENCORE1 study. The present analysis sought to evaluate EFV PK-PD and the putative minimum effective concentration (MEC ≥1.0mg/L at mid-dose interval) in ENCORE1 patients.

Materials & Methods: Patients were randomised to receive 400mg or 600mg EFV with tenofovir disoproxil fumarate/emtricitabine (300/200mg) once daily. Single blood samples were drawn 8-16h post-dose on weeks 4 and 12 and additional intensive sampling also performed in a sub-group of patients (4-8 weeks). Plasma concentrations were quantified by validated LC-MS/MS and genotyping conducted using TaqMan assays and PCR-based allelic discrimination. Nonlinear mixed effects modelling was applied (NONMEM v. 7.2) to estimate EFV PK parameters and variability. Covariates weight, age, sex, ethnicity and *CYP2B6* 516G>T and 983T>C genotypes were investigated. Associations between log-transformed mean individual predicted EFV PK parameters [CL/F, $AUC_{0\text{-}24}$, C_{max}, trough concentration (C_{24}), concentration 12h post-dose (C_{12}) representing mid-dose interval] and plasma viral load (VL) <200copies/mL at 48 weeks were evaluated by logistic regression. Categorical covariates (EFV dose, genotype and screening VL ≤/>100,000copies/mL) were assessed by exact chi-square. Missing VLs were excluded.

Results: 606 patients (32% female, 30% Caucasian, 33% Asian, 37% African) were included (400mg, n=311; 600mg n=295; 46/606 also had intensive sampling), providing 1491 samples in total (1-9 samples/patient; 1-3 occasions). Median (range) age, weight, baseline CD4 and VL were 35yr (18-69), 65kg (39-148), 270cells/mm^3 (40-679) and 56,803copies/mL (162-10,000,000), respectively. Genotypes were available for 574 patients. A one-compartment model best described the data with *CYP2B6* G516T/T983C composite genotype (defined below) and weight significantly associated with EFV CL/F (interindividual and interoccasion variability: 38% and 21%, respectively). EFV CL/F decreased by 34, 27, 71 and 65% for 516GG/983TC or CC, GT/TT, GT/TC or CC and TT/TT, respectively compared to wild-type (GG/TT). At 48 weeks 97% of patients with available VL achieved <200copies/mL (97% *vs.* 98% for 400mg and 600mg EFV, respectively). Of the PK parameters assessed, $logC_{24}$ was associated with VL <200copies/mL at 48 weeks (odds ratio, 95% CI: 3.1, 1.6-5.9; p=0.001). Due to the low proportion of virological failures, multivariate analysis was not feasible; however dose, genotype and screening VL were not significant in univariate analyses (chi-square; p>0.05 all comparisons). In participants with C_{12} <1.0mg/L and ≥1.0mg/L, incidence of VL ≥200copies/mL was 21% and 2% at 48 weeks, respectively (chi-square; p=0.001). Of the 4 participants with both VL ≥200 copies/mL and C_{12} <1.0mg/L, 1 and 3 received 400mg and 600mg EFV, respectively.

Conclusions: Virological efficacy was comparable between doses despite lower concentrations in the 400mg EFV arm. Relationships between *CYP2B6* polymorphisms and weight with EFV PK were consistent with previous reports. The number of patients with VL ≥200copies/mL at 48 weeks were very low, although higher in those with EFV C_{12} <MEC (1.0mg/L). As virological outcomes were not related to dose allocation, other drivers of virological response such as adherence may be involved.

No conflict of interest

Abstract: O_02

PK-PD of Drug Efficacy and Toxicity

Reduced darunavir dose is as effective in maintaining HIV suppression as the standard dose in virologically suppressed HIV-infected patients.

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Introduction: The global economic crisis has prompted interest in dose optimization strategies aimed at reducing the cost of antiretroviral treatment (ART) while maintaining its efficacy. The DRV600 study compares the efficacy and safety of a reduced dose with the standard dose of darunavir (DRV) in virologically suppressed HIV-infected patients.

Materials & Methods: The DRV600 study (eudraCT 2011-006272-39) was a multicenter, randomized, open-label clinical trial in HIV-infected patients with a plasma viral load (pVL) <50 copies/mL while on ART including DRV 800mg once daily (QD) plus two nucleos(t)ide reverse transcriptase inhibitors (NRTIs). Documented DRV resistance-associated mutations or prior virologic failure while receiving ART with protease inhibitors were considered exclusion criteria. Participants were randomized either to continue on the standard DRV 800mg QD dose (DRV800) or to reduce the dose to 600mg QD (DRV600). All patients continued receiving ritonavir 100mg QD and the same NRTIs. Treatment failure was defined as two consecutive pVL >50 copies/mL or discontinuation of study treatment by week 48. The trial had 80% power to show non-inferiority for the DRV600 arm (delta=-15%) in the intention-to-treat non-completer=failure (ITT NC=F) population.

Results: A total of 100 patients were included in the study (DRV800=50; DRV600=50). Of these, 81% were male and 20% were co-infected by HCV. Mean (SD) CD4+ T cell count at baseline was 562 (303) cells/mm^3, with no differences between study arms. Two patients from the DRV800 arm and three from the DRV600 arm developed virologic failure by week 48. Additionally, one patient from each arm was lost to follow up and one patient from the DRV600 arm died of septic shock. Thus, the proportion of patients with pVL<50 copies/mL at week 48 in the ITT NC=F analysis was 90% in the DRV600 and 94% in the DRV800 arm (difference -4%; 90% CI: -12.9; 4.9; p=0.46). CD4 cell counts remained stable during follow up in both arms. DRV trough concentrations in plasma were comparable between the two study groups. There was no difference in the frequency of adverse events between study arms.

Conclusion: Compared to the standard dose of DRV (800mg QD), a reduced dose (600mg QD) resulted in comparable DRV concentrations in plasma and showed non-inferior virologic efficacy in previously virologically suppressed HIV-infected patients, over 48 weeks. This strategy has the potential to reduce treatment cost of ART and allow more patients to be treated.

No conflict of interest

Abstract: O_03

Drug Drug Interactions

Reduced artemether-lumefantrine exposure in HIV-infected Nigerian subjects on nevirapine-based antiretroviral therapy

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Introduction: Artemether/lumefantrine is the most widely used first-line antimalarial. Given the overlapping HIV and malaria epidemics, frequent coadministration of artemether/lumefantrine with antiretroviral therapy (ART) is expected, but not without the potential for clinically relevant drug-drug interactions. Artemether and lumefantrine are primarily metabolized by cytochrome P450 (CYP) 3A4 enzymes and nevirapine is a known inducer of CYP3A4. Dihydroartemisinin, the active metabolite of artemether, is subsequently eliminated via uridine 5'-diphospho-glucuronosyltransferase enzymes. While exposure to artemether and dihydroartemisinin have been shown to be lower in combination with nevirapine-based ART, conflicting data exist regarding the impact of nevirapine on lumefantrine exposure. Therefore, we set out to evaluate the disposition of artemether/lumefantrine in HIV-infected, Nigerian subjects receiving nevirapine-based ART.

Materials & Methods: This was an open-label pharmacokinetic study in HIV-infected adult subjects who received co-formulated artemether/lumefantrine (80/480 mg) twice daily for three days while on steady state nevirapine-based ART. Serial pharmacokinetic sampling was performed at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 48, 72, and 96 hours following the last dose of artemether/lumefantrine. Artemether, dihydroartemisinin, and lumefantrine were quantified using validated liquid chromatography tandem mass spectrometry methods; pharmacokinetic parameters were determined using non-compartmental analysis via the linear up-log down trapezoidal rule using WinNonlin 5.2.1 (Pharsight Corporation, Mountain View, CA). Artemether, dihydroartemisinin, and lumefantrine pharmacokinetic parameters were compared to historical HIV-uninfected controls not receiving ART using the Wilcoxon rank sum test. Demographic information is presented as percentage or median (range) and pharmacokinetic parameters are presented as geometric means.

Results: A total of 11 HIV-infected subjects underwent intensive pharmacokinetic sampling. They were predominately female (81.8%), 37 years of age (31-59 years), 66 kg (56-92 kg), and had been on nevirapine-based ART for 3.5 years (2-5.6 years). Results were compared to historical HIV-uninfected controls not on ART (n=16) with similar body weight. Exposure to artemether, as estimated by the area under the concentration time curve (AUC_{last}), decreased by 65% in subjects receiving nevirapine-based ART as compared to controls (18.9 vs. 53.9 hr•ng/mL; p=0.02). No significant change in dihydroartemisinin parameters were noted between groups (180 vs. 177 hr•ng/mL; p=0.88). Exposure to lumefantrine was 60% lower in those on nevirapine-based ART as compared to controls (150 vs. 374 hr•mcg/mL; p=0.01), with a corresponding shorter half-life (1.6 vs. 4.8 days, respectively; p<0.001).

Conclusions: Exposure to both artemether and lumefantrine are significantly reduced in HIV-infected, malaria-uninfected, Nigerian adults receiving nevirapine-based ART. These data support prior reports of decreased exposure to both artemether and lumefantrine. The potential for suboptimal antimalarial response due to inadequate artemether/lumefantrine exposure warrants urgent evaluation in malaria-infected patients receiving nevirapine-based ART.

No conflict of interest

Abstract: O_04

Defining the therapeutic range of ribavirin in the era of DAA-telaprevir based triple therapy for HCV infection: is it possible?

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Background: In Phase III trials of telaprevir plus pegylated interferon and ribavirin, the concentrations of ribavirin were weakly associated with sustained virologic response (SVR) (area under the curve [AUC] receiver operating characteristics [ROC] curve 0.55), while the association between ribavirin concentrations and the development of anemia was much stronger (AUC ROC curve 0.70).[1] This analysis aims to further explore how ribavirin concentrations change over time and whether a therapeutic range for ribavirin concentrations can be defined for the optimal balance of anemia and SVR with telaprevir treatment.

Materials & Methods: Treatment-naïve patients from phase III studies ADVANCE, ILLUMINATE and OPTIMIZE using telaprevir-based triple therapy and who had a ribavirin concentration available at Week 4 of treatment were included in the analysis. Ribavirin concentrations were measured throughout the study period including at Weeks 1, 2, 4 and 8. Multivariable logistic regression analyses were performed to evaluate whether ribavirin plasma concentrations were an independent predictor of SVR (undetectable viral load 24 weeks after treatment) or clinically significant anemia (hemoglobin level <8.5 g/dL). Odds ratios (OR) were adjusted for known predictors of SVR and anemia. ROC analyses were performed to determine the optimal cut-off values for each available time point. The percentage of patients within these proposed therapeutic ranges were calculated with their associated chances for response.

Results: In total, Week 4 ribavirin concentrations were available for 904 patients. Patients were predominantly male (61%), Caucasian (93%) with mean (range) age of 48 (18–70) years and a mean BMI (range) of 27 (17–53) kg/m^2. Most patients were HCV genotype 1a (59%) and had a high baseline viral load (>800,000 IU/mL; 82%) and 20% of patients had cirrhosis.
Ribavirin concentration increased over time, with mean (SD) ribavirin concentrations at Weeks 1, 2, 4 and 8 of 1.86 (0.81), 2.34 (0.93), 2.97 (1.05) and 3.28 (1.18) mg/L, respectively and declined after stopping telaprevir. At all time points ribavirin concentrations were significantly associated with anemia (1.78<OR<2.61); however, this was only the case for SVR with ribavirin concentrations at Week 8.
From the ROC analyses, the following cut-off values of ribavirin for anemia were defined at Weeks 1, 2, 4 and 8: 2.3, 2.5, 3.1 and 3.5 mg/L, respectively. The cut-off value for SVR at Week 8 was 3.0 mg/L, resulting in a therapeutic range for ribavirin concentrations at Week 8 of 3.0–3.5 mg/L. Overall, 17% of patients had a ribavirin concentration within this range, 83% of whom achieved SVR and 6.7% reported developing severe anemia.

Conclusions: Although other known patient- and virus-related predictive factors influence the response to treatment, the potentially modifiable ribavirin concentration early after the start of treatment is clearly associated with anemia.

References: 1) Gordon SC, et al. EASL 2013. Poster 1116.

No conflict of interest

Abstract: O_05

Pharmacogenetics

ITPA activity and Ribavirin Ctrough are both predictive of ribavirin-induced anemia in HIV-HCV patients receiving boceprevir-based triple therapy (ANRS HC27)

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Introduction: Inosine triphosphatase (ITPA) variants causing ITPA deficiency have been shown to protect against ribavirin (RBV)-induced anemia. Moreover, RBV concentration was also reported to be a predictor of anemia during pegylated-interferon (PegIFN) plus RBV treatment in HCV or HCV/HIV patients. We explored the association between ITPA activity, plasma RBV Ctrough and the development of anemia in patients treated with boceprevir(BOC)/PegIFN/RBV.

Materials and Methods: In this multicenter open-label phase 2 trial, patients received PegIFNα2b (1.5 µg/kg/wk) + RBV (800-1400 mg/day) + BOC (800 mg tid) for 44 weeks after a 4-week lead-in of PegIFN/RBV. RBV plasma Ctrough was determined (W4 and W8) by HPLC. ITPA polymorphisms, rs1127354 and rs7270101, were genotyped using Taqman Real-Time PCR method. ITPA deficiency is defined by the presence of at least one variant allele among both polymorphisms and is classified as mild (heterozygosity for only rs7270101), moderate (heterozygosity for only rs1127354 or homozygosity for only rs7270101) or severe (heterozygosity for both variants or homozygosity for only rs1127354). Patients who received EPO substitution or had a RBV dose adjustment before W4 and/or W8 were excluded from the analysis. Statistical analysis was performed using non-parametric tests (Wilcoxon-Mann-Whitney test), Fisher exact test and Pearson correlations.

Results: Overall, 64 patients were included and ITPA genotypes were available for 63/64 and RBV Ctrough for 59/64 at W4 and 48/64 at W8. Median (IQR) RBV Ctrough at W4 and W8 were 1.7 µg/ml (1.4; 2.1) and 2.7 µg/ml (2.2; 3.1), respectively. RBV Ctrough was significantly higher at W8 (p<0.0001) after excluding patients for whom RBV dose was adjusted. ITPA deficiency was present in 21 (33%) patients (13 mild, 7 moderate and 1 severe). No difference on RBV Ctrough was observed between patients with a lower or a functional ITPA activity at W4 (1.6 *vs.* 1.7 µg/ml. p=0.644) and W8 (2.5 *vs*. 2.8 µg/ml; p=0.155). Hemoglobin (Hb) values were available for 54/64 at W4 and 41/64 at W8. We observed a significant difference between patients presenting an ITPA deficiency and those with a functional ITPA activity on the W4 Hb (14.3 g/dl vs. 12.8 g/dl; p=0.003), Hb decline at W4 (-1 g/l *vs*. -2.05 g/dl; p=0.022) and Hb decline at W8 (-2.7 g/dl *vs*. -4.05 g/dl; p=0.05). EPO substitution use between J0 and W8 was significantly higher in non deficient patients (functional ITPA): 11 (26.2%) *vs*. 0 (p=0.011). We also observed a significant correlation between W4 RBV Ctrough and W4 Hb (p=0.005), W8 Hb (p=0.006) and the Hb decline at W8 (p=0.042) but not at W4.

Conclusion: This is the first study reporting in HIV-HCV patients, a significant protective effect of ITPA deficiency on anemia during BOC-based triple therapy, associated with a lower use of EPO. Moreover, RBV Ctrough remains predictive of anemia in the context of a triple therapy with BOC, highlighting the usefulness of maintaining RBV TDM to manage RBV-induced anemia. ITPA genotyping may be useful to identify patients for whom a lower RBV dose

would be required to avoid severe anemia particularly in such regimen at higher risk of anemia.

No conflict of interest

Abstract: O_06

Drug Drug Interactions

Drug interactions between direct acting anti-HCV antivirals Sofosbuvir and Ledipasvir and HIV antiretrovirals

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Introduction: A once daily fixed-dose combination tablet composed of NS5A inhibitor ledipasvir (LDV) 90 mg and NS5B inhibitor sofosbuvir (SOF) 400 mg is in Phase 3 clinical trials for the treatment of chronic HCV infection. We conducted a Phase 1 study in healthy volunteers to evaluate potential DDIs between LDV and an integrase inhibitor raltegravir [RAL], and LDV/SOF and NNRTI-based ARV regimens efavirenz (EFV)/emtricitabine (FTC)/tenofovir DF (TDF) [Atripla®; ATR] or FTC/rilpivirine (RPV)/TDF [Complera®; CPA] before recommending their co-use in HIV/HCV co-infected patients.

Materials & Methods; This was a multiple-dose, randomized, cross-over DDI study. Group 1 subjects (N=30, fed) received LDV 90 mg QD, RAL 400 mg BID and LDV+RAL each for 10 days. Group 2 subjects (N =32, fasted) received LDV/SOF 90/400 mg alone followed by co-administration with ATR (600 mg/200 mg/300 mg) QD or ATR alone followed by co-administration with LDV/SOF, for 14 days. Group 3 subjects (N=32, fed) received LDV/SOF alone followed by co-administration with CPA (200 mg/25 mg/300 mg) QD or CPA alone followed by co-administration with LDV/SOF, for 10 days.
LDV, SOF, GS-331007 (predominant circulating nucleoside metabolite) and ARV plasma concentrations were analyzed on the last day of dosing for each treatment and PK parameters were calculated. Geometric least-squares means ratios % and 90% confidence intervals (combination vs. alone) for LDV, SOF, GS-331007, and ARV AUC_{tau}, C_{max} and C_{tau} were estimated using a linear mixed effect model with fixed treatment, period and sequence effects, and random subject effects, and compared against pre-specified lack of PK alteration boundaries of 70-143%. Safety assessments were conducted throughout the study.

Results: Twenty-eight of 30 subjects (Group 1) and 29 of 32 subjects (Groups 2 and 3) completed the study. The majority of adverse events (AEs) were Grade 1. The most frequent AEs were constipation (Group 1), headache and dizziness (Group 2), and nausea (Groups 2 and 3). Two subjects in Group 1, 1 subject in Group 2, and 1 subject in Group 3 discontinued due to an AE.
LDV or LDV/SOF PK was unaffected by RAL or CPA, respectively. A modest (~34%) decrease in LDV exposure with no impact on SOF or GS-331007 PK with ATR, and small (< 20%) changes in RAL PK with LDV, were observed on co-dosing. These changes were not deemed clinically relevant. EFV, RPV, or FTC PK was not affected by LDV/SOF. TFV exposure increases (ATR: ~1.8-2.6-fold; CPA: ~1.3-1.9-fold) were observed with LDV/SOF; overall, TFV absolute AUC values in the test (combination) treatments were comparable to those achieved when FTC/TDF is administered with ritonavir-boosted PIs, which do not warrant dose adjustment.

Conclusion: Study treatments were generally well tolerated. Cumulatively, results from this study and a previous DDI study between SOF and ARVs demonstrate that LDV/SOF may be administered with ATR, CPA, RAL, with a backbone of FTC/TDF.

Conflict of interest : Authors are employees of Gilead Sciences and may own stock

Abstract: O_07

Drug Drug Interactions

Evaluation of transporter and cytochrome P450-mediated drug-drug interactions between pan-genotypic HCV NS5A inhibitor GS-5816 and phenotypic probe drugs

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Introduction: GS-5816 is an HCV NS5A inhibitor with potent in vitro activity against HCV genotypes 1-6 that is in Phase 2 clinical development for the treatment of chronic HCV infection. In vitro studies demonstrate that GS-5816 is an inhibitor of transporters OATP, P-gp, and BCRP, and a substrate for P-gp and CYP3A4 (minor) and CYP2C8 (minor) enzymes. This Phase 1 study evaluated the potential of GS-5816 to be a perpetrator or victim of drug-drug interactions using phenotypic probe substrates (pravastatin, rosuvastatin, or digoxin) or inhibitors and inducers of enzymes and drug transporters (ketoconazole, rifampin, or cyclosporine) implicated in its disposition.

Materials & Methods: This was an open-label, single-and multiple-dose, five-cohort crossover study in healthy subjects. Within each cohort, subjects were randomized to receive both test (GS-5816 100 mg + probe) and reference (GS-5816 or probe) treatments. Treatments were separated by appropriate washouts for the respective compounds used in each cohort. Serial blood samples were collected over 72 hours (Cohort 1: pravastatin) or 96 hours (Cohorts 2-5: rosuvastatin, digoxin, cyclosporine, GS-5816) for the PK analyses. Geometric-least squares means ratios and 90% confidence intervals were estimated for AUC and C_{max} of probe drugs and GS-5816, as appropriate, and compared against pre-specified lack of PK alteration boundaries of 70 to 143%.

Results: The study enrolled 76 subjects into 5 cohorts. All subjects except one, described below, completed the study. Study drugs were generally safe and well tolerated. Treatment emergent AEs were generally of mild severity (Grade 1). In Cohort 2, a Grade 3 AE (panic attack) was reported 2 days after receiving a single oral dose of digoxin 0.25 mg and before GS-5816 was administered, and led to study discontinuation.
GS-5816 as Perpetrator: Coadministration of GS-5816 with OATP1B1/1B3 substrate pravastatin resulted in AUC and C_{max} increases of ~35% and ~28%, respectively. A larger increase in OATP/BCRP substrate rosuvastatin AUC (~170%) and C_{max} (~161%) was observed following coadministration with GS-5816. Coadministration of GS-5816 with P-gp substrate digoxin resulted in AUC and C_{max} increases of ~34% and ~88%, respectively.
GS-5816 as Victim: Administration of a potent CYP3A/CYP2C8/P-gp inducer rifampin decreased GS-5816 AUC and C_{max} by ~82% and ~71%, respectively; whereas, administration of a potent CYP3A/CYP2C8/P-gp inhibitor ketoconazole increased GS-5816 AUC and C_{max} by ~70% and ~29%, respectively. Administration of a selective OATP1B1/1B3 inhibitor rifampin increased GS-5816 AUC and C_{max} by ~47% and ~28%, respectively. Coadministration of a mixed OATP/P-gp/MRP2/CYP3A inhibitor cyclosporine and GS-5816 did not alter cyclosporine PK but resulted in GS-5816 AUC and C_{max} increases of ~102% and ~56%, respectively.

Conclusions: All study treatments were safe and well-tolerated. Clinical results are consistent with preclinical characterization of GS-5816. As a substrate of CYP3A, CYP2C8, and drug transporters such as P-gp and OATP, the disposition of GS-5816 is affected by potent inhibitors and inducers of the enzyme/drug transporter systems. GS-5816 is a weak (P-gp, OATP) to moderate (BCRP) transport inhibitor and clinically relevant drug-drug interactions between GS-5816 and OATP, P-gp, and CYP450 substrates are not anticipated.

Conflict of interest: All authors are employees of the study sponsor, Gilead Sciences, Inc.

Abstract: O_08

Pharmacokinetics for Pediatrics, Pregnancy and other Special Populations

Mucosal tissue pharmacokinetics of maraviroc and raltegravir in women: implications for chemoprophylaxis.

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Background: The poor adherence rates demonstrated by heterosexual women in recent PrEP trials necessitate second-generation PrEP strategies that allow for intermittent or as-needed dosing. PK/PD modeling will inform the design of these dosing strategies, but better characterization of antiretroviral exposure in mucosal tissues is needed. This investigation was performed to examine the single dose pharmacokinetic profile and dose proportionality of maraviroc(MVC) and raltegravir(RTG) as potential PrEP agents.

Materials & Methods: 48 healthy women were given single oral doses of MVC or RTG at 50%, 100% or 200% of the licensed treatment doses. 13 plasma samples were collected over 48h. Vaginal tissue(VT), cervical tissue(CT) and rectal tissue(RT) were collected at 6, 12, 24, and 48hrs for pooled sample analysis. Drug concentrations were measured by LC-MS/MS. Concentrations were analyzed with WinNonlin® and SigmaPlot®. Dose proportionality was declared if the 90% confidence interval(CI) around the slope(β_1) of log-transformed $AUC_{0\text{-}48h}$÷dose was within 0.64-1.36. Linear regression determined if plasma concentrations predicted mucosal tissue exposure. Data are reported as median(min,max).

Results: No difference in MVC or RTG exposure was noted between VT and CT(Tmax, Cmax, and $AUC_{0\text{-}48h}$,$p>0.4$), and the data were combined for subsequent analyses. MVC and RTG demonstrate rapid distribution to VT/CT(Tmax=6(6,6)h for MRV and RTG). Distribution to RT was more variable(Tmax= 6(6,24)h for MVC and 24(6,48)h for RTG). Cmax in VT/CT for MVC at 50/100/200% doses were 53/351/535ng*g^{-1} and for RTG were 127/329/274ng*g^{-1}. Cmax in RT for MVC at 50/100/200% doses were 740/1201/4749ng*g^{-1} and for RTG were 151/9893/4394ng*g^{-1}. Compared to VT/CT, RT Cmax was 8-fold higher for MRV and 15-fold higher for RTG. Likewise, RT $AUC_{0\text{-}48h}$ was 10-fold higher than VT/CT for MRV and 28-fold higher for RTG.
No dose-exposure relationship met statistical dose proportionality criteria. However, MVC demonstrated a linear relationship between dose and $AUC_{0\text{-}48h}$ in CT/VT (β_1=1.2,r^2=0.95) and RT(β_1=1.6,r^2=0.95). A linear relationship was found for RTG in VT/CT(β_1=0.84,r^2=0.84) but not RT (β_1=2.4,r^2=0.56), where it plateaued with higher doses. VT/CT concentrations were correlated with plasma for MVC (r^2=0.72, $p<0.001$) and RTG (r^2= 0.76, $p\leq0.001$). RT concentrations did not correlate with plasma(r^2=0.04 for MVC and r^2=0.001 for RTG, $p\geq0.4$).

Conclusions: To our knowledge, this is the first report of MRV and RTG PK in multiple mucosal tissues in women. Our findings indicate MVC and RTG rapidly distribute to the FGT making them potentially well-suited for chemoprophylaxis in women. Different distribution patterns were seen in RT. As previously determined in separate studies of men and women, MRV and RTG exposure was 2-11-fold higher in RT than in VT/CT. While MRV exposure in VT/CT and RT increased 5-9-fold across a 4-fold dosing range, RTG did not. This could indicate saturation of RTG transport in tissues, as we have recently found MDR1 transporter expression in VT/CT and RT. These tissue data will be used to create PK models for modeling and simulation studies of intermittent chemoprophylaxis doses. Characterizing the tissue concentrations required for protection is an important next step in discerning these agents' role for HIV prevention.

No conflict of interest

Abstract: O_09

PK/PD modeling

A multi-compartment single and multiple dose pharmacokinetic comparison of rectally applied tenofovir 1% gel and oral tenofovir disoproxil fumarate

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Introduction: Oral tenofovir (TFV)-containing regimens have demonstrated efficacy in HIV prevention. The primary objective of the Phase 1 RMP-02/MTN-006 clinical trial was to evaluate the systemic safety of TFV 1% gel when applied topically (rectum). Built into this study were comprehensive pharmacokinetic evaluations comparing systemic and compartmental pharmacokinetics within/between oral TDF and rectal TFV 1% gel users. This is the first study to quantify human rectal mucosal pharmacokinetics after topical administration of tenofovir in multiple compartments concurrently to enable within-subject compartment comparisons for topical and oral dosing each comparing differing compartment concentrations over time. A secondary goal was to determine whether less-invasive compartment sampling (such as rectal fluid) correlated with tissue biopsies/isolated CD4+ cells from biopsies, potentially simplifying sampling in large clinical trials.

Materials & Methods: This previously reported Phase 1, randomized, two-site, double-blind, placebo-controlled study enrolled 18 subjects with each receiving a single 300-mg dose of oral tenofovir disoproxil fumarate (TDF) with subsequent randomization (2:1) to receive single and then 7-daily rectal exposures of vaginally-formulated TFV 1% gel or a hydroxyethyl cellulose (HEC) placebo gel. Blood, rectal/vaginal mucosal fluids, and colorectal biopsies were collected at designated timepoints (30min to 12days) after the single oral and topical dosings as well as 30min following the last 7-day dosing. Samples were processed to quantify extracellular concentrations of TFV (plasma, rectal/vaginal fluids, tissue) and intracellular analysis of the active metabolite TFVdp in tissue as well as peripheral blood mononuclear cells (PBMCs) and isolated mucosal mononuclear cells (MMC), including CD4+ and CD4- cell subsets from both.

Results: TFV plasma concentrations were 24-33 fold lower and half-life was 5h shorter following the single topical rectal exposure compared to the single oral exposure ($p=0.02$). TFVdp concentrations undetectable in PBMCs after single-dose rectal exposure. However, rectal tissue concentrations of both TFV and TFVdp were 2-4 $\log_{10}$ higher after single rectal dosing compared to single oral dosing. TFVdp was 4.5-fold higher in tissue after 7-day dosings. These rectal tissue concentrations of TFVdp were predictive (residual standard error, RSE=0.47) of MMC TFVdp concentration. Interestingly, the CD4+ MMCs averaged a 2-fold higher TFVdp concentration than CD4- cells. TFV concentrations from rectal sponges was a modest surrogate indicator for both rectal tissue TFV and TFVdp (RSE=0.67, 0.66, respectively) as well as plasma TFV (RSE=0.38). Vaginal fluid TFV concentrations were detected after both oral and rectal dosing with rectal dosing driving significantly higher vaginal concentrations ($p<0.01$).

Conclusions: Rectally-applied topical TFV gel delivers lower systemic exposure and higher vaginal exposure than do similar doses of oral delivery, with rectal tissue accumulation of TFVdp over time, likely due to the long intracellular half-life. An unexpected yet biologically interesting finding was the 2-fold higher concentrations of TFVdp in rectal mucosal CD4+ versus CD4- cells. TFV rectal fluid concentrations of TFV correlate with tissue concentrations and may be reasonable bio-indicators rectal tissue/cell concentrations,

providing coarse but less-invasive methods to estimate adherence and TFV concentrations in target tissues.

No conflict of interest

Abstract: O_10

PK-PD of Drug Efficacy and Toxicity

Estimated onset and duration of PrEP activity for daily TDF/FTC using the EC90 from iPrEx

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Background: Critical questions for the field of PrEP include the number of daily TDF/FTC doses required to establish protection from HIV acquisition (onset of action) and the number of days after stopping TDF/FTC that protection is maintained (duration of action). A substudy of the iPrEx trial estimated that 16 fmol/million cells of tenofovir-diphosphate (TFV-DP) in viably cryopreserved PBMC (vPBMC) was associated with a 90% reduction in HIV acquisition risk relative to placebo (EC_{90}) in men who have sex with men (MSM). The aim of this study was to estimate the number of daily TDF/FTC doses required to reach the EC_{90} and how long the concentration remained above the EC_{90} after drug discontinuation from steady-state conditions.

Materials & Methods: HIV-negative adults were enrolled in an intensive pharmacokinetic study of daily TDF/FTC for 30 days. PBMC were collected at first dose, days 3, 7, 20, and 30, and off-drug on days 5, 15, and 30 of washout. Rectal biopsies were performed once during an on-drug visit and mononuclear cells were isolated, counted, and lysed. Paired vPBMC and freshly lysed PBMC were collected once per participant. vPBMC were harvested using the same procedures as in iPrEx and TFV-DP/FTC-TP were quantified in all samples with validated LC-MS/MS. The conversion between TFV-DP in vPBMC versus freshly lysed PBMC was determined using multiple imputation based on paired samples from the current and past studies. With each daily dose, the proportion of individuals achieving the iPrEx EC_{90} was assessed and the inferred HIV risk reduction was calculated with the exponential regression model from iPrEx [PMID: 22972843] using viable-corrected PBMC values.

Results: Twenty-one participants were included, 11 male, 10 female, median age: 31 years, weight: 81.1kg, race: 10 Caucasian, 10 African American, 1 Hispanic. Nineteen subjects completed all visits. No differences were observed between males and females in TFV-DP concentrations after the first dose or at steady state ($p \geq 0.29$). After 8 doses, 93% (95% CI 71% - 98%) of participants reached the iPrEx EC_{90}. At this time, the ln(TFV-DP) concentration was 96% of steady state in rectal mononuclear cells (1438 fmol/million cells). Greater than 90% of participants remained above the iPrEx EC_{90} until two days after stopping drug, at which time the percentage fell to 86% (63% - 95%). The inferred HIV risk reduction was 95% (92% - 98%) after 3 doses, 99% (98% - 100%) after 8 doses, and 98% (96% - 100%) two days after stopping drug. The inferred HIV risk reduction remained greater than 95% for 6 days after stopping drug from steady-state conditions.

Conclusions: These data indicate that high PrEP efficacy and high rectal tissue concentrations can be achieved in MSM after approximately one week of daily dosing. They also suggest that following daily dosing to steady state in MSM, a high level of protection may persist for several days after the last dose taken.

No conflict of interest

Abstract: O_11

PK/PD modeling

Population analysis of Tenofovir plasma and intracellular pharmacokinetics in female HIV-1 seropositive patients

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Introduction: Pre-exposure prophylaxis (PrEP) is an HIV-1 preventative strategy whereby healthy individuals use antiretroviral (ARV) medications, such as tenofovir (TFV), prior to HIV exposure to reduce the likelihood of viral infection. However, ARV concentrations needed in compartments such as blood plasma (BP), the female genital tract (FGT), and peripheral blood mononuclear cells (PBMCs) for maximal reduction in HIV transmission have not been extensively studied. Our work assesses the steady-state exposure of TFV in BP, PBMCs, cervicovaginal fluid (CVF), and cervical cells (FGT cells) of HIV-infected women and uses population modeling methods to simulate TFV doses needed in each biological compartment in the context of an HIV-1 PrEP strategy.

Materials & Methods: Thirty HIV-infected women (median age of 49 years) receiving once-daily Atripla™ (co-formulated tenofovir disoproxil fumarate/emtricitabine/efavirenz, 300/200/600 mg) were enrolled in a prospective pharmacokinetic study. BP, PBMCs, CVF, and FGT cells samples were collected and ARV drug concentrations were measured using a validated high-performance liquid chromatography coupled with tandem mass spectrometry assay. Pharmacokinetic (PK) modeling was achieved using a nonlinear mixed effects approach in ADAPT5. A two-compartment model with first order absorption was used to describe the TFV concentration-time profile in plasma, while a sequential analysis approach model was selected for evaluating the CVF and FGT cells samples. The intracellular PBMC TFV concentrations were analyzed using a one-compartment model. The TFV concentrations in each of the four biological compartments were also simulated and compared to TFV concentrations believed to reduce or eliminate HIV transmission.

Results: The apparent clearance (CL/F), apparent volume of the central compartment (Vc/F), peripheral compartment volume (Vp/F), apparent inter-compartment clearance (Q/F) and absorption rate constant (Ka) of the TFV plasma model were 56.3 L/h, 205 L, 751L, 0.908 h^{-1} and 147 L/h, respectively. The rate constants from the plasma central compartment to the FGT cells and CVF were 5.42 h^{-1} and 1.49 h^{-1}, respectively. The rate constants from the FGT cells to the plasma central compartment and CVF were 0.012 h^{-1} and 0.0836 h^{-1}, respectively. The rate constant from the CVF to the FGT cells was 2.15 h^{-1}, and the elimination rate out of the CVF was 0.674 h^{-1}. The half-life of TFV in the CVF and FGT cells was 22 h for both compartments. The clearance (CL_{PBMC}/F), volume of the central compartment (V_{PBMC} /F) and absorption rate constant (Ka_{PBMC}) of the TFV PBMC model were 0.0742 L/h, 4.36 L, and 2.37 h^{-1}, respectively. The calculated half-life in PBMCs was 40.8 h. Finally, the US Food and Drug Administration-recommended TFV treatment dosage (300 mg daily) proved to be the most efficient dosage for prophylactic administration, with an adequate TFV concentration maintained for 76-100% of the dosing period in all four compartments.

Conclusion: The development of a novel PK TFV model linking four biological compartments allowed for the simulation of alternative dosing strategies of TFV for its use in PrEP.

No conflict of interest

Abstract: O_12

PK-PD of Drug Efficacy and Toxicity

Translational studies to understand the mechanism of liver delivery by Sofosbuvir

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Background: The nucleotide prodrug sofosbuvir delivers a nucleoside analog monophosphate to the liver for subsequent phosphorylation in hepatocytes to form the pharmacologically active triphosphate metabolite that inhibits the hepatitis C virus NS5B RNA-dependent RNA polymerase. Results from multiple experimental systems including in vitro incubations, animal studies, and the measurement of sofosbuvir metabolite levels in liver explants taken from patients treated with sofosbuvir pre-transplant were used to gain a comprehensive understanding of liver delivery.

Materials & Methods: In vitro bidirectional permeability assays were performed using Caco-2 monolayers. Intracellular metabolism of sofosbuvir was assessed in primary human hepatocytes from 14 donors following 2-hour pulse incubation. Plasma pharmacokinetics were determined in intact and portal vein cannulated dogs and liver pharmacokinetics were determined in intact dogs. Liver metabolite levels were determined in 25 consenting patients enrolled in study P7977-2025 (NCT01559844) exploring the clinical efficacy of sofosbuvir and ribavirin administered prior to liver transplantation to prevent HCV recurrence post-transplant.

Results: Hepatic extraction was anticipated for sofosbuvir based on instability in hepatic extracts, making it difficult to assess gastrointestinal absorption based on systemic pharmacokinetics. Therefore, the absorption of sofosbuvir was assessed in bi-directional permeability studies through Caco-2 cells in vitro and in portal vein cannulated dogs following oral administration. Consistent with results in Caco-2 assays, sofosbuvir was absorbed into the portal veins of cannulated dogs with a fraction absorbed as intact prodrug of 40%. High first-pass hepatic extraction (74%) was calculated for sofosbuvir based on the exposures observed in the portal and jugular veins. Reflecting first-pass metabolism, oral administration to dogs resulted in the rapid appearance of the intermediate alanine nucleoside analog monophosphate metabolite (GS-566500), followed by the nucleoside analog (GS-331007), the predominant circulating metabolite. First-pass hepatic extraction coupled with intracellular conversion to a pharmacologically active triphosphate metabolite that does not itself circulate in plasma made assessment of the intracellular metabolism of sofosbuvir in hepatocytes essential to fully understanding its pharmacology. Sofosbuvir was efficiently activated in primary human hepatocytes and, once formed, the triphosphate persisted with a half-life of >12 hours following pulse incubations in vitro. Consistent with these results, high mean liver levels of total sofosbuvir (71 µM) and ribavirin (560 µM) metabolites were observed in liver explants from subjects treated for between 3 and 32 weeks prior to liver transplantation (study P7977-2025). Additionally, the triphosphate was also efficiently formed in dog livers following oral administration, achieving a maximal concentration of 47 µM following oral administration at a dose of 5 mg/kg. Dog pharmacokinetic studies proved to be predictive of clinical liver levels with dose and surface area adjusted maximal liver concentrations within 2-fold of those observed in humans.

Conclusions: Combining these results with findings from biochemical studies assessing the enzymes involved in prodrug activation and nucleotide phosphorylation provides a thorough understanding of the mechanism for efficient liver delivery and potent antiviral activity following administration of sofosbuvir.

Work presented, in part, previously at the 64th Annual Meeting of the American Association for the Study of Liver Diseases, November 1-5, 2013, Washington, DC, USA.

Conflict of interest: Some authors are employees of Gilead Sciences, Inc.

Abstract: O_13

PK-PD of Drug Efficacy and Toxicity

A novel microdose approach to assess bioavailability, intestinal absorption, gut metabolism and hepatic clearance of simeprevir in healthy volunteers

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Background: Simeprevir (SMV, TMC435) is a one pill, once-daily (QD), hepatitis C virus (HCV) NS3/4A protease inhibitor approved in Japan, Canada, and the USA, and under regulatory review in Europe for treatment of chronic HCV genotype 1 infection. This sequential, single-dose Phase I study assessed the pharmacokinetics (PK) and absolute bioavailability (F_{abs}) of single oral SMV doses of 50 mg and 150 mg followed by an intravenous (i.v.) microdose of [^{3}H]-SMV 100 µg in healthy volunteers. The proportion of the i.v. dose excreted in urine and faeces, and information from the oral dose was used to determine the contribution of intestinal absorption, and intestinal- and hepatic-metabolism in the PK of simeprevir.

Materials and Methods: Six healthy male volunteers (median age 47.0 years) received two sequential treatments separated by a washout period. Treatment Period 1: single oral dose of SMV 50 mg followed 5 hours later by a single 10-minute i.v. infusion of 100 µg [^{3}H]-SMV (100µCi). Treatment Period 2: single oral dose of SMV 150 mg followed 5 hours later by [^{3}H]-SMV (dosing as before). SMV and [^{3}H]-SMV plasma PK profiles, and total plasma radioactivity were determined for both treatments 0–72 hours after oral SMV administration. Urine per 24-hour interval and faeces were collected for at least 96 hours after oral SMV administration. Urine and faeces were analysed for total radioactivity and metabolite profiling was performed on faeces. Safety was assessed by laboratory examination, electrocardiogram, vital and clinical signs.

Results: Systemic clearance was saturable between single oral doses of SMV 50 mg and 150 mg, decreasing from 6.23 L/h to 4.75 L/h, respectively. Volume of distribution decreased from 94.4 L for the 50 mg dose to 75.3 L for the 150 mg dose. Elimination half-lives were 10.8 h and 11.5 h, respectively, for the 50 mg and 150 mg doses. These changes are consistent with saturation of hepatic uptake of simeprevir at the 150 mg dose. The SMV plasma exposure was more than dose-proportionally higher for SMV 150 mg compared with 50 mg.
With both treatments, radioactivity was excreted mainly in the faeces (~85% of total radioactive dose) and only ~2% of the total radioactive dose was recovered in urine.
Mean values for fraction absorbed (F_a) (0.75±0.07 for 50 mg, 0.83±0.06 for 150 mg) and fraction escaping gut-wall elimination (F_g) (0.69±0.07 for 50 mg and 0.81±0.03 for 150 mg) were higher for SMV 150 mg versus SMV 50 mg. Mean F_{abs} of SMV was higher after a single oral dose of 150 mg vs 50 mg (62.1% versus 46.0%, respectively).
Both treatments were generally well tolerated in healthy male volunteers, with no serious adverse events (AEs), fatal AEs, grade 3/4 AEs or AE-related treatment discontinuations.

Conclusions: The absolute bioavailability of orally administered SMV was dose-dependent; 46% at 50 mg and 62% at 150 mg. Intestinal absorption, metabolism and hepatic uptake were saturable, with a greater fraction absorbed and lower fraction metabolized at the higher dose.
This study was funded by Janssen.

Conflict of interest: All authors are employees of Janssen Infectious Diseases

Abstract: O_14

PK/PD modeling

Towards physiologically-based pharmacokinetic modelling of darunavir/ritonavir in pregnancy

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Introduction: Limited pharmacokinetic data from clinical studies shows that during pregnancy the exposure to darunavir/ritonavir (DRV/RTV) is reduced. Physiologically-based pharmacokinetic (PBPK) modelling is an *in silico* approach to predict drug exposure, taking *in vitro* pharmacokinetic and physicochemical drug properties as well as human physiology as starting points. Literature data suggest that DRV can interact with liver drug transporters. Here we use mechanistic modelling studies to delineate the potential impact of drug transporters on DRV pharmacokinetics (PK) and identify current knowledge gaps that limit the accurate PBPK modelling of DRV/RTV exposure in pregnancy.

Materials & Methods: Simcyp version 13.0 was used for PBPK modelling, exploring both well-stirred and permeability-limited models for hepatic clearance in healthy subjects and pregnant females. DRV and RTV physicochemical and *in vitro* pharmacokinetic parameters were retrieved from literature, including DRV Km and Vmax for CYP3A4-mediated biotransformation and Kinact/Ki values of RTV against CYP3A4, hepatic influx (OATPs) and canalicular efflux (P-gp) transporters. Sensitivity analyses were performed to address uncertainty in available *in vitro* parameters concerning transporters. For validation of the DRV model, with and without RTV boosting, simulation results were compared to available previously published or in-house clinical data.

Results: We found that using the well-stirred liver model following an oral single dose of 600mg DRV in healthy subjects, C_{max} and exposure were overestimated: $C_{max,simulated}$ and $C_{max,observed}$ being 4.4 (95%CI: 3.7-5.3) mg/L and 1.6 mg/L respectively; $AUC_{simulated}$ was 21.5 (95%CI: 16.2-28.4) mg/L*h versus $AUC_{observed}$ of 6.8 mg/L*h. To include possible influence of OATPs and P-gp, a permeability-limited hepatic model was used. Sensitivity analyses revealed that over a pharmacologically relevant range of $CL_{passive\ diffusion}$ conditions (1-100 µl/min/million hepatocytes), simulated DRV exposure proved sensitive to variation of $CL_{int,active\ transport}$ of uptake and efflux processes between 1-500 µl/min/million hepatocytes. Simulation of DRV exposure also proved sensitive to efficiency of enteral reuptake of excreted unchanged drug. Indeed, simulation of DRV PK improved including active hepatic influx and efflux transports and partial enteric reuptake of unchanged drug was allowed: $C_{max,simulated}$ of 1.8 (95%CI: 1.4-2.3) mg/L vs $C_{max,observed}$ of 1.6 mg/L, $AUC_{simulated}$ of 6.1 (95%CI: 4.7-7.9) mg/L*h vs $AUC_{observed}$ of 6.8. With regard to RTV boosting, the simulated C_{max} (3.2 (2.7-3.8)) and AUC ratio (8.6 (6.6-11.1) were well in line with the observed C_{max} ratio (3.4) and AUC ratio (8.6). Simulating the change in DRV exposure for the DRV/RTV 600/100 BID and 800/100 QD regimen at steady-state during pregnancy, yielded a decrease in $AUC_{simulated}$ of 29% and 21% versus a decrease in $AUC_{observed}$ of 17% and 37% respectively.

Conclusions: Our data support the presence of a clinically relevant role of hepatic transporters in DRV pharmacokinetics. Moreover, the described model could approximate boosting by ritonavir and the decrease in maternal DRV exposure during pregnancy. However, to ensure a better mechanistic basis of PBPK simulations, future *in vitro* experiments should focus on generating quantitative data concerning passive and transporter-mediated DRV uptake in hepatocytes, transporter abundance as well as data on the enteral re-uptake of unchanged DRV excreted via the bile.

No conflict of interest

Abstract: O_15

Pharmacokinetics for Pediatrics, Pregnancy and other Special Populations

Total and unbound pharmacokinetics of once-daily darunavir/ritonavir in HIV-1–infected pregnant women

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Introduction: Antiretroviral therapy during pregnancy reduces risk of mother-to-child transmission (MTCT). Physiologic changes during pregnancy can affect pharmacokinetics. A previous analysis of darunavir/ritonavir 600/100mg twice-daily showed lower total but not unbound darunavir exposure in HIV-1–infected pregnant women, and no MTCT. This study was extended to HIV-1–infected pregnant women receiving once-daily darunavir/ritonavir.

Materials & Methods: Phase IIIb study, HIV-1–infected pregnant women ≥18 years old, in 2nd trimester of pregnancy, receiving darunavir/ritonavir 800/100mg once-daily with other antiretrovirals. Fifty-nine percent (10/17 patients) had viral suppression (<50 copies/mL) at study entry. Darunavir (total and unbound) and ritonavir (total) plasma concentrations were evaluated predose, 1, 2, 3, 4, 6, 9, 12 and 24 hours postdose (3, 6, 12h timepoints only analyzed for total concentrations), during the 2nd and 3rd trimesters, and postpartum. Total darunavir and ritonavir plasma concentrations were determined using a validated HPLC-MS/MS assay. Darunavir unbound fraction was determined by separation through ultrafiltration of ^{14}C darunavir-fortified plasma samples and liquid scintillation counting. Pharmacokinetic parameters were derived using non-compartmental analysis. Safety and efficacy were evaluated at each visit.

Results: 17 women (5 Black, 2 Hispanic, 7 White, 3 Other) enrolled; 16 had evaluable pharmacokinetic data. Total darunavir AUC_{24h}, C_{min} and C_{max} were lower by 34% (LSMeans ratio, 90% CI: 0.66, 0.60-0.74), 32% (0.68, 0.56-0.83) and 34% (0.66, 0.59-0.75) during the 2nd trimester and by 35% (0.65, 0.57-0.74), 50% (0.50, 0.35-0.73) and 31% (0.69, 0.63-0.77) during the 3rd trimester, versus postpartum. Unbound darunavir AUC_{24h}, C_{min} and C_{max} were lower by 24% (0.76, 0.67-0.85), 13% (0.87, 0.69-1.10) and 25% (0.75, 0.65-0.87) during the 2nd trimester, and by 20% (0.80, 0.71-0.89), 38% (0.62, 0.43-0.90) and 16% (0.84, 0.74-0.96) during the 3rd trimester, versus postpartum. Unbound darunavir was >10-fold above the unbound EC_{50} for wild-type HIV (2.75 ng/mL) in all subjects at all times. Ritonavir pharmacokinetic parameters decreased by approximately 45-50% during the 2nd and 3rd trimesters, versus postpartum. Albumin and α_1-acid glycoprotein (AAG) concentrations were 20-27% and 46% lower, respectively, during pregnancy versus postpartum (median % decrease). Viral suppression was maintained in >88% of subjects at all times during gestation. CD4+ counts increased in the 2nd and 3rd trimesters and 6-12 weeks postpartum, with lower values observed in-between (2-5 weeks postpartum). Six serious adverse events were reported in the treatment phase, all considered pregnancy-related; only 1 (gestational diabetes) was considered possibly related to darunavir/ritonavir. Three of 16 infants were born prior to 37 weeks (33, 36 and 36 weeks), there were no birth defects, and all infants were HIV-1–negative (standard PCR testing).

Conclusions: Total darunavir decreased during pregnancy possibly due to pregnancy-related albumin and/or AAG dilution and/or decreased ritonavir concentrations. The decrease in unbound darunavir during pregnancy was less pronounced than for total darunavir, although

larger than previously reported in HIV-1–infected pregnant women treated with twice-daily darunavir/ritonavir. Unbound darunavir was >10-fold above the wild-type EC_{50}, high viral suppression rates were maintained throughout the study, and there was no MTCT. The regimen was well tolerated. No dose adjustment is required for darunavir/ritonavir 800/100mg once-daily in pregnant women.

Conflict of interest: Herta Crauwels is an employee and stockholder of Johnson & Johnson.

Abstract: O_16

Large scale utilisation of dried blood spots (DBS) for the characterisation of efavirenz (EFV) pharmacokinetics (PK) in the ENCORE 1 study

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Background: Analysis of plasma concentrations continues to be the method of choice for PK studies of antiretroviral drugs. However, plasma collection requires specialised training and facilities (cold storage/transport) which can be problematic in resource-limited environments. Dried blood spot (DBS) measurement could provide a cheap and easier alternative.
ENCORE1 is a randomised, double-blind, placebo-controlled trial comparing the safety and efficacy of a reduced 400 mg od dose of EFV (+ TDF/FTC) with the standard 600 mg od dose in antiretroviral-naïve patients. EFV concentrations were measured at steady state in plasma and in matched DBS samples at various time-points over the study, as a means of assessing the suitability of DBS as a measure for EFV PK. The relationship between EFV concentrations by DBS and paired plasma was explored, both in the main study population and a cohort undergoing intensive PK sampling.

Materials and Methods: Plasma and DBS samples (Whatman 903 Protein Saver cards) were obtained from the ENCORE1 clinical trial. 1094 paired plasma and DBS samples, (579 400mg, 515 600mg; 348 female) were collected at weeks 4 (n=561) and 12 (n=533) (8-16hr post dose; pd) at 39 sites in the main study. An additional 46 patients (28 400mg, 18 600mg; 15 female) underwent intensive 24-hour PK sampling between weeks 4 and 8 at 4 sites. EFV [concentrations] were measured in plasma $[plasma]^{M}$ and DBS using LC-MS/MS. Predicted plasma $[plasma]^{P}$ were derived from [DBS] using the formula $[DBS]/(1\text{-haematocrit})]\times f_{bpp} = [plasma]^{P}$, assuming a standardised haematocrit of 0.45 L/L and f_{bpp} of 0.995 (where f_{bpp} is the fraction of drug bound to plasma proteins). Linear regression and Bland-Altman plots (SigmaPlot 12) were used to compare $[plasma]^{M}$ and $[plasma]^{P}$.

Results: EFV [DBS] showed a significant correlation with $[plasma]^{M}$ (R^2=0.904, P<0.001; n=1094), with [DBS] on average (±SD), 53% ±9.5 lower than the corresponding $[plasma]^{M}$. $[Plasma]^{P}$ were correlated with $[plasma]^{M}$ concentrations in both the main (slope=0.85 week 4; slope=0.89 week 12) and intensive (slope=0.93; 12 hr pd; slope =0.99 16 hr pd) groups (R^2>0.900, P<0.001). In the Bland Altman plots the mean difference (95% CI) between EFV $[plasma]^{P}$ and $[plasma]^{M}$ was 86.3 ng/ml (-5.7 to 178; 12 hr pd) and 75.1 ng/ml (-9.7 to 160; 16 hr pd) in the intensive study. In the main study a mean difference (95%CI) of -451 ng/ml (-504 to -398) and -431ng/ml (-483 to -379) in weeks 4 and 12 was observed.

Conclusions: DBS may be a valuable sampling tool for use in small controlled PK studies at a limited number of sites. However, application of this methodology to a large-scale multicentre trial across diverse health resource settings resulted in significant underestimation of EFV concentrations, possibly arising from inter-operator differences in accuracy of sampling volumes or spotting technique, which need to be addressed before widespread utilisation of DBS in a global field setting.

No conflict of interest

15th International Workshop on Clinical Pharmacology of HIV & Hepatitis Therapy

Abstracts
Best of Poster presentations

Abstract: PP_01

Drug Drug Interactions

Simulation of the interaction between erlotinib and ritonavir using a physiologically based pharmacokinetic model

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Background: Incidence of non-AIDS defining cancers continues to rise in HIV-infected patients. Many chemotherapeutic agents are substrates of metabolizing enzymes that may be induced or inhibited by antiretroviral drugs, leading to potential drug-drug interactions. However, specific clinical trials assessing these interactions are difficult to run in clinical practice. Erlotinib (ERL) is an inhibitor of the epithelial growth factor receptor tyrosine kinase which is used to treat patients with non-small lung or pancreatic cancer. ERL is mainly metabolized by CYP3A4 but also by CYP3A5, CYP1A1 and CYP1A2 isoforms of the cytochrome P450, providing a rationale for drug interactions with antiretroviral drugs. The objective of this study was to simulate the interaction between ERL and ritonavir (RTV) using a physiologically based pharmacokinetic (PBPK) model.

Materials & Methods: *In vitro* data describing chemical properties, absorption, distribution, metabolism and elimination (ADME) of ERL and RTV, as well as the inhibition and induction potential of RTV were obtained from the literature. Steady state ERL and RTV concentrations in plasma were simulated in a virtual population of 50 individuals receiving ERL 150mg QD with and without RTV 100mg QD. ERL C_{trough}, C_{max} and AUC_{0-24} with and without RTV were compared by using the geometric mean ratio and its 90% confidence interval (GMR, 90% CI). Additionally, the effect of an ERL dose reduction in presence of RTV was also evaluated. Simulations were performed using a PBPK model using Simbiology (Matlab, version R2013b). Simulated ERL and RTV pharmacokinetic parameters as well as the magnitude of the inhibition of CYP3A4 by RTV were compared with values from literature.

Results: The simulated parameters of ERL and RTV given separately were in agreement with reference values from literature. The GMR (90%CI) for ERL with RTV 150/100mg QD relative to ERL 150mg QD without RTV was 3.01 (2.74-3.31) for C_{trough}, 2.51 (2.33-2.71) for C_{max}, and 2.74 (2.52-2.98) for AUC_{0-24}. An ERL dose reduction to 50mg QD ameliorated the increase in ERL exposure. The GMR (90%CI) for ERL 50mg QD with RTV 100mg QD relative to ERL 150mg QD alone was 0.97 (0.88-1.06) for C_{trough}, 0.81 (0.75-0.87) for C_{max}, and 0.88 (0.81-0.96) for AUC_{0-24}.

Conclusion: The developed PBPK model predicted the *in vivo* pharmacokinetics of ERL and RTV and their interaction. The increase in ERL exposure driven by RTV 100mg QD may be mitigated by reducing the ERL dose to 50mg QD. However, these results should be validated in clinical practice. PBPK may be a useful tool for both prediction of drug-drug-interactions and selection of doses to explore in prospective clinical trials.

No conflict of interest

Abstract: PP_02

Pharmacokinetic of raltegravir (800 mg) once-daily in switching strategies in HIV-1-infected patients with suppressed viremia

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Background: Raltegravir (RAL) is a first generation integrase inhibitor, active on HIV-1 and HIV-2. RAL metabolism avoids CYP450 pathways and it is preferentially biotransformed by UGT1A1, limiting the occurrence of drug-drug interactions (DDI). RAL Pharmacokinetic demonstrates high between (~212%) and within variability (~122%) and short plasma half-life (~9hours). All this properties bring a twice-daily administration of RAL (400mg BID) for virological efficacy, avoiding the selection of resistant HIV. To improve adherence and quality-life of treated-patient some physicians prescribed RAL in once-daily administration (800mg QD) using the actual approved galenic formulation (poloxamer OCT, Oral Compressed Tablet).
The aim of this study is to evaluate RAL plasma Concentration 24 hours (C24h) after 800mg QD and immune-virological response at week 24 in switching strategies in HIV-1-infected patients with suppressed viremia. Secondary objectives are to describe the impact of inter-patient variability and ARV backbone on RAL pharmacokinetic.

Materials & Methods: multicenter, observational cohort, conducted in HIV-1 infected patients older than 18 years, with plasma Viral Load (pVL) $\leq$50copies/mL and a stable antiretroviral (ARV) treatment for at least 6 months, naïve for integrase inhibitors or receiving 400 mg BID without previous history of virological failure on RAL. Written informed consent was obtained from all participants. RAL C24h was measured by UPLC-MS/MS (Waters® Acquity UPLC/Waters® Acquity TQD System) (LOQ<5ng/ml). Statistical analyses were made with StatView® (Abacus Concepts, Berkley, California, USA).

Results: On the 71 enrolled-patients switching for RAL 800mg QD, 17 were pre-treated with 400mg QD, 46 years, 47 males, 15 years since HIV diagnosis, 9 CDC stage C, 588 CD4/mm^3, 14 years of ARV duration, 5 previous ARV lines and 62 months on viral suppression. ARV backbone was 42 TDF/FTC, 13 ABC/3TC, 6 ETR, 3 NVP, 3 ATV/r, 1 ATV. Among them, 4 received omeprazole co-medications. Reasons for switching to RAL 800mg QD were: 47 for intolerance, 6 for DDI, 4 for simplification, 15 others. Geometric Mean (CV%) RAL C24h were determined on 61 patients 50ng/mL (122%) with 19% below 14ng/mL (31nM) the *in vitro* IC_{95} against HIV1 in 50% human serum (Rizk ML, AAC 2012) and 20% below 22ng/ml (45nM) the i*n vivo* supposed active C24h (lowest quartile of Mean Geometric C24h from QDMrck. At W24, 99% of patients had pVL$\leq$50copies/ml and CD4~589/mm^3. Apparently, no deleterious impact of ARV backbone had been found. For information, administration of 1200mg QD as 400mg x 3 OCT and 600mg x 2 reformulated tablet in the fasted state resulted in a day 5 geometric mean (CV%) Ctrough of 40ng/ml (53%) and 39ng/ml (72%), respectively (Rizk ML, CROI 2014, Abs. 523).

Conclusions: switching to RAL OCT formulation (800mg QD) containing regimen maintains virological suppression at W24 in all patients except one, with 80% of adequate RAL C24h despite a large inter-patient variability compared with the new formulation at 1200mg QD in healthy subjects.

No conflict of interest

Abstract: PP_03

Pharmacokinetics for Pediatrics, Pregnancy and other Special Populations

Age and gender effects on the pharmacokinetics of HCV NS5A inhibitor MK-8742

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Introduction: MK-8742 is a potent, once-daily inhibitor of the hepatitis C virus (HCV) nonstructural protein NS5A being developed for the treatment of chronic HCV infection. This study was the first comparison of MK-8742 pharmacokinetics between males and females, as well as the first comparison between healthy young males and healthy elderly subjects.

Materials & Methods: This was a double-blind, placebo-controlled, randomized, single-dose study designed to evaluate the safety, tolerability, and pharmacokinetics of MK-8742 in healthy elderly male and female subjects. Panel A and Panel B consisted of 14 healthy elderly male (age 65-78 years) and 14 healthy elderly female (age 65-80 years) subjects respectively. Twelve (12) subjects per panel were randomized to receive a single oral dose of 100 mg MK-8742, and 2 subjects per panel received matching placebo. Panel C consisted of 8 young (age 22-45 years) male subjects; 6 received MK-8742 and 2 received placebo.

Results: A single dose of 100 mg MK-8742 was well tolerated in the healthy elderly males and females and healthy young males in this study. The MK-8742 AUC0-∞, Cmax, and C24h geometric mean ratios (GMRs) (90% confidence intervals [90% CIs]) for the comparison of a single dose of 100 mg MK-8742 administered to healthy elderly females versus healthy elderly male subjects were 1.67 (1.12, 2.48), 1.75 (1.16, 2.66) and 1.58 (1.07, 2.33), respectively. Additional exploratory analyses were conducted to adjust for body weight or BMI. The resulting AUC0-∞ GMRs (90% CIs) for the comparison of a single dose of 100 mg MK-8742 administered to healthy elderly female versus healthy elderly male subjects were 1.33 (0.83, 2.14), when adjusted for body weight, and 1.64 (1.10, 2.45), when adjusted for BMI. Similar results were obtained for the Cmax and C24h parameters following these additional analyses. The MK-8742 AUC0-∞, Cmax, and C24h GMRs (90% CIs) for the comparison of a single dose of 100 mg MK-8742 administered to healthy elderly males versus healthy young males were 1.02 (0.69, 1.53), 0.91 (0.60, 1.38), and 0.97 (0.66, 1.44).

Conclusions: The plasma exposures following a single 100 mg dose of MK-8742 in healthy elderly female subjects is approximately 70% greater than that observed in healthy elderly male subjects. The plasma AUC0-∞ is approximately 33% greater in healthy elderly female subjects when adjusted for weight, suggesting that the observed gender effect may partially be explained by gender differences in body weight. A single 100 mg administration of MK-8742 results in similar exposures in healthy elderly male and healthy young male subjects. MK-8742 was well-tolerated in the healthy elderly male and female subjects in this study.

Conflict of interest Authors affiliated with Merck & Co INC are current employees of Merck & Co INC

Abstract: PP_04

Novel Drugs and Formulations

Plasma concentrations of the novel HCV entry inhibitor, ITX 5061, in liver transplant patients

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Introduction: ITX 5061 is a first-in-class hepatitis C virus (HCV) entry inhibitor that acts through blockade of scavenger receptor B-1. Parallel trans-Atlantic phase Ib open-label studies measured the plasma concentrations of ITX 5061 in HCV-infected patients undergoing liver transplantation peri- and post-operatively.

Materials & Methods: Patients with HCV undergoing liver transplantation due to end-stage liver disease or hepatocellular carcinoma were recruited at University Hospital Birmingham (Birmingham, UK) and Mount Sinai Hospital (New York, US). For US patients, a 300-mg dose of ITX 5061 was administered orally prior to surgery and a second dose administered (via nasointraduodenal tube) on arrival to the ICU. Six additional oral doses of 300-mg were given every 24 hours during the post-anhepatic phase. Thereafter, patients received ITX 5061 150-mg once daily for an additional 21 days. For UK patients, a similar protocol was followed, however, ITX 5061 was dosed at 150-mg throughout the study for one week. On the day of surgery, US patients had plasma samples collected for the measurement of ITX 5061 concentrations post-transplant upon arrival to the ICU, and 8, 12, 16, and 24 hours following the second dose (post-reperfusion). For UK patients, plasma concentrations were collected at induction of anesthesia and after reperfusion. During the post-anhepatic stage, trough samples were collected on days 2, 3, 4, 5 (both US and UK patients), and days 14, 21, and 28 (US patients only). Analyses of samples were performed using reverse phase liquid chromatography and mass spectrometry detection. The summary data of ITX 5061 plasma concentration is presented as geometric means [with interquartile range] and time since last dose (TSLD) as medians.

Results: Data were available from 9 patients in the US and 10 patients in the UK. After administration of dose 1, patients from the UK had mean concentrations at induction (median TSLD, 1 hour) and after reperfusion (median TSLD, 4.1 hours) of 274 [190] ng/mL and 97 [111] ng/mL, respectively. For patients from the US, mean plasma concentration after reperfusion was 65 [77] ng/mL. For US patients, following administration of the second dose, the mean concentrations (ng/mL) of ITX 5061 at 8, 12, 16, and 24 hours were 60.5 [40.0], 45.4 [54.0], 27.6 [12.5], and 22.4 [25], respectively. The mean trough concentrations of ITX 5061 for UK and US patients during the post-anhepatic phase were 48.8 [47.2] and 45.0 [35.8], respectively. Mean concentrations collected during days 14, 21 and 28 for US patients were 36.3 [53.4].

Conclusions: Pharmacokinetic studies of ITX 5061 were successfully completed in HCV-infected patients before and after liver transplantation and achieve concentrations that exceed in vitro target values. On average, trough concentrations of ITX 5061 exceeded the concentration at which >90% of infectious HCV is inhibited (30 ng/mL). ITX 5061 represents a novel anti-HCV agent warranting further study in the setting of liver transplantation of HCV-infected patients.

No conflict of interest

Abstract: PP_05

PK/PD modeling

Population pharmacokinetics of tenofovir-diphosphate in red blood cells in HIV-negative and HIV-infected adults.

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Introduction: The predominant factor that impacts antiretroviral drug exposure is adherence, but no gold standard objective measure of adherence is clinically available. Tenofovir-diphosphate (TFV-DP) accumulates in red blood cells (RBCs) with a half-life of ~17 days, a unique pharmacological characteristic that makes it a potential tool for monitoring long-term antiretroviral adherence. The objective of our study was to construct a population model to assess the pharmacokinetics (PK) of TFV-DP in RBC in HIV-negative and HIV-infected individuals.

Materials and Methods: Data were included from an intensive 60-day PK study of daily co-formulated tenofovir-disoproxil-fumarate/ emtricitabine (TDF/FTC) for 30 days followed by 30-day washout in HIV-negative adults and daily TDF/FTC (plus efavirenz) for 60 days in HIV-infected individuals. RBC samples were collected at varying times (1, 2, 4, 8, 24 hrs) after first dose and on days 3, 7, 20 and 30 from participants. A single RBC sample was collected on days 5, 15, and 30 off-drug for HIV-negative individuals and on day 60 for HIV-infected individuals. RBCs were counted, lysed, and TFV-DP was measured using validated LC-MS/MS. Nonlinear mixed effects modeling (NONMEM 7.2.0) using First Order Conditional Estimation with Interaction was used to develop the population model and explore the influence of covariates including gender, race, age, HIV status, weight, estimated glomerular filtration rate, plasma TFV oral clearance and hematocrit. Model selection was based on graphical assessments (goodness of fit, residuals vs. predicted and residuals vs. time), accuracy and meaningfulness of parameter estimates, significant decrease in objective function value (OFV) and visual predictive checks. Final models were evaluated using stepwise inclusion/backward elimination.

Results: 39 individuals (18 HIV-infected, 13 women, 16 Black, 5 Hispanic) contributed 324 samples for analysis. A one-compartment Base Model with a first order absorption rate constant (Ka) term (representing TFV-DP formation) best described the PK of intracellular TFV-DP in RBCs. The typical value (95% CI) of the elimination rate constant (K) was estimated to be 0.0374 day-1 (0.0332 to 0.0415) with an inter-individual coefficient of variation (CV) of 21.7%, corresponding to a half-life of 18.5 days. The apparent volume (V) was estimated to be 27.8 L (24.6 to 30.9), CV 34.1% (representing a scalar). The corresponding Css was 131 fmol/106 RBC. Ka was 7.29 day-1 (4.40 to 10.17), CV 110%. Residual variability was 24.7%. Ka was fixed for covariate evaluation. Weight and race had a significant influence on K after forward inclusion ($\Delta OFV > 3.84; p < 0.05$), but neither remained significant after backward elimination ($\Delta OFV < 7.81; p > 0.01$), thus they were not included in the Final Model. No significant effects on K or V were observed for any of the remaining covariates.

Conclusions: A one compartment model adequately described the PK of TFV-DP in RBCs in HIV-negative and HIV-infected individuals. This model confirms the long elimination half-life and the Css of TFV-DP in RBCs and extends previous work in HIV-negative individuals to HIV-infected individuals. These results also provide the basis for future research on its application as an objective measure of drug adherence in clinical trials and routine patient care.

No conflict of interest

15th International Workshop on Clinical Pharmacology of HIV & Hepatitis Therapy

Abstracts
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Abstract: P_01

Novel Drugs and Formulations

A novel Ritonavir pediatric powder formulation is bioequivalent to Norvir® oral solution with a similar food effect

A.H. Salem[1], Y.L. Chiu[2], J.M. Valdes[3], A.M. Nilius[3], C.E. Klein[1]

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Introduction: AbbVie is developing a ritonavir powder formulation to eliminate the alcohol and propylene glycol contents in the current Norvir® oral solution for pediatric use. Two studies were conducted to assess the bioequivalence of the powder to the Norvir ® oral solution and to evaluate the effect of food and different vehicles on its bioavailability.

Materials and Methods: Study 1 was a randomized, partial crossover, 4-period study in 48 HIV-negative adult subjects. In Period 1 and 2, all subjects received the powder formulation in water and the oral solution following a moderate-fat meal. In Period 3 and 4, 24 subjects received the powder formulation in water under fasting conditions and following a high-fat meal and 24 subjects received the powder formulation in either chocolate milk or pudding following a moderate-fat meal. Study 2 was a randomized, complete crossover, 4-period study in 24 HIV-negative adult subjects. Subjects were randomized to a sequence of the oral solution and powder formulation in water, infant formula and apple sauce; all following a moderate-fat meal. Bioavailability comparisons were assessed by the 90% confidence intervals for the difference of the least square means obtained from the analyses of the natural logarithms of C_{max}, AUC_t and AUC_∞.

Results: Ritonavir powder formulation in water was bioequivalent to Norvir ® oral solution. Ritonavir powder formulation administered in chocolate milk, pudding, infant formula or apple sauce was bioequivalent to the powder formulation administered in water. Compared with fasting conditions, moderate-fat and high-fat meals were associated with approximately 25-40% and 35-50% reduction in ritonavir concentrations, respectively.

Conclusions: The novel ritonavir powder formulation is bioequivalent to Norvir ® oral solution under moderate-fat conditions with a similar effect of meals. None of the vehicles tested negatively affected the bioavailability of the novel formulation which suggests the potential for use of a broad range of vehicles.

Conflict of interest The design, study conduct, and financial support for the clinical trials were provided by AbbVie. AbbVie participated in the interpretation of data, review, and approval of the publication. All authors are employees of AbbVie and have no additional conflicts of interest to disclose.

Abstract: P_02

Novel Drugs and Formulations

Evaluation of the pharmacokinetics and formulation performance of Tenofovir disoproxil fumarate oral powder under fed conditions

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Background: Tenofovir disoproxil fumarate (TDF) tablets are approved for use in HIV-and HBV-infected adults. TDF tablets are also approved for use in pediatrics with a range of tablet sizes (150, 200, 250 and 300 mg). An oral powder formulation of TDF is also available allowing for dosing flexibility and ease of administration for younger children and some adults who may have difficulty swallowing tablets. The present study evaluated the pharmacokinetics (PK) and formulation performance of TDF oral powder, relative to TDF oral tablet, under fed conditions in healthy subjects.

Materials & Methods: This was a randomized, open-label, single-dose, two-cohort, two-way crossover (per cohort) study. All subjects (n=28) received TDF 300 mg as an oral powder and as an oral tablet in a crossover manner separated by a seven day washout period. Cohort 1 subjects received treatments with a light meal (approximately 390 kcal and 12 g fat). Cohort 2 subjects received treatments with a high-fat meal (approximately 800 kcal and 44 g fat). Intensive PK was assessed for 72 hours post dose. Statistical comparisons of tenofovir (TFV) exposures were made using geometric mean ratios (GMR) and associated 90% confidence interval (CI) bounds of 70-143% (>90% power to conclude clinical equivalence), with the oral powder serving as the test treatment and the oral tablet serving as the reference treatment. Safety assessments were performed throughout the study and during follow-up.

Results: Study treatments were well tolerated. Twenty-seven of the 28 enrolled subjects completed study drug and one discontinued after withdrawing consent. No Grade 2, 3 or 4 adverse events were observed except for one subject that experienced Grade 2 otitis media while receiving the oral tablet with a high-fat meal. Following administration of TDF as oral powder versus tablet formulations under both fed conditions, TFV AUC_{last} and AUC_{inf} were within the protocol defined equivalence boundary (GMR (90% CI) for AUC_{last} and AUC_{inf} were 92.0 (86.8, 97.4) and 94.0 (89.7, 98.4), respectively [light meal]; and 85.2 (79.8, 90.9) and 85.8 (81.5, 90.4), respectively [high-fat meal]). TFV C_{max} was modestly lower following administration of the oral powder versus the tablet formulation under both fed conditions (21% lower with light meal; 44% lower with high-fat meal) but not considered clinically meaningful, as TFV AUC across treatments/conditions were in the range of exposures associated with TDF efficacy.

Conclusions: There were no clinically relevant differences in TFV systemic exposures between oral powder and tablet formulations of TDF under fed conditions. The comparable TFV exposures observed following administration of the oral powder under both fed conditions indicated similar formulation performance regardless of meal type. These results are consistent with the established PK profile of TFV from the oral powder formulation under fasted conditions.

Conflict of interest All coauthors are employees and shareholders of Gilead Sciences.

Abstract: P_03

Novel Drugs and Formulations

Lopinavir/ritonavir/lamivudine as a fixed-dose combination tablet: assessment of bioequivalence and effect of food on bioavailability

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Introduction: AbbVie is developing a novel protease-inhibitor based fixed-dose combination (FDC) tablets of lopinavir, ritonavir and lamivudine. AbbVie conducted two studies to assess the bioequivalence of the new FDC formulation to the reference marketed

lopinavir/ritonavir and lamivudine tablets and to evaluate the effect of meals on the FDC.

Materials and Methods: Study 1 was a randomized, 2-way crossover study in 108 HIV-negative adult subjects. Subjects were randomly assigned in equal numbers to a sequence of the FDC and reference products administered under fasting conditions. Study 2 was a randomized, 3-way crossover study in 24 HIV-negative adult subjects. Subjects were randomly assigned in equal numbers to one of six sequences of three regimens; FDC under fasting, moderate-fat and high-fat meal conditions. Single doses of lopinavir/ritonavir 400/100 mg and lamivudine 150 mg were administered on Study Day 1 of each period, separated by at least 5 days. Serial blood samples were drawn for 36 hours and pharmacokinetic parameters were calculated in Phoenix WinNonlin (v.6.3). The relative bioavailability of the FDC was assessed by the 90% confidence intervals for the difference of the least square means obtained from the analyses of the natural logarithms of C_{max}, AUC_t and AUC_∞ in SAS (v.9.2).

Results: The novel FDC was bioequivalent to the marketed lopinavir/ritonavir and lamivudine products. Following administration of the FDC tablets under moderate and high fat meal conditions, there was a minimal change in lamivudine concentrations. Compared with fasting conditions, there were 34-41% and 21-27% increases in lopinavir and ritonavir concentrations, respectively, when the FDC is taken with a moderate-fat meal. Compared with fasting conditions, there were 21-41% and 37-40% increases in lopinavir and ritonavir concentrations, respectively, when the FDC is taken with a high-fat meal.

Conclusions: The study demonstrated the bioequivalence of the novel protease-inhibitor based FDC of lopinavir, ritonavir and lamivudine to the marketed products under fasting conditions. The food effect on the FDC is similar to that for the marketed products. This fixed dose formulation can be dosed either once or twice daily, with additional flexibility for selection of the third agent in the combination antiretroviral regimen.

Conflict of interest The design, study conduct, and financial support for the clinical trials were provided by AbbVie. AbbVie participated in the interpretation of data, review, and approval of the publication. All authors are employees of AbbVie and have no additional conflicts of interest to disclose.

Abstract: P_04

Novel Drugs and Formulations

Assessment of bioequivalence and food effect for a complete antiretroviral fixed-dose combination of Lopinavir, Ritonavir, Lamivudine and Zidovudine

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Introduction: AbbVie is developing a novel protease-inhibitor (PI)-based fixed-dose combination (FDC) tablets of lopinavir, ritonavir, lamivudine and zidovudine.

Materials and Methods: Study 1 was a randomized, 3-way crossover study in 108 HIV-negative adult subjects. Subjects were randomly assigned in equal numbers to a sequence of the FDC, US and EU reference products administered under fasting conditions. Study 2 was a randomized, 3-way crossover study in 24 HIV-negative adult subjects. Subjects were randomly assigned to a sequence of FDC under fasting, moderate-fat and high-fat meal conditions. Single doses of lopinavir/ritonavir 400/100 mg, lamivudine 150 mg and zidovudine 300 mg were administered on Study Day 1 of each period. Serial blood samples were drawn for 36 hours and pharmacokinetic parameters were calculated in Phoenix WinNonlin (v.6.3).

The relative bioavailability of the FDC was assessed by the 90% confidence intervals for the difference of the least square means obtained from the analyses of the natural logarithms of C_{max}, AUC_t and AUC_∞ in SAS (v.9.2).

Results: The novel FDC was bioequivalent to both US and EU sourced reference products. Following administration of the FDC tablets under moderate and high-fat meal conditions, there was a minimal change in lamivudine concentrations. Moderate-fat conditions increased lopinavir C_{max} by ~ 28% and AUC by ~35% compared with fasting conditions. High-fat conditions did not have a statistically significant effect on lopinavir C_{max} with fasting conditions, but increased the lopinavir AUC by 30% compared with fasting conditions. Moderate-fat conditions did not have a statistically significant effect on ritonavir C_{max} compared with fasting conditions, but increased ritonavir AUC by ~15% compared with fasting conditions. High-fat conditions had a minimal effect on ritonavir C_{max} but increased AUC by ~20% compared with fasting conditions.
Under fed conditions, the mean C_{max} of zidovudine was decreased by 22% to 26% compared with fasting conditions. Food did not have a statistically significant effect on zidovudine AUC compared with fasting conditions.

Conclusions: The study demonstrated the bioequivalence of the FDC of lopinavir, ritonavir, lamivudine and zidovudine to the marketed products under fasting conditions. The food effect on the FDC is similar to that for the marketed products.

Conflict of interest:The design, study conduct, and financial support for the clinical trials were provided by AbbVie. AbbVie participated in the interpretation of data, review, and approval of the publication. All authors are employees of AbbVie and have no additional conflicts of interest to disclose.

Abstract: P_05

Novel Drugs and Formulations

Resistance analysis in subjects receiving daclatasvir in combination with asunaprevir and BMS-791325 for hepatitis C virus genotype 1 infection

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Introduction: The all-oral, ribavirin-free combination of daclatasvir (DCV; NS5A inhibitor), asunaprevir (ASV; NS3 inhibitor), and BMS-791325 (Non-nucleoside NS5B inhibitor) achieved sustained virologic response (SVR) in > 90% of treatment-naive patients with chronic HCV genotype (GT) 1 infection treated for 12 or 24 weeks. In this report, we examined the impact of baseline (BL) polymorphisms on virologic response and resistance emergence.

Materials & Methods: Subjects were assigned to receive DCV (60-mg, once daily [QD] or 30-mg twice daily [BID]), ASV (200-mg, BID) and BMS-791325 (75 or 150-mg, BID) for 12 or 24 weeks. The NS3, NS5A and NS5B genes from available BL and failure samples were analyzed from 232 HCV GT-1 (185 GT-1a and 47 GT-1b) subjects enrolled in groups 1-6 of Study AI443014 to determine the presence of resistance associated variants (RAVs) known to affect drug susceptibility in vitro by >3-fold.

Results: Baseline NS3 resistance-associated variants (RAVs) at R155 was detected in 1/184 (0.5%) GT-1a subjects with available NS3 sequence; the one subject with NS3-R155K relapsed. Baseline NS5A RAVs at M28, Q30, L31, and Y93, and associated with a loss in DCV potency, were detected in 14/183 (7.7%) GT-1a subjects with available NS5A sequence. Four of these subjects were on-treatment failures while the remaining 10 achieved SVR. NS5B RAVs at

P495 were not detected in any of the 180 available BL NS5B sequences from subjects infected with GT-1a.
Virologic failure (breakthrough or posttreatment relapse) was experienced by 14/232 (6.0%) subjects (13 GT-1a and 1 GT-1l) receiving 12 or 24 weeks of treatment. Of the 13 GT-1a failures, 6 received 75-mg BID BMS-791325 and 7 received 150-mg BID BMS-791325. The NS3 RAV R155K was detected in 12/13 (92.3%) GT-1a subjects at failure. NS5A RAVs at M28A/T, Q30E/H/R/S, L31M and Y93H/N were observed in the majority (12/13 [92.3%]) of GT-1a failures. There was one subject who relapsed and did not have detectable NS5A substitutions that reduce DCV potency. This lack of DCV-resistant substitutions was confirmed by both population sequencing and deep sequencing. Emergent NS5B RAVs at P495L/S were observed in 7/13 (53.8%) GT-1a failures. For 5 of the 6 virologic failures with no detectable NS5B RAVs, deep sequencing analysis (clonal analysis and Ion Torrent) did not identify any minor variants at P495.
There was one virologic failure designated as being infected with GT-1b by the study central laboratory. Sequence analysis of NS3, NS5A and NS5B revealed a close similarity with the recently identified GT-1l genotype. This subject had NS3 (Q80L), NS5A (L28M, R30Q, L31M), and NS5B (V499A) at baseline. In vitro, these substitutions individually affected drug susceptibility by < 3-fold. At failure, RAVs similar to those in GT-1a were observed and included NS3-R155K, NS5A-Y93C, and NS5B-P495S.

Conclusions: In the all-oral, interferon-free/ribavirin-free regimen of DCV, ASV and BMS-791325, no clear association between BL NS3, NS5A, and NS5B polymorphisms and virologic outcome was apparent. Failure was associated with the co-emergence of RAVs in NS3 and NS5A and to a lesser degree NS5B.

Conflict of interest: Employee of BMS.

Abstract: P_06

Novel Drugs and Formulations

Pharmacokinetics and safety of IDX21437, a novel nucleotide prodrug for the treatment of hepatitis C virus (HCV) infection, in healthy subjects

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Introduction: IDX21437, a novel uridine nucleotide analog prodrug, is a potent and selective pan-genotypic HCV NS5B inhibitor. IDX21437 produces high levels of nucleotide triphosphate metabolite in the liver. There is no evidence of geno, mitochondrial or cardiac toxicity associated with IDX21437. We assessed the tolerability, safety, and pharmacokinetics (PK) in healthy subjects.

Materials & Methods: Six sequential cohorts of 8 subjects for a total of 48 subjects were randomized 2:6 to receive placebo or IDX21437 at single doses of 10, 25, 50, 150, 300 mg or multiple doses at 300 mg once daily (QD) x 7 days. Subjects stayed at the clinical facility for up to 13 days for PK and safety evaluation. Plasma samples were obtained up to 120 h postdose and measured for IDX21437 and its nucleoside metabolite, IDX20664, levels using a validated LC/MS/MS methodology.

Results: All subjects completed the study. Single and multiple doses of IDX21437 were safe and well tolerated. There were no serious adverse events, patterns of adverse events or laboratory abnormalities related to IDX21437. Under fasting conditions at single ascending doses from 10 mg to 300 mg, IDX21437 was rapidly absorbed with Cmax reached within 1h. The parent drug was quickly cleared at a short half-life of ~1h while the nucleoside metabolite IDX20664 gradually appeared and reached

Cmax within 3-4 h. IDX20664 exhibited a longer plasma half-life of 20-30 h, supporting QD dosing. Plasma exposures of IDX21437 and IDX20664 increased with increasing doses in the studied dose range. IDX21437 and IDX20664 reached steady state after 4-5 QD doses of 300 mg/day. IDX21437 did not accumulate with multiple doses while total exposure of IDX20664 increased by 36 percent. Based on in vitro data, the steady-state exposures are expected to produce clinical antiviral activity in HCV-infected patients.

Conclusions: IDX21437 was safe and well tolerated at single and multiple doses up to 300 mg QD for 7 days and achieved plasma exposures expected to produce clinical anti-HCV activity. Its PK profile supports QD dosing. A 7-day proof-of-concept study in subjects infected with HCV genotype 1-3 is ongoing.

Conflict of interest: Employee, shareholder or contracted to conduct to presented clinical study

Abstract: P_07

Improving interlaboratory precision of intracellular Tenofovir diphosphate measurements: results from a pilot study

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Introduction: In increasing number of non-traditional specimen types, such as peripheral blood mononuclear cells (PBMC), are collected for HIV clinical research in the areas of HIV prevention, treatment and eradication for the measurement of antiretroviral (ARV) concentrations in clinical studies sponsored by the National Institutes of Health (NIH). The pivotal nature of drug concentration data within these research initiatives as well as the developing NIH policy for raw data sharing necessitates verification that the precision of measurements reported by different laboratories are acceptable.

Materials and Methods: Three NIH-supported clinical pharmacology laboratories measuring intracellular tenofovir diphosphate (TFV-DP) concentrations in PBMC participated in an exchange of low, medium and high quality controls from each laboratory (QC exchange). The study was coordinated and analyzed by the NIH Clinical Pharmacology Quality Assurance (CPQA) program. Four laboratories shipped 8 replicates of each QC level to the CPQA using a custom-made kit and instructions. One complete set of 12 blinded samples was subsequently shipped back to each laboratory for analysis. Results were reported using the CPQA proficiency data management system. After this first round (RD1) of testing, de-indentified results were shared to assist each laboratory in determining inconsistencies with the others. A second round (RD2) of testing was conducted after re-blinding the same QC samples. Data was analyzed using summary statistics since lab assigned values of each QC were potentially inaccurate. One laboratory did not complete RD2 and was excluded. Absolute differences (AD) were calculated as the absolute difference of two values normalized by the mean of the two values. Interlaboratory variability was calculated as percent relative standard deviation (RSD). The log of concentration reported during round 2 versus AD was regressed to determine any laboratory relationships.

Results: The range of quantitation (30-, 800-, and 1000-fold) and lower limits of quantitation (12.5 – 250 pg/mL QC) for lab methods varied and 2/12 controls were excluded from analysis due to unreportable values. During RD1 the interlaboratory variability (median RSD) was 36%; 8/10 RSDs were >30%. One lab's values were ~50-60% higher than the other two. Subsequent root cause analysis revealed that the purity of the reference compound was inaccurate and a new vendor was utilized for RD2. Interlaboratory variability improved during

RD2 yielding a median RSD of 10%; only 1 of 10 values was > 20%.
After % purity was factored, individual lab interassay AD over RD1 and RD2 was determined to be 6-9% and each lab maintained a distinct positive or negative bias from others throughout both rounds. The correlations between increasing interassay AD and decreasing QC concentration was not significant ($p>0.05$ for slopes, $R2<0.32$).

Conclusions: The CPQA-coordinated, interlaboratory QC exchange strategy provided a venue for confidential performance assessment which brought about better congruency during RD2. Lack of accurate purity data for TFVDP reference standard was identified as the source of the RD1 discordancy. Therefore, perhaps use of one vendor source amongst all labs might further decrease bias in lab values. Blinded inter-laboratory exchange, such testing of QC, is recommended to assure interlaboratory precision when proficiency testing is not available.

No conflict of interest

Abstract: P_08

Antiviral quantification in paired blood and liver tissue or hepatocytes

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Introduction: A critical question in designing Hepatitis C virus (HCV) therapy in persons with advanced liver disease is whether blood concentrations for the direct acting antiviral drugs (DAA) reflect their liver concentrations. Patients with advanced liver disease may have portal-systemic shunting or alterations in membrane transporter and/or phosphorylation enzyme expression or function that could affect DAA concentrations in the liver. The objective of this work was to quantify antiviral drugs in liver tissue and the active, phosphorylated forms of nucleos(t)ide analogs in hepatocytes obtained from a fresh liver explant and compare these values to drug concentrations in paired blood and peripheral blood mononuclear cells (PBMCs).

Materials & Methods: Using an IRB-approved protocol, tissue was obtained from a fresh liver explant from a 50 year old HIV/HCV-coinfected male with decompensated liver disease who underwent liver transplantation. The patient received two antiviral regimens, switching therapy five days prior to transplant. The total list of drugs in the two regimens included tenofovir disoproxil fumarate, emtricitabine, lamivudine, raltegravir, darunavir, atazanavir, and ritonavir. In the operating room, an 18-gauge biopsy needle was used to remove cores from the liver explant and a small liver tissue sample was collected. A paired blood sample was obtained from the patient to measure drug in plasma and PBMCs. PBMCs and hepatocyte concentrations are expressed as femtomole per million cells (fmol/10^6 cells).

Results: We successfully isolated 100,000 hepatocytes and quantified all 3 nucleos(t)ide analogs from the core biopsy samples and paired PBMCs and measured the other antiviral agents in the liver tissue and in plasma. Tenofovir diphosphate (TFV-DP) concentrations in hepatocytes and PBMCs were 157 and 262 fmol/10^6 cells, respectively. Lamivudine triphosphate (3TC-TP) concentrations in hepatocytes and PBMCs were 3750 and 17700 fmol/10^6 cells, respectively. Emtricitabine triphosphate (FTC-TP) concentrations in hepatocytes and PBMCs were 618 and 1630 fmol/10^6 cells, respectively. The corresponding ratios of hepatocyte:PBMC concentrations for TFV-DP, 3TC-TP, and FTC-TP were 0.6, 0.2, and 0.4, respectively. Tenofovir, emtricitabine, raltegravir, atazanavir, and ritonavir concentrations in liver tissue vs. plasma were 572 and 94 ng/mL, 377 and 117 ng/mL, 2217 and 4539 ng/mL, 6869 and 882 ng/mL, and 4785 and 1132 ng/mL, respectively. The corresponding ratios of liver:plasma concentrations for tenofovir, emtricitabine,

raltegravir, atazanavir, and ritonavir were 6.1, 3.2, 0.51, 8.2, and 4.4, respectively.

Conclusions: Antiviral drugs, including the phosphorylated anabolites of the nucleos(t)ide analogs, can be quantified in liver samples and hepatocytes. Our approach differs from previous efforts to measure liver concentrations of nucleos(t)ide analogs because we isolated fresh hepatocytes and measured the individual nucleotide triphosphate moieties normalized to a cell count. This methodology may also be useful in measuring DAAs in patients undergoing HCV treatment.

No conflict of interest

Abstract: P_09

Characterizing antiretroviral distribution within active viral reservoirs using mass spectrometry imaging

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Introduction: HIV infection persists despite long-term antiretroviral (ARV) treatment. Inadequate ARV exposure in certain anatomic sites may contribute to continued viral replication within tissue reservoirs. Detailed evaluations of the contribution of ARV disposition to the formation and persistence of these reservoirs would greatly inform HIV cure efforts. Recent studies have demonstrated differential ARV penetration into suspected reservoirs using tissue homogenates; however this method of evaluating ARV exposure in tissues is limited in its scope and ability to describe within-tissue ARV distribution. Mass spectrometry imaging (MSI) allows for the visualization of small molecule biodistribution within anatomic sites. Here, we use a novel MSI technique to characterize the distribution of two commonly prescribed ARVs within the lymph node, which has been implicated as an active viral reservoir.

Materials & Methods: A single healthy uninfected rhesus macaque was dosed to steady-state with 30mg/kg tenofovir disoproxil fumarate (TDF) given subcutaneously, and 200mg efavirenz (EFV) given orally once daily. At necropsy, an inguinal lymph node was removed and frozen on dry ice. A single ten micron slice from each tissue was analyzed using an infrared matrix-assisted laser desorption electrospray ionization (IR-MALDESI) source coupled to a Thermo Q-Exactive mass spectrometer. MSI data were analyzed using MSiReader software. In order to relate observed IR-MALDESI findings to tissue architecture, serial sections were fixed and stained with hematoxylin and eosin (H&E).

Results: IR-MALDESI imaging revealed non-homogenous ARV distribution within the tissue compartment. TFV and EFV were both detected in the lymph node, though their respective signals showcased unique tissue distribution. Visual inspection of the supporting H&E stain show that TFV signal was concentrated throughout the medullary sinuses, while EFV signal was predominantly visualized near a small section of the lymph node capsule.

Conclusions: This is the first report of visualizing ARV distribution within a tissue implicated as a viral reservoir. Observed distributional patterns identified by IR-MALDESI, when coupled with H&E stains from serial slices, agree with tissue homogenate studies that have shown that TFV and EFV achieve measurable concentrations in the lymph nodes. The distinct distributional pattern of EFV compared to TFV suggests that ARV exposure within viral reservoirs cannot be assumed to be the same between individual agents. Further, apparent preference of TFV for the vascularized medullary sinus over the lymphoid follicles may suggest inadequate concentrations at the site of action. Importantly, the distributional variation observed between TFV and EFV would not have been captured with standard analytical methods and showcases the advantage of using MSI for future

studies. Because the tissues evaluated in this study were removed from a dosed animal, the observed results are likely representative of ARV disposition during in vivo dosing scenarios. This study provides sound proof of concept for future evaluations defining drug distribution in animals and humans.

No conflict of interest

Abstract: P_ 10

A comparison of intracellular antiretroviral concentrations following conventional cell washing vs. a rapid spin through oil.

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Introduction: Accurate determination of antiretroviral drug concentrations is a key necessity for research into intracellular reservoirs of HIV. Considerable variation exists in reported intracellular drug concentrations among research groups. One potential cause for this variation is due to differences in washing cells during processing. One approach that has been used to minimize this variability is to spin cells through an oil solution, as opposed to repeated washes through saline solutions as is commonly done.

Materials & Methods: We compared intracellular drug concentrations of raltegravir (RAL), atazanavir (ATV), darunavir (DRV), efavirenz (EFV), lopinavir (LPV), and ritonavir (RTV) in the CEM.ss T-cell line. We assessed drug concentrations via a validated LC-MS-MS methodology in cells washed one, two, and three times with Hank's buffered saline solution (HBSS) as compared with cells spun through oil. We additionally assessed drug concentrations in the wash solutions. Finally, we compared drug concentrations in samples spun through oil with samples processed immediately and samples left in HBSS for 2 hours at room temperature or on ice.

Results: Samples spun through oil had higher measured intracellular concentrations for all drugs compared with samples washed three times with HBSS, with at least a 3 fold difference in intracellular concentrations. These samples had higher intracellular concentrations for all drugs except for ATV when compared with samples washed two times with HBSS. When we assessed drug remaining in the wash buffer there was a significant decline in remaining drug present in the wash buffer between the first wash and the second or third washes. There was no detectable ATV, DRV, LPV, or RTV in the second and third wash samples, and very low concentrations for RAL and EFV. Finally, we observed that oil spun samples had higher detected intracellular concentrations than those left in HBSS either on ice or at room temperature, with samples left in HBSS for 2 hours having intracellular concentrations ranging from ¾ to ½ of that of samples spun through oil.

Conclusions: The decline in intracellular antiretroviral concentrations that occurs with repeated washes in saline solutions as compared with a spin through oil shows the utility of the spin through oil methodology. While intracellular drug concentrations of samples spun through oil did not show significant differences compared with samples washed once with HBSS, the large amount of drug present in the wash solution suggests that this may be due to incomplete washing of the cells. Similarly, the higher intracellular concentrations in samples processed with oil compared with samples left in HBSS for an extended amount of time shows the advantages of a spin through oil. Traditional intracellular processing methods require multiple washes with a saline solution, and significant portions of intracellular drug can be lost. Utilizing a spin through oil results in high intracellular drug concentrations, and can be done in a fast and efficient manner.

No conflict of interest

Abstract: P_11

An LC-MS/MS method for quantification of rilpivirine in plasma, cervicovaginal-fluid (CVF), rectal-fluid (RF), vaginal and rectal tissues (VT/RT)

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Background: Long-acting antiretrovirals can improve adherence to therapy and could become the preferred agents for HIV pre-exposure prophylaxis (PrEP) and for chronic treatment of HIV infection. TMC278-LA is an investigational long-acting injectable nanosuspension formulation of rilpivirine (RPV) and is currently under investigation as a potential agent for PrEP. Studies investigating drug accumulation at sites of HIV transmission, including genital and rectal fluids and tissues require robust, accurate, precise and highly sensitive methodologies. Here we describe a LC-MS/MS method for quantification of RPV in plasma, genital/rectal fluids and mucosal tissues.

Materials & Methods: CVF samples were self-collected from the upper vagina via direct aspiration using a volumetric aspirator (Rovumeter™). CVF and RF aspirates (10-100µl) were also collected via adsorption using ophthalmic Weck Cel® spears. VT and RT samples were collected by biopsy and homogenised in drug-free plasma. Plasma, CVF (direct aspirates) and tissue homogenate were extracted using protein precipitation (acetonitrile/water; 5:1 v/v). CVF and RF absorbed onto ophthalmic spears were extracted by protein precipitation followed liquid-liquid extraction (hexane/ethyl acetate; 80:20 v/v). A stable isotope labelled internal standard (^{13}C-d4-RPV) was used, and the assay validated over a concentration range of 0.5-400 ng/ml. Quantification was performed using SRM in positive mode on a triple quadrupole TSQ Vantage mass spectrometer (Thermo Scientific). Validation of the method was carried out as per FDA guidelines. Short and long-term stability under various storage conditions were evaluated.

Results: Chromatographic separation of the E and Z isomer forms of RPV was achieved on a reverse phase column and steps were taken to ensure that interconversion of the isomers did not occur under normal laboratory processing conditions. The extraction techniques demonstrated a high percentage recovery for all matrices (>75%), with minimal interference from the sample matrix. Inter and Intra-assay precision and accuracy at the LLQ, and for LQC, MQC and HQC concentrations were <15%. QC samples were stable for up to 4 hours at room temperature and following heat inactivation and 3 freeze/thaw cycles. Plasma/spear samples were stable following 1 year in storage and incurred tissue samples (intact and homogenised) were stable for up to 3 months (-70ºC).

Conclusions: A sensitive, specific and reproducible LC–MS/MS methodology has been developed and validated for accurate measurement of RPV in plasma and female genital tract/rectum. The method has been utilised in phase I studies characterising the pharmacokinetics (PK) of RPV in the plasma, female genital tract (CVF and VT) and female and male rectal compartment (RF & RT) of HIV negative volunteers receiving single intramuscular doses (300, 600, 1200mg) of TMC278-LA over 3-4 months.

No conflict of interest

Abstract: P_12

LC-MS/MS analysis of endogenous deoxy-nucleotide-triphosphate (dNTP) pools in HIV-negative versus HIV-positive adults

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Introduction: Many anti-viral drugs are nucleoside analogs (NA), which interact with the cellular machinery that regulates endogenous dNTP, potentially perturbing cellular dNTP pools. The presence of HIV infection is also associated with effects on endogenous pools through influences on immune activation state and SAMHD-1 pathways. Thus an understanding of the interaction of endogenous dNTP pools with HIV status and with NAs treatment will help elucidate the pathophysiology of HIV infection, and treatment outcomes with NAs. Due to the lack of reliable and sensitive analytical methods, few studies have systematically and comprehensively characterized the effect of HIV or NAs on dNTPs. The goal of this study was to develop a sensitive and reliable analytical method for quantifying endogenous dNTPs in human cell samples, including 2' deoxycytidine (2dCTP), 2' deoxyadenosine (2dATP), 2' deoxyguanosine (2dGTP), and thymidine triphosphate (TTP) using LC-MS/MS technology, and to apply this method to clinical research samples.

Materials & Methods: The method utilized a strong anion exchange isolation of mono-(MP), di-(DP), and tri-phosphates (TP) from intracellular matrix. The TP fraction was then dephosphorylated to the parent moiety (dNs) yielding a molar equivalent to the original nucleotide analog intracellular concentration. Reverse phase and weak cation exchange mix mode purification were then utilized for desaltation. PBMC were collected from 19 HIV negative subjects and 17 HIV positive subjects who were not taking any antiretroviral drug treatments. PBMC were isolated with identical procedures then were counted, and lysed. Endogenous dNTP levels were quantified and compared using Welch's t-test and variances were evaluated with F test.

Results: Simultaneous quantitation for dNs was achieved using a PFP kinetex column with isocratic flow of a mobile phase containing 0.5% IPA and 0.02% acetic acid. The quantifiable range was 25-2500 fmol/sample for each dN. The dN calibration curves were fit to a quadratic (1/conc weighted) curve over the concentration range with average r^2 values of 0.9985. Accuracy and precision values were ≤ 13.2% for QCs. Specificity was shown with blank analysis providing background less than 20% of the LLOQ. The method was successfully applied to 36 clinical research samples. The sex of the participants was (HIV negative/HIV positive) 8/3 females and 11/14 males, and the average age and weight were 32.9/34.9 years and 82.4/80.3 kg. The median (interquartile range) of dGTP, dCTP, TTP and dATP was 267.5 (226.0, 335.5), 866.5(681.8, 1070.0), 425.0 (312.5, 616.8) and 158.5 (129.0, 178.8) fmol/10^6 PBMCs, respectively. dGTP levels were significantly lower in HIV infected persons (256.1 vs 334.5; p=0.02), and a decrease trend was seen for dATP (p=0.29), dCTP (p=0.07) and TTP (p=0.08). Variances were lower for all dNTPs in HIV infected versus HIV-negative adults (p<0.01).

Conclusions: An accurate, precise, sensitive, and specific analytical method was developed for intracellular dNTPs. Application of this method to clinical samples revealed significant differences in endogenous nucleotide pools between HIV infected versus HIV negative adults. These findings are consistent with SAMHD-1 activity in HIV-infected individuals, providing a basis for further evaluation of dNTPs for relationships with HIV-pathophysiology and treatment outcomes with NAs.

No conflict of interest

Abstract: P_13

Drug Drug Interactions

The effect of calcium and iron supplements on the pharmacokinetics of Dolutegravir in healthy subjects

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Introduction: Dolutegravir (DTG) is a 2-metal-binding integrase inhibitor (INI) with a novel resistance profile that is currently approved in the US and EU. Antacids containing high levels of metal cations significantly reduce DTG exposure via chelation; therefore dosing separation is recommended. The objective of this study was to evaluate the effects of calcium and iron supplements on the pharmacokinetics (PK) of DTG, both fasted and with food (as these are often taken with food to improve tolerability), and to determine a dosing strategy when DTG is co-administered with these supplements.

Materials & Methods: This was an open-label, randomized, 4-period cross-over study in healthy adult subjects. Subjects were randomized into one of two cohorts (calcium cohort and iron cohort) and received each of four treatment regimens in a randomized fashion: A single dose of DTG 50 mg administered 1) alone under fasted conditions; 2) with a single dose of calcium carbonate 1200 mg or ferrous fumarate 324 mg under fasted conditions; 3) with a single dose of calcium carbonate or ferrous fumarate with a moderate-fat meal (approximately 30% fat); 4) under fasted conditions 2 hours prior to administration of a single dose of calcium carbonate or ferrous fumarate. There was a washout period of at least 7 days between periods. Safety evaluations were performed throughout the study and serial PK samples were collected after each treatment. Within each cohort, noncompartmental PK analysis was performed and geometric least squares mean ratios (GLS-MR) and 90% confidence intervals (CI) were generated by the mixed effect model for within-subject treatment comparisons.

Results: There were twelve evaluable subjects in the calcium cohort and eleven in the iron cohort. No Grade 3 or 4 adverse events (AEs), deaths or SAEs were reported during the study. Only one drug-related AE was observed in the study (Grade 1 nasal congestion). Co-administration of DTG with calcium carbonate under fasted condition resulted in reduction in plasma DTG AUC(0-∞), Cmax, and C24 by 39%, 37%, and 39%,respectively. Co-administration of DTG with ferrous fumarate under fasted condition resulted in reduction in plasma DTG AUC(0-∞), Cmax, and C24 by 54%, 57%, and 56%, respectively. Co-administration of DTG with calcium carbonate or ferrous fumarate under fed condition, or dosing DTG 2 hours prior to the administration of these supplements yielded DTG exposures similar to those when DTG was given alone under fasted conditions.

Conclusions: Calcium and iron supplements (which have lower amounts of chelating cations when compared to antacids) are frequently taken with food; DTG and calcium or iron supplements can be co-administered if taken with a meal. Under fasted conditions, DTG should be given 2 hours prior or 6 hours after calcium or iron supplements.

Conflict of interest Employee of GlaxoSmithKline

Abstract: P_14

Drug Drug Interactions

Influence of separated and concomitant administration of ritonavir on the anticoagulant effect of dabigatran etexilate in healthy volunteers

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Introduction: Potential interactions between antiretrovirals and anticoagulant medications are of particular for HIV patients requiring short-term or chronic anticoagulation. Dabigatran etexilate (DE), an oral anticoagulant that directly inhibits thrombin, is a substrate for the efflux protein, P-glycoprotein (P-gp); it is neither a substrate nor a modulator of cytochrome P450 enzymes. The HIV protease inhibitor, ritonavir (RTV) is a P-gp inhibitor with the potential to interact with DE when taken simultaneously. Separating DE and RTV administration however, may avoid this putative interaction. To address this question, we compared the effect of concomitant vs. separated administration of DE and RTV on thrombin time (TT) in healthy volunteers.

Materials & Methods: The present study was conducted as a single-center, open-label, fixed-sequence, intra-subject, pharmacokinetic/pharmacodynamics (PK/PD) study. Sixteen healthy volunteers received a single dose of DE 150mg alone (Phase 1). After a five-day washout period, subjects took RTV 100mg daily for 2 weeks. A second single dose of DE was then given two hours before the RTV dose (Phase 2), and one week later a third single dose of DE was given concomitantly with the RTV dose (Phase 3). After each DE dose, blood was collected serially over 24 hours and TT was determined according to standard laboratory procedures. DE PD parameters (area under the effect curve [AUEC], maximum effect ratio over baseline [ERmax], and time to maximum thrombin time [TT-tmax]) were derived using noncompartmental methods. Geometric mean ratios (GMR) with 90% confidence intervals (CI) were calculated and compared between Phases 1 and 2, and between Phases 1 and 3 using a 2-tailed paired t-test. A change in PD parameter was accepted as statistically at $p < 0.05$.

Results: A 13% decrease in AUEC was observed between Phase 2 compared with Phase 1 ($p = 0.048$), and a 6% decrease in AUEC was observed between Phase 3 compared with Phase 1 ($p = 0.6$). There was no significant change in ERmax in Phase 2 or Phase 3 compared to Phase 1 (-6%, and no change, respectively, $p > 0.05$, both comparisons). The mean TT-tmax ranged from 2.56 to 3.36 hours, with an 11% decrease in Phase 2 vs. Phase 1 and a 16% increase in Phase 3 vs Phase 1 ($p > 0.05$, both comparisons).

Conclusions: P-gp inhibition, mediated by RTV, was expected to result in an increase in DE AUEC when RTV and DE were given concomitantly. This interaction was expected to be circumvented by separating DE and RTV administration. Instead, we observed a decrease in DE AUEC in the presence of RTV. This decrease was statistically significant during separated -not concomitant- DE and RTV administration. Although statistically significant, the minor decrease we observed in AUEC between phases 1 and 2 would appear to be of limited clinical relevance. Correlation of these results with dabigatran concentrations and the more sensitive clotting assay, ECT, are warranted to confirm these preliminary findings.

No conflict of interest

Abstract: P_15

Drug Drug Interactions

Effect of food and acid reducing agents on the relative bioavailability and pharmacokinetics of Ledipasvir/Sofosbuvir fixed dose combination tablet

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Introduction: A single fixed-dose combination tablet composed of the NS5A inhibitor ledipasvir (LDV) 90 mg and NS5B inhibitor sofosbuvir (SOF) 400 mg is being developed for the treatment of HCV infection. Prior to implementation of LDV/SOF tablet into Phase 3 clinical development, two Phase 1 studies were conducted to examine the effect of food and acid reducing agents on the relative bioavailability and pharmacokinetics of LDV/SOF.

Materials & Methods: Study 1 was a randomized, single-dose, cross-over food effect evaluation in healthy volunteers (N=30) who received LDV/SOF under fasted conditions, with a moderate-fat meal (~ 600 kcal, 25% to 30% fat) or a high calorie/high-fat meal (~ 1000 kcal, ~ 50% fat) with a 9-day washout between treatments.
Study 2 was a 2-group, single and multiple-dose, fixed sequence, cross-over evaluation of the effect of acid-reducing agents on LDV/SOF PK in healthy subjects. Group 1 subjects (N=12; fed) received LDV/SOF alone on Day 1 , simultaneously with a representative H2-receptor antagonist (H2RA) famotidine (40 mg) on Day 12, and 12 hours after famotidine on Day 24. Group 2 subjects (N=16; fasted) received LDV/SOF on Day 1, a representative proton pump inhibitor (PPI) omeprazole (20 mg QD) on Days 12-16 alone and then with LDV/SOF SD on Day 17. LDV, SOF and GS-331007 (predominant circulating nucleoside metabolite) plasma concentrations were analyzed on the last day of dosing for each treatment and PK parameters were calculated. Geometric least-squares means ratios % and 90% confidence intervals (test vs. reference) for LDV, SOF and GS-331007 AUC and C_{max} were estimated using a linear mixed effect model and compared against pre-specified lack of PK alteration boundaries of 70-143%. Safety was assessed throughout the study.

Results: Twenty-eight of 30 subjects completed Study 1; two subjects withdrew consent. All subjects completed Study 2. All adverse events (AE) in Study 1 and Study 2 (Group 1) were Grade 1. There were no AEs in Study 2, Group 2. Food did not alter LDV PK. SOF AUC and C_{max} increased by < 2-fold and < 1.3-fold, respectively, with food. For GS-331007, ~18-30% lower C_{max} with no change in AUC were observed. As SOF exposure increase was modest and GS-331007 AUC was not altered, an increase in SOF PK was not considered clinically meaningful.
Coadministration of famotidine (simultaneous or staggered) with LDV/SOF resulted in ~ 17-20% lower LDV C_{max} without an alteration in AUC. Administration of simultaneous famotidine increased SOF C_{max} by ~ 15% without an impact to SOF AUC or GS-331007 AUC and C_{max}. Staggered famotidine did not alter SOF or GS-331007 AUC or C_{max}. With omeprazole, LDV AUC_{inf} and C_{max} were ~ 4% and 11% lower with no impact on the AUC or C_{max} of SOF or GS-331007.

Conclusion: Study treatments were well tolerated. LDV/SOF may be administered without regard to meals. LDV/SOF may be administered with H2RAs at a dose that does not exceed famotidine 40 mg twice daily. PPI dose comparable to omeprazole 20 mg can be administered simultaneously with LDV/SOF or up to 2 hours after taking LDV/SOF.

Conflict of interest All authors are employees of Gilead Sciences and may own company stock

Abstract: P_16

Drug Drug Interactions

Establishment of an interdisciplinary online expert-forum (INXFO) specialized in HIV and hepatitis in Germany

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Introduction: The continuous progress being made in the diagnosis and treatment of HIV and hepatitis, as well as an aging HIV-infected population with potential comorbidities, have led to an increasing complexity in the management of these infections. In response, INXFO was founded as an internet-based forum for health care providers to obtain anonymous, case-specific, free-of-charge and independent recommendations from an interdisciplinary team of experts.

Materials & Methods: INXFO went on-line in April 2012 (www.inxfo.de). The forum was promoted to health care providers through the distribution of flyers, information booths at conferences and web-site links. After an initial, free online registration, health care providers present their case and ask their question(s) by filling in a template. This is then directed to at least one expert team-member specialized in that field, who can provide a response or obtain more information from the user. Every answer of an expert is checked by a second expert prior to release. The team of experts consists of the following specialties: cardiology, dermatology, endocrinology, gynecology, hepatology, HIV-treatment and resistance, immunology, infectious diseases, internal medicine, lipidology, microbiology, nephrology, neurology, oncology, pediatrics, pharmacy, psychiatry and virology. Additionally, INXFO writes newsletters on various topics and presents cases of interest. Aim of INXFO is to provide recommendations that are fast, tailored to individual cases and applicable to routine clinical care.

Results: In 2013, 113 questions concerning the management of complex cases were answered by INXFO with an increase from 21 in the first quarter to 36 in the fourth. Most frequently, questions were directed at pharmacy (32.7%) and virology (31.0%). Drug interactions was the most common topic (28.3%), followed by co-morbidities and side effects (17.7%), therapy failure (15.9%) and hepatitis (8.0%). 78.8% of cases were reported to be HIV-infected and 8.0% with each hepatitis B and C. One-third (32.7%) were reported to have at least one co-morbidity, of which depression was the most prevalent (11%). The goal is to provide an answer within 3 to 5 working days. 59.3% of questions were answered within 2 days. Three newsletters dealt with the following: 1. interactions between antiretroviral therapy (ART) and antidepressants, 2. ART and cytostatic agents and 3. interactions between ART and anticoagulants. In the most recent quarter, eight case presentations responded to questions in HIV/hepatitis and the following fields: endocrinology, gynecology, hepatology, infectious diseases, nephrology and 2x virology.

Conclusion: Considering the complexity of HIV and hepatitis treatment, an interdisciplinary online expert-forum is a valuable tool for discussion of individual cases. A steady increase of questions over the one-year period examined suggests an increasing awareness and acceptance of INXFO. The next step will be a 'conversation-function' within the forum to allow online discussion of cases and the responses/recommendations provided by the experts.

Conflict of interest The inxfo online forum receives financial support through an unconditional grant from AbbVie Deutschland GmbH & Co. KG.

Abstract: P_17

Drug Drug Interactions

The effects of a single dose of Peginterferon Lambda-1a on Cytochrome P450 activity in healthy subjects

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Introduction: Peginterferon lambda-1a (Lambda), a type III interferon, is in phase 3 development for HCV infection. Therapeutic type I interferons are known to alter human cytochrome P450 (CYP) activity *in vivo*. This study was conducted to understand the effects of a single dose of Lambda on human CYP activity *in vivo*.

Materials & Methods: An open-label, single-sequence study was conducted in healthy male subjects to assess the pharmacokinetics (PK) of a modified 'Cooperstown 5+1 cocktail' containing oral substrates of CYP1A2 (caffeine, 200 mg), CYP2C9 (warfarin, 10 mg), CYP2C19 (omeprazole, 40 mg), CYP2D6 (dextromethorphan, 30 mg) and CYP3A4 (midazolam, 5 mg), and their major metabolites, before and after a single subcutaneous dose of Lambda (180 mg). Subjects (N=24) received the cocktail on Days 1 and 15 and serial PK samples were collected through 96 hours post-dose; subjects were dosed with Lambda on Day 8. Lambda effects on each substrate were assessed by point estimates and 90% confidence intervals (90% CI) for the Day15:Day 1 ratio of geometric means (GMR) for C_{max}, AUC_{inf} and the metabolite:parent (M:P) AUC ratio, using linear mixed models on log-transformed data.

Results: Lambda inhibited the activity of all five CYPs tested, evidenced by increased AUCs and reduced M:P ratios. Day 15:Day 1 GMRs (90% CI) for each substrate were as follows: caffeine C_{max} 0.96 (0.87–1.06), AUC_{inf} 1.73 (1.58–1.88), M:P AUC_{0-T} 0.63 (0.56–0.71); warfarin C_{max} 1.08 (1.03–1.12), AUC_{inf} 1.40 (1.34–1.45), M:P AUC_{0-T} 0.82 (0.78–0.87); omeprazole C_{max} 1.65 (1.33–2.06), AUC_{inf} 2.11 (1.81–2.47), M:P AUC_{inf} 0.64 (0.58–0.70); dextromethorphan C_{max} 1.84 (1.58–2.14), AUC_{inf} 2.06 (1.81–2.34), M:P AUC_{inf} 0.49 (0.43–0.56); midazolam C_{max} 1.46 (1.32–1.60), AUC_{inf} 1.75 (1.58–1.93), M:P AUC_{inf} 0.77 (0.69–0.85). Twenty-one subjects completed the study. Two subjects withdrew for adverse events (ALT elevation, CPK elevation) and one subject withdrew consent. A single dose of Lambda 180 mg resulted in asymptomatic, reversible ALT elevations in 45% of healthy subjects, but was otherwise generally well tolerated.

Conclusions: Following single-dose administration, Lambda has broad effects on human CYP activity *in vivo*, being a mild inhibitor of CYP1A2, CYP2C9 and CYP3A4, and a moderate inhibitor of CYP2C19 and CYP2D6. Dose adjustments for concomitant drug substrates are unlikely, though caution may be warranted with extensively CYP-metabolized drugs with narrow therapeutic indices.

Conflict of interest M Hruska, E Colston, M Stonier, M Hesney, H Myler and R Bertz are employees, and maybe shareholders, of Bristol-Myers Squibb. M Furlong has no conflicts of interest and was an employee of Bristol-Myers Squibb at the time of the study,

Abstract: P_18

Drug Drug Interactions

Boceprevir and antiretroviral pharmacokinetic interactions in HIV/HCV coinfected persons – AIDS clinical trials group study A5309S

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Introduction: In healthy volunteers, boceprevir (BOC) was found to interact with several antiretroviral (ARV) agents. However, data are limited in HIV/HCV co-infected patients. The objectives of this study were to estimate the effects of (1) BOC on ARV pharmacokinetics (PK) and (2) ARV on BOC PK.

Materials & Methods: HIV/HCV co-infected persons receiving peginterferon, ribavirin and BOC through AIDS Clinical Trials Group (ACTG) protocol A5294 could participate in this PK substudy. Subjects received 2 NRTIs plus efavirenz (EFV), raltegravir (RAL), ritonavir (RTV)-boosted atazanavir (ATV), or twice daily RTV-boosted darunavir (DRV) or lopinavir (LPV). Subjects underwent intensive PK sampling for ARV 2 weeks before (week 2) and 2 weeks after initiating BOC (week 6), and intensive PK sampling for BOC at week 6. ARV and BOC AUC were determined using non-compartmental methods. C_{max} and C_{min} were observed. Geometric mean ratios (GMRs) and associated 90% confidence intervals (CI) were used to compare ARV PK at weeks 2 and 6 and BOC PK to historical data (HD) in healthy volunteers.

Results: Sixty four patients (16% cirrhotic) enrolled. ARV PK are available for 54 subjects. EFV PK (n=19) was not affected by BOC. RAL (n=17) AUC and C_{max} were increased with BOC with GMRs (90% CI) of 1.56 (1.03 to 2.35) and 1.87 (1.13 to 3.09), respectively; RAL C_{min} was not significantly increased [1.10 (0.74, 1.64)]. ATV (n=11) AUC and C_{min} were reduced by BOC with GMRs (90%CI) of 0.70 (0.55 to 0.87) and 0.57 (0.42 to 0.78), respectively; ATV C_{max} was lower with BOC (GMR 0.84), but not significantly (0.62 to 1.14). DRV (n=5) AUC, C_{max}, and C_{min} were reduced with BOC with GMRs (90%CI) of 0.58 (0.53 to 0.63), 0.68 (0.64 to 0.71) and 0.36 (0.27 to 0.48), respectively. BOC PK are available for 48 subjects. BOC AUC and C_{max} were lower in patients on EFV (n=19) vs. HD with GMRs (90% CI) of 0.89 (0.79 to 1.0) and 0.73 (0.62 to 0.85), respectively; BOC C_{min} was lower than HD (GMR 0.79) but not significantly (0.5, 1.2). BOC AUC was higher with RAL (n=14) vs. HD (GMR=1.18; 90%CI=1.02 to 1.37), with no differences in BOC C_{max} [1.04 (0.88, 1.23)] or C_{min} [1.08 (0.75, 1.55)]. BOC PK were not different in those on ATV/RTV vs. HD. BOC C_{min} was higher with DRV/RTV vs. HD [1.93 (1.37 to 2.73)], with no differences in BOC AUC [1.03 (0.72, 1.46)] or C_{max} [0.85 (0.54, 1.36)]. No statistical tests were performed in the 2 subjects on LPV/RTV due to the small sample size, but reductions in both BOC and LPV were observed.

Conclusions: With the exception of higher RAL with BOC, effects of BOC on ARV PK in these HIV/HCV co-infected patients were very similar to effects in healthy volunteers. A greater decline in BOC C_{min} with EFV and a reduction in BOC exposures with DRV/RTV were expected, but not observed. The impact of these drug interactions on antiviral safety and efficacy in co-infected individuals undergoing HCV treatment is forthcoming upon availability of A5294 trial data.

Conflict of interest: This study was supported in part by Merck.

Abstract: P_19

Drug Drug Interactions

Pharmacokinetics of simeprevir, JNJ-56914845 and ritonavir-boosted TMC647055 when co-administered in healthy volunteers

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Background: Simeprevir is a hepatitis C virus (HCV) NS3/4A protease inhibitor approved for the treatment of chronic HCV genotype 1

infection. TMC647055 is an investigational non-nucleoside polymerase inhibitor with broad genotype coverage and JNJ-56914845 is an investigational NS5A inhibitor. Simeprevir is an inhibitor of CYP3A, OATP1B1/3 and P-glycoprotein. JNJ-56914845 is an inhibitor of OATP1B1/3 and P-glycoprotein. TMC647055 induces CYP3A and therefore low-dose ritonavir (a potent CYP3A inhibitor) is used to counteract this effect. Because of the complex interplay between CYP and hepatic transporters, the pharmacokinetic interactions of these three direct antiviral agents (DAAs) were assessed.

Materials & Methods: A Phase I, open-label, randomized, 2-panel, 3-way crossover study in 48 healthy volunteers was conducted. Healthy volunteers were randomised within one of two treatment panels, each panel consisted of three 7-day treatments in randomised order with 7-day washout periods in between. Panel 1 (n=24) treatments were JNJ-56914845; simeprevir 150 mg; and JNJ-56914845 + simeprevir 150 mg. Panel 2 (n=24) treatments were JNJ-56914845; simeprevir 75 mg + TMC647055/ritonavir; and JNJ-56914845 + simeprevir 75 mg + TMC647055/ritonavir. JNJ-56914845 and TMC647055/ritonavir were dosed 60 mg and 450/30 mg, respectively. All treatments were administered once-daily with food. Plasma samples for simeprevir, JNJ-56914845, TMC647055 and ritonavir were collected, as appropriate, over 24 hours on Day 7 of each treatment and assayed using validated LC-MS/MS methods. Pharmacokinetic parameters (C_{max}, C_{min}, AUC_{24h}) were determined using non-compartmental analysis (WinNonlin). Safety was monitored throughout the study.

Results: Co-administration of simeprevir increased JNJ-56914845 C_{max}, C_{min} and AUC_{24h} by 1.9-, 3.9- and 2.6-fold, respectively. Similarly, co-administration of simeprevir with TMC647055/ritonavir increased JNJ-56914845 C_{max}, C_{min} and AUC_{24h} by 1.9-, 2.9- and 2.3-fold, respectively. Addition of JNJ-56914845 to simeprevir and TMC647055/ritonavir slightly increased TMC647055 exposure (19-25%).
Co-administration of JNJ-56914845 with or without TMC647055/ritonavir slightly increased simeprevir exposure (17-34%). Simeprevir exposures were comparable between Panels 1 (150 mg once-daily) and 2 (75 mg once-daily with TMC647055/ritonavir with or without JNJ-56914845).
No serious adverse events or deaths were reported. Overall, JNJ-56914845 alone or in combination with simeprevir with or without TMC647055/ritonavir; simeprevir alone or in combination with JNJ-56914845, TMC647055/ritonavir or JNJ-56914845 with TMC647055/ritonavir; and TMC647055/ritonavir with simeprevir with or without JNJ-56914845 was generally safe and well tolerated.

Conclusions: In healthy volunteers, co-administration of simeprevir increased exposure (AUC_{24h}) of JNJ-56914845 2.6-fold with no apparent additional effect when TMC647055/ritonavir was co-administered. Co-administration of JNJ-56914845 resulted in a small increase in the plasma concentrations of simeprevir and TMC647055 that is not considered to be clinically relevant for either DAA. Single, dual and triple DAA regimens consisting of simeprevir, JNJ-56914845 and TMC647055/ritonavir were safe and well tolerated.

Conflict of interest: TN Kakuda: Employee of Janssen Research and Development LLCK Spittaels: Employee of Janssen Infectious Diseases BVBAR Verloes: Employee of Janssen Infectious Diseases NVI Vanwelkenhuysen: Employee of Janssen Research and Development NVC Truyers: Employee of Janssen Infectious Diseases BVBAP van Remoortere: Employee of Janssen Research and Development LLC

Abstract: P_20

Drug Drug Interactions

In vitro drug interaction profile of the HIV integrase inhibitor, GSK1265744, and demonstrated lack of clinical interaction with midazolam

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Introduction: GSK1265744 is a potent HIV integrase inhibitor in Phase 2 clinical development as a long-acting (LA) injectable formulation for the treatment and prevention of HIV infection. This work summarizes the drug-drug interaction profile of GSK1265744 based on results from in vitro drug transport and metabolism experiments and clinical drug-drug interaction studies.

Materials & Methods: In vitro studies were conducted to assess the drug metabolism and transport of GSK1265744 and its potential to cause and be subject to drug interactions. The in vitro data were incorporated into mechanistic and dynamic PBPK models (SimCYP) to predict potential clinical drug interactions. The effect of GSK1265744 (30 mg orally once daily x 14 days) on the single dose pharmacokinetics of oral midazolam (3 mg) was investigated in healthy subjects (n=12).

Results: GSK1265744 is primarily metabolized by glucuronidation via UGT1A1 and, to a lesser extent, UGT1A9. Any CYP-mediated metabolism of GSK1265744 is expected to be minimal based on preliminary metabolism information. GSK1265744 is a substrate for P-glycoprotein (Pgp) and Breast Cancer Resistance Protein (BCRP), but due to its high permeability these transporters are not expected to affect GSK1265744 intestinal absorption. In vitro GSK1265744 is not a CYP inducer and does not inhibit (IC_{50} > 30 uM) the transporters Pgp, BCRP, multidrug resistance protein (MRP) 2/4, organic anion transporting polypeptide (OATP) 1B1/3, organic cation transporter (OCT) 1/2, bile salt export pump (BSEP), or any CYP or UGT enzymes (except UGT1A3; IC_{50} = 12uM). In human subjects GSK1265744 has no effect on the pharmacokinetics of midazolam. GSK1265744 inhibits the renal multidrug and toxin extrusion transporters (MATE) 1/2-K (IC_{50}= 14 - 18 uM) and OAT1/3 (IC_{50}= 0.4 - 0.8 uM). Based on EMA and FDA regulatory DDI guidelines, mechanistic and PBPK modeling indicate GSK1265744 has a low potential to cause or be subject to clinically significant drug interactions, except for co-administration with sensitive OAT1/3 substrates.

Conclusions: Other than sensitive OAT substrates with a narrow therapeutic index (e.g. methotrexate), these in vitro and in vivo studies demonstrate a low propensity for GSK1265744 to cause or be subject to clinically significant interactions with antiretrovirals or other commonly co-administered drugs, consistent with the current safety profile of GSK1265744 in humans.

Conflict of interest: All authors are employees of GlaxoSmithKline

Abstract: P_21

Drug Drug Interactions

Enzyme induction not alterations in protein binding contribute to reduced Etravirine exposures with Boceprevir

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Introduction: Drug-drug interactions (DDI) between antiretroviral agents and Hepatitis C virus (HCV) therapies are the primary consideration when treating HIV/HCV coinfected persons. We previously found the area under the curve (AUC), maximum concentration (Cmax), and minimum concentration (Cmin) of the HIV non-nucleoside reverse transcriptase inhibitor, etravirine (ETV), were reduced 23%, 24%, and

29%, respectively when combined with the HCV protease inhibitor, boceprevir (BOC). The aim of this study was to determine if enzyme induction or alterations in protein binding were responsible for the reduction in ETV concentrations when combined with BOC.

Materials & Methods: ETV metabolites were identified in vitro using human liver microsomal (HLM) incubations and LC/MS-MS. Metabolite formation and fraction unbound (fu) were determined in vivo using samples from 20 HIV-1/HCV-seronegative men and women who previously completed a DDI study with BOC and ETV. For this DDI study, subjects received three treatment sequences in random order: (i) BOC 800 mg every 8 hours; (ii) ETV 200 mg every 12 hours, and (iii) BOC 800 mg every 8 hours plus ETV 200 mg every 12 hours. At the completion of two weeks of each of the three sequences, subjects underwent intensive pharmacokinetic sampling following a standardized moderate fat breakfast. Metabolite and parent ETV concentrations were determined using LC/MS-MS and the metabolite:parent AUC over the dosing interval ($AUC_{0,\tau}$) ratios were compared (two-sided paired t-test) with and without concomitant BOC. ETV protein binding was determined using equilibrium dialysis and LC/MS-MS at three time points during the dosing interval: at the Cmax, 12 hours post-dose (C12) and one point in between Cmax and C12 (Cmid). Fu was calculated by dividing the unbound ETV concentration by the total ETV concentration. The average (Cavg) of Cmax, Cmid, and C12 was also calculated. ETV fu was compared (two-sided paired t-test) with and without concomitant BOC. $P<0.05$ was considered statistically significant.

Results: Six ETV phase I metabolites were observed in vitro via HLM incubations and LC/MS-MS analysis. Four metabolites were observed in the human plasma (HP) samples: two di-oxygenated (HP-M1 and HP-M2) and two di-alkyl-hydroxy (HP-M3 and HP-M4) products; however, HP-M3 was present only in trace amounts and not quantified. HP-M2 was predominately produced via the 2C19 pathway, while metabolite HP-M4 was produced by all cytochrome P450 (CYP) bactosomes tested with a formation rate trend of CYP2D6 < CYP2B6 < CYP3A5 << CYP2C19 < CYP3A4 ~ CYP2C9. In vivo, ETV metabolite:parent $AUC_{0,\tau}$ ratios for the HP-M1, HP-M2, and HP-M4 metabolites were 2.32- ($p=0.001$), 1.62- ($p=0.029$), and 1.18-fold ($p=0.0414$) higher, respectively in the presence of BOC. Time-dependent protein-binding was not observed with ETV alone ($p=0.36$) or with the combination ($p=0.57$). Mean (CV%) ETV Cavg fu was not significantly different with [0.269 (22.9%)] vs. without BOC [0.296 (20.3%)].

Conclusions: The elevated ETV metabolite:parent $AUC_{0,\tau}$ ratios in the presence of BOC suggest that BOC induces microsomes in vivo, primarily CYP2C9/19. An increase in the ETV fu was not observed with BOC. Thus, enzyme induction, not an increased fraction of unbound ETV, contributes to the reduced ETV exposures with BOC.

Conflict of interest: This study was supported by a research grant from the Investigator-Initiated Studies Program of Merck Sharpe & Dohme Corp (to J. Kiser). J Kiser also receives research funding from Janssen.

Abstract: P_22

Drug Drug Interactions

The effect of steady-state BMS-791325, a non-nucleoside HCV NS5B polymerase inhibitor, on the pharmacokinetics of midazolam, in healthy Japanese and Caucasian males.

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Introduction: BMS-791325 is a potent, thumb 1 allosteric inhibitor of the HCV NS5B RNA-dependent RNA polymerase, active *in vitro*

against HCV genotypes 1, 3, 4, 5 and 6 and currently under clinical investigation as part of an all-oral regimen with daclatasvir (NS5A inhibitor) and asunaprevir (NS3 inhibitor) in genotypes 1 and 4. BMS-791325 inhibits CYP3A and induces CYP3A4 *in vitro*. Many concomitant agents used in patients with chronic disease are metabolized by CYP3A4. The effect of BMS-791325 on CYP3A4 activity *in vivo* was assessed.

Materials & Methods: This was an open-label, exploratory phase 1 study (AI443-006) of both the pharmacokinetics (PK) of multiple-dose BMS-791325 in healthy, HCV-uninfected Japanese and Caucasian subjects, and of the effects of steady-state BMS-791325 on the plasma PK of midazolam (MDZ), a sensitive metabolic probe of CYP3A4 activity. For the midazolam interaction part of the study, 16 Japanese and 16 Caucasian subjects received a single fasted (8 hours) oral dose of 5 mg MDZ on Day 1, followed by BMS-791325 150 mg BID (n=8, 8 respectively) or 300 mg BID (n=8, 8) on Days 2–15, and a final AM-only dose on Day 16. On Day 15, subjects also received a second fasted AM dose of MDZ with their AM dose of BMS-791325. Blood samples were collected predose and through 24 hours postdose on Day 1 without BMS-791325, and on Day 15 with BMS-791325, and were analyzed for plasma MDZ and its 1-hydroxymidazolam (1-OH MDZ) metabolite concentrations using validated LC-MS/MS assays. Noncompartmental PK parameters were derived. Point estimates and 90% confidence intervals (90%CI) for ratios of geometric means (GMR) for MDZ C_{max} and AUC_{inf} with and without BMS-791325 were calculated from linear mixed-effects models on log-transformed data.

Results: One subject (150 mg BMS-791325) discontinued the study for a protocol deviation. Study drugs were generally well tolerated: all adverse events were of mild intensity and there were no discontinuations due to adverse events. Individual ratios of MDZ parameters with (Day 15) versus without (Day 1) BMS-791325 appeared similar between Japanese and Caucasians, and these two groups were pooled for analysis. In the 150 mg BMS-791325 panel, GMRs and 90%CI for MDZ C_{max} and AUC_{inf} were 0.66 (0.57–0.76) and 0.50 (0.45–0.57), respectively. In the 300 mg panel, these values were 0.52 (0.47–0.57) and 0.44 (0.40–0.48), respectively. The geometric mean 1-OH MDZ/MDZ metabolite-to-parent AUC_{inf} ratio increased 2–3-fold when MDZ was coadministered with BMS-791325, from 0.36 (20% coefficient of variation) to 0.78 (33%) in the 150 mg panel, and from 0.43 (35%) to 1.20 (30%) in the 300 mg panel.

Conclusions: BMS-791325 is a moderate inducer of CYP3A4 *in vivo* in healthy Japanese and Caucasians, as evidenced by reduced PK exposure to MDZ and increased exposure to 1-OH MDZ under co-administration. Concomitant use of BMS-791325 and CYP3A substrate medications should be undertaken with caution, especially for medications with a narrow therapeutic index.

Conflict of interest: M AbuTarif, R Bertz, W Li, M Wind-Rotolo and K Sims are employees and shareholders of Bristol-Myers Squibb. J Pursley, K Zhu, Y Ding and B He are employees of Bristol-Myers Squibb. B Rege was an employee of Bristol-Myers Squibb at the time of the study is now employed by Eisai Inc and is a shareholder of Bristol-Myers Squibb and Seattle Genetics.

Abstract: P_23

Drug Drug Interactions

ACTG precautionary and prohibited medications database: a novel informatics resource for antiviral agents for hepatitis C virus and HIV infection:

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Introduction: The AIDS Clinical Trials Group (ACTG) Precautionary and Prohibited Medication Database (PPMD) is a novel human immunodeficiency virus type-1 (HIV-1) informatics resource that has grown and extended to include antivirals for hepatitis C

infection. The database provides emerging pharmacokinetic information on drug interactions for use during protocol development and facilitates human subject protection during study enrollment. The database has primarily focused on antivirals for HIV-1, and now includes approved and investigational drugs for hepatitis C virus (HCV) infections.

Materials & Methods: A survey of the PPMD was performed to evaluate the current status of approved direct-acting antiviral (DAA) agents in the database. With the rapid development of DAAs and the anticipation of significant changes in treatment and outcome of HCV infection, this area was chosen as a focus. The origin of the data contained in the database was collected primarily from scientific conferences. The data were extracted, summarized and subject to review by the international editorial reviewers. Upon final approval, drug information summaries are publicly searchable and available in the PPMD.

Results: The database had approximately 1200 entries and included all of the 4 current FDA approved DAAs, boceprevir, telaprevir, simeprevir and sofosbuvir. Of the 45 current entries for these agents, 58% involve co-administration with ARVs (protease inhibitors n=11, non-nucleoside reverse transcriptase inhibitors n=6, nucleoside reverse transcriptase inhibitors n=2 and integrase inhibitors n=7). The next largest groups were HMG-CoA reductase inhibitors (16%) and immunosuppressants (13%). Lastly, entries including herbal, opioid, acid-reducing agent, anti-psychotic, anti-TB and oral contraceptive were included. Interaction mechanisms include protein binding, metabolism and membrane transporters. Currently, 7 ACTG protocols have incorporated HCV drug interaction data from the PPMD. A mechanism was added to provide drug interaction data for investigational drugs when pharmacokinetic studies were investigated but not presented.

Conclusions: The PPMD is an integral resource for ACTG protocol development and human subject protection. The content contained within this database is growing to meet investigational protocol needs for HCV monoinfection and HIV/HCV co-infection and identify future areas of drug interaction research. Upcoming plans include utilizing the PPMD as a mechanism to identify gaps in pharmacokinetic knowledge, complex drug interactions and identify comparative data from healthy volunteers versus HIV-HCV infected patients.

No conflict of interest

Abstract: P_24

Drug Drug Interactions

Co-prescription of non-HIV medications in HIV-infected individuals in five European countries and the possible impact of interactions with Stribild® (FTC/TDF/EVG/COBI)

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Background: Introduction of combination antiretroviral therapy (ART) has enabled HIV-infected individuals to live longer and with considerably better quality of life. However, age-related comorbid conditions may elevate the risk of polypharmacy in HIV-infected individuals. Drug-drug interactions (DDIs) between ARV drugs and the co-prescribed non-ARV medications may pose an important challenge in treating elderly patients with HIV. The consequences of DDIs between ARV drugs and other medications may include sub-optimal ARV drug levels with consequent loss of virologic control, development of resistance, lack of efficacy of the co-prescribed medication or increased toxicity. This study evaluated the co-prescription of non-HIV medications in HIV-infected individuals in five European countries

and examined the impact of possible interactions with Stribild (FTC/TDF/EVG/COBI).

Materials & Methods: This retrospective study analyzed the records of HIV-infected patients in care from five European countries (France, Germany, Italy, Spain, and the United Kingdom) during July 2012 to June 2013. Patients diagnosed with HIV-1 at any time as indicated by their general practitioners' patient record and those receiving ARTs and at least one co-prescribed medication were included in the analysis. The most common co-prescribed medications were identified and ranked. Potential DDIs were identified based on the Stribild SmPC and/or the University of Liverpool HIV DDI database (www.hiv-druginteractions.org). Clinically significant DDIs were identified and categorized as requiring close clinical monitoring (CCM), or contraindicated when listed as per at least one of the above-mentioned sources.

Results: Demographic and drug prescription data were analyzed from 9243 patients (males 65%) distributed as follows: 52.7% from France, 9.2% from Germany, 6.4% from Italy, 23.3% from Spain, and 8.4% from the United Kingdom. In total, 255 non-ARV medications, including combinations, were identified to be commonly co-prescribed for HIV-infected individuals. Among these co-medications, information on the possible DDI with Stribild, based on SmPC and/or Liverpool HIV DDI database, was available for 129 drugs. The analysis identified five drugs (1.96%), including combinations, as contraindicated with Stribild, among which the most commonly co-prescribed drugs were salmeterol and simvastatin (percentage of co-prescriptions being 0.25% and 0.15%, respectively). Twenty-nine (11.39%) of the co-medications required CCM. The most frequently co-prescribed medication requiring CCM was alprazolam (1.18%). The overall rates of co-prescription of drugs designated as contraindicated and requiring CCM were 0.71%, and 13.23%, respectively.

Conclusions: In HIV-infected patients that were receiving any co-medication and not currently treated with Stribild, contraindicated medications were not likely to be prescribed by HIV clinicians (0.71%). Additionally, the co-prescription of non-ARV drugs that required CCM was also appreciably low in HIV-positive patients (13.23%). Knowledge of the severity, frequency, and distribution of these DDIs can help clinicians to optimize the care of HIV-infected patients.

Conflict of interest: Many of the authors are from Gilead sciences none of the non-Gilead presenters have been paid by Gilead to be part of this research

Abstract: P_25

Drug Drug Interactions

Effect of food on the steady-state pharmacokinetics of rilpivirine when administered as a fixed-dose combination in HIV-1 infected Ugandan adults

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Background: In single-dose studies, rilpivirine exposure was increased during administration with food. This study aimed to investigate the effect of food on the steady-state pharmacokinetics (PK) of rilpivirine when administered as a fixed dose combination tablet containing tenofovir disoproxil fumarate, emtricitabine plus rilpivirine (TDF/FTC/RPV) in HIV-1 infected patients using an East African meal.

Materials & Methods: The clinical study was conducted at the Infectious Disease Institute, Kampala, Uganda. Consenting HIV-1 infected adults were switched at enrolment from an efavirenz-based regimen to TDF/FTC/RPV one tablet administered once daily for 56 days. Enrolled patients underwent 24-hour blood

sampling with TDF/FTC/RPV dosing in the fasted state (day 42), with low fat meal (353 Kcal, day 49) and with a moderate fat meal (589 Kcal, day 56). Both study meals contained a local banana staple (*matooke*). Rilpivirine concentrations in plasma were determined by liquid chromatography-tandem mass spectrometry. Non-compartmental analysis was performed. PK parameters (AUC_{0-24}, C_{24} and C_{max}) in plasma were calculated for rilpivirine and presented as geometric means and 90% confidence intervals (CI). Using the moderate fat meal as reference, data comparisons were performed using geometric mean ratios (GMR) and 90% CI.

Results: All 15 enrolled subjects (9 female) completed the study. Median (interquartile range, IQR) age and weight were 40.8 (36.4-44.3) years and 58.5 (51-67) kg. Rilpivirine AUC_{0-24} (90% CI) was 2392 (2157 – 2918) ng.h/mL with a moderate fat meal, 2582 (2336 – 3108) ng.h/mL with a low fat meal and 2007 (1819 – 2499) ng.h/mL in the fasted state. Rilpivirine C_{24} (90% CI) was 80 (72 – 102) ng/mL with a moderate fat meal, 92 (82 – 117) ng/mL with a low fat meal and 63 (57 – 85) ng/mL in the fasted state. Rilpivirine C_{max} (90% CI) was 159 (141 – 204) ng/mL with a moderate fat meal, 175 (156 – 217) ng/mL with a low fat meal and 157 (143 – 195) ng/mL in the fasted state. Rilpivirine AUC_{0-24} was significantly decreased by 16% (GMR, 90% CI, 0.84, 0.73 – 0.96) during administration in the fasted state when compared to AUC_{0-24} during administration with a moderate fat meal. Similarly, rilpivirine C_{24} was significantly decreased by 21% (0.79, 0.65 – 0.97) in the fasted state compared with a moderate fat meal. Rilpivirine C_{max} was similar under the 3 meal conditions. PK parameters were unchanged during administration with a low fat meal, except for C_{24}, which was significantly increased by 15% (1.15, 1.01 – 1.30) when compared with the moderate fat meal.

Conclusion: Steady-state PK parameters of rilpivirine were significantly lower when TDF/FTC/RPV was administered in the fasted state compared to the moderate fat meal. However PK parameters were similar during dosing with either a low fat or moderate fat local meal. The TDF/FTC/RPV formulation should be administered with food.

Conflict of interest: This Investigator-Initiated Study (IIS) was funded by Janssen Pharmaceutica NV

Abstract: P_26

Drug Drug Interactions

Consumption of recreational drugs, alcohol and tobacco in HIV patients at a care center in Chile

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Introduction: The use of recreational drugs, alcohol and tobacco may directly affect the response to antiretroviral therapy (ART). The large number of drug-drug interactions may impair the efficacy of HIV treatment and the consumption of these substances can directly affect ART adherence.

Materials & Methods: 1562 surveys were conducted to 1070 patients during a 6 month period at Fundación Arriarán (FA), an HIV clinical care center in Santiago, Chile. Patients were asked anonymously about alcohol, tobacco and recreational drugs (marihuana, cocaine, crack, coca paste, heroin and methamphetamines) consumption in the last 7 days prior to survey. Patients with ART were also consulted about number of missed doses of HIV treatment. General demographic data was collected. The study was approved by the local ethical committee.

Results: 1562 surveys were performed in 1070 patient. Surveys were conducted in medical, laboratory or nurse/midwife regular visits at FA. Participant's mean age was 41.7 years (interquartile range –IQR 33.7-48.9). Of the

whole, female population was 11.8% and patients with ART were 89.6% (1400). Rate of main drugs consumption was: marihuana 7.5%, cocaine 1.2%, coca paste 0.3%, methamphetamine, crack, and heroine 0%. Alcohol 53.1% and tobacco 42.2%.
Among 1400 surveys from patients with ART, 74.7% reported 100% for adherence to HIV treatment in the 7 days prior to the survey. Mean age in this group was 43.2 years (IQR 33.5-43.3), 11.2% were female. Patients that failed to have 100% adherence, reported a mean of 1 missed dose of ART (IQR 1-2), the mean age was 39.9 years (33.5-43.3) ($p < 0.0001$), and 13% were female. Amid the sub group of drugs consumers: 40.2% of marihuana users missed at least one dose of ART vs 24.2% of non consumers ($p = 0.001$), 58.8% of cocaine users missed at least one dose of ART vs 24.9% of non consumers ($p = 0.0035$). 30.7% of alcohol consumer skipped at least one dose of ART vs 19.3% of non alcohol drinkers ($p = 0.0001$); 27.6% of tobacco users missed at least one dose of ART vs 23,4% of non smokers ($p = 0.09$). Of the combined subgroup of alcohol + tobacco consumers, 32.5% skipped at least one ART dose. In the marihuana + alcohol users, 46.7% missed at least on dose of ART.

Conclusions: On a 7 days period retrospective survey, one quarter of patients reported to have failed to take all ART medication. These patients were significantly younger than those with complete adherence. The use of recreational drugs and alcohol consumption significantly affects ART adherence, decreasing complete ART intake in a variable range depending on the recreational drug. Tobacco consumption did not influence ART adherence. Recreational drugs affect the ART effectivity not only by drug-drug interactions and the corresponding PK-PD alterations, but also treatment adherence with an expected decrease ART plasmatic levels.

Conflict of interest: This work is part of a project financed by NIH.

Abstract: P_27

Drug Drug Interactions

Pharmacokinetic interaction of HCV NS5A inhibitor MK-8742 and ketoconazole in healthy subjects

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Introduction: MK-8742 is a potent, once-daily inhibitor of the hepatitis C virus (HCV) nonstructural protein NS5A being developed for the treatment of chronic HCV infection. In rats, MK-8742 was mainly eliminated as oxidative metabolites that are formed predominantly through CYP3A4. In rat, dog, and human in vitro liver preparations**,** oxidative metabolites formed through CYP3A4 metabolism were detected. These data suggest the potential for MK-8742 to be a victim of drug interactions with known inhibitors of CYP3A4. This study evaluated the effect of multiple oral doses of ketoconazole, a potent inhibitor of CYP3A4 and P-glycoprotein (P-gp), on the single dose pharmacokinetics of MK-8742 in healthy male subjects.

Materials & Methods: This was a double-blind, randomized, placebo-controlled, 2-period, fixed-sequence study to evaluate the effect of multiple oral doses of ketoconazole on the pharmacokinetic parameters (AUC0-∞, Cmax, and C24h) of a single oral dose of MK-8742 in 10 healthy male adult subjects ages 23-49. In Period 1, subjects received a single,oral dose of either 50 mg MK-8742 (N = 8) or placebo (N = 2) on Day 1, followed by a 9 day washout. In Period 2, subjects received 400 mg of ketoconazole once daily (QD) for 9 days starting on Day 1 with a single dose of either 50 mg MK-8742 or placebo co-administered on Day 2. The same subjects received MK-8742 or placebo in both periods.

Results: The co-administration of multiple oral doses of 400 mg ketoconazole with a single oral dose of 50 mg MK-8742 was generally safe and well tolerated in the healthy male subjects in this study. The MK-8742 AUC0-∞, Cmax, and C24h geometric mean ratios (GMRs) (90% confidence interval [90% CI]) for the comparison of a single dose of 50 mg MK-8742 co-administered with multiple doses of 400 mg ketoconazole versus a single dose of 50 mg MK-8742 alone were 1.31 (0.73, 2.35), 0.88 (0.44, 1.77), and 1.38 (0.75, 2.54), respectively. An additional statistical analysis, which excluded a single subject who had an anomalous decrease in MK-8742 exposure following ketoconazole administration, demonstrated an AUC0-∞ GMR (90% CI) of 1.80 (1.41, 2.29). The MK-8742 median Tmax was approximately 3.50 hours postdose with and without co-administration with ketoconazole. The mean apparent terminal t½ was lengthened by approximately 5 hours when MK-8742 was co-administered with ketoconazole.

Conclusions: The plasma MK-8742 AUC0-∞ after co-administration of a single oral dose of 50 mg MK-8742 with multiple doses of 400 mg QD ketoconazole, a strong CYP3A4/P-gp inhibitor, is increased by approximately 31% to 80% compared to administration of a single oral dose of 50 mg MK-8742 alone. These results demonstrate that MK-8742 is a CYP3A4 substrate in humans with modest increases in concentrations following coadministration of strong CYP3A4 inhibitors.

Conflict of interest: All of the authors affiliated with Merck & Co INC are current employees of Merck & Co INC

Abstract: P_28

Drug Drug Interactions

Efavirenz pharmacokinetics in HIV infected persons receiving rifapentine and isoniazid for TB prevention in ACTG 5279

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Background: AIDS Clinical Trials Group (ACTG) Study A5279 is a phase III clinical trial (N=3000) comparing 4 weeks of daily rifapentine + isoniazid (RPT/INH) to 9 months of daily INH for the prevention of active TB in HIV-infected individuals. RPT is a known CYP inducer, while EFV is a CYP substrate leading to concern for decreased EFV exposure and risk of virologic failure. The pharmacokinetics (PK) of this combination have not been evaluated. An objective of A5279 was to evaluate the effect of RPT/INH on EFV PK in the first 90 participants who enrolled on a stable EFV-containing regimen.

Materials & Methods: Participants receiving ART containing EFV (600mg PO QD) randomized to the weight based RPT/INH (RPT, ≈ 10mg/kg; INH, 300mg) treatment arm of A5279 were evaluated. Mid interval plasma samples were collected at week 0 (pre-RPT/INH) and weeks 2 and 4 during concomitant RPT/INH. EFV apparent oral clearance (CL/F) was modeled using Bayesian estimation (ADAPT). Week 2 and 4 EFV concentrations were combined to estimate EFV CL/F on RPT/INH. EFV PK were evaluated in real time. The geometric mean ratio (GMR) and 90% confidence interval (CI) of the pre and during RPT/INH EFV CL/F values were calculated. EFV PK data were to be judged acceptable if >80% of participants had EFV concentrations ≥1 mg/L.

Results: Demographic and baseline data from the 87 evaluable participants were: female, 47 (54%); Black Non-Hispanic, 48 (55%); median age (range), 35y (13-61); median BMI, 23.2; mean $CD4^+$ count, 537 cells/mm^3 (164-1570); 79 (93%) had undetectable (<40 copies/mL) HIV-1 RNA at randomization. 75 of the 87 evaluable

participants had week 8 HIV-1 RNA levels available, 71 (95%) were undetectable at week 8. Median (IQR) EFV concentrations were: Week 0, 2.59 mg/L (1.85-3.83); week 2, 2.46 mg/L (1.47-3.81); week 4, 2.54 mg/L (1.44-3.83). Median (IQR) EFV CL/F was: Pre-RPT/INH 9.3 L/hr (6.42-13.22), on RPT/INH 9.8 L/hr (7.04-15.59). The GMR (90% CI) for EFV CL/F was 1.04 (0.97-1.13). The numbers of participants with EFV concentrations ≥ 1 mg/L were: week 0, 85 (98%); week 2, 81 (93%); week 4, 78 (90%); weeks 2 and 4, 75 (86%). Median (IQR) RPT concentrations were 9.18 mg/L (6.2-12.7).

Conclusions: Overall, the CL/F of EFV with and without RPT/INH was equivalent, as judged by the GMR and 90% CI. A decrease in the percentage of participants with EFV concentrations ≥ 1 mg/L during RPT/INH therapy suggests induction of EFV CL/F, presumably from RPT. Importantly, the proportion did not cross below the pre-specified threshold of >80%. These drug-drug interaction data and pre and post HIV-RNA data provide support that RPT/INH for 4 weeks can be co-administered with EFV-containing ART, and provide the necessary PK evidence for continuing the efficacy assessment of RPT/INH ultra-short therapy for the prevention of TB in HIV-infected individuals.

Presented at the Conference on Retroviruses and Opportunistic Infections (CROI) 2014, Boston, MA. March 5, 2014.

No conflict of interest

Abstract: P_29

Drug Drug Interactions

The induction effect of rifampicin on efavirenz is time-dependent: systematic review of 12 drug interaction studies.

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Background: Efavirenz is primarily metabolised by the hepatic cytochrome iso-enzymes CYP2A6 and CYP2B6. Efavirenz exhibits interindividual pharmacokinetic variability caused by genetic differences in cytochrome P450 (CYP) expression. Efavirenz induces its own metabolism, and 4-16 weeks of treatment are required for efavirenz to reach steady-state plasma concentrations. Most tuberculosis (TB) drugs interact with the CYP metabolizing enzymes. Rifampicin is known to lower the plasma concentrations of several antiretrovirals. There have been discordant results from different drug interaction studies of efavirenz and rifampicin.

Materials & Methods: a systematic search of MEDLINE and EMBASE identified sequential or cross-over studies evaluating efavirenz and rifampicin. The studies were analysed by duration of efavirenz-rifampicin treatment before pharmacokinetic evaluation. Results from two longitudinal studies of efavirenz-treated patients with or without TB were used as supportive evidence.

Results: 12 pharmacokinetic studies were identified. Six studies evaluated <8 days of combined efavirenz-rifampicin treatment, with reductions in efavirenz Cmin of -19% to -54%, compared with efavirenz alone. Effects on efavirenz in these seven studies were as follows: Study 1, healthy volunteers, n=33, single dose, EFV Cmin -45%. Study 2, healthy volunteers, n=10, single-dose, EFV AUC -54%. Study 3, healthy volunteers, n=8, single-dose, EFV AUC -39%. Study 4, HIV+, n=8, 7 days, EFV Cmin -22%. Study 5, healthy volunteers, n=12, 7 days, EFV Cmin -32%. Study 6, healthy volunteers, n=11, 8 days, EFV Cmin -19%. One study (7) of 2-6 weeks of efavirenz-rifampicin treatment showed mean Cmin reductions of -34%. Five longer-term studies evaluated 4-24 weeks of combined efavirenz-rifampicin treatment, with increases in efavirenz Cmin of +6% to +26%. Effects of rifampicin-based treatment on efavirenz in these five studies were as follows: Study 8, HIV+, n=34, 4 weeks, EFV Cmin +9%. Study 9, HIV+, n=21, EFV Cmin +11%. Study 10, n=91 HIV+, 24 weeks, EFV Cmin +6%, Study 11,

HIV+, n=20, 24 weeks, EFV Cmin +26%, Study 12, HIV+, n=17, 24 weeks, EFV Cmin +22%. In two longidudinal studies, differences in efavirenz Cmin between rifampicin treated and untreated patients were only observed in the first 1-4 weeks of combined treatment, with no significant effects on efavirenz concentrations during longer-term treatment.

Conclusions: In this systematic review of 12 drug-drug interaction studies, rifampicin only lowered efavirenz concentrations in the first 1-4 weeks of treatment. By contrast, there were non-significant increases in efavirenz levels after 4-24 weeks of combined treatment. The results suggest that dose modification of efavirenz is not needed during co-administration with rifampicin-based treatment for tuberculosis.

No conflict of interest

Abstract: P_30

Pharmacogenetics

Effect of CYP3A4*22 (rs35599367) on lopinavir pharmacokinetics in HIV-positive adults

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Background: The *CYP3A4**22 (rs35599367) has been associated with lower CYP3A4 activity and/or the pharmacokinetics (PK) or pharmacodynamics of various statins, tacrolimus, midazolam and erythromycin. We previously showed that lopinavir (LPV) is an OATP1B1 substrate and *SLCO1B1* 521T>C (rs4149056) is associated with lower LPV plasma PK exposure using a population PK approach. Here we investigated the effect of *CYP3A4* rs35599367 alone or combined with *SLCO1B1* rs4149056 on the PK of LPV through a population PK approach.

Materials & Methods: HIV-positive patients on LPV/ritonavir 400/100 mg based regimens from the Liverpool Therapeutic Drug Monitoring Registry were included. Samples were taken at random time points but with documented time post dose. Plasma was obtained and stored at -80°C before analysis. LPV plasma concentration was quantified using validated LC-MS/MS. Genotyping for *CYP3A4* rs35599367 was conducted using TaqMan® assay with ID C_59013445_10. Non-linear mixed effects modelling was applied (NONMEM v. VI 2.0) using a model previously published to describe associations of *SLCO1B1* SNPs with LPV plasma concentrations in this cohort.

Results: 375 patients were included (82% male, median age 40, median weight 72kg). Minor allele frequency for *CYP3A4* rs35599367 was 0.04 and 6 patients had a combination of *CYP3A4* rs35599367 and *SLCO1B1* rs4149056 alleles (5 with *CYP3A4* GA / *SLCO1B1* CT, 5; 1 with *CYP3A4* AA / *SLCO1B1* CT). Median (IQR) LPV concentration (ng/ml) according to *CYP3A4* rs35599367 was GG (n = 353): 5400 (3200-8100); GA (n = 18): 6600 (2500-8700); and AA (n = 4): 9600 (4900-14000). In the final model, population clearance was 5.6L/h and patients with *CYP3A4* rs35599367 AA had 35% (P = 0.002) lower clearance compared to non-carriers. A 1.7-fold higher LPV trough concentration (C_{trough}) was observed for individuals with *CYP3A4* rs35599367 AA genotype or *SLCO1B1* rs4149056 CC genotype and 4.5-fold higher C_{trough} in homozygotes for both alleles compared to non-carriers. Individuals with *CYP3A4* rs35599367 AA, *SLCO1B1* rs4149056 CC, or both combined were predicted to achieve a mean C_{trough} of 4050 (3410-4200), 4200 (4050-4350) or 10600 (10200-10900) ng/ml, respectively, with a simulated 200/100 mg LPV/ritonavir, which is well above the minimum effective concentration (1000 ng/ml).

Conclusions: We observed an association of LPV C_{trough} with *CYP3A4* rs35599367 and *SLCO1B1* rs4149056 SNPs, which if confirmed could impact on strategies to improve benefit versus risk (e.g. gastrointestinal intolerance, lipid abnormalities) of LPV/ritonavir. PK modelling and simulation represents a valuable tool to

quantitatively assess risk-benefit, through incorporation of genetic and environmental factors.

No conflict of interest

Abstract: P_31

Pharmacogenetics

The effect of CYP3A5 genotype on pharmacokinetics of maraviroc in healthy volunteers

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Introduction: We have demonstrated in vitro that the polymorphic enzyme cytochrome P450 3A5 (CYP3A5) plays a major role in the oxidative metabolism of the anti-HIV drug maraviroc. The present study evaluated the impact of CYP3A5 genotype on the pharmacokinetics of maraviroc.

Materials & Methods: Of the sixteen subjects enrolled, 8 subjects carried the CYP3A5*1 allele (3 CYP3A5*1 homozygous and 5 heterozygous) and 8 subjects did not carry the CYP3A5*1 allele. Subjects received an oral dose of 300 mg maraviroc and blood was sampled over a period of 32 hr. Plasma maraviroc concentrations were determined using liquid chromatography-mass spectrometry and pharmacokinetic parameters including area under the plasma concentration-time curve (AUC_{inf}), peak concentration (C_{max}), and clearance were calculated.

Results: The pharmacokinetic parameters did not differ between the group carrying the CYP3A5*1 allele versus those not carrying a CYP3A5*1 allele. However, the CYP3A5*1 homozygous group exhibited 55% and 52% lower AUC_{inf}, 97% and 84% higher apparent clearance, and 65% and 59% lower C_{max}, respectively, as compared to the subjects that were heterozygous for CYP3A5*1 and those not carrying the CYP3A5*1 allele.

Conclusions: C_{max} and AUC_{inf} were decreased while clearance was increased in subjects carrying two CYP3A5*1 alleles. The results indicate maraviroc has the potential to be used as a CYP3A5 clinical phenotyping probe.

The data will also be presented at Experimental Biology 2014 (San Diego, CA) April 26-30, 2014.

No conflict of interest

Abstract: P_32

Pharmacogenetics

Assessment of correlation of asunaprevir with polymorphisms in liver uptake transporters (OATP1B1 and 2B1): results of an integrated population PK analyses

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Introduction: Asunaprevir (ASV) is a selective inhibitor of HCV NS3 protease with activity against genotypes 1 and 4, under review as part of combination regimens for HCV. ASV AUC_{tau} and C_{max} are approximately 2-fold higher in Japanese than US/EU patients at the dose of 200 mg twice daily (BID). ASV is a substrate of the liver uptake transporters organic anion transport polyprotein (OATP) 1B1 and 2B1 in vitro. Single dose rifampin markedly increases plasma exposure of ASV, confirming OATP-mediated transport of ASV in vivo. Previously, the effect of OATP single nucleotide polymorphisms (SNPs) and haplotypes was

explored graphically and by evaluating the effect of selected SNPs on ASV AUC_{tau} using a small data set (n=18) including Japanese and non-Japanese HCV infected subjects. No OATP1B1 or 2B1 SNPs or haplotypes appeared to strongly associate with plasma AUC of ASV. The current work describes the effects of OATP haplotypes on ASV exposures as part of an integrated population PK (PopPK) analysis in Japanese and non-Japanese subjects using a larger dataset.

Materials & Methods: Effect of OATP haplotypes on ASV exposure was evaluated graphically and using PopPK with an integrated dataset (total N=1239 with n=873 with OATP1B1 data). PopPK analysis was conducted using data from 5 Phase 2 and Phase 3 studies in Japanese and non-Japanese subjects receiving multiple dosing regimens of ASV (200 mg QD, 200 mg BID, 600 mg QD and 600 mg BID of Phase 2 tablet and 100 mg BID of Phase 3 softgel capsule). Covariates screened for effect on ASV PK included age, body weight, sex, and race. OATP1B1 haplotypes were categorized as *1B/*1B, *1A/*1B, *1A/*1A, other (all other haplotypes were combined into this category) or missing. The base PopPK model was used to evaluate the effect of OATP1B1 haplotypes on V/F and CL/F graphically. Additionally, OATP1B1 haplotypes were tested as a covariate on ASV CL/F. Correlations between individual OATP2B1 genotypes and ASV AUC were also explored in a subset of subjects (n=122).

Results: Graphical exploration did not identify a clear relationship between OATP1B1 haplotypes and ASV exposure. No clear relationship between OATP1B1 haplotypes and ASV V/F was identified from the base PopPK model. OATP1B1 haplotypes were not identified as significant covariates on ASV CL/F in the univariate screening at $p < 0.05$ and were not included in the full model. Exploratory analysis in a subset of subjects did not identify strong associations between OATP2B1 genotypes and ASV exposure. These results are consistent with the results of the graphical analysis and the previous analysis evaluating the relationship between OATP SNPs and ASV PK.

Conclusions: Graphical exploration and population PK analysis did not identify OATP1B1 haplotypes as significant covariates for ASV CL/F, or strong associations between OATP2B1 genotypes and ASV exposure. These data indicate that differences in the allelic frequencies of OATP SNPs may not contribute meaningfully to the ethnic differences observed in ASV PK.

Conflict of interest: T Garimella is an employee of Bristol-Myers Squibb and a shareholder of Abbvie. R Bertz, T Delmonte, L Hui, P Chan, M Wind-Rotolo and W Li are employees and shareholders of Bristol-Myers Squibb. T Eley, E Hughes, L Zhu and B He are employees of Bristol-Myers Squibb.

Abstract: P_33

PK/PD modeling

Population pharmacokinetic analysis of Ledipasvir (GS-5885) in healthy and hepatitis C virus infected subjects

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Background: Ledipasvir (LDV) 90 mg, a once daily potent hepatitis C virus (HCV) NS5A inhibitor in a fixed dose combination with a once daily NS5B inhibitor sofosbuvir (SOF) 400 mg is in Phase 3 clinical development for the treatment of chronic HCV-infection. A population based pharmacokinetic (POPPK) model was developed to understand the clinical covariates of the PK of LDV in subjects with chronic HCV infection.

Materials & Methods: The POPPK model for LDV was developed using LDV plasma concentration data from pooled intensive and sparse samples from 9 studies in healthy subjects (n=391), and 5 studies in treatment naïve (TN) and experienced (TE) HCV genotype 1 infected subjects (n=1759). A nonlinear mixed effects modeling approach using first-order conditional estimation with interaction (FOCEI) method in NONMEM version 7.1.2 was used for the POPPK analysis. Covariates including age,

body weight, sex, race, cirrhosis, disease status (healthy/HCV-infected, or healthy/TN/TE), ribavirin (RBV) usage and concomitant medications including anticoagulants, selective serotonin reuptake inhibitors, statins, calcium channel blockers, H2 receptor antagonists and diuretics were evaluated using a forward addition and backward subtraction methodology for their effect on LDV PK. Clinical significance of statistically significant covariates was determined by a sensitivity analysis of their impact on the steady-state LDV exposure parameters AUC_{tau}, C_{max}, and C_{tau}.

Results: Plasma PK of LDV was best described by a two-compartment model with first order absorption, first order elimination from the central compartment and an absorption lag time. The PK model was parameterized in clearance (CL), central volume (V_c), distribution clearance (Q), peripheral volume (V_p), relative bioavailability (F1), absorption rate constant (k_a), and lag time (T_{lag}). Statistically significant parameter-covariate relationships were identified for CL (sex, body weight, RBV usage and disease status [healthy/HCV-infected]), V_c (body weight), and F1 (disease status [healthy/TN/TE]). For a typical TN male HCV-infected subject weighing 80 kg without RBV usage, CL was 13.1 L/hr, V_c was 399 L, Q was 28.5 L/hr, V_p was 620 L, k_a was 0.326 1/hr, T_{lag} was 0.442 hr, and elimination half-life was 22.7 hr. Inter-individual variability was 48% for CL, 56% for V_c, 78% for V_p and 46% for k_a. The sensitivity analysis showed the magnitude of effect of sex, body weight, disease status, and RBV usage on LDV steady-state exposure was modest (AUC_{tau} <49%, C_{max} <33%, C_{tau} <47%) for subjects with extreme covariate values (5^{th} to 95^{th} percentile) relative to the typical subject. Considering the range of LDV exposure seen in the Phase 3 population (AUC_{tau} range: 416-49,140 ng•h/mL), the favorable safety profile of LDV/SOF, and high response rates (>90% SVR12) across Phase 3 studies, the difference in LDV exposure due to sex, body weight, disease status, and RBV usage was not considered clinically relevant.

Conclusions: Demographic variables such as age, body weight, sex, race, cirrhosis, RBV usage, disease status, and concomitant medications do not have a clinically relevant impact on LDV exposures in HCV-infected subjects.

No conflict of interest

Abstract: P_34

PK/PD modeling

Population pharmacokinetic (PK) modeling of tenofovir (TFV), emtricitabine (FTC), and their intracellular metabolites in HIV+ subjects

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Background: Understanding the intracellular PK of tenofovir diphosphate (TFV-DP) and emtricitabine triphosphate (FTC-TP) is critical for prevention, treatment, and cure. Recent models describing the disposition of these metabolites have used indirect response models with parent concentrations as the driver of effect. We present a steady-state PK model in infected patients using transit compartments and fractional apparent oral clearance (CL/F) to describe parent and metabolite PK as an alternative that can be utilized to incorporate viral dynamic modeling linked to metabolite disposition.

Materials & Methods: TFV, FTC in plasma, and TFV-DP, FTC-TP concentrations in PBMCs were determined at 4 timepoints in HIV+ adults receiving TFV/FTC with either efavirenz or atazanavir/ritonavir. Concentrations were analyzed with validated LC-MS/MS methods. Population PK modeling was performed using the FOCE-ELS algorithm in Phoenix NLME. Structural models were compared using Akaike's

Information Criterion, and the likelihood ratio test was used with forward addition/backward elimination (α = 0.01, 0.001) to determine covariate effects. Molar units were used for each moiety.

Results: Subjects (n=43) ranged in age from 22-73yr (median 48yr). Mean ± SD body mass index (BMI) was 27.9 ± 5.7 kg/m^2 and creatinine clearance was 99.3 ± 27.2 ml/min. Nineteen Caucasians (1 Hispanic), and 24 African Americans were included in this analysis; 14/43 were female. For TFV and FTC, a 2-compartment model with first-order absorption and elimination best described the data. The first-order absorption rate constant was fixed, as only trough and 2 hour post-dose concentrations were collected. FRAC, a parameter applied to the CL/F to transfer parent to metabolite, was estimated for TFV and FTC. A one-compartment model with input as (1-FRAC) x CL/F and linear clearance described TFV-DP and FTC-TP concentrations. A proportional error model was used for both parents and metabolites. Parameter estimates and variability were comparable to literature values for parent. The estimated fraction of drug converted to metabolite was 1.7% and 5.7% for TFV and FTC, respectively. The metabolite CL estimate for TFV-DP was 0.972 L/hr and 0.147 L/hr for FTC-TP. In the TFV model, interindividual variability was estimated for the CL/F (41% CV) and metabolite CL (46% CV). For the FTC model, interindividual variability was estimated for the CL/F (36% CV), central volume (46% CV), and metabolite CL (32% CV). Covariates tested included sex, background regimen, age, creatinine clearance, frailty score, and BMI. In the final models for each parent drug, creatinine clearance on FTC CL/F and age on TFV-DP clearance were significant covariate effects. Goodness of fit plots and visual predictive checks indicate the models describe both parent and metabolite PK well.

Conclusions: The model developed here is a novel, simplified way to describe TFV-DP and FTC-TP disposition, and lends itself well to incorporation of virologic pharmacodynamics effects at the metabolite level. Although BMI and creatinine clearance are reported elsewhere as significant covariates for TFV and FTC disposition, this was not consistently observed here. The potential relationship between age and TFV-DP clearance is a new finding and will be explored further in this completed cohort and in future mechanistic studies.

No conflict of interest

Abstract: P_35

PK/PD modeling

Telaprevir population pharmacokinetic modeling and pharmacokinetic-dynamic associations

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Introduction: The addition of telaprevir (TVR) to peginterferon alfa and ribavirin (PR) therapy for the treatment of chronic hepatitis C virus (HCV) has greatly increased the rates of sustained virologic response (SVR). However, TVR+PR is not a universal cure. Some patient populations do not respond as well to this therapy including prior null responders, cirrhotics, and African Americans. In addition to clinical factors, TVR pharmacokinetics may also contribute to the likelihood of SVR. We developed a population pharmacokinetic model for telaprevir, investigated the effect of covariates on telaprevir pharmacokinetics, and explored pharmacokinetic-dynamic relationships for this drug utilizing a two-stage approach.

Materials & Methods: TVR pharmacokinetics (PK) was determined in HCV-infected, genotype 1, treatment naive subjects receiving TVR+PR. Subjects underwent sparse PK sampling at first dose and weeks 1, 2, 4, and 12. TVR in plasma was measured using a validated HPLC-MS/MS assay. A population pharmacokinetic model for TVR was developed using non-linear mixed effects modeling (NONMEM, v7.2). Model-estimated steady-state TVR area-under-the-concentration-time curves from 0-8 hours (AUC0-8) were compared by race (black vs. non-black) and gender using an unpaired t-test.

AUC0-8 was compared between METAVIR fibrosis stages using one way ANOVA. The associations between TVR AUC0-8 and age, weight, ribavirin steady-state AUC0-12, hemoglobin decline and the two phases of HCV viral decline were determined using Pearson correlation coefficients. TVR AUC0-8 was also compared in those achieving rapid virological response (RVR; undetectable virus at week 4 of treatment) vs. no RVR and in those with hemoglobin levels <10g/dL vs >10g/dL using the unpaired t-test.

Results: Two hundred thirty samples from 18 (12 male; 3 African American) subjects (mean±SD age 51.4±8.5yrs and weight 81.8±16.5kg) were used to develop the model. A one compartment model best described TVR pharmacokinetics. Mean (95% CI) TVR CL/F was 35.4 L/hr (29.7, 41.1) and V/F was 229 L (98.1, 360). Absorption rate, Ka, was fixed at 0.23 h^{-1}. TVR AUC0-8 was positively correlated with ribavirin steady state AUC0-12 (rho=0.62, p=0.02). Mean (SD) TVR AUC0-8 was lower in blacks vs. non-blacks, 18,467 ng*hr/mL (927) vs. 23,863 ng*hr/mL (1038), respectively (p=0.035). Gender, age, weight, rapid virological response, hemoglobin drop below 10 g/dL and fibrosis stage were not associated with plasma TVR AUC0-8 and there was no significant correlation between TVR exposure and slope of viral decline or hemoglobin decline.

Conclusions: TVR AUC0-8 was lower in blacks and this may contribute to reduced SVR rates in this population. TVR AUC0-8 was positively correlated with ribavirin AUC0-12 which may support a potential drug interaction or an effect on other processes such as clearance or absorption of these agents.

No conflict of interest

Abstract: P_36

Drug Drug Interactions

A mechanistic SimCYP simulation evaluating dolutegravir and efavirenz pharmacokinetics following a switch from once-daily efavirenz to once-daily dolutegravir

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Introduction: Dolutegravir (DTG) is a once-daily unboosted integrase inhibitor approved for the treatment of HIV-1. Dolutegravir is primarily metabolized through UGT1A1 with CYP3A4 as a minor route, and co-administration with the efavirenz (EFV), an inducer of UGT1A1 and CYP3A4, results in decreases in DTG maximum plasma concentration, area-under-the-curve, and plasma trough concentration of 39%, 57%, and 75%, respectively.. This results in the need for twice-daily dosing of DTG when co-administered with EFV as part of a stable dosing regimen. Because patients may switch from an HIV treatment regimen containing EFV to one including DTG, it is necessary to understand whether once-daily dosing of DTG is sufficient to maintain an effective DTG plasma concentration as EFV plasma concentration declines following an immediate switch from once-daily EFV to once-daily DTG.

Materials & Methods: SimCYP pharmacokinetic simulation models were developed for both DTG and EFV using mechanistic in vitro data on elimination, enzyme induction, and variance data from a previous population pharmacokinetic analysis of DTG. Model validation was performed by simulation and comparison to observed pharmacokinetics in a clinical drug-interaction study between DTG and EFV. Using the final model, DTG and EFV plasma concentrations were predicted following a switch from EFV 600mg once daily to DTG 50mg once daily. Predicted trough plasma concentrations of DTG and EFV were then compared to

established minimum effective concentrations (MEC) for EFV (1 mg/mL) and DTG (0.3 mg/mL) in order to assess the potential for post-switch viral breakthrough. Predictions of DTG and EFV concentrations following the switch were also made for CYP2B6 poor metabolizer population (for EFV) as well as a hypothetical population with lower turnover rate for regeneration of CYP3A4/UGT1A1.

Results: Following the switch from EFV 600 mg once daily to DTG 50mg once daily, EFV concentrations stayed above MEC up to 3 days post switch (after EFV dose was stopped) and DTG trough concentrations achieved MEC 3 days post switch (after DTG dose was initiated). In the CYP2B6 poor metabolizer population, EFV concentrations stayed above MEC up to 8 days post switch and DTG trough concentrations achieved MEC 6 days post switch. In the hypothetical slow CYP3A4/UGT1A1 turnover population, EFV concentrations stayed above MEC up to 3 days post switch and DTG trough concentrations achieved MEC 3 days post switch. These simulation results demonstrated that DTG trough concentrations achieved MEC before EFV concentrations fell below MEC following a switch from once-daily EFV dosing to DTG 50mg once daily.

Conclusions: Simulations predict that once-daily dolutegravir dosing following a switch from once-daily efavirenz dosing is sufficient to maintain plasma concentrations of either dolutegravir or efavirenz above their respective minimal effective concentration during the post-switch time period.

Conflict of interest: Employees of GlaxoSmithKline.

Abstract: P_37

Pharmacokinetics for Pediatrics, Pregnancy and other Special Populations

Pharmacokinetics of Hepatitis C Virus Protease Inhibitor MK-5172 in Volunteers with Mild and Moderate Hepatic Impairment

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Introduction: MK-5172 is a potent, once-daily hepatitis C virus (HCV) NS3/4A protease inhibitor that is being developed for the treatment of chronic HCV infection. This study evaluated the pharmacokinetic profile and safety of MK-5172 in non-HCV-infected subjects with mild and moderate hepatic impairment.

Materials & Methods: This was a Phase 1, open-label, multiple-dose study in non-HCV infected subjects with either Child-Pugh (CP)-A (8 subjects) or CP-B (8 subjects) liver impairment. In addition, 16 healthy matched control subjects were included. CP-A subjects received MK-5172 200 mg once-daily (QD) for 10 days, while CP-B subjects received 100 mg QD for 10 days. The pharmacokinetic profile of MK-5172 was obtained. Safety was monitored by clinical and laboratory evaluations.

Results: The steady-state $AUC_{0\text{-}24h,}$ $C_{max,}$ and C_{24h} of MK-5172 were increased in CP-A subjects with geometric mean ratios (GMRs) [90% confidence intervals (CIs)] for MK-5172 (mild HI/healthy) of 1.62 [1.03, 2.56], 1.28 [0.77, 2.12], and 1.92 [1.40, 2.62], respectively. The steady-state $AUC_{0\text{-}24h,}$ $C_{max,}$and C_{24h} of MK-5172 were increased in CP-B subjects with GMRs [90% CIs] for MK-5172 (moderate HI/healthy) of 4.88 [2.62, 9.08], 5.52 [2.54, 11.96], and 3.90 [1.91, 7.96], respectively. MK-5172 was safe and well-tolerated in subjects with mild and moderate hepatic impairment.

Conclusions: MK-5172 exposures increased ~2-fold in CP-A subjects and ~5-fold in CP-B subjects compared with matched healthy controls. The C_{max} of MK-5172 in non-HCV-infected CP-B subjects was comparable to that in HCV-infected CP-A patients. Dosing recommendations for CP-B and CP-C patients will be based on results of further studies.

Conflict of interest: Authors affiliated with Merck & CO INC are current employees of Merck & CO INC.

Abstract: P_38

Pharmacokinetics for Pediatrics, Pregnancy and other Special Populations

Pharmacokinetics of an increased Nelfinavir dose during the third trimester of pregnancy

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Background: Nelfinavir (NFV) continues to be used during pregnancy because of its favorable safety and side effect profile in this population. NFV is metabolized to its active metabolite M8 via CYP2C19; both NFV and M8 are metabolized to inactive forms by CYP3A4. IMPAACT protocol P1026s previously demonstrated that standard 1250 mg twice daily dosing in pregnancy resulted in decreased NFV exposure by 31% and M8 exposure by 75% during 3rd trimester versus postpartum, and 44% of 3rd trimester subjects failed to meet the NFV area under the concentration-time curve (AUC) target. The goal of this study was to determine NFV pharmacokinetic (PK) parameters in women during the 3rd trimester receiving an increased dose of 1875 mg twice daily and compare NFV and M8 exposure in the same subjects receiving 1250 mg twice daily postpartum.

Materials & Methods: P1026s is an ongoing, multi-center, multi-arm, prospective study of antiretroviral PK among HIV-1 infected pregnant women receiving antiretroviral drugs (ARVs) for routine clinical care. This arm enrolled women receiving NFV 1875 mg twice daily during 3rd trimester of pregnancy and the standard 1250 mg twice daily dose postpartum as part of their routine care. Intensive steady-state 12-hour NFV and M8 PK profiles were obtained once during 3rd trimester (30-36 weeks) and once at 6-12 weeks postpartum. The target steady-state NFV 12-hour AUC was 18.5 µg h/mL (10^{th} percentile in non-pregnant historical controls). Third trimester and postpartum parameters were compared via the Wilcoxon signed-rank test and by 90% confidence intervals (CI) for the geometric mean ratios.

Results: Eighteen subjects completed 3rd trimester PK evaluation; 16 of these completed postpartum PK evaluation. During 3rd trimester 15/18 (83%) met the NFV AUC target and postpartum 14/16 (88%) met the target. The NFV AUC for the increased dose during the third trimester was nearly identical to the AUC for the standard dose postpartum, with a geometric mean ratio for third trimester to postpartum of 0.98 (90% CI 0.71-1.35). Similarly, the sum of AUCs for the NFV and M8 active moieties was comparable, with a third trimester to postpartum ratio of 0.93 (90% CI 0.68-1.26). The NFV third trimester and postpartum median AUCs were 34.2 µg*h/mL (Interquartile Range (IQR) 27.2 – 46.9) and 33.5 µg*h/mL (IQR 28.6 – 43.5) respectively. The median molar sums of NFV and M8 AUCs for third trimester and postpartum were 71.6 µM*h (IQR 54.3 – 93.1) and 73.3 µM*h (IQR 66.3 – 91.7) respectively. Consistent with previous findings, the NFV clearance was higher during the third trimester than postpartum (Wilcoxon p-value 0.04).

Conclusions: These results support an 1875mg twice daily dose of NFV during 3rd trimester of pregnancy to achieve NFV and total active moiety exposure (NFV+M8 AUCs) comparable

to the standard dose of NFV 1250mg twice daily taken postpartum.

No conflict of interest

Abstract: P_39

Pharmacokinetics for Pediatrics, Pregnancy and other Special Populations

Pharmacokinetics and safety of Tenofovir alafenamide in subjects with mild or moderate hepatic impairment

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Background: Tenofovir alafenamide (TAF), a novel tenofovir (TFV) prodrug, is in clinical development for the treatment of HIV- and HBV-infection. TAF is metabolized primarily by hydrolytic cleavage and minimally by CYP3A4-catalyzed oxidation. Carboxylesterase-1, which is highly expressed in the liver, also contributes to TAF hydrolysis. This study evaluated the effect of liver impairment on the pharmacokinetics of TAF and its metabolite, TFV.

Materials & Methods: All subjects had stable hepatic impairment (no clinically significant changes within 60 days of screening) with Child-Pugh-Turcotte (CPT) classification A (CPT score: 5 to 6; N=10 (mild)) or B (CPT score: 7 to 9; N=10 (moderate)). The control group (N=20) consisted of healthy subjects with normal liver function, each matched for age, (± 10 years), gender, and BMI (±20% of ≥ 18 and ≤ 36 kg/m^2) with a subject in each impairment group. TAF (25 mg) was administered as a single dose, with food, followed by intensive pharmacokinetic sampling. Safety evaluations were performed through 7 days post-dose and during a 10-day follow-up period. The 90% confidence intervals (CI) were constructed about the ratio of geometric means (GMR) of log-transformed TAF and TFV exposures in the impaired versus control group, with an increase in exposure of at least 100% considered to be clinically relevant, consistent with US FDA guidance. Plasma protein binding of TAF and TFV was measured using equilibrium dialysis.

Results: All 40 enrolled subjects completed the study. Mean age and BMI in all groups were ~56 years and ~27.5 kg/m^2, respectively, with males accounting for 50% (mild) and 70% (moderate) of subjects.
Hepatic impairment did not affect TAF or TFV exposures in subjects with mild or moderate hepatic impairment relative to normal matched control subjects; the upper bounds of the 90% confidence intervals were below the pre-specified clinically significant increase of 100%. The GMR (%) (90% CI) for TAF AUC_{last} and $C_{max,}$ respectively, were 91.8 (65.2, 129.4) and 89.0 (57.7, 137.3) (mild) and 115.1 (88.5, 149.6) and 118.7 (78.9, 178.5) (moderate). The corresponding values for TFV were 89.3 (67.3, 118.5) and 97.0 (75.9, 124.0) (mild) and 95.6 (75.2, 121.4) and 87.6 (70.5, 108.8) (moderate). No correlations were observed between TAF or TFV exposures versus CPT score or individual laboratory components of CPT classification (albumin, total bilirubin, prothrombin time, or INR). Mean free fraction (%) of TAF ranged from 16% to 19% (mild and their matched controls) and 14% to 23% (moderate and their matched controls); corresponding values for TFV were >99% in all groups, indicating a lack of effect of hepatic impairment on TAF or TFV protein binding.
The incidence of treatment-emergent adverse events (AEs) was comparable between impaired and control groups. Most AEs were mild in severity and considered unrelated to study treatment. No clinically relevant laboratory abnormalities were seen in either group.

Conclusions: Mild or moderate hepatic impairment does not result in clinically relevant changes in TAF or TFV exposures. This treatment was well-tolerated. Based on these data, no dose adjustment of TAF is necessary in subjects with mild to moderate hepatic impairment.

No conflict of interest

Abstract: P_40

Pharmacokinetics for Pediatrics, Pregnancy and other Special Populations

Pharmacokinetics and safety of Cobicistat boosted-elvitegravir in subjects with decreased UGT1A1 activity

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Background: The integrase inhibitor elvitegravir (EVG) and pharmacoenhancer cobicistat (COBI) are components within the single tablet regimen EVG/COBI/emtricitabine (FTC)/tenofovir disoproxil fumarate (TDF) (Stribild™) approved for HIV treatment. EVG is also in regulatory review in the United States and approved in the European Union and Canada for HIV treatment as part of an antiretroviral regimen containing a boosted protease inhibitor. EVG is primarily eliminated by CYP3A and secondarily, by glucuronidation via UGT enzymes 1A1 and 1A3. In the boosted state upon coadministration with pharmacoenhancer COBI or ritonavir, EVG metabolism is presumably mediated predominantly by UGT1A1 and/or 1A3. Although genetic variants of UGT1A1 are rare, the UGT1A1*28 homozygous variant represents the polymorphism with the largest decrease in enzymatic activity, relative to wild type (UGT1A1*1). The present study evaluated the pharmacokinetics (PK) and safety of COBI-boosted EVG in subjects with decreased UGT1A1 activity as identified by the UGT1A1*28 homozygous genotype.

Materials & Methods: This was an open-label, parallel-design, single center, multiple-dose study in subjects with decreased UGT1A1 activity (UGT1A1*28). Subjects were matched for gender, age (±20%) and BMI (±20%) with a subject in the control group (UGT1A1*1). All subjects (n=36) received EVG+COBI 150/150 mg QD for 10 days. Intensive PK was assessed for 24 hours after the final dose. Statistical comparisons of EVG exposures were made using geometric mean ratios (GMR) and associated 90% confidence interval (CI) bounds of 70-143% (>90% power to conclude clinical equivalence), with UGT1A1*28 subjects serving as the test treatment and UGT1A1*1 subjects serving as the reference treatment. For the glucuronidated metabolite of EVG (GS-9200), only descriptive PK was assessed. Safety evaluations were performed throughout the study and during follow-up.

Results: Study treatments were generally well tolerated and all enrolled subjects completed the study. No Grade 2, 3, 4 or serious adverse events were observed. Following multiple-dose administration of COBI-boosted EVG in subjects with decreased UGT1A1 activity as identified by the UGT1A1*28 homozygous genotype, versus wild type UGT1A1*1 matched control subjects, EVG PK was unaffected (GMR (90% CI) AUC_{tau}: 104 (79.9, 134), C_{max}: 97.6 (78.4, 122), and C_{tau}: 120 (95.5, 152). EVG half-life (T_{half}) was comparable between UGT1A1*28 subjects and UGT1A1*1 subjects (median (Q1, Q3) T_{half} was 9.7 (8.7, 12.9) hours versus 10.9 (9.7, 12.0) hours, respectively), indicating that EVG elimination was unchanged. Mean GS-9200 exposure (AUC) was modestly lower (37%) in UGT1A1*28 subjects versus UGT1A1*1 subjects.

Conclusions: EVG exposures are comparable and its half-life is unchanged following multiple-dose administration of boosted EVG in subjects with decreased UGT1A1 activity (UGT1A1*28), relative to wild-type matched control subjects (UGT1A1*1), while exposures of the glucuronidated metabolite of EVG (GS-9200) were modestly lower. As such, these data indicate that UGT1A1 activity does not influence overall EVG clearance, obviating any utility in screening for reduced function genotypes. Based on these study findings, no dose modification of EVG is necessary in patients with decreased UGT1A1 activity receiving EVG as part of a boosted antiretroviral regimen.

Conflict of interest: All coauthors are employees and shareholders of Gilead Sciences.

Abstract: P_41

Pharmacokinetics for Pediatrics, Pregnancy and other Special Populations

Pharmacokinetics and safety of hepatitis C virus non-structural protein 5a inhibitor MK-8742 in cirrhotic patients with mild and moderate hepatic insufficiency

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Introduction: MK-8742 is an HCV NS5A inhibitor being developed for the treatment of chronic HCV infection. This study evaluated the pharmacokinetic profile of MK-8742 in individuals with mild and moderate hepatic insufficiency.

Materials & Methods: This was a multi-center, open-label, fixed-sequence, sequential panel 2-part study in adult cirrhotic male and female patients with either Child-Pugh A (8 patients) or Child-Pugh B (7 patients) liver disease who were administered one 50 mg dose of MK-8742. The plasma concentration profiles and pharmacokinetics of hepatically insufficient patients were compared to those of historical healthy control subjects. Safety was monitored throughout the study by repeated clinical and laboratory evaluations. Plasma samples for MK-8742 concentrations were obtained predose and at selected time points postdose.

Results: Administration of MK-8742 was generally safe and well-tolerated by the patients in this study. Single 50 mg oral doses of MK-8742 in patients with mild hepatic insufficiency resulted in $AUC_{0-\infty}$, C_{max}, and C_{24h} geometric mean ratios (GMRs, MK-8742 Mild Impaired/MK-8742 Healthy) [90% confidence intervals (CIs)] of 0.758 [0.480, 1.197], 0.579 [0.346, 0.970], and 0.733 [0.474, 1.135] respectively. Following administration of 50 mg of MK-8742 to patients with moderate hepatic insufficiency $AUC_{0-\infty}$, C_{max}, and C_{24h} GMRs (MK-8742 Mild Impaired/MK-8742 Healthy) [90% confidence intervals (CIs)] of 0.858 [0.595, 1.240], 0.686 [0.485, 0.972], and 0.830 [0.575, 1.196] respectively.

Conclusions: The plasma PK of MK-8742 after administration of one 50 mg dose of MK-8742 is not meaningfully altered in individuals with Child-Pugh A or B liver disease, supporting the administration of MK-8742 to patients with mild and moderate hepatic dysfunction.

Conflict of interest: Authors affiliated with Merck & Co INC are current employees of Merck & Co INC

Abstract: P_42

Pharmacokinetics for Pediatrics, Pregnancy and other Special Populations

The effect of lopinavir and nevirapine pharmacokinetics on long term virological outcomes in protease inhibitor-experienced HIV-infected children

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Background: Adequate exposure to antiretroviral drugs is necessary to achieve long-lasting virological suppression. However, several factors may influence drug levels, leading to increases or decreases that results in toxicities or virological failure.
Aim: We assessed the relationship between plasma lopinavir and nevirapine concentrations and long term viremia.

Materials & Methods: Data were from the post-randomization phase of the Neverest study in South Africa. One hundred and ninety five children were randomized to either remain on lopinavir based regimen or switched nevirapine based regimen. Baseline investigations at randomization included, age, viral load, CD4%, sex, weight for age and height for age z-scores. Concomitant TB medication and resistance mutation were investigated after randomization. Viral load and lopinavir or nevirapine concentrations were measured at clinic visits 4, 8, 12, 16, 20, 24, 36, 52, 64 and 76 weeks post-randomization. Cox multiple failure event models were used to estimate the crude and adjusted effect of lopinavir or nevirapine concentrations on hazard of viremia (viral load >50 copies/mL).

Results: Ninety-nine children were randomized to remain on lopinavir whereas ninety-five were switched to nevirapine. The median (IQR) time of randomization CD4% was 29.70(24.40-35.90) and (29.10 (21.6a0-28.59) for children on lopinavir and nevirapine respectively. The median [MS1] viral loads were 50 (50-130) and 50(50-80) for children on lopinavir and nevirapine. The median WFA and HFA z-scores were -0.56(-1.28-0.08) and -3.26(-4.03 to -2.01) for children on lopinavir whereas the median WFA and HFA z-scores were -0.66(-1.41-0.23) and -2.99(-4.12 to -2.12) for children on nevirapine. The crude and adjusted Cox models revealed a significant association between viremia viral load and lopinavir and nevirapine concentrations. We showed that lower lopinavir and nevirapine concentrations increased the hazard of viremia.

Conclusion: Low plasma lopinavir and nevirapine concentrations are associated with long term virological outcomes in children.

No conflict of interest

Abstract: P_43

Pharmacokinetics for Pediatrics, Pregnancy and other Special Populations

The effect of renal impairment on single-dose pharmacokinetics to daclatasvir, an HCV NS5A inhibitor

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Background: Daclatasvir (DCV) is a potent, pangenotypic HCV NS5A replication complex inhibitor with *in vitro* activity against HCV genotypes 1–6. DCV is primarily excreted in feces; renal excretion represents <10% of elimination. Study AI444-063 —an open-label, oral single-dose adaptive study— assessed the pharmacokinetics and safety of DCV 60 mg in HCV-uninfected subjects with renal impairment (RI), and in controls with normal renal function.

Materials & Methods: Twelve subjects with end-stage renal disease (ESRD, eGFR <15 mL/min/1.73 m^2 [MDRD equation]) and 12 subjects with normal renal function (creatinine clearance [CL_{CR}] ≥90 mL/min [Cockroft-Gault estimation]) who were matched by age (± 10 years), weight (± 20%) and gender, received DCV 60 mg QD on Day 1. Noncompartmental DCV pharmacokinetics were derived from validated LC/MS/MS analysis of serial blood samples collected through Day 4. Ratios of geometric means (GMR) and 90% confidence intervals (90%CI) for DCV AUC_{inf} were estimated using an ANCOVA model on log-transformed data. Pre-specified criteria for study expansion (ESRD versus normal renal function AUC_{inf} upper GMR 90% CI limit >1.5) were met in an interim analysis so six subjects with moderate RI (eGFR 30–59 mL/min/1.73 m^2) and six with severe RI (eGFR 15–29 mL/min/1.73 m^2) were

then enrolled. The relationship between log-transformed DCV AUC_{inf} and estimated renal function was analyzed by linear regression (ESRD data excluded; CL_{CR} as an independent variable). The primary analysis using CL_{CR} to assess renal function is reported.

Results: Thirty-six subjects (male, n=30; female, n=6; White, n=18; Black/African American, n=16; mean age, 53 years) were treated and completed the study. DCV AUC_{inf} was higher in subjects with ESRD receiving hemodialysis *versus* control subjects (GMR [90%CI], 1.27 [0.99–1.62]). A statistically significant relationship was observed with DCV AUC_{inf} increased with decreasing CL_{CR} (regression analysis slope, -0.008; *P* <0.001). Compared with a normal CL_{CR} (90 mL/min), estimated GMR and 90%CIs for total DCV AUC_{inf} at a CL_{CR} of 60, 30 and 15 mL/min were 1.26 [1.14–1.40], 1.60 [1.30–1.96] and 1.80 [1.39–2.32], respectively; similar estimated increases in the AUC_{inf} of unbound free DCV were also observed (1.18 [1.07–1.30]; 1.39 [1.14–1.70] and 1.51 [1.18, 1.94], respectively). Compared to the normal function group, AUC_{inf} was higher in the moderate RI, severe RI and ESRD groups, with GMRs (90%CIs) of 2.10 (1.36–3.24), 1.94 (1.42–2.63) and 1.27 (0.99–1.62), respectively. DCV C_{max} was unaffected by RI. DCV was generally well tolerated in controls with normal renal function, subjects with ESRD, and subjects with moderate and severe RI.

Conclusions: The total AUC and unbound AUC of DCV were estimated to be increased by 1.8- and 1.5-fold, respectively in HCV-uninfected subjects with severe renal impairment. The increase in DCV exposure was within the exposures observed in the population PK and exposure-safety assessment which has not shown a correlation between these higher exposures and adverse events.

Conflict of interest: Employee of Bristol-Myers Squibb

Abstract: P_44

Pharmacokinetics for Pediatrics, Pregnancy and other Special Populations

Accumulation of antiretroviral drugs in amniotic fluid in HIV-infected pregnant women

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Background: The rate of mother-to-child transmission (MTCT) of HIV-1 is as low as 0.5% in non breast feeding mothers who delivered at term while receiving HAART with a plasma HIV-RNA<500c/mL in the French ANRS perinatal cohort (Tubiana R, CID, 2010). Based on National Guidelines, usual HAART as boosted PIs associated with 2 NRTIs is proposed in HIV-infected pregnant women. Then, the foetotoxicity risk is partly proportional to the degree of foetal exposure, directly dependent on the amount of placental transfer of drugs. Several mechanisms are involved in becoming of xenobiotics in amniotic fluid (AF) as transplacental passive diffusion and depending on ARV chemical properties (ionization state, molecular weight, liposolubility, protein binding) and several physiological parameters (pH and concentration gradient, exchange surface area, volume of distribution, blood flow, CYP450 placental activity, etc.). Besides, active efflux transporters as P-glycoproteins, are responsible for AF's detoxification via foeto-maternal transfer. While recommended by Guidelines, Therapeutic Drug Monitoring of ARV in HIV-infected pregnant women is more used to detect adherence difficulties or pharmacokinetic modifications than accumulation in AF and foetotoxicity. The aim of this study is to determine the *in vivo* AF

accumulation of ARV in HIV-infected pregnant women.

Materials & Methods: multicenter, retrospective study conducted between 2005 and 2014, based on the pharmacological database availability of ARV concentrations in mother/infant/AF at delivery. ARV concentration was measured using UPLC/MS/MS (Waters® Acquity UPLC/Waters® Acquity TQD System) except T20 measured by HPLC/fluorimetry (Waters® Acquity HPLC/Water® fluorimeter).
Concentrations ratio between Maternal and cord blood (as foetal) named CP/MP ratio, cord blood and AF named AF/CP ratio were calculated and expressed in median (IQR25-75%).

Results: On the 66 mother/infant couples, 20 received ZDV/3TC (300/150mg BID) and 14 IV ZDV, 4 ABC/3TC (600/300mg QD) and 15 TDF/FTC (300/200mg QD), possibly associated with 31 LPV/r (400/100mg BID), 6 DRV/r (800/100mg QD), 2 DRV/r (600/100mg BID), 6 ATV/r (300/100mg QD) and 1 unboosted ATV (400mg QD), 4 APV/r (700/100mg BID), 9 RAL (400mg BID), 3 T20 (90mg BID).
CP/MP ratio's for NRTIs are: FTC=1.52 (0.46-1.20)>ZDV=1.30 (0.77-3.41)>3TC=1.32 (0.80-3.37)>TDF=1.00 (0.63-1.33)>ABC=0.88 (0.46-3.37). CP/MP ratio's for PI: DRV=0.24 (0.14-0.36)> APV=0.18 (0.13-0.56)>LPV=0.16 (0.08-0.22)>ATV=0.15 (0.15-0.26) and RTV=0.15 (0.07-0.79). For other ARV, CP/MP ratio are: RAL=1.88 (0.80-4.80) and T20=0.18 (0.09-0.30).
AF/CP ratio's for NRTIs are: TDF=11.36 (5.79-24.42)>FTC=7.15 (3.12-11.61)>3TC=6.83 (4.78-11.38) >ZDV=2.50 (1.01-4.17)>ABC=0.40 (0.39-8.49). AF/CP ratio's for PI: ATV=2.07 (1.49-3.27)> DRV=1.74 (1.44-2.32)>APV=1.12 (0.66-2.06)>LPV=0.75 (0.38-1.67) and RTV=0.42 (0.12-1.73). For other ARV, AF/CP ratio's are: RAL=1.05 (0.67-1.19) and T20=0.82 (0.44-1.21).

Conclusions: Because of their favourable physicochemical and pharmacokinetic characteristics, NRTIs could accumulate in the amniotic compartment. Amniotic exposures are the most important for TDF, FTC and 3TC. Regarding the probable foetal UGT immaturity, RAL is poorly eliminated in AF while demonstrating a high CP/MP ratio. Whatever, T20 (peptide with high molecular weight) cannot diffuse through placental membrane. Finally, PIs had low placental transfer and poor AF's accumulation.

No conflict of interest

Abstract: P_45

Pharmacokinetics for Pediatrics, Pregnancy and other Special Populations

Marked increase in lopinavir clearance occurs between early and late second trimester of pregnancy: a population analysis of a diverse clinical cohort

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Background: Globally, ritonavir-boosted lopinavir (LPV/r) remains a preferred protease inhibitor for use in HIV-infected pregnant women. To overcome physiologic changes that result in lower lopinavir exposure during pregnancy, the U.S. guidelines recommend increasing the LPV/r dose to 600/150 mg twice daily during the second and third trimesters. However, existing lopinavir pharmacokinetic (PK) data during the second trimester was measured after 20 weeks gestation; therefore, the ideal gestational age at which to make the recommended dose adjustment remains uncertain. To explore this question, a population pharmacokinetic (PK) model was developed to characterize lopinavir clearance during all stages of pregnancy and post-partum.

Materials & Methods: HIV-infected pregnant women who were receiving LPV/r-based antiretroviral therapy for at least one week were enrolled. A sparse sampling approach was used to collect plasma samples at each antepartum and postpartum clinical visit. Adherence to LPV/r was assessed at each visit and subjects documented the time of their last LPV/r dose prior to each PK sampling. Plasma lopinavir concentrations were determined by a validated LC/MS/MS assay with a lower limit of quantitation of 20 ng/mL. Population PK analysis was performed using NONMEM version 7.2 (PDx-Pop version 5) with a FOCE-I subroutine. Apparent oral clearance (CL/F) and volume of distribution were estimated while the absorption constant (Ka) was fixed at 0.8 hr^{-1}. Lopinavir concentration data were pooled from each of the following time periods to estimate lopinavir CL/F: first trimester (T1; weeks 0-13), early second trimester (early T2; weeks 14-20), late second trimester (late T2; weeks 21-27), early third trimester (early T3; weeks 28-33), late third trimester (late T3; weeks 34 to delivery), and postpartum (PP).

Results: 151 steady state pharmacokinetic samples (median (interquartile range (IQR) 3.4 (3.6) hours post-dose) were collected from 24 HIV-infected pregnant women. Subjects had a median (IQR) age of 31 (4) years, were racially diverse (38% African American, 38% Caucasian, and 25% Black African), and 17% were of Hispanic ethnicity. Plasma samples available for lopinavir analysis and included in the model were as follows: T1 (n=4), early T2 (n=17), late T2 (n=37), early T3 (n=40), late T3 (n=39), and PP (n=14). A one-compartment model with first order absorption and elimination was found to best fit the data. Population CL/F estimates (% relative standard error) were: T1 4.54 L/hr (14.1%), early T2 5.18 L/hr (15%), late T2 7.17 L/hr (14.1%), early T3 6.81 L/hr (12.5%), late T3 7.95 L/hr (12.2%), PP 3.78 L/hr (14.6%).

Conclusions: Among a racially and ethnically diverse U.S.-based cohort of HIV-infected pregnant women receiving LPV/r-based ART, population-based estimates of lopinavir plasma clearance markedly increased and remained at least 80% higher throughout the later half of pregnancy compared to postpartum (non-pregnant) estimates. The model estimated that the largest change in clearance (38.4% increase) occurred between early and late second trimester, relative to the other gestational age groups. These data support findings from prior studies in later pregnancy, while also highlighting that the LPV/r dose increase may be most important in the later half of the second trimester.

No conflict of interest

Abstract: P_46

PK-PD of Drug Efficacy and Toxicity

CSF viral load and darunavir concentrations in pts receiving DRV/r 600/100 mg or 800/100 mg once daily (OD) plus two nucleosides.

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Background: Darunavir/r (DRV/r) is currently used at a dose of 800/100 mg once daily (OD) in a high proportion of patients. Pharmacokinetic data suggest that 600/100 OD may be effective, reducing toxicity and cost. However, drug concentrations in reservoirs such as cerebrospinal fluid (CSF) might not be adequate to inhibit viral replication. We aimed to evaluate concentrations of DRV and HIV-1 viral load (VL) in CSF patients receiving DRV 600/100 mg OD.

Materials & Methods: DRV600 is an ongoing randomized open study comparing DRV/r 800/100 mg (DRV800) vs. 600/100 mg (DRV600) OD plus TDF/FTC or ABC/3TC in 100 virologically suppressed patients (eudraCT

2011-006272-39). Here we present the results of a CSF sub-study. A lumbar puncture (LP) was performed in participating patients after at least 6 months of inclusion in the study, 20-28 h after a dose of DRV/r. VL (PCR, LOD 40 copies/mL) was determined in CSF and in plasma. DRV concentrations were quantified in CSF by liquid chromatography mass spectrometry (LC/MS/MS) and in plasma using high-performance liquid chromatography (HPLC).

Results: Sixteen patients were included (8 in each arm). All DRV600 patients and 4 out of 8 DRV800 patients received TDF/FTC, and the other 4 ABC/3TC. 75% were males, median (range) age was 48 (17-71) years, CD4 cell count 532 cells/ml (190-1,394). Median total time on DRV/r was 30 (11-57) months, and since the beginning of the study 8 (6-12) months in DRV800 and 10 (7-12) months in DRV600 patients. LP was performed a median of 26 (24-28) hours after the last DRV/r + TVD or KVX dose. In DRV600 patients the median DRV plasma levels were 1,674 (326-3,742) ng/ml, CSF levels 17.08 (5.79-30.19) ng/mL and DRV CSF:plasma ratio 0.0084 (0.0028-0.0388), while in the DRV800 arm, median DRV plasma levels were 1,707 (958-3,910) ng/ml, CSF levels 13.23 (3.47-32.98) ng/mL and DRV CSF:plasma ratio 0.0104 (0.0018-0.0262). All pts had VL < 40 copies/mL in plasma and 14 patients VL < 40 copies/mL in CSF. Two pts (1 in each arm, and taking TDF/FTC) had detectable VL in CSF (280 and 159 c/mL). These patients had the lowest CSF DRV concentrations (5.47 and 3.47 ng/mL), with plasma DRV concentrations of 802 and 958 ng/mL respectively.

Conclusions: CSF DRV concentrations and CSF VL were similar between patients receiving DRV/r 800/100 mg or 600/100 mg OD. Low CSF DRV concentrations might be associated with viral escape in CNS. This may be taken into account in patients receiving OD DRV/r. Larger studies should confirm these findings.

No conflict of interest

Abstract: P_47

PK-PD of Drug Efficacy and Toxicity

Evaluation of the effect of Ledipasvir on the QT/QTc interval in healthy subjects

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Background: Ledipasvir (LDV) 90 mg, a once daily potent hepatitis C virus (HCV) NS5A inhibitor in a fixed dose combination with a once daily NS5B inhibitor sofosbuvir (SOF) 400 mg is in Phase 3 clinical development for the treatment of chronic HCV-infection. In vitro, LDV did not display significant inhibition of hERG channel activity (IC_{50} > 0.5 μM), however, in accordance with the ICH E14 requirement for clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential of non-antiarrhythmic drugs, a Phase 1 study was conducted to evaluate the effect of supratherapeutic LDV on QTc interval.

Materials & Methods: Healthy volunteers (N=60) were enrolled into one of 6 treatment sequences and received in a randomized fashion blinded LDV 120 mg BID (supratherapeutic exposure) and LDV placebo for 10 days each, and a single dose of open-label moxifloxacin (moxi; positive control). Active and placebo treatments were followed by a 14-day washout; moxi treatment was followed by a 6-day washout. Triplicate time-matched ECGs were collected at baseline and after each treatment. Serial plasma samples for LDV concentration analysis were collected over 24-hours after each treatment. Change from baseline in QTc for LDV or moxifloxacin vs placebo was determined using several correction formulas including QTcF (primary), QTcN and QTcI (PD analysis). Pharmacokinetics (PK) and exposure-QT relationships (PK/PD) were evaluated. Safety was monitored throughout the study.

Results: Fifty-nine out of 60 subjects completed the study. Fifty-nine subjects were included in the PK and PD analyses; 58 subjects were included in the PK/PD analysis. One subject discontinued due to an adverse event [AE] (exacerbation of pre-existing hernia) and was excluded from PK and PK/PD analyses; another subject was excluded from PD and PK/PD analyses due to a damaged Holter flash card for placebo postdose ECGs.
Study treatments were well tolerated. The percentage of subjects with treatment-emergent AEs in the placebo and LDV arms was similar (21.7% vs. 20.3%) The majority of the AEs were Grade 1 in severity.
LDV AUC_{0-24} and C_{max} were approximately 3.7-fold and 4.2-fold higher, respectively, relative to therapeutic LDV 90 mg dose within LDV/SOF. The lower bound of the 2-sided 96.67% CI for the mean difference in QTcF, QTcN and QTcI for moxifloxacin vs placebo was > 5 msec at 3, 3.5 and 4 hours post-dose, establishing assay sensitivity. Following supratherapeutic LDV dosing, the upper bound of the 2-sided 90% CIs for the mean difference in time-matched baseline-corrected QTc between LDV vs placebo was < 10 msec at all time points using all evaluated correction methods. Categorical analyses did not demonstrate marked effects of LDV on QTc intervals. The relationships between LDV plasma concentrations and QTc intervals did not reveal an association using QTcF, QTcN or QTcI methods.

Conclusion: The results from this study met the ICH E14 definition of a negative 'thorough QT/QTc study'. Collectively, the results from this study and a previous TQT evaluation for SOF demonstrate that LDV/SOF is not expected to prolong QTc interval in healthy adults.

Conflict of interest: All authors are employees of Gilead Sciences and may own company stock

Abstract: P_48

PK-PD of Drug Efficacy and Toxicity

No clinically meaningful effect of single and multiple dose administration of Peginterferon Lambda-1a (lambda) on the QTC interval

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Introduction: Lambda (180µg) is in phase-3 development for chronic HCV infection. Preclinical data have not revealed a signal related to QT prolongation. To further understand the potential of Lambda to prolong the QT interval, integrated analyses of clinical data were conducted.

Materials & Methods: Triplicate electrocardiograms were obtained pre- and post-dose from two studies for which abnormal QTc at baseline was exclusionary: a single-ascending dose study in healthy subjects (Lambda 80,120,180, 240µg or placebo) and a phase-2b study in patients with chronic HBV (Lambda 180µg, or peginterferon alfa-2a (alfa) 180µg weekly for 48 weeks [24-week data analyzed]). Central tendency, and categorical analyses were conducted using QTc (Fridericia's method [QTcF]), change in QTcF from baseline (ΔQTcF), heart rate (HR), QRS and PR interval data. AEs potentially related to QT prolongation were evaluated. Exposure-response analyses were conducted examining relationship between serum concentrations and ΔQTcF.

Results: Single-dose Lambda showed no evidence of a QTc effect. Following multiple-dose Lambda 180mg, at Week 12, mean ΔQTcF (upper bound 90% CI) was 3.5 (5.5) msec; upper bound was below the E14-defined 10 msec effect level. One subject in each of the Lambda (1.3%) and alfa (1.2%) groups had ΔQTcF >30 msec and ≤60 msec, while none had ΔQTcF >60 msec observed during dosing. No subjects in the study had maximum QTcF intervals >480 msec. Single- and multiple-dose Lambda administration had no effect on HR or QRS/PR intervals and no AEs related to arrhythmias were identified. No

clinically meaningful relationship between Lambda exposure and ΔQTcF was observed.

Conclusions: Lambda had no clinically meaningful effects on the QTc interval following single- or multiple-dose administration.

Conflict of interest: M Hruska, D Xu, C Jurkowski, D Bounous, E Cooney, S Srinivasan and R Bertz are all employees, and maybe shareholders, of Bristol-Myers Squibb.

Abstract: P_49

PK-PD of Drug Efficacy and Toxicity

PK and PD of darunavir 800mg qd when coadministered with cobicistat 150mg qd in HIV-1-infected patients with no darunavir RAMs: GS-US-216-0130 week 48

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Introduction: Cobicistat is a pharmacoenhancer of select antiretrovirals, including darunavir. Previous studies in healthy volunteers demonstrated comparable darunavir exposure when darunavir 800mg once-daily was coadministered with cobicistat 150mg once-daily or ritonavir 100mg once-daily. A single-tablet co-formulation of darunavir/cobicistat is in development.

Materials & Methods: GS-US-216-0130 is a Phase III, open-label, single arm, multicenter study evaluating the pharmacokinetics, safety and efficacy of darunavir/cobicistat 800/150mg once-daily (as single-agents) plus two NRTIs in HIV-1 infected adults with no darunavir resistance-associated mutations (RAMs).
Sparse samples for darunavir were collected at Weeks 2, 4, 8, 12, 16, 24 and 48 in all patients. An optional substudy assessed cobicistat, darunavir, emtricitabine and tenofovir pharmacokinetics. Between Week 2 and 8, steady-state pharmacokinetic parameters (C_{max}, C_{min} and AUC_{24h}) were obtained by non-compartmental analysis (WinNonlin) using plasma samples collected pre-dose, 1, 2, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12 and 24 hours post-dose.
An existing 2-compartment model with first-order absorption was updated with the substudy data and was then used to derive individual empirical Bayes estimates of darunavir exposure (AUC_{24h} and C_{0h}) using NONMEM. Pharmacokinetic/pharmacodynamic relationships were assessed using darunavir exposure and virologic response (<50 copies/mL) at Week 48. The absence or presence of select adverse events (AEs: diarrhea, nausea, rash or vomiting) and worst change in laboratory parameters (ALP, ALT, AST, amylase, lipase, glucose, total cholesterol, LDL-cholesterol, HDL-cholesterol, or triglyceride) by darunavir AUC_{24h} was also evaluated.

Results: Of the 313 patients enrolled, the majority (96.2%) received tenofovir/emtricitabine as the 2 NRTIs. Mean baseline viral load and $CD4^+$ cell count were 4.8 $\log_{10}$ copies/mL and 368 cells/mm^3, respectively. No patient discontinued due to lack of efficacy. Overall virologic response was 80.8% at week 48 (FDA snapshot analysis); $CD4^+$ cell count increased 190 cells/mm^3 from baseline. The most common AEs were diarrhea (27.5%) and nausea (23.0%); there were no deaths.
Overall mean (SD) population pharmacokinetic-derived darunavir AUC_{24h} and C_{0h} at week 48 were 102,000 (33,100) ng.h/mL and 2,150 (1,320) ng/mL (n=298), respectively. Sixty patients enrolled in the pharmacokinetic substudy. Mean (SD) C_{max} (ng/mL), C_{24h} (ng/mL) and AUC_{24h} (ng.h/mL) were respectively for darunavir: 7,663 (1,920), 1,310 (969) and 81,646 (26,322); cobicistat: 991 (331), 33 (95) and 7,596 (3,657); tenofovir: 382 (118), 78 (33) and 3,613 (1,203); and emtricitabine: 1,862 (491), 113 (101) and 11,793 (3,490). These pharmacokinetic parameters were comparable to historic data.
There were no clinically relevant relationships between darunavir exposure and virologic

response at Week 48, AEs or laboratory parameters.

Conclusions: Darunavir/cobicistat 800/150mg once-daily was generally safe and well tolerated with virologic and immunologic response similar to historic data (darunavir/ritonavir 800/100mg once-daily). No clinically relevant relationship was observed between darunavir AUC_{24h} or C_{0h} and virologic response at Week 48. Overall there were no apparent relationships between darunavir pharmacokinetics and safety.

Conflict of interest: Employee of Janssen.

Abstract: P_50

PK-PD of Drug Efficacy and Toxicity

Seminal pharmacokinetics and antiviral efficacy of once-daily maraviroc plus lopinavir/ritonavir in HIV-positive patients.

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Introduction: Sexual transmission of HIV-1 is currently the major way of viral spread worldwide: the quantification of HIV-1 RNA has been clearly linked to the risk of transmission. Occasional HIV-1 shedding has been demonstrated despite effective systemic therapy, and insufficient penetration of antiretrovirals has been advocated as one of the possible explanation. Primary aim of this study was to describe the seminal pharmacokinetics of maraviroc (150 mg once-daily) when given in association with lopinavir/ritonavir; secondary objective was to analyze seminal HIV-1 replication in patients receiving this dual regimen.

Materials & Methods: Adult male patients enrolled in the VEMAN study (TDF/FTC plus lopinavir/ritonavir vs maraviroc 150 mg once-daily plus lopinavir/ritonavir in naive subjects) were considered, if inclusion/exclusion criteria were fulfilled (no concomitant systemic nor genital illness, a confirmed viral load below 37 copies/mL, to be on protocol between weeks 48 and 96, and no coadministration of potentially interacting drugs). Blood plasma and seminal plasma levels were measured by a validated ultra-performance liquid chromatography coupled with triple-quadrupole mass spectrometry method (UPLC-MS-MS) with a limit of detection of 0.125 ng/mL. Plasma HIV RNA was measured through kinetic PCR molecular system while seminal plasma HIV RNA was measured through the NucliSENS EasyQ® HIV-1 v2.0 Data are expressed as medians (interquartile ranges).

Results: Ten male patients were enrolled [aged 39.6 years (34.3-45.8) and with a body mass index of 23.5 mg/Kg^2 (22.2-29.4)]. CD4 cell count was 619/uL (547-683). Maraviroc plasma and seminal concentrations were 223 ng/mL (103.9-312, 55.4%) and 527 ng/mL (234-852, 89.8%): seminal plasma to plasma ratio ($ratio_{SP-P}$) was 291.6% (103.9-405.1, 80.5%). Lopinavir plasma and seminal concentrations were 7935 ng/mL (6269-8958) and 233 ng/mL (136-803): lopinavir $ratio_{SP-P}$ was 4.3% (2.6-11.7). Ritonavir plasma and seminal concentrations were 275 ng/mL (224-773) and 21 ng/mL (7-31): ritonavir $ratio_{SP-P}$ was 8.3% (IQR 4.6-10.7). The included patients were compared to five patients in the control arm (receiving tenofovir/emtricitabina plus lopinavir/ritonavir): seminal HIV RNA was undetectable in all seminal samples (n=13, 2 not amplified).

Conclusions: This is the first report of maraviroc pharmacokinetics in seminal plasma when dosed at 150 mg once-daily with a boosted PI: maraviroc confirmed to accumulate in seminal plasma and compartmental maraviroc concentrations were found to be adequate, well above the protein-free IC_{90} (0.5 ng/mL) in all included subjects. Interestingly in our patients both plasma and seminal maraviroc exposure resulted to be comparable to the values

previously reported for maraviroc at double dosing (150 mg bid) with darunavir/r. In conclusion, once-daily maraviroc at 150 mg administered with lopinavir/ritonavir showed adequate seminal exposure and full antiviral activity in the male genital tract.

No conflict of interest

Abstract: P_51

PK-PD of Drug Efficacy and Toxicity

Pharmacokinetics of BMS-791325, a non-nucleoside HCV NS5B inhibitor, and its active metabolite in healthy Japanese and Caucasian subjects

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Introduction: BMS-791325 is a potent, allosteric inhibitor of the HCV NS5B RNA-dependent RNA polymerase, active *in vitro* against HCV genotypes 1, 3, 4, 5 and 6 and currently under clinical investigation as part of an all-oral regimen with daclatasvir (NS5A inhibitor) and asunaprevir (NS3 protease inhibitor) in genotypes 1 and 4. The potential for differences in drug exposures between different race groups exists and, as a result, the pharmacokinetics (PK) of BMS-791325 and its equipotent N-desmethyl metabolite, BMS-794712, were evaluated in healthy Japanese and Caucasian subjects.

Materials & Methods: This was an open-label, sequential, ascending multiple-dose, phase 1 study (AI443-006) of both the steady-state PK of BMS-791325 and BMS-794712, and the effects of BMS-791325 on the PK of midazolam, in healthy Japanese and Caucasian subjects. For the assessment of BMS-791325 and BMS-794712, 24 Japanese and 24 Caucasian males received oral BMS-791325 twice-daily for 14 days at 75, 150 or 300mg (8 Japanese and 8 Caucasian per group) plus a single AM dose on the 15th day. Blood samples were collected before the AM dose and through 12 hours postdose on day 1 and predose and through 48 hours on dosing day 15. Plasma concentrations of BMS-791325 and BMS-794712 were analyzed using a validated LC-MS/MS assay. Noncompartmental PK parameters were derived. For comparison between Japanese and Caucasian subjects, point estimates and 90% confidence intervals (90%CI) for ratios of geometric means (GMR) for C_{max}, AUC_{tau} and C_{12} at steady-state (day 15) were calculated from linear mixed-effects models on log-transformed data with treatment, race, and treatment-by-race interaction, with and without subject weight as a covariate. Steady-state BMS-791325 dose proportionality was assessed by race and for all subjects.

Results: Two subjects discontinued due to withdrawal of consent (75mg arm) and protocol violation (150mg arm). BMS-791325 was generally well tolerated: all adverse events were mild and there were no adverse event-related discontinuations. Relative to Caucasian subjects, Japanese subjects receiving BMS-791325 demonstrated a higher steady-state BMS-791325 exposure of 29–36% and a higher BMS-794712 exposure of 31–47%. GMR and 90%CI for C_{max}, AUC_{tau} and C_{12} (all treated subjects) were 1.32 (1.14–1.52), 1.32 (1.14–1.53) and 1.32 (1.01–1.73), respectively, for BMS-791325, and 1.36 (1.19–1.56), 1.38 (1.19–1.60) and 1.41 (1.12–1.77) for BMS-794712. When exposure was adjusted for body weight, these racial differences were reduced (90%CI for each parameter GMR crossed 1.0 at all doses). No racial difference in BMS-794712/BMS-791325 metabolite-to-parent ratio was evident at any dose. Exposures to BMS-791325 increased proportionally following twice-daily 75–300mg doses; C_{max} and AUC_{tau} GMR 90%CI crossed 1.0 in both Caucasian and Japanese subjects and across all subjects.

Conclusions: BMS-791325 plasma exposure parameters in healthy Japanese subjects are 29–36% higher for a given dose than in Caucasian subjects; these differences were smaller when adjusted for body weight. BMS-791325 exposures were dose proportional following multiple twice-daily 75–300mg doses. Similar safety and efficacy outcomes observed with both 75mg and 150mg doses of BMS-791325 in HCV clinical studies suggest that these differences are unlikely to be clinically relevant.

Conflict of interest: M AbuTarif, R Bertz, W Li, M Wind-Rotolo and K Sims are employees and shareholders of Bristol-Myers Squibb. J Pursley, K Zhu, Y Ding and B He are employees of Bristol-Myers Squibb. B Rege was an employee of Bristol-Myers Squibb at the time of the study is now employed by Eisai Inc and is a shareholder of Bristol-Myers Squibb and Seattle Genetics.

Abstract: P_52

PK-PD of Drug Efficacy and Toxicity

Expression and localization of ATP-binding cassette (ABC) and solute-carrier (SLC) membrane drug transporters in human testicular tissue

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Background: A major obstacle to the complete eradication of HIV in infected patients is persistent viral infection in both cellular and anatomical reservoirs. Recent studies have suggested that the testis may act as a viral reservoir due in part to low antiretroviral drug permeability across the blood-testis barrier. Our group and others have shown that drug transporters pertaining to the ATP-binding cassette (ABC) superfamily, solute-carrier (SLC) superfamily, as well as drug metabolic enzymes belonging to the cytochrome P450 (CYP450) family can interact with antiretroviral compounds and regulate their tissue distribution. In addition, we have previously reported that drug efflux transporters, P-gp, MRP1, and BCRP, are functionally expressed at the blood-testis barrier in rodent testicular cell culture systems and primary cultures of human testicular tissues. However, the rarity of human testicular samples has led to very few studies demonstrating the expression and localization of drug transporters and drug metabolic enzymes in this tissue. This study aims to investigate the expression and localization of drug transporters and drug metabolic enzymes in the testis of healthy and HIV-infected patients receiving antiretroviral therapy in order to gain further insight on the factors regulating antiretroviral drug disposition in this tissue.

Methods: At this stage**,** eight uninfected patients choosing to undergo elective orchiectomy for transsexual modification at the Metropolitan Centre of Plastic Surgery in Montreal, Canada, have been enrolled. Total RNA was prepared from frozen testicular samples collected from the patients and qPCR was used to assess mRNA expression levels of several key drug transporters and metabolic enzymes. Whole tissue lysates were also extracted and western blot analysis was used to detect protein expression. In addition, sections of testicular tissue from a single uninfected individual were prepared for immunofluorescent staining and laser scanning confocal microscopy was used to identify the localization of selected drug transporters and metabolic enzymes.

Results: mRNA expression levels of ABC transporters, P-gp, MRP1, MRP4 and BCRP, were detected in uninfected testis, while MRP2 expression was very low. SLC transporter OATP2B1 was detected in uninfected testis, while OATP1A2, OATP1B1, and CNT1 were detected at very low levels. All mRNA expression results showed high variability between individuals. Protein expression of ABC

transporters P-gp, MRP1, MRP2, MRP4 and BCRP as well as SLC transporters OATP1B1, OATP2B1 and OAT1 were expressed in all uninfected individuals. Immunofluorescence imaging revealed localization of P-gp, MRP1, MRP2, MRP4, BCRP, OATP1A2, OATP1B1, OATP2B1, OAT1, CNT1 and ENT2 in the seminiferous epithelium. OATP1B1, OATP2B1 and OAT1 also localized in the interstitial tissue.

Conclusions: Our data demonstrate significant interindividual variability in mRNA expression of ABC and SLC drug transporters with robust protein expression of P-gp, MRP1, MRP2, MRP4 and BCRP in uninfected human testicular tissue. We also observed that ABC transporters localized primarily at the seminiferous epithelium, while SLC transporters were distributed throughout the testis. Together these data suggest that drug disposition in testicular tissues can be highly regulated by drug transporters. *(Supported by CIHR)*

No conflict of interest

Abstract: P_53

PK-PD of Drug Efficacy and Toxicity

Asunaprevir does not have an effect on QTCF interval in healthy subjects

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Background: Unanticipated effects of new drugs on cardiac repolarization are a potentially serious safety issue that require careful evaluation. Asunaprevir (ASV)—a selective inhibitor of HCV NS3 protease with activity *in vitro* against genotypes 1, 4, 5 and 6—is currently in phase 3 development as a soft capsule formulation dosed twice daily (BID) at 100 mg with daclatasvir (NS5A inhibitor) ± BMS-791325 (non-nucleoside NS5B polymerase inhibitor) or peginterferon alfa/ribavirin. ASV displays time-dependent pharmacokinetics, with maximum exposure (ME) on Days 2-3 of dosing and steady-state (SS) achieved by Day 10. Clinically significant electrocardiogram (ECG) alterations have not been seen at any dose of ASV studied to date. The ECG effects of a supratherapeutic dose of ASV were evaluated in healthy subjects.

Materials & Methods: This was a randomized, multiple-dose, double-blind, parallel group, placebo-controlled and positive-controlled study in healthy subjects (N=120) with a nested crossover for the placebo and positive control (moxifloxacin [MOX]). Subjects were randomized 2:1:1 to 3 treatment sequences (S1, S2 and S3) to receive on Day 1: ASV-placebo BID (all sequences); Day 2: single-dose MOX 400 mg (S2) or MOX-placebo (S1+S3); Days 3-12: ASV soft capsule 300 mg (S1) or ASV-placebo (S2+S3) BID; Day 13: single-dose MOX 400 mg (S3) or MOX-placebo (S1+S2). Serial, triplicate 12-lead ECG measurements were collected predose and up to 12-hours post-morning dose on Days 1, 2, 5 (ASV ME), 12 (ASV SS) and 13. Placebo-corrected changes from baseline (ΔΔ) and 90% confidence intervals (CIs) for key ECG parameters and the relationship between plasma ASV concentration and ΔQTcF (change in Fridericia-corrected QTc) were estimated using linear mixed-effects models. PK samples were analyzed for ASV using a validated LC/MS/MS method. Noncompartmental PK parameters for Days 5 and 12 were derived. Subjects were monitored for adverse events throughout the study.

Results: No clinically relevant QTcF prolongations were observed following administration of ASV 300 mg BID; all upper-bounds of CIs for ΔΔQTcF were <10 msec. The multiplicity corrected lower-bounds of CIs for moxifloxacin were >5 msec at pre-specified time points (2-4 hours postdose), confirming the assay sensitivity. ASV had no clinically relevant effect on heart rate, QRS interval, PR interval, or waveform morphology. No concentration–response trend was noted in a random coefficient regression model examining ΔQTcF versus ASV concentration. As expected, ASV

concentrations were higher on Day 5 (ME) compared to Day 12 (SS). ASV 300 mg BID was generally well tolerated in this population.

Conclusions: A supratherapeutic ASV dose of 300 mg BID did not have any clinically relevant effect on QTc interval, waveform morphology, or other ECG parameters.

Conflict of interest: Employee and Stockholder of Bristol-Myers Squibb

Abstract: P_54

PK-PD of Drug Efficacy and Toxicity

Thorough QT/QTC trial to evaluate the effect of the HIV-1 attachment inhibitor BMS-626529, administered as its prodrug, BMS-663068, on QTC intervals

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Background: New antiretroviral drugs are needed for treatment-experienced HIV-1-positive patients with limited therapeutic options. BMS-663068 is a prodrug of BMS-626529, an attachment inhibitor that binds directly to HIV-1 gp120, preventing the initial interaction between virus and host cell. This study evaluated the effect of BMS-626529, following BMS-663068 administration, on QT/QTc (QT interval corrected for heart rate [HR]) in healthy adults following the International Conference on Harmonisation E14 guidance for evaluation of non-antiarrhythmic drugs.

Materials & Methods: The study included a sentinel cohort (Part I) and main study (Part II). Part I evaluated the safety, tolerability and pharmacokinetics (PK) of BMS-663068 2400 mg BID to select a supratherapeutic dose for Part II. Part II was a randomized, double-blind, four-period, crossover, placebo-controlled, active-controlled study assessing the effect of the active drug, BMS-626529, on time-matched change from baseline QTc intervals versus placebo, corrected via Fridericia's method (ΔΔQTcF). The effects of BMS-626529 on HR, QRS and PR intervals, and changes in electrocardiogram (ECG) waveforms and relationship between BMS-626529 plasma concentration and ΔΔQTcF were also assessed. Sixty subjects were randomized to four treatment sequences (n=15 per sequence) each comprising four 7-day treatment periods: BMS-663068 1200 mg QD, BMS-663068 2400 mg BID, placebo (Days 1-6) and moxifloxacin 400 mg (Day 7 only), or placebo alone; separated by 10-day washouts. ECGs were collected in triplicate pre-dose and up to 22.25 hours post-dose on Day 7 of each treatment. Physical examinations, vital signs, laboratory evaluations and adverse events (AEs) were monitored during the study. Serial blood samples for PK analysis were collected post-morning-dose on Day 7. The effects of BMS-626529 on ECG-derived endpoints were analyzed using a mixed linear-model to derive differences from placebo. Non-inferiority of BMS-663068 versus placebo was assessed using 10 ms thresholds. Intersection union tests were performed using 90% two-sided CIs for the estimated ΔΔQTcF at each post-dose ECG measurement. Exposure-response relationships between BMS-626529 plasma concentration and ΔΔQTcF utilized random-coefficients mixed linear-models.

Results: In Part I, no dose-limiting AEs or intolerabilities arose with BMS-663068 2400 mg BID. In Part II, administration of BMS-663068 1200 mg QD produced no clinically meaningful effect on QTcF (maximum ΔΔQTcF 90% CI upper limit = 6.34 ms at 6 hours); however, administration of BMS-663068 2400 mg BID for 7 days had a QTcF prolongation (maximum ΔΔQTcF 90% CI upper limit = 13.30 ms at 5 hours). Moxifloxacin effects on ΔΔQTcF confirmed assay sensitivity. Regardless of BMS-663068 dose, BMS-626529 had no meaningful effects on HR, QRS and PR intervals, or ECG waveform morphology. The relationship between BMS-626529 plasma concentration and change in QTcF was statistically significant (P=0.0001).

BMS-663068 1200 mg QD was well tolerated; however, BMS-663068 2400 mg BID was associated with one SAE (headache) and a higher frequency of headache and gastrointestinal AEs.

Conclusions: At a therapeutic dose of BMS-663068 (1200 mg QD), BMS-626529 produced no clinically meaningful effect on QTc interval; however, QTc interval prolongation was observed following BMS-663038 2400 mg BID. BMS-626529 does not affect other ECG-derived endpoints. BMS-663038 was generally well tolerated. These data support continued development of BMS-663068.

Conflict of interest: Dr Savant is an employee of, and holds stock options, in Bristol Myers Squibb

Abstract: P_55

PK-PD of Drug Efficacy and Toxicity

Should the dose of tenofovir be reduced to 200-250mg/day, when combined with protease inhibitors?

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Background: The approved dose of tenofovir disproxil fumarate, 300mg once daily, was established in clinical trials in combination with efavirenz, which does not significantly affect tenofovir concentrations. Combining tenofovir with lopinavir/r, darunavir/r or atazanavir/r increases tenofovir concentrations, which could raise the risk of renal adverse events. Newly approved tenofovir tablets are available at lower strength (200 or 250mg) for use in paediatrics.

Materials & Methods: A literature search was used to assess the effects of lopinavir/r, darunavir/r and atazanvir/r on tenofovir plasma Cmax, AUC and Cmin (Geometric Mean Ratio and 90% confidence intervals). Assuming linear dose-proportional pharmacokinetics (as observed in dose-ranging studies), the 250mg tablet was predicted to achieve plasma concentrations 17% lower than the 300mg dose, and the 200mg tablet to achieve plasma levels 33% lower. Effects on tenofovir plasma Cmax, AUC and Cmin concentrations were assessed for combined dosing of each protease inhibitor with 250 or 200mg daily doses of tenofovir, versus standard dose tenofovir (300mg daily) without protease inhibitors.

Results: In drug-drug interaction studies, lopinavir/ritonavir significantly increased tenofovir Cmax (GMR 1.15 , 95% CI 1.07-1.22), AUC (GMR 1.32, 95% CI 1.25-1.38) and Cmin (GMR 1.51, 95% CI 1.37-1.66). Atazanavir/ritonavir significantly increased tenofovir Cmax (GMR 1.34, 95% CI 1.20-1.51), AUC (GMR 1.37, 95% CI 1.30-1.45) and Cmin (GMR 1.29, 95% CI 1.21-1.36). Darunavir/ritonavir also significantly raised tenofovir Cmax (GMR 1.24, 95% CI 1.08-1.42), AUC (GMR 1.22, 95% CI 1.10-1.35) and Cmin (GMR 1.37, 95% CI 1.19-1.57). Effects of each PI on tenofovir Cmin were greater than effects on Cmax or AUC. Using a 250mg paediatric dose of tenofovir with lopinavir/ritonavir, the tenofovir Cmin was predicted to remain higher than tenofovir 300mg used with efavirenz (GMR =1.26, 95% CI 1.14-1.38). Similar results were observed for use of tenofovir 250mg with atazanavir/ritonavir (GMR 1.07, 95% CI 1.01-1.13) and with darunavir/ritonavir (GMR 1.14, 95% CI 0.99-1.31). Tenofovir AUC levels for the 250mg dose with protease inhibitors were all predicted to be within the bioequivalence range, relative to use with efavirenz. Using a 200mg paediatric dose of tenofovir with lopinavir/ritonavir, the tenofovir Cmin was predicted to be bioequivalent to tenofovir 300mg used with efavirenz (GMR =1.02, 95% CI 0.92-1.11). Similar results were observed for use of tenofovir 200mg with atazanavir/ritonavir (GMR 0.86, 95% CI 0.82-0.91) and with darunavir/ritonavir (GMR 0.92, 95% CI 0.80-1.05). All three results were within the bioequivalence limits of 0.8-1.25. Tenofovir AUC levels for the 200mg dose with protease inhibitors were predicted to be 8-18% lower than for tenofovir 300mg used with efavirenz.

Conclusions: Use of approved paediatric doses of tenofovir (200-250mg once daily) in combination with lopinavir/r,darunavir/r or atazanavir/r could compensate for known drug interactions. This dose modification could potentially lower the risk of tenofovir related renal adverse events, while maintaining consistent levels of efficacy. These potential dose reductions need to be assessed in prospective pharmacokinetic studies, including analysis of intracellular triphosphate concentrations.

Conflict of interest: Andrew Hill has worked as a consultant for Janssen, not connected with this project

Abstract: P_56

Relationship between the early boceprevir-S isomer plasma concentrations and the onset of breakthrough during anti-HCV genotype 1 treatment.

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The standard of care for treatment of HCV-1 is now the association of Ribavirin (RBV) and Peg-Interferon-α (Peg-IFNα) with Direct Acting Antivirals (DAAs, Boceprevir, BOC or Telaprevir, TEL), improving SVR rate. However an emerging issue is viral resistance resulting in virological breakthrough (BT). Resistance phenomenon is usually ascribable to a sub-optimal exposure to antimicrobial drugs: in this work.
We aimed to evaluate the plasma concentrations of the BOC-S isomer (the active one) and of RBV after 2 weeks of triple therapy, evaluating a possible correlation with the onset of BT. 18 patients, previously treated with dual therapy and now re-treated with BOC. have been enrolled. BOC-S isomer and RBV plasma concentrations were determined by validated and previously published methods.

8 patients out of 18 (44.4%) experienced BT. BOC-S plasma concentrations resulted significantly lower (median value was 55 ng/mL; I.Q.R. 44–63 ng/mL; p=0.034) in patients with BT respect to the others (100 ng/mL; I.Q.R. 58–981 ng/mL). Differences in RBV plasma concentrations between these groups did not reach the statistical significance (p=0.101). Moreover, we identified a cut-off value of 65 ng/mL for BOC-S concentration under which there is a higher risk of developing BT (AUROC=0.80, p=0.033; sensibility 87.5%, specificity 70%).

BT resulted to be an issue in the treatment with BOC correlated to the early low plasma exposure to the active isomer of BOC. So, the monitoring of this pharmacokinetic parameter could be a good tool to prevent the occurrence of BT.

No conflict of interest

Abstract: P_58

ARRIBA: Evaluation of a test dose of ribavirin to achieve adequate exposure directly from start of HCV therapy

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Background: Adequate exposure to ribavirin is essential for optimal sustained virological response (SVR) rates in the treatment of chronic hepatitis C virus (HCV) infections. Due to the long elimination half-life of ribavirin, steady-state is not reached before week 8 and therefore interventions based on measuring ribavirin concentrations may come too late. Loustaud-Ratti *et al*. (Hepatology 2008) have proposed that the $AUC_{0\text{-}4h}$ of the first weight-based dose of ribavirin should be ≥1.755 mg.h/L to guarantee the highest chance of SVR. Here, we introduce a new concept (ARRIBA) that takes a test dose of ribavirin to select the optimal starting-dose for each individual HCV infected patient. In this study, we evaluate whether adequate ribavirin concentrations ($AUC_{0\text{-}4h}$ ≥1.755 mg.h/L) can be achieved after a dose advice based on the $AUC_{0\text{-}4h}$ of a single weight-based dose of ribavirin.

Materials & Methods: HCV-treatment experienced patients were selected who had tolerated ribavirin in the past and were either cured or not yet eligible for subsequent HCV treatment. They received a single dose of ribavirin based on body weight (<75kg: 400mg; ≥75kg: 600mg) on day 1 with a standardized breakfast. Seven blood samples were taken to measure plasma ribavirin concentrations and to calculate $AUC_{0\text{-}4h}$. If ribavirin $AUC_{0\text{-}4h}$ was ≥1.755 mg.h/L, subjects received the same dose on day 29. If the $AUC_{0\text{-}4h}$ was <1.755 mg.h/L, an adjusted dose of ribavirin was administered on day 29, based on a predefined algorithm. Blood samples were taken again on day 29 to measure plasma ribavirin concentrations and to calculate $AUC_{0\text{-}4h}$.
The primary outcome was the proportion of subjects with an $AUC_{0\text{-}4h}$ ≥1.755 mg.h/L after the second dose. With a planned sample size of 50 subjects we would have sufficient power to demonstrate an increase in the proportion of subjects with an adequate AUC from 50 to 75%.

Results: We present the data from a planned interim analysis after approximately 50% of the patients were enrolled. 26 patients (17 males) completed both pharmacokinetic days. Median (+range) age and BMI were 50 (20-70) years and 23 (18-35) kg/m^2, respectively. All subjects were Caucasian. Twelve subjects received an initial dose of 400 mg and 14 subjects received 600 mg on Day 1.The geometric mean (95% CI) $AUC_{0\text{-}4h}$ of ribavirin on day 1 was 1.67 (1.44-1.92) mg.h/L with only 9 out of 26 (35%) subjects reaching the AUC target. At day 29, 17 subjects (65%) received an adjusted dose of ribavirin, ranging from 600 to 1200mg. At day 29 the geometric mean (95% CI) $AUC_{0\text{-}4h}$ increased to 1.90 (1.62-2.21) mg.h/L and now 16 subjects (62%) had an $AUC_{0\text{-}4h}$ ≥ 1.755 mg.h/L, which is significantly higher than day 1 ($p<0.05$, McNemar). From the subjects with a dose intervention, 7 (41%) had an adequate $AUC_{0\text{-}4h}$ at day 29.

Conclusions: Our ARRIBA concept of a test dose of ribavirin leads to an increased proportion of patients with an adequate AUC vs. the traditional weight-based dose of ribavirin: 62% vs. 35%. As there still remains a significant proportion of patients underdosed, alternative dosing algorithms should be explored.

Conflict of interest: Supported in part by a research grant from Roche

Abstract: P_59

Impact of demographic and therapeutic factors on Rilpivirine plasma concentrations after oral administration in HIV-infected patient

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Background: Rilpivirine (RPV) is a Non Nucleotide Reverse Transcriptase Inhibitor (NNRTI) used for the treatment of HIV-1

infections in combination with NRTI. Previous study has shown accumulation of other NNRTIs (nevirapine and efavirenz) in adipose tissue due to their physicochemical properties. Indeed, RPV is a diarylpyrimidine, with a low molecular weight (366g/mol), high lipophilicity (logP=4.86) and long half-life ($T_{1/2}$=51 hours), conferring a high affinity to adipose tissue. Repartition of adipose tissue can be differed between gender, ethnicity and age, and may affect the RPV disposition. Indeed, clinical trials ECHO and THRIVE have shown a significant effect of gender and ethnicity on RPV plasma pharmacokinetic, attributed by difference of oral clearance, with probable low clinical relevance. Another pharmacokinetic study of long-acting RPV after subcutaneous administration, have shown a significant correlation between RPV AUC and gender and body mass index (BMI).
The aim of this study is to identify parameters which can affect RPV plasma concentration 24 hours (RPV C24h) after the last oral intake: gender, ethnicity, age, weight, BMI and previous treatment. A second objective is to correlate BMI modification and duration of RPV treatment.

Materials & Methods: multicenter, retrospective study conducted between 2012 and 2014. The main inclusion criteria were: availability of RPV C24h from 2 to 5 months after treatment initiation, plasma viral load<50 copies/mL, demographic and therapeutic data. Transgender were excluded. Written informed consent was obtained from all participants. RPV C24h was measured by UPLC-MS/MS (Waters® Acquity UPLC/Waters® Acquity TQD System). Statistical analyses were made with StatView® (Abacus Concepts, Berkley, California, USA).

Results: On the 83 enrolled HIV-1 infected patients, 34 were women, 31 Caucasian, 44 African and 8 Hispanic. For those patients, median age was 47 (IQR25-75%: 40-55 years), weight 73kg (64-84) and BMI 24.69kg/m² (22.63-27.93). Among them, 8 patients had stopped RPV, 5 for virological failure, 2 for adverse events (neurotoxicity and digestive intolerance) and 1 for deleterious drug-drug interactions. RPV was prescribed in 6 patients in initiation, 43 in switch from protease inhibitors, 27 from NNRTIs and 7 from others: anti-integrase, NRTIs or combination. In this study, median RPV C24h was 89ng/ml (55-149) and 17 patients had RPV C24h<50 ng/mL (efficacy threshold) and 9 with RPV C24h$\geq$ 200 ng/mL (toxicity risk threshold). RPV C24h was not statistically related with gender, ethnicity, weight and previous treatment. However, RPV C24h was significantly related with age ($p \simeq 0.03$) and BMI ($p \simeq 0.04$). Besides, higher BMI was not related to duration of RPV treatment.

Conclusions: Steady-state RPV C24h is not influenced by demographic parameters (as gender, ethnicity, and weight) and previous treatment after switch. Influence of BMI and age on RPV C24h are in accordance with results found in long-acting formulation. Based on these results, such study might be conducted in obese patients (BMI$\geq$30 kg/m²). In conclusion, RPV can be orally administered without discrimination of gender, race, age, weight, BMI and previous treatment.

No conflict of interest