



Reviews

in Antiviral Therapy
INFECTIOUS DISEASES

4
2015

JOURNAL OF ABSTRACTS AND CONFERENCE REPORTS FROM INTERNATIONAL WORKSHOPS ON INFECTIOUS DISEASES & ANTIVIRAL THERAPY

Abstract Book

16th International Workshop on Clinical Pharmacology of
HIV & Hepatitis Therapy

26 - 28 May 2015, Washington, DC, USA

16th International Workshop on Clinical Pharmacology of HIV & Hepatitis Therapy

26 – 28 May 2015, Washington, DC, USA

Abstracts Oral Presentations

Abstract: 1*Session 1***Sensitivity of liver function classification systems for exposure changes***I. Younis¹*

¹US Food and Drug Administration, Office of Clinical Pharmacology Office of Translational Sciences CDER, Silver Spring, USA

Background: Assessment of liver function in pharmacokinetic studies in subjects with hepatic impairment has generally been conducted using the Child-Pugh classification criteria (CPC). Other static methods have been developed such as NCI criteria (NCI), model for end stage liver disease (MELD), and Maddrey discriminant function (MDF). This work compares the sensitivity of these 4 systems to detect exposure changes in subjects with hepatic impairment.

Materials & Methods: A database of individual level data from pharmacokinetics studies in subjects with hepatic impairment was constructed. Data collected included demographics, PK parameters (AUC, C_{max}, CL, t_{1/2}, protein binding), medical history, and laboratory measurements (hematology and biochemistry). Liver function was originally classified in these studies using CPC. To conduct the comparison, subjects were also classified using NCI, MELD, and MDF.

Results: The database contains data from 65 hepatic impairment studies with a total of 1841 subjects. The number of subjects (based on CPC) in the normal, mild, moderate, and severe hepatic impairment groups was 692, 351, 512, and 286 respectively. When CPC was used the probability of observing AUC ratio (hepatic impairment/ normal) ≥ 2 was 0.1, 0.24, and 0.35 in the mild, moderate, and severe hepatic impairment groups respectively. The average AUC ratio increased with increasing CPC score. When NCI was used the probability of observing AUC ratio (hepatic impairment/ normal) ≥ 2 was 0.14, 0.24, 0.36, and 0.46 in the mild group 1, mild group 2, moderate, and severe hepatic impairment arms. When

MELD was used the probability of observing AUC ratio (hepatic impairment/ normal) ≥ 2 was 0.33 for MELD score > 10 . Linear regression of AUC ratios vs MELD score produced a significant slope ($p < 0.0001$, $R^2=0.11$). Linear regression of AUC ratios vs MDF score produced a significant slope ($p < 0.0001$, $R^2=0.02$)

Conclusions: All of the four liver function classification systems showed sensitivity to measure exposure changes in subjects with hepatic impairment. The NCI criteria appear to be a more robust system for detecting exposure changes. Further adjudication of cases where exposure changes as a function of liver impairment were not observed is warranted. In addition, ways to improve the ability of the various liver impairment classification systems to detect exposure changes is needed.

No conflict of interest

Abstract: 2*Session 1***Evaluation of PK/PD Relationships between Ribavirin and Sustained Virologic Response in HCV-Genotype 3 Infected Subjects in the Sovaldi® Phase 3 Program**

B. Kirby¹, L. Ni², N. Bekele², D.M. Brainard³, B.P. Kearney¹, A. Mathias¹

¹Gilead Sciences, Clinical Pharmacology, Foster City, USA;

²Gilead Sciences, Biometrics, Foster City, USA; ³Gilead Sciences, Clinical Research, Foster City, USA

Background: Sofosbuvir (SOF; Sovaldi®), a potent, once-daily, orally administered nucleotide analog prodrug inhibitor of the HCV NS5B polymerase is approved in the US, EU, Canada and other regions for the treatment of HCV infection as a component of an antiviral regimen. Within the Phase 3 registrational program, sustained virologic response (SVR12) rates in subjects infected with genotype 3 (GT3) HCV were lower than in GT 2 subjects receiving administered SOF 400 mg + weight based ribavirin (1000 or 1200 mg/day) for 12 or 16 weeks. In GT2 subjects, no associations between SVR rates and clinical factors or drug exposure metrics were noted. Regression analyses in GT3 subjects indicated that treatment duration was the primary driver of efficacy with variable associations between SVR12 and prior treatment experience, sex, cirrhosis, weight-adjusted RBV dose (mg/kg) or exposure of the primary metabolite of sofosbuvir (GS-331007). We performed additional PK/PD analyses to evaluate the contribution of RBV exposure, measured as AUC, on SVR12 rate.

Materials & Methods: HCV GT3-infected subjects (n=388) enrolled in the POSITRON, FISSION, and FUSION trials with available RBV plasma concentration data were included in this analysis. Steady-state RBV AUC was estimated utilizing a previously published RBV population PK model. Average daily RBV AUC was

calculated for each subject based on individual considerations of dose modifications/interruptions, and utilized in the further analyses. Univariate analyses evaluated the SVR12 rate observed across population quartiles of RBV AUC for all subjects, and by subgroups including treatment duration and presence of cirrhosis. Multivariate logistic regression evaluated the relationship between SVR12 and various clinical factors including treatment duration, sex, prior treatment experience, cirrhosis, GS-331007 exposure (primary metabolite of sofosbuvir), and RBV exposure.

Results: Mean (CV%) daily RBV AUC was 63.3 ug*h/mL (34.1%) with a range of 5.31 to 186 ug*h/mL. Univariate regression analyses indicated that increased RBV exposure was associated with increased SVR12 rate in GT3 infected subjects, irrespective of treatment duration (12 or 16 weeks) and presence of cirrhosis. Multivariate regression indicated that treatment duration, prior treatment experience, RBV AUC, cirrhosis and sex were statistically significant predictors of SVR12 whereas GS-331007 AUC was not. The influence of RBV AUC changing from the 25th to 75th percentile (54.0 – 80.0 ug*h/mL) equated to an Odds Ratio of ~2.0, whereas the Odds Ratio for longer treatment duration (16 vs. 12 weeks) was ~4.8.

Conclusions: These regression analyses indicate that in addition to treatment duration, RBV systemic exposure was a significant predictor of efficacy in GT 3 HCV infected subjects administered SOF+RBV for 12 or 16 weeks. SVR12 rates are notably higher with 24 weeks of SOF+RBV in GT3 HCV infected subjects and the impact of RBV exposure with this regimen is currently unknown.

Conflict of interest; All authors are employees of and own stock in Gilead Sciences Inc.

Abstract: 3*Session 1***Population viral kinetic modeling: SVR prediction in HCV GT-3 cirrhotic patients with 24 weeks of Daclatasvir + Sofosbuvir administration**

E. Tafoya¹, Y. Lu¹, M. Luo¹, P. Narasimhan¹, N. Thanneer¹, B. Cirincione¹, T. Eley¹, N. Zhou¹, D. Hernandez¹, F. McPhee¹, T. Leil¹

¹Bristol-Myers Squibb, Research and Development, Princeton, USA

Background: Effective treatments for Hepatitis C virus (HCV) genotype (GT) 3 remains a significant unmet medical need, especially given emerging data showing increased rates of liver cancer and liver decompensation in patients infected with this genotype compared to other HCV genotypes. In the ALLY-3 Phase 3 study (Study AI444218; 12 weeks of Daclatasvir (DCV) + Sofosbuvir (SOF) in HCV GT-3 chronically infected patients), a subgroup analysis showed a lower sustained virologic response rate at 12 weeks after completion of therapy (SVR12) in cirrhotic (63 %) vs. non-cirrhotic (96 %) patients. HCV GT-3 cirrhotic patients may benefit from longer treatment duration without RBV. This was explored by using population viral kinetic (PVK) modeling to replicate the response with 12 weeks of DCV+SOF with the aim of providing a mechanistic interpretation of the observed SVR12, and to predict SVR12 and sustained virologic response at 24 weeks after completion of therapy (SVR24) rates for 24 weeks of DCV+SOF treatment.

Materials & Methods: The PVK model in treated patients was characterized by a competition between a drug-susceptible strain and a drug-resistant strain in an HCV two-strain model. The drug-resistant strain was defined as the most significantly resistant variant identified by population-based sequencing data of HCV RNA for each treated subject in AI444218 (N=152 Subjects) and resistance profiles established by

using cell-based HCV replicon assays. The replication capacity of the each patient's resistant strain and their cirrhosis status were included in the PVK model as covariate effects. The PVK model was fitted to HCV RNA plasma concentration records in AI444218 (N=1608 records). A Markov chain Monte Carlo (MCMC) Bayesian Laplacian algorithm in NONMEM version 7.2 was used for model development. Prior information on the drug-independent model parameters and drug effectiveness were determined based on prior PVK model data. To evaluate the quality of the predictions relative to the observed data from Study AI444218, a visual predictive check (VPC) of VK during and after treatment was conducted by generating predictions from the posterior samples of the MCMC Bayesian estimation. Stochastic simulation using the posterior MCMC Bayesian samples was performed to evaluate SVR12 and SVR24 rates in GT-3 cirrhotic and non-cirrhotic subjects with 12 and 24 weeks of DCV+SOF administration.

Results: The predictions of SVR12 and SVR24 rates following 12 weeks of treatment were comparable to those observed in the cirrhotic and non-cirrhotic GT-3 sub-populations studied in Study AI444218 (median SVR12 rate: 63 % (observed) and 59 % (simulated)). Furthermore, the predictions demonstrated no clear benefit of increased treatment duration on SVR12 and SVR24 rates in non-cirrhotic subjects. However, SVR12 and SVR24 rates were predicted to rise from 63 % to 89% in GT-3 cirrhotic patients with 24 weeks of treatment.

Conclusions: A mechanistic PVK model was used to effectively characterize the 12 week DCV+SOF treatment efficacy data, and to predict the efficacy of 24 weeks of therapy in GT-3 cirrhotic and non-cirrhotic patients. This PVK approach supports 24 weeks of DCV+SOF without ribavirin for HCV GT-3 cirrhotic patients, a population with high unmet medical need.

No conflict of interest

Abstract: 4*Session 1***Physiologically based pharmacokinetic model to predict drug-drug interaction in patients receiving antiretroviral and antineoplastic therapies**

J. Moltó¹, R. Rajol², D. Back², M. Valle³, A. Owen², B. Clotet⁴, M. Siccardi²

¹Hospital Universitari Germans Trias i Pujol, Fundació Lluita contra la Sida, Badalona, Spain; ²University of Liverpool, Department of Molecular and Clinical Pharmacology, Liverpool, United Kingdom; ³Institut de Recerca HSCSP-IIB St Pau, PKPD Modeling and Simulation, Barcelona, Spain; ⁴Hospital Universitari Germans Trias i Pujol Badalona, Institut de Recerca de la Sida IrsiCaixa, Badalona, Spain

Background: The co-administration of antineoplastic regimens with antiretrovirals in HIV-infected patients is challenging since several antineoplastic agents are implicated in drug-drug interactions (DDIs). However, specific clinical trials assessing such DDIs are difficult to conduct. Erlotinib (ERL) and gefitinib (GEF) are two drugs used to treat patients with non-small cell lung cancer. ERL is usually dosed at its maximum tolerated dose (MTD) while GEF is dosed at one third of its MTD. Both, ERL and GEF are metabolized by CYP3A4, implicated in many DDIs with antiretroviral drugs. The objective of this study was to simulate the interaction between ERL or GEF with ritonavir (RTV), efavirenz (EFV) and etravirine (ETR) and to predict dose adjustments using a physiologically based pharmacokinetic (PBPK) model.

Materials & Methods: *In vitro* data describing chemical properties, absorption, distribution, metabolism and elimination (ADME) of ERL, GEF, RTV, EFV and ETR, as well as the effect of RTV, EFV or ETR on CYP3A4 activity were obtained from the literature. Steady state drug concentrations in plasma were simulated in a virtual population of 50 individuals receiving ERL 150mg QD or GEF 250 mg QD alone or with RTV 100mg QD, EFV 600 mg QD, or ETR 200 mg BID.

ERL and GEF AUC₀₋₂₄ and C_{max} with and without the antiretrovirals were compared by using the geometric mean ratio and its 90% confidence interval (GMR, 90% CI). Additionally, different dose-adjustment strategies were evaluated. Simulations were performed using a PBPK model using Simbiology (Matlab, version R2013b). Simulated pharmacokinetic parameters as well as the magnitude of the induction or the inhibition of CYP3A4 by EFV, ETR or RTV were compared with literature values.

Results: The simulated parameters of each drug given separately were in agreement with literature reference values. The GMR (90%CI) for ERL AUC₀₋₂₄ with antiretroviral drugs relative to ERL 150mg QD alone was 4.53 (4.11-4.99) for RTV, 0.85 (0.76-0.95) for EFV, and 0.40 (0.37-0.44) for ETR. Similarly, the GMR (90%CI) for GEF AUC₀₋₂₄ with antiretrovirals relative to GEF 250mg QD alone was 3.85 (3.62-4.09) for RTV, 0.67 (0.60-0.75) for EFV, and 0.46 (0.42-0.51) for ETR. Based on these predictions, dose-adjustment strategies may consist of dosing ERL at 25 mg QD with RTV, 200 mg QD with EFV, or 300 mg QD with ETR, and dosing GEF at 125 mg QD with RTV or 500 mg QD with either EFV or ETR.

Conclusion: PBPK models predicted the *in vivo* pharmacokinetics of the antineoplastic ERL and GEF, the antiretrovirals RTV, EFV, ETR, and drug-drug interactions between them. The simulated dose-adjustments may represent valuable strategies to optimise antineoplastic therapy in HIV patients receiving these key antiretrovirals.

No conflict of interest

Abstract: 5*Session 1***Doravirine Efficacy Exposure-Response Analysis at Week 48 and Implications**

K. Yee¹, X. Xu², H. Teppler³

¹Merck & Co., Pharmacokinetics Pharmacodynamics and Drug Metabolism, Kenilworth, USA; ²Merck, BARDS, Kenilworth, USA; ³Merck & Co., Clinical Research, Kenilworth, USA

Background: Doravirine is a novel, once-daily, non-nucleoside reverse transcriptase inhibitor (NNRTI) being developed for treatment of human immunodeficiency virus -1 (HIV-1) infection in combination with other antiretroviral therapy (ART). Doravirine is a potent inhibitor *in vitro* of HIV-1 Wild-Type (WT) virus and K103N, Y181C, and K103N/Y181C mutant viruses. In a Phase 2 trial in combination with TRUVADA, doravirine has been shown to be efficacious in treating ART-naïve HIV-1 infected patients over the investigated 25 mg-200 mg dose range as compared with efavirenz at Week 48. The pharmacokinetics (PK) of doravirine were characterized in this trial based on sparsely sampled plasma concentrations and population PK modeling. Exposure-response (ER) relationships were explored based on efficacy results at Week 48.

Materials & Methods: Part 1 of a 2-part dose-ranging study examined the safety, tolerability, PK, and efficacy of 4 doses of doravirine (25, 50, 100, and 200 mg qd) vs. efavirenz (600 mg qhs), each administered with TRUVADA. Sparse doravirine PK data, available from 167 of 208 pts enrolled, were pooled with densely sampled Phase 1 PK data in a population PK model to obtain individual post hoc estimates of steady state PK parameters. Individual steady state PK estimates and Week 48 viral RNA (vRNA) results were matched and PK/PD trends were explored graphically. Additionally, individual Ctrough estimates were binned into equal-sized groups and plotted against the proportion of patients in each bin with undetectable vRNA levels.

Results: No correlation between doravirine Ctrough, AUC0-24, or Cmax and Week 48 vRNA was observed. There was also no difference in exposure-response trends for vRNA data stratified by baseline vRNA (< vs ≥100,000 c/mL). No trends between doravirine PK parameters and the proportion of patients with undetectable vRNA levels were observed over a wide range of PK values achieved with once daily doses of 25 to 200 mg. To examine the influence of both Ctrough and baseline viral load on the antiviral response, steady state Ctrough was plotted against baseline vRNA, with different symbols representing if a patient did or did not achieve undetectable vRNA levels at Week 48. The distribution of patients with undetectable viral loads suggest no trend between achievement of undetectable vRNA and steady state Ctrough irrespective of baseline viral load. Overall, there is no evidence of an exposure-response relationship for vRNA viral load or the proportion of subjects achieving undetectable vRNA at Week 48.

Conclusions: The lack of an exposure-response relationship between doravirine plasma levels and both vRNA and the proportion of subjects with undetectable vRNA levels at Week 48, regardless of baseline viral load stratification, indicates attainment of a plateau over the dose range 25 – 200 mg QD evaluated in this Phase 2 trial. Based on the overall benefit-risk assessment, which includes consideration of potential drug interactions, activity against common mutant HIV-1 strains, and forgiveness of missed doses, these data support the selection of 100 mg QD for evaluation in Phase 3 trials.

Conflict of interest: Employee of Merck.

Abstract: 6*Session 2***The pharmacokinetics of tenofovir and tenofovir diphosphate following administration of tenofovir alafenamide versus tenofovir disoproxil fumarate**

J. Custodio¹, W. Garner², C. Callebaut³, M. Fordyce⁴, A. Plummer⁵, L. Zhong², M. Miller³, S. McCallister⁴, B. Kearney¹, J. Zack¹

¹Gilead Sciences, Clinical Pharmacology, Foster City, USA;

²Gilead Sciences, Biometrics, Foster City, USA; ³Gilead Sciences, Clinical Virology, Foster City, USA; ⁴Gilead Sciences, Clinical Research, Foster City, USA; ⁵Gilead Sciences, Clinical Operations, Foster City, USA

Introduction: Tenofovir alafenamide (TAF) is an investigational prodrug of tenofovir (TFV) with distinct metabolism designed to maximize antiviral potency and clinical safety. Compared to tenofovir disoproxil fumarate (TDF 300 mg; Viread®), which is a preferred NtRTI but is associated with renal and bone toxicity, TAF is more stable in plasma, has a lower dose, provides higher intracellular levels of the active moiety tenofovir-diphosphate (TFV-DP), and has lower circulating tenofovir (TFV). TAF 10 mg has been coformulated into a single tablet regimen containing elvitegravir 150 mg (EVG, E), cobicistat 150 mg (COBI, C) and emtricitabine 200 mg (FTC, F) (E/C/F/TAF), which provides TAF exposure comparable to TAF 25 mg single agent due to intestinal Pgp inhibition by COBI. The pharmacokinetics (PK) of plasma TFV and intracellular TFV-DP in peripheral blood mononuclear cell (PBMC) was compared in subjects receiving either E/C/F/TAF or the approved E/C/F/TDF (Stribild®, STB).

Materials & Methods: Intensive steady state substudy data was pooled from one Phase 2 and two Phase 3 randomized, double-blind, multi-site studies evaluating the safety and efficacy of E/C/F/TAF vs STB in antiretroviral treatment-naïve adult subjects. Fifty-five subjects in the

E/C/F/TAF group and 36 subjects in the STB group participated in the plasma PK substudy; 31/55 of those on E/C/F/TAF and 19/36 of those on STB participated in the PBMC PK substudy at sites equipped for PBMC processing. Bioanalysis of plasma and PBMC PK samples was conducted by QPS (Newark, DE, USA) and the PK parameters of plasma TFV and intracellular PBMC TFV-DP were determined via WinNonLin v6.3 (Pharsight, Mountain View, CA, USA). Statistical comparisons of TFV and TFV-DP exposure were made using geometric mean ratios (GMR) and associated 90% confidence intervals (CI) with E/C/F/TAF serving as the test treatment and STB serving as the reference treatment.

Results: Plasma TFV exposure (AUC_{tau}) following once daily administration of E/C/F/TAF was 91% lower than the TFV exposure observed following once daily administration of STB (GMR (90% CI) TFV AUC_{tau} : 8.90 (8.20, 9.65)). Conversely, the intracellular PBMC TFV-DP exposure (AUC_{tau}) was 4.4-fold higher in subjects receiving E/C/F/TAF, relative to subjects receiving STB (GMR (90% CI) TFV-DP AUC_{tau} : 437 (286, 669)). These data are consistent with the proof of concept study in HIV-infected subjects, which demonstrated reduced systemic TFV exposure (~86% lower) and higher intracellular TFV-DP concentrations (5-7-fold higher) following 10 day monotherapy of TAF 25 mg vs TDF 300 mg.

Conclusions: Administration of E/C/F/TAF resulted in substantially lower plasma TFV with markedly higher intracellular TFV-DP concentrations relative to STB. The lower plasma TFV exposures from E/C/F/TAF versus STB or other TDF-containing regimens may potentially reduce off-target effects associated with TFV, in particular renal and bone toxicity. Additionally, the higher intracellular concentrations from E/C/F/TAF versus STB demonstrate stable and effective loading of the active moiety TFV-DP into the target cells by TAF.

Conflict of interest :Authors are employees and shareholders of Gilead Sciences.

Abstract: 7*Session 2***Microboosting of atazanavir 300 mg with 50 mg versus 100mg of ritonavir daily in HIV-infected patients**

P. Giguère¹, C. la Porte², J. Angel³, G. Zhang², I. Seguin², E. Sabri⁴, D.W. Cameron³

¹The Ottawa Hospital, Pharmacy Department, Ottawa, Canada; ²Ottawa Hospital Research Institute, Clinical Investigational Unit, Ottawa, Canada; ³University of Ottawa, Faculty of Medicine, Ottawa, Canada; ⁴Ottawa Hospital Research Institute, Clinical Epidemiology Unit, Ottawa, Canada

Background: Ritonavir (RTV) is used as a pharmacokinetic enhancer with protease inhibitors. Even at low dose, RTV may be associated with gastrointestinal intolerance and metabolic toxicities. The optimal boosting dose of RTV has not been well characterized. Some reports using RTV at doses of 50mg dose with saquinavir and atazanavir, have shown similar boosting effect than conventional dosing. In this study, we hypothesized that 50mg of RTV (one-half of a RTV tablet) would provide similar atazanavir exposure than 100mg.

Materials & Methods: This was an open-label multiple dose, 2-period pharmacokinetic study looking at the differences in ATV and RTV exposure between ATVr 300/100mg and 300/50mg once daily. Participants were HIV positive adults, stable on ATVr 300/100mg with a viral load < 40 copies/mL. Use of acid reducing agents and known CYP inducers/inhibitors were excluded. During the first period, participants took ATVr 300/100mg in AM with a standardized meal for 7 days. Serial pharmacokinetic sampling was performed 10 minutes before and at 1, 2, 3, 4, 6, 8, 10 and 24 hours after drug dosing. Thereafter, participants took ATVr 300/50 (1/2 tab of 100mg RTV) and after 7 days, the same pharmacokinetic sampling were performed. Ritonavir and atazanavir pharmacokinetic concentrations were quantified using a validated HPLC tandem mass spectrometry method. Pharmacokinetic

parameters (AUC, Cmax, C24) were calculated using non compartmental pharmacokinetic analysis. Following calculation of the geometric mean ratio (GMR) and 90% confidence intervals, the classical bioequivalence approach with boundaries of 0.80 to 1.25 was used. Changes in total cholesterol, LDL-C, HDL-C, triglycerides and total bilirubin were assessed using wilcoxon signed-rank test.

Results: The study included 12 adults, of whom 9 were male and 3 were black. Median (interquartile range) age, weight, and BMI were 50 (44-59) years old, 78 kg (70-96) and 25.5 kg/m² (23.8-32.6) respectively. All patients had an undetectable viral load and the median CD4 count was 507. No patients were HBV or HCV co-infected. Five patients were on tenofovir-based regimen. ATV GMR (90% CI) of ATVr 300/50 over 300/100 were: 0.905 (0.724, 1.132) for AUC, 0.968 (0.765, 1.1225) for Cmax, 0.717 (0.537, 0.957) for Cmin. For RTV, GMR (90% CI) were 0.359 (0.307, 0.421) for AUC, 0.380 (0.311, 0.465) for Cmax and 0.429 (0.339, 0.543) for Cmin. Three patients had ATV Cmin below 0.15 mg/L while on the lower dose of RTV. No patients experienced virological failure. No clinical nor statistical differences in lipids or total bilirubin were noted between the 2 groups.

Conclusion: This is the first study looking at reduced dosage of RTV with atazanavir in HIV-infected patients. Consistent with previous report in healthy volunteers, ATV exposure was marginally reduced when co-administered with 50mg of RTV compared to 100mg. However, this study failed to show bioequivalence due to high interpatient variability. No metabolic benefits were observed likely due to the small sample size and short duration of the study. A clinical study is warranted to confirm the clinical efficacy and safety of this new treatment strategy.

Conflict of interest: Study sponsored by Bristol-Myers Squibb (A1424-979)

Abstract: 8*Session 3***Pharmacokinetics of GS-331007 Triphosphate in Red Blood Cells in HCV-infected Subjects Receiving Sofosbuvir plus Ribavirin in the SPARE trial**

J.E. Rower¹, E.G. Meissner², L.C. Jimmerson¹, Z. Sims³, L.R. Bushman¹, S. Kottlil³, J.J. Kiser¹

¹University of Colorado Denver, Skaggs School of Pharmacy and Pharmaceutical Sciences, Aurora, USA; ²Medical University of South Carolina, Infectious Diseases, Charleston, USA; ³National Institutes of Health, National Institute of Allergy and Infectious Diseases, Bethesda, USA

Background: Sofosbuvir (SOF), an inhibitor of the hepatitis C virus (HCV) NS5B polymerase, is a uridine nucleotide analog pro-drug. In cells, SOF is metabolized by host enzymes to the pharmacologically active GS-331007 (007) triphosphate (TP). We previously described 007-phosphate pharmacology in peripheral blood mononuclear cells (PBMC) in 45 patients receiving various SOF-based HCV treatments and identified a median 007-TP concentration of 859 fmol/10⁶ cells and a half-life of 26 hours. The objectives of the current study were to determine 007-TP concentrations in red blood cells (RBC), to examine the association between clinical covariates and 007-TP concentrations, and to evaluate relationships between 007-TP concentrations and sustained virologic response (SVR24).

Materials & Methods: HCV infected genotype 1 subjects received 400mg SOF plus either low-dose (600mg daily) or weight-based (1000 or 1200mg daily) ribavirin (RBV) for 24 weeks as part of the NIH/NIAID SPARE trial. 007-TP concentrations were determined on day 3, and weeks 4, 12, and 24 of treatment using a validated LC-MS/MS assay linear from 50-50000 fmol/sample. The effect of clinical covariates on 007-TP was investigated using linear regression. A one compartment population PK model [NONMEM v7.2] was used to determine 007-TP

elimination rate and to evaluate its association with clinical covariates. The association between 007-TP and SVR24 was assessed using both univariate and multivariable regression.

Results: 180 RBC samples were obtained from 47 subjects: 32 males, 37 African-Americans, 14 with an HAI fibrosis score of ≥ 3 , and 22 receiving low-dose RBV. 29 of the 47 subjects (62%) achieved SVR24. Median (range) 007-TP concentrations in RBC at day 3, weeks 4, 12 and 24 were 1.44 (0.53, 18.3), 2.43 (0.25, 5.84), 2.91 (1.14, 10.4), and 2.50 (0.39, 18.4) fmol/10⁶ cells, respectively. Week 12 (steady-state) 007-TP were univariately associated with sex (42% lower in men, $p=0.005$) and RBC RBV-TP concentrations (1.3 fmol/10⁶ cells increase per 100 pmol/10⁶ cells RBV-TP, $p=0.04$). Modeled accumulation phase data suggested a 69 hour (95%CI: 64-75) half-life for 007-TP in RBC. No clinical covariates had a significant impact on modeled 007-TP elimination rate. Higher 007-TP trended towards an association with SVR24 at day 3 and week 24 ($p=0.17$ and $p=0.13$, respectively) but baseline HCV RNA $<800,000$ ($p=0.03$), female sex ($p=0.05$), and fibrosis stage ≤ 2 ($p=0.07$) were stronger univariate predictors of SVR24. The trend for an association between 007-TP and SVR24 remained when controlling for these covariates in a multivariable model, but only fibrosis ($p=0.04$) and baseline HCV-RNA ($p=0.02$) were statistically predictive of SVR24.

Conclusions: Compared to 007-TP pharmacology in PBMC, which we previously defined in another patient cohort, 007-TP concentrations in RBC were ~ 300 -fold lower, but longer lived (69 vs. 26 hours). These data demonstrate cell-specific differences in the uptake and/or phosphorylation of SOF *in vivo*. More work is needed to define 007-TP concentrations in various cell types and to determine any clinical implications of the sex and RBV-TP associations with RBC 007-TP. A trend was identified between 007-TP and SVR24 suggesting additional study of this association may be warranted.

No conflict of interest

Abstract: 9*Session 3***HIV-1 Attachment Inhibitor Prodrug BMS-663068: Exposure-Response Modeling in Predicting QTcF Interval Prolongation for Quantitative Dose Selection for the Phase 3 Program**

J. Landry¹, M. Luo¹, D.W. Boulton¹, M. Abutarif¹

¹Bristol-Myers Squibb, Clinical Pharmacology, Princeton NJ, USA

Background: BMS-663068 is an oral prodrug of BMS-626529, a first in class attachment inhibitor that binds to HIV-1 gp120, preventing initial viral attachment and entry into host CD4+ T-cells. The effects of BMS-663068 on ECG parameters were evaluated in a multiple dose thorough QT (tQT) study (AI438016), that showed the potential for BMS-626529 to prolong the QTcF interval at a supratherapeutic dose (2400 mg BID) but not a therapeutic dose (1200mg QD). BMS-663068 is not quantifiable in human plasma after oral dosing. BMS-663068 may be used with ritonavir (RTV)-boosted protease inhibitors in heavily treatment experienced patients. Ritonavir increases the C_{max} of BMS-626529 by 31-79%. Based on the observed dose-response (HIV-1 viral load) relationship from the Phase 2b(AI438011) study, two dosing regimens, 1200 mg QD and 600 mg BID, were further evaluated for dose selection prior to Phase 3 study. The objective of this analysis was to characterize BMS-626529 systemic exposure versus QTcF interval changes using the data from AI438016 study and then use this model-based analysis to predict QTc F effects of the two potential BMS-663068 Phase 3 doses (1200 mg QD; 600 mg BID) when administered with RTV.

Materials & Methods: Several models were explored to fit the BMS-626529 systemic exposure and placebo and time-match QTcF ($\Delta\Delta\text{QTcF}$) data including linear, direct response and indirect response sigmoid E_{max} models with

and without Hill coefficients. The models were specified in terms of fixed (either Kin, Kout, E_{max}, EC₅₀, Hill Coefficient and E₀) and random-effect parameters that were estimated by nonlinear regression using NONMEM software. The final model was evaluated by visual predictive check (VPC) comparing the 90% confidence intervals for the 5th, 50th and 95th percentiles of the prediction intervals to the observed data from the two doses from the tQT study. The relative risk of $\Delta\Delta\text{QTcF}$ prolongation of 600 mg BID and 1200 mg QD with and without RTV were evaluated using simulations of 1000 trials using final model estimates.

Results: The concentration-response relationships for the $\Delta\Delta\text{QTcF}$ effects for BMS-626529 were best described using indirect response sigmoid E_{max} with Hill coefficient with additive error model and -first order conditional estimation with interaction (FOCEI). The eta distribution of E₀, E_{max}, Kout, EC₅₀ appeared to be normally distributed. VPC indicated that the model adequately describes variability of the data around the central tendency. The relative $\Delta\Delta\text{QTcF}$ prolongation risk for two proposed clinical doses (600 mg BID, 1200 mg QD) with RTV showed that 1200 mg QD with RTV (mean 5.42 msec, UCL 7.94 msec) has higher likelihood of being associated with clinically meaningful QTcF prolongations compared to 600 mg BID with RTV (mean 2.98 msec, UCL 5.58 msec).

Conclusions: An indirect response sigmoid E_{max} model with Hill coefficient best described the relationship between individual observed $\Delta\Delta\text{QTcF}$ and plasma exposure of BMS-626529. BMS-663068 600 mg BID, a dose not studied clinically, was selected as the Phase 3 dose since 600 mg BID with ritonavir was predicted to have a lower risk of QTcF prolongation compared to 1200 mg QD with ritonavir

No conflict of interest

Abstract: 10*Session 3*

Prediction of Intracellular (IC) Tenofovir Diphosphate (TFV-DP) and Emtricitabine Triphosphate (FTC-TP) Concentrations Following Drug Intake Cessation

L. Dickinson¹, H.M. Yapa², A. Jackson², G. Moyle², L. Else¹, A. Amara¹, S. Khoo¹, D. Back¹, Z. Karolia², C. Higgs², M. Boffito²

¹University of Liverpool, Department of Molecular & Clinical Pharmacology, Liverpool, United Kingdom; ²St. Stephen's Centre, Chelsea & Westminster Foundation Trust, London, United Kingdom

Background: Pharmacokinetic (PK) data describing prolonged time-courses of anti-retrovirals in plasma and peripheral blood mononuclear cells (PBMCs) are important for understanding and management of late or missed doses and to assess appropriateness for pre-exposure prophylaxis (PrEP). PK of coformulated tenofovir disoproxil fumarate (DF)/emtricitabine/rilpivirine in plasma were evaluated in healthy volunteers up to 9 days following drug cessation. Use of non-linear mixed effects modelling was also explored to predict IC anabolites, TFV-DP and FTC-TP.

Materials & Methods: Individuals received daily tenofovir DF/emtricitabine/rilpivirine (245/200/25 mg) for 14 days. Drug intake was stopped and serial sampling occurred prior to the final dose and up to 216h (9 days) post-stopping drug. Concentrations were determined by LC-MS/MS. Separate population PK models were developed for tenofovir and emtricitabine (NONMEM v. 7.2) and all plasma and IC data were modelled simultaneously. Plasma tenofovir, emtricitabine and time-matched TFV-DP and FTC-TP concentrations from a previous healthy volunteer study (n=16) investigating tenofovir/emtricitabine/efavirenz PK after drug cessation (EFV study) were used to describe the relationship between plasma and IC anabolite concentrations. Plasma PK parameters for the present study were fixed to their individual Bayesian estimates and

population parameters obtained for the relationship between plasma concentrations and IC anabolites used as prior information to predict IC TFV-DP and FTC-TP concentration-time profiles for the present study (0-168h; 7 days).

Results: Eighteen volunteers (11 female) completed the study. Two-compartment oral models described plasma tenofovir and emtricitabine [CL/F (RSE%): 67L/h (7%) and 20L/h (6%), respectively]. Inclusion of weight and creatinine clearance significantly improved the tenofovir model and tenofovir relative bioavailability was 33% higher for the present study than the EFV study due to food intake. Creatinine clearance was associated with emtricitabine CL/F. Plasma and PBMC compartments were linked by first-order rate constant, k_{24} [TFV-DP: 3.20h⁻¹ (18%); FTC-TP: 0.15h⁻¹ (22%)] and elimination of TFV-DP and FTC-TP described by k_{40} [0.0059h⁻¹ (18%) and 0.019h⁻¹ (6%), respectively]. Geometric mean (90% CI) TFV-DP and FTC-TP AUC₀₋₂₄, AUC₀₋₁₆₈, C_{max} and C₂₄ were 1456fmol.h/10⁶ cells (1302-2193) and 87.8pmol.h/10⁶ cells (79.2-150), 7495fmol.h/10⁶ cells (6792-11486) and 273pmol.h/10⁶ cells (252-440), 92.2fmol/10⁶ cells (83.8-135) and 6.2pmol/10⁶ cells (5.7-10.5), 54.0fmol/10⁶ cells (48.2-87.9) and 3.1pmol/10⁶ cells (2.9-5.6), respectively. Model-derived IC half-lives (0-168) were 116h (TFV-DP) and 37h (FTC-TP). Twenty-four, 36, 48 and 72h after stopping drug, 6%, 0%, 1% and 4% of predicted TFV-DP and 56%, 78%, 83% and 83% of FTC-TP were <16fmol/10⁶ cells and 3.7pmol/10⁶ cells, respectively (iPrEx HIV prevention targets). Plasma tenofovir and emtricitabine terminal elimination plasma half-life within 216h was longer than 0-24 [tenofovir: 31h (27-40) vs. 13.3h (12.5-15.1); emtricitabine: 41h (36-54) vs. 6.4h (5.9-7.6)]. Plasma rilpivirine at 216h was 4.5ng/mL (4.2-6.2) and half-lives 0-216 and 0-24 were 47h (41-59) and 35h (28-46), respectively.

Conclusions: Inclusion of plasma and IC data from a previous study as prior information allowed prediction of IC TFV-DP and FTC-TP from plasma concentrations. Although adherence to antiretrovirals should be promoted, these data contribute to our understanding of drug behaviour following treatment interruption.

Conflict of interest: The clinical study was performed with financial support from Gilead Sciences Ltd

Abstract: 11**Session 3****Disulfiram Reactivates Latent HIV Infection in a Dose-Dependent Manner**

S.A. Lee¹, J.H. Elliott², J. McMahon², W. Hartogenesis¹, N.N. Bumpus³, C. Chang⁴, J. Lifson⁵, P. Bacchetti¹, S.G. Deeks¹, S.R. Lewin⁴, R.M. Savic⁶

¹UCSF- San Francisco General Hospital, Medicine Infectious Diseases, San Francisco, USA; ²Alfred Hospital and Monash University, Medicine Infectious Diseases, Melbourne, Australia; ³Johns Hopkins University, Pharmacology and Molecular Sciences, Baltimore, USA; ⁴Peter Doherty Institute for Infection and Immunity University of Melbourne, Medicine Infectious Diseases, Melbourne, Australia; ⁵National Cancer Institute – Frederick, AIDS and Cancer Virus Program, Bethesda, USA; ⁶UCSF, Bioengineering and Therapeutic Sciences, San Francisco, USA

Background: HIV genomes are stably integrated within long-lived resting memory CD4+ T cells ('latent HIV'). Most curative strategies for HIV infection require agents that activate latent HIV, leading to the production of virus and clearance of these cells. Here, we evaluated the pharmacokinetics (PK) and pharmacodynamics (PD) of a phase I study of disulfiram, an FDA-approved drug for the treatment of alcohol dependence, in activating latent HIV measured as a change in HIV RNA in CD4+ T-cells or plasma.

Materials & Methods: We analyzed data from 30 HIV-infected individuals on suppressive antiretroviral therapy (ART) enrolled in a dose-escalation study of disulfiram at 500 mg (N=10), 1000 mg (N=10), and 2000 mg (N=10), given daily for a total of 3 consecutive days. Disulfiram and four metabolites (M1: N,N-diethyldithiocarbamate; M2: diethyldithiocarbamate-methyl ester; M3: S-methyl-N,N-diethylthiolcarbamate sulfoxide; and M4: carbamathione) were measured pre-dosing (hour 0) and post-dosing on days 1 (hours 2 and 6), 2, 3 (hours 2 and 6), 4, and 8. Changes in cell-associated unspliced (CA-US) HIV RNA (in CD4+ T cells) and plasma HIV RNA were quantified by PCR. All longitudinal data were analyzed using the nonlinear mixed effects approach available in

the NONMEM program. Pharmacokinetics of the parent drug and each metabolite were linked to the PD endpoints using an indirect response model.

Results: A one-compartment disposition model with first-order absorption best described the pharmacokinetics of disulfiram and its metabolites. The estimated clearance was 0.35 L/hr, (CV%=20%), the volume of distribution was 1.6L and the absorption constant=0.12 hr⁻¹. The AUC for 500, 1000 and 2000 mg groups were 573, 2845, and 8355 mg-hr/L, respectively. Higher-than-dose-proportional increases in disulfiram exposure were due to dose-dependent increases in relative bioavailability, likely secondary to saturation of first pass effect. This supra-proportional increase was also observed for the M1 and M4 metabolites. PD modeling demonstrated that there was a significant sigmoidal exposure-response relationship with parent drug and all metabolites. In general, an increase in PK exposure resulted in significant increases in both CA-US RNA (E_{\max} =60% effect half-life of 4 days, $P<0.001$) and plasma HIV RNA levels (E_{\max} =20% effect half-life of 32 days, $P<0.001$). For CA-US RNA, the exposure-response relationship was most significant when using M2, while for plasma HIV RNA, exposure to M2 and M4 showed the strongest association. Though all subjects responded to disulfiram, 10% of the population exhibited much higher efficacy (e.g. E_{\max} =300%) compared to E_{\max} predicted by PK estimates alone.

Conclusions: Disulfiram results in an exposure-response effect at all doses for both CA-US RNA and plasma HIV RNA. Exposure to DDTC-Me strongly predicts increases in CA-US RNA while exposure to DDTC-Me and carbamathione best predict increases in plasma HIV RNA. These findings suggest that disulfiram metabolites may be driving activation of latent HIV, and therefore, disulfiram dosing should optimize exposure to these specific metabolites for use in HIV cure strategies. We also observed 'enhanced' responders for whom viral reactivation was not determined by drug exposure alone, suggesting that additional non-pharmacologic mechanisms likely contribute to individuals' responses to disulfiram.

No conflict of interest

Abstract: 12*Session 5***CYP3A5*1 Allele Not Associated with Lower Maraviroc Exposures in the Phase 2b/3 MERIT Study**

M. Vourvahis¹, L. McFadyen², S.R. Valluri³, B. Weatherley², L.S. Wood⁴, J.C. Marshall⁴, P.L.S. Chan², A. Clark⁵, A. Rinehart⁶, K.Y. Smith⁶, J. Heera⁷

¹Pfizer Inc, Clinical Pharmacology, New York NY, USA; ²Pfizer Inc, Pharmacometrics, Sandwich, United Kingdom; ³Pfizer Inc, Biostatistics, New York NY, USA; ⁴Pfizer Inc, Clinical Pharmacogenomics, Groton CT, USA; ⁵ViiV Healthcare, London, United Kingdom; ⁶ViiV Healthcare, Research Triangle Park NC, USA; ⁷Pfizer Inc, Clinical, Groton CT, USA

Background: Maraviroc (MVC) is a substrate for CYP3A4/5, P-glycoprotein and SLCO1B1. Data from Lu et al (2014) suggested that MVC average exposures (C_{avg}) are significantly lower in subjects with CYP3A5*1/*1 wild-type genotype (n=8) compared to those with CYP3A5 mutant alleles (*3,*6 and/or *7; n=8). While rare in Whites, the prevalence of CYP3A5*1/*1 is high (39-70%) in Blacks. The aim of this post-hoc analysis of MERIT, a Phase 3 study, was to describe the prevalence of and assess the effect of CYP3A5 genotype on MVC C_{avg} when dosed in combination with zidovudine/lamivudine.

Materials & Methods: DNA was extracted from 864 blood samples (MVC and efavirenz arms) and genotyped for CYP3A5 (*1,*3,*6,*7). Population PK estimates of C_{avg} for MVC 300 mg BID derived from BID and QD/open-label BID data from the original MERIT analysis were utilized. The results were statistically analyzed by the Mann-Whitney U test, logistic regression and tested for Hardy-Weinberg equilibrium (HWE) by chi-square test.

Results: Prevalence of the CYP3A5 genes (n=863, 1 subject excluded due to lack of a result for CYP3A5 genotype) for the study population was 60.7%, 28.5% and 10.8% for those with no CYP3A5*1 alleles (mutant), one CYP3A5*1 allele

and two CYP3A5*1 alleles (wild-type), respectively. The majority of Whites (83.8%) had no CYP3A5*1 alleles while the majority of Blacks had at least one CYP3A5*1 allele (77.9%; 49.5% with one CYP3A5*1 allele and 28.4% with two CYP3A5*1 alleles). CYP3A5 allelic frequencies by race were in HWE and were consistent with previous population studies. There were 494 subjects who received MVC in this study that had both MVC PK and CYP3A5 genotype data available. In the overall population, the median MVC C_{avg} [n; % of subjects with $C_{avg} \geq 75$ ng/mL (exposure associated with near-maximal MVC efficacy)] for those with no CYP3A5*1 alleles, one CYP3A5*1 allele and two CYP3A5*1 alleles was 137.7 ng/mL (n=314; 89.8%), 144.9 ng/mL (n=127; 93.7%) and 165.2 ng/mL (n=53; 92.5%), respectively. Subjects with CYP3A5*1/*1 genotype had statistically significantly higher MVC C_{avg} compared to those with two CYP3A5 mutant alleles (p=0.048). This pattern was also observed in Blacks, however did not reach statistical significance (p=0.343). In Blacks (n=138), the median MVC C_{avg} (% of subjects with $C_{avg} \geq 75$ ng/mL) for those with no CYP3A5*1 alleles, one CYP3A5*1 allele and two CYP3A5*1 alleles was 144.4 ng/mL (n=33; 93.9%), 166.0 ng/mL (n=61; 96.7%) and 169.6 ng/mL (n=44; 93.2%), respectively.

Conclusions: The prevalence of CYP3A5*1/*1 was higher in Blacks than in Whites (28% vs 1%). Importantly, CYP3A5*1/*1 was not associated with lower MVC exposures across the overall population as well as in Blacks. MVC administered at recommended doses yielded a $C_{avg} \geq 75$ ng/mL in $\geq 90\%$ of patients, irrespective of CYP3A5 genotype or Black race.

Conflict of interest: Employee of Pfizer Inc, and hold stock/stock options in Pfizer Inc.

Abstract: 13*Session 5***Pharmacokinetics (PK) of once-daily dolutegravir (DTG) and elvitegravir/cobicistat (EVG/COBI) following drug cessation**

E. Elliot¹, A. Amara², A. Jackson^{1,2}, G. Moyle¹, L. Else², S. Khoo², D. Back², A. Owen², M. Boffito^{1,3}

¹Chelsea and Westminster Hospital, St Stephens Centre, London, United Kingdom; ²University of Liverpool, Department of Molecular & Clinical Pharmacology, Liverpool, United Kingdom; ³Imperial College, London, United Kingdom

Background: Plasma PK data after cessation of antiretroviral drugs are important to understand the management of late and missed doses, and may also inform the appropriateness of specific compounds for HIV pre-exposure prophylaxis (PrEP). DTG and EVG (the latter combined with the booster COBI; EVG/COBI) are new antiretrovirals, which belong to the integrase strand transfer inhibitor (INSTI) class. *In vivo* data on DTG and EVG/COBI concentration decay after intake cessation have not been previously described. This study aimed to independently evaluate the plasma PK of DTG and EVG/COBI in HIV-negative volunteers up to 10 days after drug cessation.

Materials & methods: This was an open-label, two-session, PK trial. Healthy volunteers received DTG 50 mg once-daily for 10 days, then underwent a nine-day wash-out period. Subsequently, volunteers received EVG/COBI as part of co-formulated Stribild® (245 mg of tenofovir disoproxil fumarate, 200 mg of emtricitabine, 150 mg of EVG and 150 mg of COBI) for 10 days. Serial PK sampling occurred prior to the final dose of each course and at regular intervals for up to 216 hours (10 days) after stopping each drug. Concentrations were determined by LC-MS/MS and PK parameters were calculated using WinNonlin Phoenix v. 6.3. All data are given as geometric mean (GM) with 90% confidence intervals (90% CI) unless otherwise stated.

Results: Seventeen volunteers completed the study. Plasma half-life within the dosing interval (0-24 hours) of DTG was similar to its terminal elimination half-life to the last measurable concentration within 216 hours: 14.3 (12.9-15.7) hours *versus* 16.4 (15.4-17.5) hours. Plasma half-life within the dosing interval (0-24 hours) of EVG was longer than its terminal elimination half-life to the last measurable concentration: 10.8 (9.7-13.0) hours *versus* 4.4 (4.2-4.8) hours. AUC₀₋₂₄ for DTG and EVG were 55505.0 (51368.1-59641.9) and 22964.8 (21483.4-25591.8) ng.h/mL. C_{max}, C₂₄ and C₄₈ for DTG, EVG and COBI were (ng/mL): 3908.4 (3571.7-4245.1), 1324.1 (1177.9-1470.3) and 427.3 (361.8-492.8); 1674.7 (1556.5-1883.6), 418.7 (387.2-500.9) and 16.8 (13.2-22.6) (n=7), and 1273.3 (1184.4-1437.7), 25.8 (22.7-46.1) and not detected. After 36 hours, DTG concentrations were detectable and above the protein-adjusted (PA) IC₉₀ (64 ng/mL) in all subjects, ranging from 229.8 to 1181.9 ng/mL; EVG concentrations were detectable in all subjects and above the PA-IC₉₅ (45 ng/mL) in 11/17 subjects, ranging from 11.3 to 296.5 ng/mL. After 48 hours, DTG concentrations were detectable and above the PA-IC₉₀ in all subjects (range 109.0-791.4 ng/mL); EVG concentrations were detectable in 7/17 subjects but below the PA-IC₉₅ (range 12.2-33.4 ng/mL). After 60 hours, DTG concentrations were detectable in all subjects (range 49.1-532.2 ng/mL) and above the PA-IC₉₀ in 16/17 subjects; EVG concentrations were not detected in any of the subjects.

Conclusions: This study investigated the PK forgiveness of two recently approved INSTIs. Detectable drug concentrations were measurable for up to 36 hours post-dose for both DTG and EVG and up to 60 hours post-dose for DTG (16/17 above PA-IC₉₀). These data contribute to our understanding of drug behaviour following a missed dose or treatment interruption with these drugs.

No conflict of interest

Abstract: 14*Session 5*

Pharmacokinetic- Pharmacodynamic Modeling and Simulation of the Virologic Response of Dolutegravir in HIV-Infected Patients with Integrase Inhibitor Resistant Virus

I. Song¹, K. Adkison¹, M. Lovern², J. Chiu², J. Huang³, C. Vavro⁴, M. Ait-Khaled⁵, B. Wynne⁶, S. Min⁷

¹GSK, CPMS, Research Triangle Park, USA; ²Quantitative Solutions, East Coast Office, Bridgewater, USA; ³GSK, Clinical Statistics, Toronto, Canada; ⁴GSK, ID Clinical Virology, Research Triangle Park, USA; ⁵GSK, MD ID, Stockley Park, United Kingdom;

⁶GSK, MD ID, Upper Marion, USA; ⁷GSK, MD ID, Research Triangle Park, USA

Background: Dolutegravir (DTG), a integrase inhibitor (INI), is currently approved at the 50mg twice daily (BID) dose for the treatment of HIV-1 infections in patients with integrase-resistant (INI-r) virus based on demonstrated efficacy and safety in 3 studies (VIKING, VIKING-3, VIKING-4). The objective of this analysis was to (1) describe the DTG exposure-Week 24 viral response relationship and (2) use model-based simulations to assess the impact of a higher dose of DTG or co-administration with food (known to increase DTG exposures) or enzyme inducing drugs and metal cation-containing dietary supplements (known to lower DTG plasma exposures) on response in the overall INI-r population, as well as subpopulations harboring the less sensitive Q148 viral mutations.

Materials & Methods: Using pooled data from 247 subjects, the probability of virologic responder (response rate) at Week 24 as defined by Snapshot/TLOVR (HIV-1-RNA<50c/mL) was modeled as a logistic function of DTG plasma exposure (Cmin or Cavg estimated by an existing PopPK model) and covariates of interest including baseline viral load, baseline integrase resistance (fold change in IC50, integrase mutation

category), phenotypic or genotypic susceptibility score of background antiretroviral therapy, prior raltegravir/elvitegravir use and duration of use, HIV risk factors, CDC category, baseline CD4+. Model building was performed in NONMEM and covariates were selected based on forward inclusion and backward elimination. The final model was validated by comparing the model predictions to the observed responses. Simulations based on observed and simulated subjects were performed to predict response rates for various scenarios including 100mg BID and dosing with food, metal cation-containing dietary supplements, or enzyme-inducing drugs.

Results: The logistic regression analysis based on either Cmin or Cmax arrived at the same final model, where baseline integrase mutation category, baseline viral load, and baseline CD4 were significant covariate effects. Based on the simulations, increasing dose from 50mg BID to 100mg BID assuming dose-proportional PK and a 45% increased exposure when dosed with food (best case scenario that conservatively assumed observed cases were fasted) is predicted to increase the Week 24 median predicted response rate from 80% to 88% for the 'No Q148' category, from 60% to 71% for the 'Q148+1' category, and from 30% to 48% for the 'Q148+≥2' category, respectively, using the Cmin-based model. However there was significant overlap in the 90% prediction intervals between 50mg BID and 100mg BID for all three mutation categories, and DTG PK was previously shown to be less than dose-proportional from 50mg to 100mg. Co-administration with strong inducers resulted in lower predicted response rates for the 50mg BID regimen by 5%, 8%, and 5% in the No Q148, Q148 + 1, and Q148 + ≥2 mutation categories. Co-administration with metal-cation dietary supplements was predicted to have a negligible impact on virologic response.

Conclusions: A logistic regression model was developed and validated to describe the relationship between the virologic response at Week 24 and DTG exposure in INI-r subjects. The simulation results support the current dose recommendation of 50mg BID for the treatment of HIV infection in patients with integrase-resistant viruses.

Conflict of interest: Employee of GSK

Abstract: 15

Session 5

Model-Based Pediatric Dosing of Ritonavir-Boosted Darunavir: An Alternative to WHO GuidelinesA. Brochot¹, P. Mohammed², Y. van Delft², H. Crauwels¹¹Janssen Pharmaceutica, Research and Development, Beerse, Belgium; ²Janssen Pharmaceutica, Global Public Health, High Wycombe, Belgium

Background: More treatment options are needed for antiretroviral (ARV)-experienced pediatric patients with HIV. Approved pediatric dosing regimens for ritonavir-boosted darunavir (DRV/rtv) differ from those recommended by the World Health Organization (WHO), as different weight bands have been used. To simplify administration of ARV drugs, WHO recommends 5 weight bands from 10 kg to ≥ 35 kg and a constant 6:1 ratio of darunavir to ritonavir, which allows simpler DRV/rtv fixed-dose combinations (FDCs). The approved (United States Package Insert) regimen uses 8 weight bands from 10 kg to ≥ 40 kg, and DRV:rtv ratios ranging from 7.5:1 to 5.8:1. This pharmacokinetic (PK) simulation was conducted to evaluate a regimen that conforms with the WHO weight bands and constant DRV:rtv ratio, while reaching DRV exposures comparable to those in adults thereby allowing extrapolation of safety and efficacy to pediatric patients.

Materials & Methods: A population pharmacokinetic model of DRV/rtv has been previously established based on rich pooled sampling data from adult and pediatric populations. Simulations were performed using both R (version 12) and NONMEM software (version 7.1), with a G Fortran compiler. Pediatric b.i.d dosing regimens using WHO weight bands and a fixed 6:1 DRV/rtv ratio (240/40mg FDC) were determined, which target (80 – 130%) the exposure (AUC, area under the curve) observed in ARV-experienced adults on DRV/rtv 600/100mg b.i.d. These were also compared to the exposure expected with the approved

regimen and weight bands with DRV and rtv as separate agents.

Results: The simulated AUC while applying the current WHO recommended dosing was below 80% of the adult reference value of 62.3 $\mu\text{g}\cdot\text{h}/\text{ml}$ in the lower weight band of 14 to <20 kg (1 pediatric tablet [240/40mg]) and above 130% of the adult reference value in the weight band of 25 to <35 kg (1 adult tablet [600/100mg]), while the other weight bands were more comparable. Further simulations of AUC and pharmacokinetic profiles after administration of DRV/rtv as 240/40mg tablets allowed selection of a new dosing schedule that reached DRV exposures between 80% and 130% of the adult reference value in all WHO weight bands: 1 tablet [240/40mg] for 10kg to <14 kg; 1.5 tablets [360/60mg] for 14kg to <20 kg and 20kg to <25 kg; 2 tablets [480/80mg] for 25kg to <35 kg; and adult dose as of 35kg). These exposures were also comparable to those anticipated with the approved DRV/rtv regimen.

Conclusions: Population PK modelling can help guide effective and practical pediatric ARV regimens. These simulations suggest that DRV dosing according to current WHO guidelines might lead to either under-dosing in a lower weight band or over-dosing in a higher weight band. Simple changes to the current WHO recommended dosing schedule could improve DRV exposure in children while still keeping to the number of weight bands and a standard DRV/rtv dosing ratio. Manufacturers could thereby simplify treatment by developing DRV/rtv FDCs which allow dosing aligned with recommendations across the unified WHO weight bands.

Conflict of interest: Employees of Janssen

Abstract: 16

Session 7

Drug-Drug Interactions of Commonly Used Medications with Direct Acting Antiviral HCV Combination Therapy of Paritaprevir/r, Ombitasvir and Dasabuvir

A.R. Polepally¹, J.R. King¹, D.L. Shuster¹, E.O. Dumas², A. Khatri¹, J. Wu¹, T.J. Podsadecki², R.M. Menon¹

¹Abbvie, Clinical Pharmacology and Pharmacometrics, North Chicago, USA; ²Abbvie, Infectious Disease Development, North Chicago, USA

Background: The 3 direct acting antiviral (DAA) combination (3D) of paritaprevir/r (nonstructural 3/4A [NS3/4A] protease inhibitor identified by Abbvie and Enanta dosed with ritonavir), ombitasvir (NS5A inhibitor) and dasabuvir (NS5B polymerase inhibitor) has been approved for the treatment of hepatitis C virus (HCV) genotype 1 infection. Results of drug-drug interaction (DDI) studies with 30 concomitant medications in healthy volunteers have been reported previously. In this abstract, additional DDI studies with the 3D regimen and commonly used medications including diazepam, hydrocodone bitartrate/acetaminophen combination, sulfamethoxazole/trimethoprim combination, metformin, carisoprodol and cyclobenzaprine are presented.

Materials & Methods: Three pharmacokinetic Phase 1, single center, open-label, two-arm (two different evaluations), sequential design studies that included administration of concomitant medications (diazepam [2 mg], hydrocodone bitartrate/acetaminophen [5/300 mg], sulfamethoxazole/trimethoprim [800/160 mg BID], metformin [500 mg], carisoprodol [250 mg] and cyclobenzaprine [5 mg]) with and without the 3D regimen (ombitasvir/paritaprevir/r 25/150/100 mg QD + dasabuvir 250 mg BID) were conducted in healthy volunteers (N= 12 -15 subjects per evaluation). The 3D regimen was administered for 14 days in all the DDI evaluations with the exception of evaluation with sulfamethoxazole/

trimethoprim. Comedications were administered alone and on 14th day of administration of 3D regimen. In case of sulfamethoxazole/trimethoprim, the DDI interaction was evaluated after single dose administration of 3D regimen alone and with steady state sulfamethoxazole/trimethoprim. Individual pharmacokinetic parameters for the DAAs, ritonavir and concomitant medications were calculated using non-compartmental analysis. Central value ratios (90% confidence intervals) for C_{max} and AUC were used to examine the potential for DDIs. Clinical relevance of changes in concomitant medication exposures were based on historical data/information.

Results: Exposures (central values of C_{max} and AUC) of acetaminophen (≤ 17% increase), sulfamethoxazole (17-21% increase), trimethoprim (17-22% increase), and metformin (~23% decrease) were not affected by the 3D regimen to a clinically meaningful extent. Upon co-administration with the 3D regimen, diazepam C_{max} increased 18% and AUC decreased 22% while nordiazepam (diazepam metabolite) C_{max} increased 10% and AUC decreased 40%. Hydrocodone exposures increased 27-90% in the presence of the 3D regimen. Carisoprodol and cyclobenzaprine exposures decreased 38-46% and 32-40%, respectively, in the presence of the 3D regimen; however, no clinically significant effect (26% difference in exposures) was observed on meprobamate (carisoprodol metabolite) or norcyclobenzaprine (cyclobenzaprine metabolite). In these DDI studies, none of the comedications had clinically significant effects on paritaprevir, ritonavir, ombitasvir or dasabuvir exposures. Co-administration of the 3D regimen with the comedications was generally well tolerated by the subjects in these studies and no serious adverse events were reported. No new or unexpected safety findings were observed.

Conclusions: Acetaminophen, sulfamethoxazole, trimethoprim, and metformin can be coadministered with the 3D regimen without dose adjustment. A 50% dose reduction is recommended for hydrocodone. An increase in dose may be needed for diazepam, carisoprodol and cyclobenzaprine based on clinical monitoring. No dose adjustment is necessary for the 3D regimen when co-administered with any of the evaluated concomitant medications.

Conflict of interest: AbbVie contributed to the study design, research, and interpretation of data, writing, reviewing, and approving the publication. All authors are AbbVie employees and may hold AbbVie stocks or options.

Abstract: 17

Session 7

Coadministration of HCV Protease Inhibitor Grazoprevir With HCV NS5A Inhibitor Elbasvir Has No Effect On Pravastatin But Increases Rosuvastatin Exposure In Healthy Subjects

L. Caro¹, W. Marshall², H. Feng¹, Z. Guo³, D. Wolford⁴, D. Stypinski⁵, M. Dupuis⁵, J. Bredja⁶, C. Mitchell⁷, J.M. Allison⁸, M. Iwamoto⁹, J. Butters², W.W. Yeh²

¹Merck & Co. Inc., Quantitative Pharmacokinetics and Pharmacometrics, West Point, USA; ²Merck & Co. Inc., Clinical Pharmacology Experimental Therapeutics, Boston, USA; ³Merck & Co. Inc., Biostatistics, Upper Gwynedd, USA; ⁴Merck & Co. Inc., Early Stage Operations, Upper Gwynedd, USA; ⁵Celerion, Pharmacokinetics, Tempe, USA; ⁶Celerion, Statistics, Tempe, USA; ⁷Celerion, Medical Writing, Tempe, USA; ⁸Celerion, Clinical, Tempe, USA; ⁹Merck & Co. Inc., Clinical Pharmacology Experimental Therapeutics, Rahway, USA

Background: Grazoprevir (GZR, MK-5172) is a once-daily (QD) inhibitor of the hepatitis C virus (HCV) NS3/4A protease and elbasvir (EBR, MK-8742) is a QD inhibitor of the HCV NS5A that are being developed as a fixed-dose combination therapy for treatment of HCV infection. This study evaluated effects of coadministration of either rosuvastatin or pravastatin with GZR QD with or without (+/-) EBR QD. Rosuvastatin is an OATP and BCRP substrate and a minor CYP3A4 substrate; pravastatin is a substrate of OATP and a minor BCRP and CYP3A4 substrate. Both GZR and EBR are BCRP inhibitors in vitro and not

OATP inhibitors in humans, while GZR is a weak CYP3A4 inhibitor in humans.

Materials & Methods: This was an open-label, 2-part study in 24 healthy subjects. In Part 1, subjects received a single oral dose of 10 mg rosuvastatin on Day 1 of Period 1 followed by a 3-day washout. In Period 2, subjects received 200 mg GZR QD on Days 1 to 9, with a single oral dose of 10 mg rosuvastatin coadministered on Day 7 with no washout between Period 2 and 3. In Period 3, subjects received 200 mg GZR QD and 50 mg EBR QD on Days 1 to 11, with a single oral dose of 10 mg rosuvastatin coadministered on Day 9. In Part 2, subjects received a single oral dose of 40 mg pravastatin on Day 1 of Period 1 with no washout. In Period 2, subjects received 200 mg GZR QD and 50 mg EBR QD on Days 1 to 9, with a single oral dose of 40 mg pravastatin coadministered on Day 9.

Results: Part 1: Multiple oral doses of GZR increased the AUC_{0-∞} and C_{max} of rosuvastatin with (rosuvastatin+GZR/rosuvastatin) geometric mean ratios (GMRs) [90% confidence intervals (CIs)] of 1.59 [1.33, 1.89] and 4.25 [3.25, 5.56], respectively. There was an added effect of EBR on the increase of rosuvastatin exposure when coadministered with grazoprevir with AUC_{0-∞} and C_{max} (rosuvastatin+GZR+EBR/rosuvastatin) GMRs [90% CI] of 2.26 [1.89, 2.69] and 5.49 [4.29, 7.04], respectively. Rosuvastatin had no significant effect on GZR or EBR exposures (AUC₀₋₂₄, C_{max}, and C₂₄ GMRs ranging from 0.93 -1.16 for GZR and 0.96- 1.11 for EBR). Part 2: Coadministration of pravastatin with GZR + EBR did not substantially affect pravastatin exposures, with AUC_{0-∞} and C_{max} (pravastatin +GZR+EBR/pravastatin) GMRs [90% CI] of 1.33 [1.09, 1.64] and 1.28 [1.05, 1.55], respectively. Pravastatin had no clinically significant effect on GZR or EBR exposures (AUC₀₋₂₄, C_{max}, and C₂₄ GMRs ranging from 1.07-1.42 for GZR and 0.97-0.98 for EBR).

Conclusions: Coadministration of GZR or GZR+EBR with rosuvastatin resulted in a greater increase in rosuvastatin C_{max} compared to AUC, indicating pre-systemic inhibition of rosuvastatin efflux by GZR or GZR+EBR in the liver and/or gut via BCRP. Grazoprevir+EBR had a larger effect than GZR alone on the increase in rosuvastatin concentrations, suggesting that both GZR and EBR are BCRP inhibitors. Coadministration of

pravastatin with GZR + EBR did not have a clinically-relevant effect on pravastatin, GZR, or EBR PK.

Conflict of interest: I am an employee of Merck & Co., Inc

Abstract: 18

Session 7

Reading HIV/HCV Coinfected Patients for HCV Treatment: Occurrence and Management of Antiviral Interactions

J. Langness¹, B. Larson², J. Bayer¹, M. Rogers¹, J. Kiser²

¹University of Colorado Hospital, Pharmacy, Aurora, USA;

²Skaggs School of Pharmacy and Pharmaceutical Sciences, Pharmacy, Aurora, USA

Background: Treatment of Hepatitis C virus (HCV) with effective, tolerable direct-acting antivirals (DAA) in patients coinfecting with HIV is becoming more accessible. The primary consideration in the use of DAA in individuals with HIV is the potential for drug interactions. The objective of this work was to assess the frequency and degree of potential drug interactions between antiretroviral agents and DAA drug in HIV/HCV co-infected patients receiving care at an academic medical center.

Methods: A cohort of 125 HIV/HCV coinfecting adults were the subjects of this retrospective study. The patients were 18 years of age and older and had an active antiretroviral prescription within the last year. The patients' antiretroviral regimen was recorded and the drug interaction potential assessed with four possible DAA regimens: simeprevir and sofosbuvir (SIM/SOF), sofosbuvir and ledipasvir (SOF/LDV), sofosbuvir and daclatasvir (SOF/DCV) and ritonavir-boosted paritaprevir, dasabuvir, and ombitasvir (3D). Antiviral drug interactions were categorized as *severe*, *moderate*, or *no significant interaction*. *Severe interactions* were defined as unsafe and the medications should not be coadministered.

Moderate interactions were defined as requiring additional monitoring and/or dose adjustments. *No significant interactions* were defined as being safe with no adjustments required. Additionally, we evaluated the frequency and severity of interactions among the patients within this cohort who were treated with SOF/LDV therapy the ability to adjust antiretroviral regimens to avoid interactions and the resolution of the identified interactions.

Results: Potential antiretroviral and DAA interactions were evaluated in 125 HIV/HCV coinfecting patients. 50 (40%) HIV regimens contained protease-inhibitors, 20 (16%) contained efavirenz, 44 (35%) contained raltegravir, and 101 (81%) contained tenofovir. Moderate or severe interactions with at least one of the four HCV regimens were identified in 88 (70.4%) patients. Potential severe and moderate interactions with antiretroviral regimens were identified in 46%, 61%, 64% and 70% of patients with SOF/DCV, 3D, SOF/LDV, and SIM/SOF, respectively. More severe interactions were identified when considering HCV treatment with SIM/SOF (64%) or 3D (40.8%), while moderate interactions were more prevalent when considering SOF/LDV (54.4%) or SOF/DCV (46.4%). 35 of the 125 patients in this cohort were prescribed SOF/LDV. Of these patients, 2 (5.7%) were on contraindicated HIV regimens requiring a treatment change, 16 (45.7%) did not have any moderate or severe interactions, and 17 (48.6%) had moderate interactions. Of the 17 patients with moderate interactions identified, 7 (41.6%) continued on their original HIV regimen during HCV treatment and 10 (58.8%) switched their HIV regimen prior to starting HCV treatment. 7 (20%) of the 35 patients would not be eligible to change their HIV regimen.

Conclusion: In HIV/HCV coinfecting patients, moderate to severe drug-drug interactions with antiretroviral agents and DAA are common and without a choice in DAA selection many patients will require a change to antiretroviral therapy or increased monitoring. However, 20% of patients in our cohort were unable to change antiretroviral agents, which presents a challenge with DAA therapies currently available in the United States.

No conflict of interest

Abstract: 19*Session 7***Sofosbuvir in haemodialysis: 400 mg daily or only the day of hemodialysis?**

A. Desnoyer¹, D. Pospai², M.P. Lê¹, J.B. Pain¹, E. Belissa¹, L. Larouy³, Y. Yazdanpanah⁴, G. Peytavin¹

¹Hôpital Bichat-Claude Bernard, Clinical pharmacology, Paris, France; ²Hôpital Bichat-Claude Bernard, Gastroenterology, Paris, France; ³Hôpital Bichat-Claude Bernard, Virology, Paris, France; ⁴Hôpital Bichat-Claude Bernard, Infectious Diseases & Tropical, Paris, France

Background: Hepatitis C virus (HCV) infection in patients requiring hemodialysis (HD) is associated with rapid liver disease progression. Currently, no dose of sofosbuvir (SOF), in patients on HD was recommended in label information. Only few data regarding its management in HD patients were published. The objective is to describe the pharmacokinetic of SOF containing regimen in HCV-infected patients requiring HD.

Methods: Multicenter, prospective and observational study, including HCV-infected patients, F3-F4 fibrosis stage, null or partial responders to previous anti-HCV treatment (PegIFN + Ribavirin), requiring HD and receiving SOF 400mg once-daily (QD) or three times a week (TIW) after HD in combination with simeprevir (SMV) 150mg QD or daclatasvir (DCV) 60mg QD. Nine patients were included; plasma samples were collected before, 4hr after HD (4h-HD) and 1.5hr after last dose intake. Plasma concentrations of SOF, SOF-007 (SOF circulating metabolite), SMV and DCV were determined using UPLC-MS/MS. Dialysance was determined using paired individual data before and after 4h-HD. SOF-007 terminal half-life ($t_{1/2}$) was determined in one patient at the end of full-daily dose treatment. All results are expressed as median (IQR25-75%). Non-parametric Mann-Whitney tests, paired and unpaired t-tests and Spearman correlation were used for statistical analysis.

Results: Nine patients: 52 yrs (45-58), 8 men, 4 Caucasians, 3 Northern Africans, 1 South American and 1 South African were included. 3 where HIV/HCV co-infected, 7 were treated with SOF QD and 2 with SOF TIW. Overall, 136 samples were analyzed, 47 before HD, 46 after HD and 43 1.5-hr post-dose (as maximal). In pre-HD: SOF concentration were <1ng/mL, SOF-007 5,862ng/mL (4,696-7,116; CV=29%), SMV 4,117ng/mL (2,532-4,845; CV=39%; n=37) and DCV 538ng/mL (404-753; CV=39%; n=10). In Post-HD: SOF were <1ng/mL, SOF-007 2,983ng/mL (2,209-3,682; CV=37%), SMV 4,072ng/mL (2,549-5,311; CV=44%; n=36) and DCV 506ng/mL (275-628; CV=42%; n=10). In 1.5hr post-dose: SOF were 813ng/mL (252-1,276), SOF-007 4,284ng/mL (3,458-5,647; CV=77%;), SMV 4,507ng/mL (3,092-5,772; CV=38%; n=37) and DCV 677ng/mL (478-836; CV=41%; n=6). No difference in SOF-007 between SOF QD and TIW measured Pre-HD ($p=0.120$) and post-HD ($p=0.148$) was observed. Moreover, no difference between Pre-HD and Post-HD was reported for SMV ($p=0.773$) and DCV ($p=0.163$). Dialysance of SOF-007 was 51% and SOF-007 $t_{1/2}$ was 38.2hr. In 2 patients receiving SOF QD no correlation between SOF, SOF-007 and treatment duration (30 consecutive HD on 12 weeks and 70 samples) was observed in Pre-HD ($r=0.197$; $p=0.257$) and Post-HD ($r=-0.021$; $p=0.906$), suggesting the absence of SOF or SOF-007 accumulation. Tolerance was good in these patients who presented a sustained virological response 4 weeks after treatment completion.

Conclusions: In this study with multiple doses of SOF, SOF-007 dialysance was consistent with historical data (53%) and not different regarding the regimen. Moreover, SOF-007 $t_{1/2}$ was not different from those observed in normal renal function patients (historical data). As expected regarding their high protein binding ratio, SMV and DCV were not significantly removed by HD. Finally, once daily dosing with SOF + SMV or DCV was effective and well tolerated. All these data are in accordance with a regimen containing SOF 400mg QD even in HD patients.

No conflict of interest

16th International Workshop on Clinical Pharmacology of HIV & Hepatitis Therapy

26 – 28 May 2015, Washington, DC, USA

Abstracts Poster Presentations

Abstract: 20*Novel Analytical Methodology***Factors Influencing Antiretroviral Quantitation in HIV-HCV Co-Infection**

R. Di Francesco¹, C.R. Taylor¹, R.W. Browne², G.D. Morse¹

¹University of Buffalo School of Pharmacy and Pharmaceutical Sciences, Translational Pharmacology Research Core, Buffalo NY, USA; ²University of Buffalo School of Medicine, Biotechnical and Clinical Laboratory Sciences, Buffalo NY, USA

Introduction: Clinical Pharmacology Laboratories (CPL) that quantitatively measure antiviral drug and metabolite concentrations employ Laboratory Developed Tests (LDT). Despite the rigor of LDT validation, a number of pre-analytical factors in patient specimens (i.e. hemolysis, lipemia and icterus) can affect the specificity or selectivity of LDTs. Pharmacokinetic studies in HIV-HCV co-infection create a need for additional specificity testing of previously validated LDTs as hyperbilirubinemia from liver disease is associated with icteric plasma samples.

Materials & Methods: The UB Clinical Pharmacology Quality Assurance (CPQA) program provided blinded samples to assure the specificity/selectivity of LDTs performed at CPLs (n=11) by including blinded icteric specificity samples in ARV proficiency testing events (PT rounds). During two PT rounds, ARVs were added at high and low concentrations to normal human plasma (control) and human plasma spiked with bilirubin at 112 micromoles/liter to simulate moderately icteric plasma. Preparations were aliquoted into cryovials, shipped frozen with routine PT samples, and stored at -80°C until analysis. CPLs tested icteric samples during LDT analysis of routine PT samples and provided ARV results to the CPQA database. The absolute percent difference (APD) measured in icteric sample compared to control was calculated: $100 \times [\text{absolute value}((\text{icteric}-\text{control})/\text{control})]$. Using Systat 13 (version 13.00.05) data were inspected for normal distribution. The Kruskal Wallis (KW) test was used to determine if CPL, target concentration (Target) and ARV were significantly

associated with APD. Least squares regression (LSR) analysis was also used to test the range of Target for significant association with APD.

Results: 289 ARV-specific, PD values for icteric samples were calculated and the data were normally distributed (skewness= - 0.105; SE= 0.143). [DR1] The APD values reported per ARV were: lamuvudine (12), abacavir (10), atazanavir (23), stavudine (6), darunavir (34), efavirenz (38), etravirine (20), emtricitabine (13), lopinavir (26), maraviroc (18), nevirapine (27), raltegravir (14), rilpivirine (6), ritonavir (25) and tenofovir (17). Overall, CPL medians for APD ranged from 1.05 to 6.39. CPL was determined to significantly effect APD (p=0.004). Target (p=0.067 KW; 0.070 LSR) and ARV (p=0.75) did not significantly effect APD. APD values were < 10% for 268 (93%), <15% for 284 (98%) and <20% for 286 (99%). Three APD values (1%) were ≥20%: etravirine (75ng/mL) and emtricitabine at one CPL (APD=20.2 and 34.3, respectively) and tenofovir (30ng/mL) at a different CPL (APD=28.6). Using the FDA APD specificity limit of 15%, 2 additional CPL exceeded limits for stavudine (PD=17.7) and atazanavir (PD=16.8). Notably, APD values ≥15% occurred at lower concentrations of these ARVs.

Conclusions: The data supported the uniqueness of each CPL and nearly all APD values indicated adequate specificity for LDT ARV concentrations in icteric plasma. However, at some CPLs, the APD values at low ARV-specific concentrations could potentially affect the specificity when the corresponding LDTs are utilized to measure these low concentrations.

No conflict of interest

Abstract: 21*Novel Drugs and Formulations***Administration of a Supratherapeutic Dose of Doravirine Does Not Result in a Clinically Meaningful Increase in QTcP**

S. Khalilieh¹, K. Yee², R. Liu³, W. Herber⁴, E. Dunzo⁵, T. Faihs⁶, I. Triantafyllou⁷, A. Hussaini⁸, M. Iwamoto¹

¹Merck & Co. Inc., Clinical Pharmacology and Experimental Therapeutics, Kenilworth, USA; ²Merck & Co. Inc., Pharmacokinetics Pharmacodynamics and Drug Metabolism, Kenilworth, USA; ³Merck & Co. Inc., Biostatistics and Research Decision Sciences, Kenilworth, USA; ⁴PAREXEL Int., EP Biostat & Prog, Baltimore, USA; ⁵PAREXEL Int., EP Clinical PK/PD, Baltimore, USA; ⁶PAREXEL Int., EP Clinical PK/PD, Bloemfontein, USA; ⁷Merck & Co. Inc., Early Stage Development Operations, Kenilworth, USA; ⁸PAREXEL Int., EP Research Physicians, Baltimore, USA

Background: Doravirine is a novel, well tolerated, once-daily, non-nucleoside reverse transcriptase inhibitor being developed for treatment of human immunodeficiency virus -1 (HIV-1) infection in combination with other anti-retroviral therapy (ART). Pre-clinically, doravirine is a potent inhibitor of HIV-1 Wild-Type (WT) virus and K103N, Y181C, and K103N/Y181C mutant viruses. In a 24-week trial in combination with TRUVADA™, doravirine has been shown to be efficacious in treating ART-naïve HIV-1 infected patients over the investigated 25 mg to 200 mg dose range. The clinical dose of doravirine is projected to be 100 mg administered once-daily (QD). While pre-clinical and clinical data do not suggest doravirine to have a clinically meaningful effect on QTc intervals, this study was conducted to evaluate the potential for doravirine to prolong QTc. A single supratherapeutic dose of 1200 mg dose was selected for evaluation as it was anticipated to cover any increases in doravirine exposure due to intrinsic or extrinsic factors. As per ICH E14, the upper limit of the 95% one-sided confidence interval (CI) of the placebo-corrected change in QTc interval from baseline must be

below 10 msec to support a lack of regulatory concern for a QT effect.

Materials & Methods: The trial was a randomized, 3-period, double-blind, placebo- and active-controlled crossover trial in healthy male (n=27) and female (n=17) subjects. The pharmacokinetics, safety, and tolerability of MK-1439 were also assessed. A single dose of doravirine 1200 mg, moxifloxacin 400 mg or MK-1439 matching placebo were administered on Day 1 of each period. In each period, continuous Holter monitoring was performed pre-dose through 24 hours post-dose, with replicate ECGs extracted at pre-specified time points. Blood samples were drawn time-matched to ECG extractions for determination of doravirine pharmacokinetics. Clinical safety parameters and adverse events (AEs) were monitored throughout the study. A pairwise analysis of covariance model was used to analyze the difference of change from baseline in population specific rate corrected QT (QTcP) for doravirine versus placebo, conducted separately at each time point. The model included a fixed-effect to account for the order in which the treatments were administered and the corresponding difference in QTcP at baseline as a covariate.

Results: Doravirine was generally well tolerated and all reported AEs were mild and transient. Five (12.2%), five (12.2%) and four (9.8%) subjects reported AEs in the doravirine, placebo and moxifloxacin treatment groups, respectively. For the analysis of the mean change from baseline in QTcP of 1200 mg doravirine versus placebo, the upper limit of the 2-sided 90% CI did not exceed 10 msec at any timepoint post-dose. For moxifloxacin versus placebo, the lower limit of the 90% CI exceeded 5 msec at relevant timepoints of 1, 2, 3 and 4 hours post-dose, demonstrating sensitivity of the study. After a single 1200 mg dose, doravirine AUC₀₋₂₄ and C_{max} were 119 µM.hr and 9240 nM, which are approximately 3.3-fold higher than steady state values associated with the 100 mg dose.

Conclusions: Administration of a supratherapeutic dose of doravirine does not result in a clinically meaningful increase in QTcP.

Conflict of interest: Employee of Merck & Co., Kenilworth, NJ

Abstract: 22*Novel Drugs and Formulations***Modelling the inhibition of transporters and enzyme for increased tenofovir bioavailability**

D.M. Moss¹, S. Park², R. Randolph², S. Wring², J. Hobson¹, S. Rannard¹, P. Domanico³, M. Watkins³, A. Owen¹, M. Siccardi¹

¹University of Liverpool, Pharmacology, Liverpool, United Kingdom; ²Scynexis, Metabolism, Durham, USA; ³Clinton Foundation, CHAI, New York, USA

Background: Tenofovir disoproxil fumarate (TDF), the clinically used prodrug of tenofovir, has oral bioavailability (25%) limited by intestinal transport (ABCB1), intestinal degradation (carboxylesterase, CES) and luminal pancreatic enzymes. We previously showed utility of physiologically-based pharmacokinetic (PBPK) modelling for estimating bioavailability from *in vitro* data without clinical data. This study aimed to investigate the contribution of transport and metabolism with the goal of informing clinical strategies to increase TDF bioavailability and reduce dose.

Materials & Methods: TDF stability was assessed at pH 6.8, 9 and 11 (1mM TDF; 22°C; 0 – 240 min). TDF stability in a range of porcine pancrelipase concentrations was assessed (0, 0.48, 4.8, 48 and 480U/mL lipase; 1mM TDF; 37°C; 0 – 30 min). Inhibition of ABCB1-mediated transport (using 0.5mg/mL TPGS) of TDF (5µM) and metabolism by CES (0-1mM propylparaben) was conducted in Caco-2 cell monolayers as a model for intestinal absorption. Samples were analyzed using mass spectrometry. TDF stability and permeation were included in a human PBPK model to predict plasma exposure following 300 mg TDF dose. Inhibition of luminal lipase, CES and ABCB1 was then simulated to assess viability of TDF dose reduction by reformulation.

Results: TDF pH stability was such that half-life was 16.7, 2.9 and 0.06 hrs at pH 6.8, 9 and 11, respectively. TDF was degraded by pancrelipase

(half-life 0.07 and 0.62 hrs using 480 and 48U/mL, respectively). TDF A-to-B Caco-2 permeation was 0.4 (control), 1.0 (1mM propylparaben) and 2.2 (0.5mg/mL TPGS) cm s⁻¹. As validation, simulated TDF PK parameters in the PBPK model after 300mg oral TDF were within 1.5-fold of previous clinical data (median simulated TFV C_{max}, T_{max}, AUC_(0-24hr) and C₂₄ of 227ng mL⁻¹, 2.5hr, 2997ng.hr mL⁻¹ and 42.7ng mL⁻¹). Inhibition of lipase, ABCB1 and CES were then simulated and dose reduction was estimated. The AUC of TDF was predicted to increase following full inhibition of either lipase (350% increase), ABCB1 (54% increase) or combined inhibition of lipase, ABCB1 and CES (550% increase). In order to achieve comparable PK to standard dose TDF, a dose reduction of 50% dose reduction was predicted when both ABCB1 and CES were fully inhibited and a dose reduction of 70% was predicted with full inhibition of luminal lipase.

Conclusions: These data further support that TDF absorption is limited by ABCB1, CES and lipase, with the most profound effect being associated with the lipase. It should be recognized that the contribution of CES and transporter inhibition cannot be delineated with the current *in vitro* data. However, the PBPK approach estimated that targeted inhibition may enable significant dose reduction, with benefits for cost and drug supply. Results suggest that TDF bioavailability may be improved by protection of TDF from intestinal transporters and enzymes, for example by nanoformulation strategies.

No conflict of interest

Abstract: 23*Novel Drugs and Formulations***Bioequivalence Assessment of Ribavirin Tablets: A Randomized, Single-Dose, Open-Label, Two-Period Crossover Study in Healthy Volunteers**

M.P. Kosloski¹, S. Dutta¹, B. Ding¹, A. Asatryan², J. Kort², W. Liu¹

¹AbbVie, Clinical Pharmacology and Pharmacometrics, North Chicago, USA; ²AbbVie, Anti-Viral Clinical Development, North Chicago, USA

Background: Treatment of Hepatitis C Virus (HCV) infections has rapidly advanced during recent years, but ribavirin remains a staple of treatments in many difficult to treat populations. Ribavirin is available in the US under the Copegus® brand name as 200 mg tablets as well as under Ribasphere® and Moderiba® brand names as 200 mg, 400 mg and 600 mg tablets. Available anti-HCV regimens typically require 1000-1200 mg of ribavirin per day administered twice daily in divided doses and formulations with higher ribavirin strength may be capable of reducing the associated pill burden by up to 67%. A bioequivalence study was conducted to compare the bioavailability of two ribavirin tablet products—600 mg Ribasphere tablets manufactured by Kadmon/DSM Pharmaceuticals (Test) and 200 mg Copegus tablets sold by Roche (Reference).

Materials & Methods: The study was a randomized, single-dose, open-label, two-treatment, two-period crossover study in twenty-four healthy volunteers (23 enrolled) with a 42 day washout period between treatments. The test and reference products were compared at a total dose of 600 mg: 1x600 mg Ribasphere tablet (Test) versus 3x200 mg Copegus tablets (Reference). Doses were administered under non-fasting conditions and blood samples were collected from 0 to 72 hours after study drug administration. Plasma concentrations of ribavirin were analyzed using a validated LC/MS-MS method. Pharmacokinetic parameters were determined

through non-compartmental methods. Bioequivalence was assessed by a two one-sided tests procedure and the antilogarithms of 90% confidence intervals for the differences of the least squares means of the natural logarithms of C_{max} , AUC_t , and AUC_{inf} were obtained within the framework of the mixed effects model.

Results: Following single dose administration under non-fasting conditions, the mean concentration-time profile of ribavirin for Ribasphere 1x600 mg tablet superimposes with the profile of Copegus 3x200 mg tablets. Both products reached T_{max} around 2 hours with an estimated harmonic mean half-life between 40 to 46 hours. The central values for C_{max} , AUC_t , and AUC_{inf} with the Test Ribasphere tablet were 1.23 µg/mL, 13.2 µg·h/mL, and 18.3 µg·h/mL; the central values for C_{max} , AUC_t , and AUC_{inf} with Reference Copegus tablets were 1.23 µg/mL, 13.6 µg·h/mL, and 18.1 µg·h/mL. The 90% confidence intervals for the central value ratios of C_{max} , AUC_t , and AUC_{inf} were within the bioequivalence range (0.80 to 1.25). There were no adverse events related to the compounds and no clinically significant abnormal vital signs, ECGs, or laboratory measurements.

Conclusion: The 600 mg Ribasphere tablet was determined to be bioequivalent to 3x200 mg Copegus tablets.

Conflict of interest: AbbVie contributed to the study design, research, and interpretation of data, writing, reviewing, and approving the publication. All authors are AbbVie employees and may hold AbbVie stocks or options.

Abstract: 24

Pharmacokinetics for Pediatrics, Pregnancy and other Special Populations

Moderate Hepatic Impairment does not affect Doravirine Pharmacokinetics

S. Khalilieh¹, K. Yee², P. Auger³, R. Liu⁴, T. Marbury⁵, K. Lasseter⁶, I. Triantafyllou⁷, D. Stypinski³, M. Iwamoto⁸

¹Merck & Co. Inc., Clinical Pharmacology & Experimental Therapeutics, Kenilworth, USA; ²Merck & Co. Inc., Pharmacokinetics Pharmacodynamics and Drug Metabolism, Kenilworth, USA; ³Celerion, Clinical Pharmacology Sciences, Lincoln, USA; ⁴Merck & Co. Inc., Biostatistics and Research Division, Kenilworth, USA; ⁵Orlando Clinical Research Center, Hepatic Division, Orlando, USA; ⁶Clinical Pharmacology of Miami, Hepatic Division, Miami, USA; ⁷Merck & Co. Inc., Early Stage Development Operations, Kenilworth, USA; ⁸Merck & Co. Inc., Clinical Pharmacology & Experimental Therapeutics, Lincoln, USA

Background: Doravirine (MK-1439) is a novel, well tolerated, once-daily, non-nucleoside reverse transcriptase inhibitor (NNRTI) being developed for treatment of human immunodeficiency virus-1 (HIV-1) infection in combination with other antiretroviral therapy (ART). Pre-clinically doravirine is a potent inhibitor of HIV-1 Wild-Type (WT) virus and K103N, Y181C, and K103N/Y181C mutant viruses. In a 24-week trial in combination with TRUVADA™, doravirine has been shown to be efficacious in treating ART-naïve HIV-1 infected patients over the investigated 25 mg-200 mg dose range. Doravirine is eliminated via CYP3A4-mediated hepatic metabolism, and is expected to be used in the treatment of HIV/hepatitis C virus (HCV) co-infected patients with hepatic impairment. The aim of this study was to evaluate the effect of moderate hepatic impairment on doravirine pharmacokinetics.

Materials & Methods: This was an open-label, parallel group study in 8 subjects with moderate hepatic impairment (Child-Pugh score ranging from 7-9) and 8 healthy subjects that were matched to the mean age (± 15) years and weight (± 20%) of the hepatic impairment cohort.

Twelve males (6 with moderate hepatic impairment and 6 healthy subjects) and 4 females (2 with moderate hepatic impairment and 2 healthy subjects) were enrolled. A single 100 mg dose of doravirine was administered to each subject on Day 1 and blood samples were collected over 144 hours post dose for subjects with hepatic impairment and over 72 hours for healthy subjects for the determination of doravirine pharmacokinetics.

The pharmacokinetics of doravirine were natural log-transformed and evaluated with an analysis of covariance model (ANCOVA). The ANCOVA model contained a categorical factor for population (moderate hepatic impairment, healthy matched control subjects) and continuous covariates age and weight. The geometric mean ratio and 90% confidence interval (moderate hepatic impairment/healthy) were computed for each PK parameter from the model.

Results: Doravirine was generally well tolerated, with no serious adverse events (AEs) reported. All reported AE's were mild and transient. Three of 8 healthy subjects reported one AE each (2 headache and 1 lower back pain), and 4 of 8 subjects with hepatic impairment reported 1 AE each (vomiting, dry mouth, postural dizziness and somnolence). Following administration of a single 100 mg dose of doravirine to subjects with hepatic impairment and to matching healthy subjects, the geometric mean ratios (GMRs, moderate hepatic impairment/healthy) and 90% confidence intervals [90% CIs] of doravirine AUC_{0-inf}, C_{max} and C₂₄ were 0.99 [0.72, 1.35], 0.90 [0.66, 1.24] and 0.99 [0.74, 1.33], respectively. The apparent terminal half-life geometric mean was ~18 hours for both groups. The median T_{max} was 2 hours (range of 1-6 hours) for subjects with moderate hepatic impairment compared to 2.5 hours (range of 1-3 hours) for healthy subjects.

Conclusions: Moderate hepatic impairment does not have a clinically meaningful effect on the pharmacokinetics of doravirine.

Conflict of interest: Employee of Merck which sponsored the study.

Abstract: 25

Pharmacokinetics for Pediatrics, Pregnancy and other Special Populations

Effect of Food on Bioavailability of Ombitasvir/Paritaprevir/Ritonavir (OBV/PTV/r) Coformulated Tablets in Healthy Japanese Subjects

J. Zha¹, P. Badri¹, B. Hu¹, N. Uchiyama², K. Alves³, R.M. Menon¹

¹AbbVie, Clinical Pharmacology and Pharmacometrics, North Chicago IL, USA; ²AbbVie GK, ADME/PK, Tokyo, Japan;

³AbbVie, Infectious Disease Development, North Chicago IL, USA

Background: The 2 direct acting antiviral combination (2D) of ombitasvir (NS5A inhibitor, OBV) and paritaprevir/r (NS3/4A protease inhibitor identified by Abbvie and Enanta dosed with ritonavir, PTV/r) is being developed for the treatment of chronic hepatitis C virus (HCV) infection in Japan. The coformulated tablet formulation of OBV/PTV/r (12.5/75/50 mg) is the to-be-marketed formulation. A Phase 1 food effect study was conducted in healthy Japanese subjects using this formulation.

Materials & Methods: This was a single-dose, open-label, randomized, two-period, crossover study designed to evaluate the effect of a high-fat meal on the bioavailability of OBV/PTV/r coformulated tablets. Twenty healthy Japanese subjects aged 20 to 45 years were enrolled and completed the study. Each subjects received two single doses of 25/150/100mg OBV/PTV/r: after an overnight fast and after a high-fat breakfast as per PMDA guideline (approximately 900 Kcal with 35% calories from fat). Plasma samples were collected to characterize pharmacokinetics of study drugs, with plasma concentrations of study drugs determined by LC/MS/MS methods. Safety was evaluated through assessment of adverse events, vital signs, ECG and clinical laboratory tests. An ethics committee approved the research. The bioavailability of the test regimen (non-fasting) relative to that of the reference regimen (fasting) was estimated along with 90% confidence interval

for the difference of the least squares means obtained from the repeated measures analyses of the natural logarithms of C_{max} and AUC.

Results: Following a single dose administration of 25/150/100mg OBV/PTV/r coformulated tablets with a high-fat breakfast to Japanese subjects, exposures of all 3 compounds increased relative to fasting conditions. The exposures (C_{max} and AUC) of PTV increased to 5-fold and 3.3-fold, respectively, of the exposures observed under fasting conditions. Administration with food increased the exposures of OBV and ritonavir to a smaller extent: 1.7- to 2-fold for OBV and 1.3- to 1.4-fold for ritonavir. The mean T_{max} of OBV and PTV was delayed by approximately 1.0 hour, while the mean T_{max} of ritonavir was delayed by approximately 1.5 hours compared to fasting conditions.

Single doses of OBV/PTV/r administered with and without food were generally well tolerated by the healthy Japanese subjects in this study.

Conclusions: A high-fat breakfast increased the bioavailability of OBV/PTV/r coformulated tablets in Japanese subjects. The magnitude of increase in bioavailability observed in Japanese subjects is similar to the food effect previously observed in Western subjects following a moderate-fat or high-fat breakfast. In Japanese subjects, the OBV/PTV/r co-formulated tablets should be taken with food, the same as in Western subjects.

Conflict of interest: AbbVie contributed to the study design, research, and interpretation of data, writing, reviewing, and approving the publication. All authors are AbbVie employees and may hold AbbVie stocks or options.

Abstract: 26

Pharmacokinetics for Pediatrics, Pregnancy and other Special Populations

Population pharmacokinetic analysis of darunavir/ritonavir in HIV-infected pregnant women

J. Moltó¹, M. Valle², A. Colbers³, V. Clotet⁴, D. Burger³

¹Hospital Universitari Germans Trias i Pujol, Fundació Lluita contra la Sida, Badalona, Spain; ²Institut de Recerca HSCSP-IIB St Pau, PKPD Modelling and Simulation, Barcelona, Spain; ³Radboud university medical center, Department of Clinical Pharmacy, Nijmegen, The Netherlands; ⁴Hospital Universitari Germans Trias i Pujol, Institut de Recerca de la Sida IrsiCaixa, Badalona, Spain

Background: During pregnancy physiological changes take place which can influence the pharmacokinetics (PK) of antiretroviral agents and lead to decreased drug exposure. Limited PK data from clinical studies shows that during pregnancy the exposure to darunavir/ritonavir is reduced. A population pharmacokinetic approach was used to characterize the pharmacokinetics of darunavir/ritonavir during pregnancy for darunavir/ritonavir 800/100 mg qd and 600/100 bid dosing regimens.

Materials & Methods: HIV-infected pregnant women treated with darunavir/ritonavir (once or twice daily) as part of their combination ART were included. Full PK curves were recorded in the third trimester and post-partum. A population analysis was performed using non-linear mixed effects modelling (NONMEN, version 7.2) The base PK model was developed by exploring typical structural models, including one- and two-compartment linear models. The effect of covariates was evaluated using a forward inclusion, backward elimination process. Visual predictive check was used to evaluate performance of the final model. The final PK model was used to simulate 1000 darunavir concentration-time profiles during 3rd trimester of pregnancy under darunavir/ritonavir 600/100 mg bid or 800/100 mg qd dosing, and darunavir concentrations were compared with the darunavir protein binding-adjusted inhibitory concentration

(IC) for HIV-1 strains with or without darunavir resistance-associated mutations (RAMs), respectively.

Results: Darunavir PK were best described by a two compartment model with an absorption lag-time (LAG), inter-individual variability (IIV) terms on clearance (CL/F) and V1/F, and proportional residual error. Pregnancy influenced LAG as well as CL/F, and IIV in CL/F and in V1/F. The population estimates of CL/F were 8.71 L/h for the 3rd trimester of pregnancy and 4.18 L/h for postpartum. All darunavir concentrations simulated with darunavir/ritonavir 800/100 mg qd dosing during 3rd trimester of pregnancy were above the protein binding-adjusted IC for wild-type HIV-1 strains (0.055 mg/L). Additionally, only 0.9% of simulated darunavir trough concentrations with darunavir/ritonavir 600/100 mg bid were below the IC of HIV-1 strains with darunavir RAMs (0.55 mg/L).

Conclusions The final population PK model developed described darunavir concentrations with no systematic bias and adequate precision. The PK of darunavir displays a two-compartmental behaviour, as previously described. Although pregnancy was identified as a major covariate influencing CL/F, explaining lower DRV concentrations in plasma during 3rd trimester of pregnancy than postpartum, no DRV dose adjustment seems to be necessary in pregnancy for HIV-infected women fully susceptible to darunavir.

No conflict of interest

Abstract: 27

Pharmacokinetics for Pediatrics, Pregnancy and other Special Populations

Ritonavir Pharmacokinetics during Pregnancy and Postpartum

A. Colbers¹, D. Burger¹

¹*Radboud university medical center, Dept. of Pharmacy, Nijmegen, The Netherlands*

Background: The use of combination antiretroviral therapy (cART) reduces the risk of mother to child transmission substantially. Perinatal guidelines recommend protease inhibitor-based cART as treatment option during pregnancy: ritonavir boosted lopinavir, atazanavir and saquinavir are preferred agents. During pregnancy physiological changes take place, influencing the pharmacokinetics of medicines. In most cases, the net effect will be a decreased exposure during pregnancy. Protease inhibitor exposure is known to be approximately 30% lower in pregnancy. In 2006/2007 pharmacokinetic changes of boosted saquinavir in pregnancy was investigated (SARA study). In 2008, a European network was established to study the pharmacokinetics of newly developed antiretroviral drugs during pregnancy (PANNA). We present ritonavir exposure in the third trimester when combined with saquinavir (SARA), atazanavir and darunavir (PANNA).

Materials & Methods: Open-label, multi-centre phase IV studies in HIV infected pregnant women recruited in HIV treatment centers in Europe and Thailand. Patients treated with boosted saquinavir, atazanavir and darunavir during pregnancy had intensive steady-state 12- or 24-hour PK profiles in the third trimester and at least 2 weeks postpartum. Where possible a cord blood (CB) and matching maternal blood samples were taken at delivery to assess placental transfer. Ritonavir plasma concentrations were determined with a validated UPLC method and an lower limit of quantification (LLOQ) of 0.045 mg/L. Pharmacokinetic parameters were calculated with WinNonlin 6.3.

Results: Forty-nine patients: 9 on saquinavir/ritonavir 1000/100mg BID; 26 on atazanavir/ritonavir 300/100mg QD; 5 on darunavir/ritonavir 600/100mg BID and 9 on darunavir/ritonavir 800/100mg QD were included in the analysis. Ratios of third trimester/postpartum ritonavir AUC_{tau} (geometric mean (90% confidence interval) were: 0.57 (0.39-0.82) for saquinavir treatment; 0.45 (0.37-0.53) for atazanavir treatment; 0.74 (0.65-0.84) for darunavir BID treatment and 0.59 (0.42-0.83) for darunavir QD treatment. Exposure (AUC_{tau}) of these protease inhibitors were 14% (saquinavir) to 34% lower during pregnancy. Ritonavir concentrations were below the LLOQ in 25 out of 26 cord blood samples. The cord blood/maternal ratio was 0.05 (0.05 / 1.06 mg/L) for this patient. Twelve samples had ritonavir concentrations below LLOQ with detectable maternal concentrations (ranging from 0.058-0.416 mg/L) at the same time point. For the remaining 13 samples both cord blood and maternal samples were below LLOQ.

Conclusions: Pregnancy influences ritonavir concentrations substantially, independent of the protease inhibitor used concomitantly. Less boosting by ritonavir can contribute to lower exposure to protease inhibitors during pregnancy. Ritonavir seems hardly to reach the foetus during pregnancy.

Conflict of interest: The PANNA network is financially supported by the "European AIDS Treatment Network (NEAT)", EC, DG Research, 6th Framework program, BMS, MSD and Janssen Pharmaceuticals N.V.

Abstract: 28

Pharmacokinetics for Pediatrics, Pregnancy and other Special Populations

A Comparison of the Pharmacokinetics of Rilpivirine during Pregnancy and Postpartum

A. Colbers¹, S. Schalkwijk², K. Kabeya³, A. Gintelmaier⁴, J. Lambert⁵, M. van der Ende⁶, D. Burger¹

¹Radboud university medical center, Dept. of Pharmacy, Nijmegen, The Netherlands; ²Radboud university medical center, Dept. of Pharmacy and Dept. of Pharmacology and Toxicology, Nijmegen, The Netherlands; ³Saint-Pierre University Hospital, Dpt. of Infectious Diseases, Brussels, Belgium; ⁴Klinikum der Universität München, Frauenklinik Innenstadt, München, Germany; ⁵Mater Misericordiae University Hospital, Dept. of Medicine (Infectious Diseases), Dublin, Ireland; ⁶Erasmus Medical Center, Dept. of Internal Medicine, Rotterdam, The Netherlands

Background: It is important to achieve effective blood concentrations of antiretroviral drugs to prevent treatment failure and the development of resistance. During pregnancy physiological changes take place, influencing the pharmacokinetics of medicines. In most cases, the net effect will be a decreased exposure during pregnancy. Limited data is available about the pharmacokinetics of rilpivirine during pregnancy and the placental passage of rilpivirine. In 2008, a European network was established to study the pharmacokinetics of newly developed antiretroviral drugs during pregnancy (PANNA). We present preliminary data on third trimester exposure to rilpivirine.

Materials & Methods: An open-label, multi-centre phase IV study in HIV infected pregnant women recruited in HIV treatment centers in Europe (PANNA Network). Patients treated with rilpivirine 25mg once daily during pregnancy had intensive steady-state 24-hour PK profiles in the third trimester and at least 2 weeks postpartum. Where possible a cord blood (CB) and matching maternal blood samples were taken at delivery to assess placental transfer. Safety and virological efficacy were evaluated. Rilpivirine plasma

concentrations were determined with a validated UPLC method and an LLOQ of 0.0063 mg/L. The minimum effective concentration of rilpivirine was defined as 0.040 mg/L based on an analysis of ECHO/THRIVE PK data. Pharmacokinetic parameters were calculated with WinNonlin 6.3.

Results: Seven patients (4 black, 1 white, 1 Asian and 1 other) with a median (range) age of 29 (19-32) years were included in the analysis. One patient did not yet deliver, hence only third trimester data is available. All patients used rilpivirine/ emtricitabine/tenofovir, one patient additionally used lopinavir/ritonavir. Median (range) gestational age at delivery was 40 weeks (34-42); birth weight was 3640 (2945-4470) gr. Approaching delivery all patients had a VL <50 cps/mL. One SAE was reported: in week 38 (gestational age) the patient was admitted to the hospital because of irregular contractions. The SAE was judged not to be related to rilpivirine. 5 children were HIV un-infected (1 unknown status) and no birth defects were reported. Seven PK curves during third trimester and 6 during postpartum were available. The results are presented as medians (range). AUC_{0-24h} (mg*h/L) was 1.73 (1.25-3.66) in the third trimester and 2.82 (1.77-6.32) post-partum. C_{max} (mg/L) was 0.13 (0.074-0.20) in the third trimester and 0.16 (0.11-0.32) post-partum. C_{through} (mg/L) was 0.056 (0.041-0.14) in the 3rd trimester and 0.11 (0.066-0.25) post-partum. Ratios of PK parameters third trimester/post-partum (median (range)) were: 0.63 (0.29-1.16) for AUC₀₋₂₄; 0.69 (0.37-1.20) for C_{max}; 0.54 (0.27-1.07) for C_{through}. 3 of the 7 patients had a subtherapeutic C_{through} in the third trimester. The ratio of cord blood/maternal plasma rilpivirine concentrations, determined in three patients, was 0.74, 0.81 and 0.48 respectively.

Conclusions: In this small population (n=7) exposure to rilpivirine was lower during pregnancy (third trimester) than postpartum, and possibly inadequate in 3 of them. This is in line with the behaviour of most antiretroviral agents used in pregnancy. Rilpivirine efficiently crosses the placenta and therefore may have potential for pre-exposure prophylaxis. These results need to be confirmed in a larger group of patients.

Conflict of interest: The PANNA network is financially supported by the "European AIDS Treatment Network (NEAT)", EC, DG Research, 6th Framework program, BMS, MSD and Janssen Pharmaceuticals N.V.

Abstract: 29

Pharmacokinetics for Pediatrics, Pregnancy and other Special Populations

Pharmacokinetics (PK) of Etravirine (ETR) in HIV-1–Infected Pregnant Women

H.M. Crauwels¹, M. Ramgopal², O. Osiyemi³, C. Zorrilla⁴, R. Ryan⁵, K. Brown⁶, V. Hillewaert⁷, B. Baugh⁶

¹Janssen Infectious Diseases, Clinical Pharmacology, Beerse, Belgium; ²Midway Immunology and Research Center, Principal Investigator, Fort Pierce FL, USA; ³Triple O Research Institute PA, Principal Investigator, West Palm Beach FL, USA; ⁴University of Puerto Rico School of Medicine, Principal Investigator, San Juan, Puerto Rico; ⁵Janssen Research & Development, Biostatistics, Titusville NJ, USA; ⁶Janssen Therapeutics, Medical Affairs, Titusville NJ, USA; ⁷Janssen Research & Development, Research & Development, Beerse, Belgium

Background: Antiretroviral (ARV) therapy during pregnancy has dramatically reduced the risk of mother-to-child transmission. Physiologic changes during pregnancy can affect the PK of ARVs.

Materials & Methods: Phase IIIb study evaluating HIV-1–infected pregnant women (age ≥18 years), in the 2nd trimester of pregnancy, receiving ETR 200mg bid with other ARVs. ETR plasma concentrations were assessed predose and 1, 2, 3, 4, 6, 9 and 12 hours postdose during the 2nd and 3rd trimesters and (6-12 weeks) postpartum. ETR PK parameters were derived using non-compartmental analysis. Safety and efficacy were investigated at each visit and summarized using descriptive statistics.

Results: Fifteen women (11 black, 2 Hispanic, 2 white) were enrolled; 13 had evaluable PK. ETR AUC_{24h}, C_{min} and C_{max} were higher by 46% (LS Means ratio, 90% CI: 1.46, 1.12-1.90), 131% (2.31, 1.26-4.22) and 39% (1.39, 1.15-1.67) during the 2nd trimester and by 28% (1.28, 0.98-1.69), 93% (1.93, 1.03-3.61) and 31% (1.31, 1.08-1.59) during the 3rd trimester, versus postpartum. ETR post-partum PK was comparable to historic controls in HIV-1 infected subjects (DUET). Though mean ETR exposures during pregnancy

were higher compared to post-partum, the observed exposures were still in range with those previously observed in HIV-1 infected subjects treated with ETR 200 mg bid. Unbound ETR PK will be explored. Median baseline (BL) viral load (VL) was 49 copies/mL; for one woman, BL VL was 54,000 copies/mL and remained detectable throughout the study. All other women had VL<400 copies/mL during pregnancy (>90% had VL<50 copies/mL). The median increases in CD4 from baseline were 29 and 45 cells/mm³ for the 2nd and 3rd trimester respectively, and were >100 cells/mm³ postpartum. Four subjects had serious adverse events (SAEs), none of which were at least possibly related to ETR (premature rupture of membranes; hypertension; headache; and one subject had 3 SAEs: pregnancy induced hypertension [twice] and premature labor). One subject had a treatment emergent adverse event (atopic dermatitis) that was at least possibly related to study drug. All infants were HIV-negative.

Conclusions: ETR exposure increased during pregnancy; this was not associated with an increased occurrence of SAEs. The regimen was well tolerated. Virologic response was maintained throughout the study and there was no mother-to-child transmission. These data indicate ETR 200 mg bid could be a treatment option for HIV-1 infected pregnant women.

These data were previously presented at the Conference on Retroviruses and Opportunistic Infections (CROI; February 23–26, 2015; Seattle, WA, USA) and the 5th International Workshop on HIV & Women (February 21-22, 2015; Seattle, WA, USA).

Conflict of interest: Herta Crauwels: employee of Janssen Infectious Diseases

Abstract: 30

Pharmacokinetics for Pediatrics, Pregnancy and other Special Populations

Association of a Senescence Biomarker with Intracellular Nucleotide Metabolite and Endogenous Nucleotide Exposures in HIV+ Subjects Receiving Tenofovir/Emtricitabine

J. Dumond¹, O. Francis², C. Trezza¹, J. Messer¹, C. Lee¹, M. Cottrell¹, H. Prince³, K. Mollan⁴, C. Sykes¹, C. Torrice⁵, K. Patterson³, A. Forrest⁶, M. Hudgens², N. Sharpless⁵, A. Kashuba⁷

¹University of North Carolina at Chapel Hill, UNC Eshelman School of Pharmacy, Chapel Hill, USA; ²University of North Carolina at Chapel Hill, Gillings School of Global Public Health, Chapel Hill, USA; ³University of North Carolina at Chapel Hill, School of Medicine, Chapel Hill, USA; ⁴University of North Carolina at Chapel Hill, School of Medicine Lineberger Comprehensive Cancer Center, Chapel Hill, USA; ⁵University of North Carolina at Chapel Hill, Lineberger Comprehensive Cancer Center, Chapel Hill, USA; ⁶State University of New York University at Buffalo, School of Pharmacy and Pharmaceutical Sciences, Buffalo, USA; ⁷University of North Carolina at Chapel Hill, UNC Eshelman School of Pharmacy School of Medicine, Chapel Hill, USA

Background: HIV infection may amplify immunologic, physiologic, and functional changes that occur with aging. The course of both aging and HIV infection are highly variable, and HIV+ patients may experience aging-related deficits at younger ages than non-infected subjects. Therefore, changes in pharmacology due to aging may not be apparent when investigating relationships with chronologic age alone. Here, we determined the associations of functional assessments (frailty phenotyping), a marker of T-cell senescence (p16^{INK4a} expression), chronologic age, and other demographics on the exposures of intracellular nucleotide metabolites (INM) and endogenous nucleotides (EN) of tenofovir (TFV) and emtricitabine (FTC).

Materials & Methods: TFV, FTC in plasma, and tenofovir diphosphate (TFV-DP), emtricitabine triphosphate (FTC-TP), deoxyadenosine triphosphate (dATP) and deoxycytidine triphosphate (dCTP) concentrations in PBMCs were collected at 4 timepoints in HIV+ adults receiving TFV/FTC with either efavirenz or atazanavir/ritonavir. Subjects underwent frailty phenotyping (Fried *et al.* method) and p16^{INK4a} expression analysis (PCR-based methods). Concentrations were analyzed with validated LC-MS/MS methods. Noncompartmental analysis (Phoenix Win Nonlinv6.3, Pharsight, St. Louis, MO) generated an area under the curve (AUC) for each analyte. Spearman rank correlation (continuous variables) and the Kruskal-Wallis test (categorical variables) were used to assess associations between AUC, demographics, and aging markers (no adjustments for multiple testing).

Results: Subjects (n=79) ranged in age from 22-73yr (median 48 yr). Mean±SD body mass index was 28.2 ± 5.5 kg/m² and calculated creatinine clearance was 116 ± 36 ml/min. Twenty-six Caucasians, 48 African Americans, and 5 subjects self-identified as Hispanic were included; 24 were female, and 50 received efavirenz. Three subjects (4%; median 56yr, range 51-60yr) demonstrated frailty, with 17 subjects (23%; median 46yr, range 26-60yr) demonstrating pre-frailty of the 75 with available frailty assessments. TFV-dp, FTC-tp, dATP, and dCTP AUCs were significantly negatively associated with p16^{INK4a} expression (Spearman rho range: -0.33 to -0.57, p-values<0.005, n = 70 evaluable). FTC AUC was associated with p16^{INK4a} expression (rho=0.35, p=0.003, n = 70 evaluable) and sex (p<0.05, n = 73 evaluable). dCTP AUC was lower in the presence of frailty/pre-frailty (p<0.05, n = 70 evaluable). TFV, FTC, and TFV-dp AUC were increased among subjects with lower renal function or higher chronologic age (p-values ≤0.05, n = 73 evaluable).

Conclusions: Associations of INM and EN exposure and a marker of T-cell senescence were observed in this cohort with 41% of subjects ≥50 years and 27% with 1+ frailty component. Expression of p16^{INK4a} induces senescence, increases with age, and may play a causal role in age-related decline. Subjects with higher levels of p16^{INK4a} expression have lower INM and EN AUCs, suggesting that senescence affects the

ability of the target cell to phosphorylate drug or alters uptake of the drug into the cell. TFV/FTC are cell-cycle independent nucleos(t)ide agents, but do appear to be affected by senescence. Due to the co-linearity of age and creatinine clearance, the associations between TFV, FTC, and TFV-dp with both of these variables are not independent and should be interpreted cautiously. This finding warrants further mechanistic study to ensure optimal treatment with these agents in the growing aging HIV+ population.

Similar analysis on a subset of these data (43 subjects) was presented at AIDS 2014, Melbourne, Australia, July 24, 2014.

No conflict of interest

Abstract: 31

Pharmacokinetics for Pediatrics, Pregnancy and other Special Populations

Pharmacokinetics of efavirenz and 8-hydroxymetabolites in pre-pubertal children and adolescents with HIV infection.

N. Rakhmanina¹, S. Rossi², H. Gordish-Dressman³, R.H.N. Van Schaik⁴, J.N. Van Den Anker⁵, K. Williams⁶, E. Capparelli²

¹Children's National Health Systems, Infectious Disease, Washington DC, USA; ²University of California San Diego, Schools of Medicine and Pharmacy, San Diego, USA; ³Children's National Health Systems, Genetics, Washington, USA; ⁴Erasmus Medical Centrum, Clinical Chemistry, Rotterdam, The Netherlands; ⁵Children's National Health Systems, Clinical Pharmacology, Washington, USA; ⁶Children's National Health Systems, Infectious Diseases, Washington, USA

Background: Functional polymorphisms in CYP2B6 result in large variability in Efavirenz (EFV) exposure among children and adolescents. Developmental changes in the metabolism of EFV are significant in early infancy and may also play a potentially important role in EFV exposure throughout pubertal maturation. This study was

aimed to evaluate developmental differences in EFV metabolism and CYP2B6 activity measured through 8-hydroxylation of EFV in HIV-infected pre-pubertal children and adolescents.

Materials & Methods: This was a cross-sectional study of HIV-infected pre-pubertal children (Tanner Stages I-II) and adolescents (Tanner Stages III-IV) on EFV-based ART. CNS toxicity was graded based on adapted ACTG questionnaire on the scale 0-70. CYP2B6 genotyping was performed at enrollment using the ABI TaqMan assay. The concentrations of EFV and its metabolites 8-hydroxy-EFV (E8F) and 8-hydroxy-EFV glucuronide (E8G), were measured at steady-state during a 24 hour PK study at time points 0, 1, 2, 4, 6, 8, 12 and 24 hours after an observed standard recommended EFV dose and were quantitated by a published validated HPLC-MS/MS method using the Sciex APT-2000. PK analyses were performed using non-compartmental methods. One-way analysis of variance methods with *post-hoc* adjustment for multiple testing were used to compare mean exposures among CYP2B6 516 genotypes. Normality of each exposure variable was confirmed and log-transformation used where necessary. All results report raw values.

Results: 21 (9 African American, 11 African, 1 Hispanic) pre-pubertal children (n=11; median age 11.7 years; 6 Females) and adolescent patients (n=10; median age 15.2 years; 5 Females) were enrolled. CYP2B6 516 genotype distribution was GG=10, GT=7, TT=4 (HWE p-value=0.21). Median EFV AUC was 59.7mcg*h/mL (range: 17.7-421.4) mcg*hr/mL and CL/F was 0.196 L/h/kg (range: 0.027-0.539). Sub-therapeutic C₂₄ (<1 mg/L) was observed in 2 subjects with CYP2B6 516 GG genotype. Patients with the CYP2B6 516 GT genotype had a significantly greater mean CL/F (13.8±6.9) than patients with the TT genotype (2.9±0.9) (p=0.045), but neither showed a significant difference to patients having the GG genotype. A similar trend was seen in EFV AUC where patients with the GT genotype showed a greater mean than patients with the TT genotype, although this did not reach statistical significance at the α=0.05 level (p=0.07). No significant differences were seen in E8F AUC, (E8F+E8G) AUC, E8F/EFV or (E8F+E8G)/EFV ratios. The median (E8F+E8G)/EFV ratio was 2.78 (range: 0.66-9.38) for GG, 8.56 (range: 0.07-27.04) for GT and 1.27 (range: 0.24-2.68) for TT

genotypes. Median CNS toxicity score was 12.5 (range: 1-23). There was no association between EFV AUC and CYP2B6 genotype with CNS toxicity. No differences in EFV AUC, CL/F and (E8F+E8G)/EFV were observed between children in Tanner Stages I-II and adolescents in Tanner stages III-IV.

Conclusions: CYP2B6 genotype was directly related to the CL/F of EFV in children and adolescents and showed a potential relationship with EFV AUC. EFV plasma exposure was not associated with CNS toxicity. In this cross-sectional study Tanner stage did not influence the PK of EFV and CYP2B6 activity. The analysis of intra-subject dynamics in PK and CYP2B6 activity while transitioning through Tanner stages is ongoing.

No conflict of interest

Abstract: 32

Pharmacokinetics for Pediatrics, Pregnancy and other Special Populations

A Comparison of the Pharmacokinetics of Abacavir during Pregnancy and Postpartum

S. Schalkwijk¹, A. Colbers², K. Kabeya³, J. Moltó⁴, C. Hidalgo-Tenorio⁵, K. Weizsäcker⁶, D. Hawkins⁷, M. van der Ende⁸, D. Burger²

¹Radboud University Medical Center, Pharmacy and Pharmacology&Toxicology, Nijmegen, The Netherlands; ²Radboud University Medical Center, Pharmacy, Nijmegen, The Netherlands; ³Saint-Pierre University Hospital, Infectious disease, Brussels, Belgium; ⁴Hospital Universitari Germans Trias i Pujol, Lluita contra la SIDA Foundation, Barcelona, Spain; ⁵Hospital Universitario Virgen de las Nieves Granada, Infectious disease, Granada, Spain; ⁶Charité Universitätsmedizin, Klinik für Geburtsmedizin, Berlin, Germany; ⁷Chelsea & Westminster Hospital, HIV and Sexual Health Services, London, United Kingdom; ⁸Erasmus Medical Center, Internal medicine, Rotterdam, The Netherlands

Background: During pregnancy physiological changes take place which can influence the pharmacokinetics (PK) of antiretroviral agents and lead to decreased drug exposure. Effective drug concentrations are important to prevent treatment failure, development of resistance and mother-to-child transmission. Abacavir (ABC) in combination with lamivudine is a preferred NRTI to be used in pregnancy according to perinatal guidelines. Pregnancy did not influence PK of the abacavir 300mg BID dose. Here, the first full PK results in pregnancy of the more frequently used 600mg QD dose are presented.

Materials & Methods: An open-label, multi-centre phase IV study in HIV infected pregnant women recruited in HIV treatment centers in Europe (PANNA Network). Patients treated with ABC 600 mg QD during pregnancy had intensive steady-state 24-h PK profiles in the 3rd trimester and at least 2 weeks postpartum. Where possible cord blood (CB) and matching maternal blood samples were taken at delivery to assess placental transfer. Safety and virological efficacy were evaluated.

Results: 9 patients (4 Black, 5 Caucasian with a median (range) age of 34 (25-39) years) were included in the analysis. None were treatment naive at conception, all used lamivudine as 2nd NRTI, 7 used a PI, 1 an NNRTI and 1 used 3 NRTIs.

Median (range) gestational age at delivery was 38 weeks (37-40); birth weight was 3200 (2060-3660) gm. Approaching delivery all patients had a VL <50 cps/mL. One SAE was reported: hospital admission to exclude pre-eclampsia. The patient was discharged after 3 days, treatment was not interrupted. 8/9 children were HIV un-infected (1 unknown status) and no birth defects were reported. Paired PK curves (3rd trimester and postpartum) were available for all patients. ABC AUC_{0-24h} was 8% (92-128%, 90% CI) higher during the 3rd trimester compared to postpartum, whereas C_{max} was 7% (75-117%) lower and t_{half} was prolonged with 19% (103-137%). Geometric mean (95% CI) for AUC_{0-24h}, C_{max} and t_{half} in the 3rd trimester were: 13.7 (10.1-18.6) mg*h/L, 3.83 (3.17-4.64) mg/L and 3.8 (2.4-6.0) h respectively. Geometric mean (95% CI) for AUC_{0-24h}, C_{max} and t_{half} postpartum were: 12.6 (10.5-15.1) mg*h/L, 4.11 (3.44-4.92) mg/L and 3.2 (2.1-4.9) h respectively. Postpartum PK parameters were comparable to reference values as reported in the

SPC text. Ratio of CB/maternal ABC concentrations (n=2) were 0.73 and 1.01.

Conclusions: Abacavir PK parameters are not influenced by pregnancy, therefore the 600mg QD dose is an appropriate dose in pregnancy. Abacavir was well tolerated during pregnancy without causing congenital abnormalities. Abacavir efficiently crosses the placenta.

Conflict of interest: The PANNA network is financially supported by the "European AIDS Treatment Network (NEAT)", EC, DG Research, 6th Framework program, BMS, MSD and Janssen Pharmaceuticals N.V.

Abstract: 33

Pharmacokinetics for Pediatrics, Pregnancy and other Special Populations

Rilpivirine Population Pharmacokinetic Modeling in Antiretroviral-Naïve HIV-1-infected adolescents in PAINT

A. Brochot¹, A. Hoogstoel¹, S. Vanveggel¹, M. Stevens¹, H.M. Crauwels¹

¹Janssen Infectious Diseases BVBA, Beerse, Belgium

Background: Rilpivirine (RPV, TMC278, Edurant®) is a non-nucleoside reverse transcriptase inhibitor (NNRTI) approved, in combination with other antiretrovirals (ARV), for the treatment of ARV-naïve HIV-1-infected, adults. PAINT (P_ediatric study in A_dolescents I_nvestigating a N_ew NNRTI T_MC278, NCT00799864) is an ongoing, open label, single arm, Phase 2 study to evaluate RPV pharmacokinetics, safety/tolerability, and antiviral activity in ARV-naïve HIV-1-infected adolescents. The current analysis examined the RPV pharmacokinetics in PAINT with population pharmacokinetic modeling.

Materials & Methods: Antiretroviral-naïve HIV-1-infected adolescents (>12 – ≤18y, n=36) were recruited from investigational sites in India,

Thailand, Uganda, South Africa and the United States. All patients were treated with RPV 25mg once daily (qd) and two nucleoside/nucleotide reverse transcriptase inhibitors. Intensive PK sampling was done (24-hour PK profile at Week 2 or 4) in a subset of patients, as previously reported. Sparse PK samples were taken in all subjects at Weeks 2, 4, 8, 12, 24 and 48. The population pharmacokinetic model that best described the pharmacokinetics of RPV was a 2-compartment disposition model in which absorption was described by a lag time followed by a sequential zero- and first-order absorption process, similar to the model previously developed for adults. The model structure and fixed effect parameters were kept the same as in the adult model, and random effect parameters were modified with the addition of inter-occasion variability on clearance. Individual values for RPV trough plasma concentrations (C_{trough}) and area under the plasma concentration-time profile over the dosing interval (AUC_{24h}) were estimated per visit; the median value across visits was used per subject for the analysis. In addition, the potential relationship between selected covariates (age, gender, bodyweight, race) and RPV pharmacokinetics was graphically evaluated.

Results: The RPV 25 mg qd pharmacokinetics and variability were similar in adolescents and adults: mean (SD) RPV C_{trough} and AUC_{24h} were 84 (39) ng/mL and 2391 (991) ng*h/mL in adolescents (n=34) and 80 (37) ng/mL and 2397 (1032) ng*h/mL in adults (n=679, pooled Phase 3 studies), respectively. The apparent oral clearance of RPV was estimated to be 13.3 L/h (inter-individual variability 32%). Age, gender and bodyweight were not found to impact the RPV apparent oral clearance in adolescents. The impact of race could not be evaluated in adolescents, as the majority of subjects were of one single race (89% black/African American).

Conclusions: The population pharmacokinetic model for RPV was updated with data from a Phase 2 study in ARV naïve HIV-1 infected adolescents (12 to <18 years). The pharmacokinetics of RPV 25 mg qd in HIV-1 infected adolescents are similar to those in adults. As in adults, no clinically relevant covariates were identified affecting the exposure to RPV in adolescents.

Conflict of interest: Employees of Janssen

Abstract: 34

Pharmacokinetics for Pediatrics, Pregnancy and other Special Populations

First human data on placental transfer of dolutegravir using an ex vivo perfusion model

S. Schalkwijk¹, R. Greupink², A. Colbers¹, J. van Drongelen³, F.G.M. Russel², D. Burger¹

¹Radboud University Medical Center, Pharmacy, Nijmegen, The Netherlands; ²Radboud University Medical Center, Pharmacology and Toxicology, Nijmegen, The Netherlands; ³Radboud University Medical Center, Obstetrics and Gynecology, Nijmegen, The Netherlands

Background: Data on fetal exposure to antiretroviral agents during pregnancy is important to estimate the potential for pre-exposure prophylaxis and toxicity. For the new antiretroviral agent dolutegravir, clinical data on the fetal disposition is not yet available. Dual perfusion of a single placental lobule (cotyledon) may provide a useful *ex vivo* model to predict the *in vivo* maternal to fetal transfer of this drug. The aim of this study was to develop and validate a placenta perfusion model to estimate fetal exposure to dolutegravir during term human pregnancy.

Materials & Methods: *Ex vivo* a fetal vein and artery of an intact cotyledon were cannulated. After successful initiation of the fetal circulation (6 ml/min) the maternal circulation (12 ml/min) was initiated by inserting 4 cannulas into the intervillous space. The perfusion medium consisted of Krebs-Henseleit buffer supplemented with 10.1 mM glucose and 0.5 ml/L heparin 5000IE to avoid coagulation of any remain blood. The buffer was oxygenated with 95% O₂ / 5% CO₂ and the pH controlled between 7.2 – 7.4. Antipyrine (100 mg/L) and inulin(-FITC) (0.73 mg/L; 4-5 kDa) were included as diffusion and leakage markers, respectively. Arterial pressure, temperature, and volume loss were monitored during the perfusion. Transplacental transport was measured after administration of dolutegravir to the maternal circulation (± 0.42 mg/L). Serial samples were taken from both

compartments over a period of 120 minutes and analyzed using HPLC-MS/MS.

Results: Perfusions were conducted with antipyrine (n=4), inulin (n=2), and dolutegravir (n=3) in a total of 6 placentae. The average fetal-to-maternal-concentration-ratios of antipyrine, inulin, and dolutegravir at t=120 min were 0.77 ± 0.09 , 0.08 ± 0.02 , and 0.35 ± 0.03 , respectively. The average dolutegravir concentration in the maternal circulation at t=1 was 0.26 ± 0.01 . At t=120 the concentration was 0.14 ± 0.02 mg/L in the maternal compartment and 0.047 ± 0.004 mg/L in the fetal compartment. As plasma proteins were not supplemented to the perfusion medium these concentrations should be interpreted as unbound drug concentration. In a previous clinical study, the unbound dolutegravir concentration in the 2-6-hour post dose window was estimated to be 0.024 mg/L after 16 weeks of treatment of HIV-1-infected adults. In this study, the average dolutegravir concentration in the maternal circulation at t=120 was about 6 times higher, and therefore may represent the upper limit of unbound concentrations found clinically. At t=120 the cumulative concentration in maternal and fetal circulation was about 70% of the concentration measured in the maternal circulation at t=1. For the purpose of mass-balance, the remaining 30% may represent placental association and/or system adherence.

Conclusions: *Ex vivo* placental transfer of antipyrine and inulin were in line with data from previous studies, demonstrating that the perfusion set-up was functional. Although more data is needed and clinical studies are warranted for confirmation, these preliminary results indicate that dolutegravir passes the placental barrier *ex vivo* and that transfer is low to moderate. This might also reflect the *in vivo* situation, which implicates exposure to dolutegravir of the newborn. Because of immaturity of the main metabolizing enzyme UGT1A1, a relatively long washout period of dolutegravir from the neonatal circulation is expected.

Conflict of interest: This study was supported by a TKI-LSH matching program.

Abstract: 35

Pharmacokinetics for Pediatrics, Pregnancy and other Special Populations

Evaluating Concentrations of Antiretrovirals : Atazanavir, Darunavir and Tenofovir in Subjects with HIV and Type 2 Diabetes Mellitus - a Pilot Study

Y.F. Yeung¹, H. Wang¹, Z. Ngan¹, M. El-Sakkary¹, V. Michaud², P.O. Hétu³, B. Lebouché⁴, N.L. Sheehan⁵

¹McGill University Health Centre and Université de Montréal, Pharmacy Department and Faculty of Pharmacy, Montreal, Canada; ²Centre de recherche du Centre Hospitalier de l'Université de Montréal and Université de Montréal, Faculty of Pharmacy, Montreal, Canada; ³Centre de recherche du Centre Hospitalier de l'Université de Montréal and Hôpital Notre-Dame Centre Hospitalier de l'Université de Montréal, Biochemistry Department, Montreal, Canada; ⁴McGill University Health Centre and McGill University, Chronic Viral Illness Service and Department of Family Medicine, Montreal, Canada; ⁵McGill University Health Centre and Université de Montréal, Chronic Viral Illness Service and Pharmacy Department and Faculty of Pharmacy, Montreal, Canada

Background: Studies reveal that patients with diabetes have varying concentrations of certain medications compared to the general population. HIV-infected patients are living longer and diabetes is twice as frequent in HIV-infected patients than in non infected patients. The pharmacokinetics of antiretrovirals (ARV) may be altered in diabetic patients. The aim of this pilot study was to assess the impact of type 2 diabetes mellitus (T2D) on the plasma concentrations at the end of the dosing interval (C_{trough}) and 4 hours post-dose (C_{4h}) of atazanavir (ATZ), darunavir (DRV) and tenofovir (TNF) in HIV-infected subjects.

Materials & Methods: A cross-sectional, single centre, pilot pharmacokinetic study in HIV-infected subjects stabilized on ATZ/ritonavir(r), DRV/r or TNF without protease inhibitors was conducted. Subjects with body mass index (BMI) above 35 kg/m², liver enzymes above 3 times the upper limit of normal, estimated glomerular

filtration rate (eGFR) below 30 (below 50 for TNF group) mL/min/1.73 m², pregnant, with acute infection, or taking medications known to interact with the ARVs were excluded. Subjects were matched (diabetic versus non diabetic) as best as possible for gender and ARV regimen. Plasma C_{trough} and C_{4h} of ARVs were measured by LC-MS/MS. Relationships and correlations between these concentrations and covariates [diabetes status, fasting plasma glucose (FPG), HOMA2-IR, glycated hemoglobin (HbA1c), genetic polymorphisms of drug transporters and cytochrome P450 isoenzymes, age, BMI and renal function] were explored using various tests (Kruskal-Wallis, Spearman rank correlation test, univariate and multivariate linear regression analyses).

Results: Forty-nine (49) subjects (22 diabetics and 27 non diabetics) completed the study (median age 53 years, 65.3% male, 49% Caucasian, median eGFR 97 mL/min/1.73 m³). The median HbA1c were 6.5% (IQR 6.0 – 7.7%) and 5.5% (IQR 5.1-5.7%) in the diabetic and non diabetic subjects, respectively. The median TNF C_{trough} for diabetic and non diabetic subjects were 0.069 and 0.051 mg/L, while the median C_{4h} were 0.192 and 0.135 mg/L, respectively. ATZ C_{trough} in diabetics was decreased by 15 to 57% (p=ns), depending on the subgroup. In diabetic subjects compared to non diabetic subjects, depending on the subgroups, ATZ C_{4h} varied by -31% to + 2%, DRV C_{trough} by -32 % to +171% and DRV C_{4h} by -22% to + 26%. A very weak positive statistically significant correlation was found between TNF C_{4h} and FPG. Although not seen in the multivariate regression, the univariate regression showed that T2D and increasing FPG were associated with increased TNF C_{4h} (β : 0.065, p=0.037; β : 0.017, p=0.037). As expected, TNF C_{trough} was positively associated with increasing age and decreasing renal function. The results are limited by small sample sizes by subgroup, large interpatient variability and a small proportion of subjects with uncontrolled diabetes.

Conclusions : T2D and FPG is associated with increased TNF C_{4h}. These factors may potentially be influencing intestinal transporters increasing TNF absorption. These observations require further validation in a larger study.

No conflict of interest

Abstract: 36

Pharmacokinetics for Pediatrics, Pregnancy and other Special Populations

Week 24 data from a Phase 3 clinical trial of E/C/F/TAF in HIV-infected adolescents

H. Kizito¹, A. Gaur², W. Prasitsuebsai³, N. Rakhmanina⁴, E. Lawson⁵, Y. Shao⁶, S. Bennett⁷, A. Cheng⁸, E. Quirk⁷

¹Joint Clinical Research Centre, NA, Kampala, Uganda; ²St.

Jude Children's Research Hospital, NA, Memphis, USA;

³HIVNAT, NA, Bangkok, Thailand; ⁴Children's National

Health System, NA, Washington D.C., USA; ⁵Gilead

Sciences Inc., Clinical Pharmacology, Foster City, USA;

⁶Gilead Sciences Inc., Biostatistics, Foster City, USA; ⁷Gilead

Sciences Inc., Clinical Research, Foster City, USA; ⁸Gilead

Sciences Inc., Dev Ops Admin, Foster City, USA

Background: EVG/COBI/FTC/tenofovir alafenamide (TAF) [E/C/F/TAF] is an integrase inhibitor-based single tablet regimen in clinical development for use in HIV-infected adolescents. Pharmacokinetics, safety and efficacy from a planned interim analysis of the first clinical trial of E/C/F/TAF in adolescents are reported.

Materials & Methods: Treatment-naïve 12 to <18 year-olds weighing ≥ 35 kg with HIV-1 RNA >1000 copies/mL (c/mL), CD4 >100 cells/ μ L and eGFR >90 mL/min/1.73m² received E/C/F/TAF once daily in a prospective, 2-part, 48-week, single-arm, open-label trial. Steady-state pharmacokinetic (PK) parameters were compared to an adult reference population by an analysis of variance (ANOVA), and related to the range of exposures associated with antiviral activity in adults. Adverse events (AE), laboratory tests, and the proportion of subjects with HIV-1 RNA < 50 c/mL were assessed through Week 24. Bone mineral density (BMD) was measured by dual-energy X-ray absorptiometry.

Results: The trial enrolled 48 adolescents with a median age of 15 years, median weight of 52 kg, 58% female, 88% Black, 13% Asian, 67% vertically infected, 35% with HIV-1 RNA > 100,000 c/mL, median CD4 count 468 cells/ μ L, and median serum creatinine [sCr] 0.57 mg/dL.

TAF, TFV, EVG, COBI, and FTC PK profiles of adolescents were consistent with those in adults. Of 23 subjects followed to Week 24, 21 (91%) had HIV-1 RNA <50 c/mL (Figure). No deaths or AE-related discontinuations occurred. The most frequent AEs were nausea (23%), upper respiratory infection (21%), and diarrhea (17%). One serious AE of visual impairment and intermediate uveitis occurred and resolved without interruption of E/C/F/TAF. The median change in sCr was +0.08 mg/dL at Week 24, consistent with cobicistat's inhibition of renal tubular Cr secretion. No renal failure or proximal renal tubulopathy occurred. From baseline to Week 24, the change in median spine BMD was +2.8% with a change in height-adjusted (HA) Z-score of +0.02 and 2/23 subjects (9%) having a decrease of $\geq 4\%$. The change in median total body less head BMD was +0.3% with a change in HA Z-score of +0.09 and no decreases of $\geq 4\%$. No fractures occurred.

Conclusions: Therapeutic plasma concentrations of all components of E/C/F/TAF were achieved, consistent with potent antiviral activity of the regimen. Treatment was generally well-tolerated through 24 weeks with a favorable renal and bone safety profile. These promising findings support E/C/F/TAF's eventual use in adolescents and its further evaluation in other pediatric populations.

Previously presented at CROI, Seattle, WA, 2015.

Conflict of interest: Employee of Gilead Sciences, Inc.

Abstract: 37*Pharmacogenetics***Genetics of nevirapine metabolite kinetics at steady state in HIV-infected Cambodians (ANRS12154 study)**

P. Eloy¹, P. Fan-Havard², C. Monidarin³, S. Gazal⁴, A. Tessier⁴, A.M. Taburet⁵, J. Bertrand⁶, D.W. Haas⁷, A. Barrail-Tran⁸

¹Hôpital Bicêtre, Clinical Pharmacy, Le Kremlin Bicêtre, France; ²University at Buffalo, School of Pharmacy and Pharmaceutical Sciences, Amherst, USA; ³Faculty of Pharmacy University of Health Sciences, Fondation Merieux Laboratory, Phnom Penh, Cambodia; ⁴INSERM, IAME UMR 1137, Paris, France; ⁵Hôpital Bicêtre, Clinical Pharmacy INSERM UMR 1184, Le Kremlin Bicêtre, France; ⁶UCL Genetics Institute, Statistical Science Department, London, United Kingdom; ⁷Vanderbilt University School of Medicine, Departments of Medicine Pharmacology Pathology Microbiology and Immunology, Nashville, USA; ⁸Hôpital Bicêtre University Paris Sud, Clinical Pharmacy INSERM UMR 1184, Le Kremlin Bicêtre, France

Background: Metabolism of nevirapine generates 4 primary hydroxylated metabolites, and involves different cytochrome P450 (CYP) isoforms. Plasma concentrations of these metabolites have been previously described in HIV-infected Cambodians who enrolled in the ANRS12154 study. In vitro studies suggest that involved isoforms are CYP3A4 for 2-hydroxy-nevirapine (2OH-NVP), CYP2B6 for 3OH-NVP, CYP3A4 and CYP2D6 for 8OH-NVP, and CYP3A4 and CYP2D6 for 12OH-NVP. The aim of this study is to explore genetic associations with nevirapine metabolites concentrations, including CYP2B6 single nucleotide polymorphisms (SNPs) associated with slower nevirapine clearance in this Asian population (rs3745274 (516G->T), rs7251950, and rs2279343).

Materials & Methods: HIV-infected patients were from the ESTHER (Ensemble pour une Solidarité Thérapeutique Hospitalière en Réseau) cohort (Calmette Hospital, Phnom Penh, Cambodia) and had consented for genetic testing. All participants were receiving nevirapine plus two nucleoside

analogs. Nevirapine, 2OH-NVP, 3OH-NVP, 8OH-NVP and 12OH-NVP pre-dose concentrations were assayed at 36 months of therapy. Nevirapine was assayed by HPLC and metabolites by LC/MS/MS with a limit of quantification of 1ng/mL. Metabolic index was defined as the ratio of metabolite concentration to nevirapine concentration. DNA was extracted from buffy coats. Genotyping for ABCB1, CYP2B6, CYP3A4, CYP3A5 and NR1I2 SNPs was as previously described (Bertrand et al., 2012). Associations between SNPs and metabolic index were characterized by univariate linear regression, and also after adjusting for CYP2B6 516G->T.

Results: Among 127 individuals with evaluable genetic data, 129 of 197 assayed loci were polymorphic. Concentrations of each metabolite in plasma were considerable less than nevirapine concentrations. Metabolic indices were low and varied considerably, ranging from 0.71 to 21.75% for 12OH-NVP, 0.13 to 2.00% for 3OH-NVP, 0.06 to 0.77% for 8OH-NVP, and <0.01 to 0.22% for 2OH-NVP. In univariate analyses, 7 CYP2B6 SNPs were associated with 3OH-NVP metabolic index (lowest P = 1.9×10^{-4}), and 10 CYP2B6 SNPs were associated with 8OH-NVP metabolic index (lowest P = 4.1×10^{-5}). These included CYP2B6 516G->T. No SNP was associated with 2OH-NVP or 12OH-NVP metabolic index. After adjusting for CYP2B6 516G->T, no other SNP was associated with 3OH-NVP or 8OH-NVP metabolic index.

Conclusion: This study shows that among HIV-infected Cambodians, CYP2B6 loss-of-function SNPs that are associated with slower plasma clearance of nevirapine also affect plasma profiles of nevirapine metabolites. Associations of CYP2B6 SNPs with metabolic indices for both 8OH-NVP and 3OH-NVP suggest that CYP2B6 is involved in generating both metabolites.

No conflict of interest

Abstract: 38*PK/PD modeling***Pharmacokinetics of Dasabuvir when Administered with Ombitasvir, Paritaprevir and Ritonavir in Healthy Volunteers***A. Polepally¹, M. Kosloski¹, A. Khatri¹, R. Menon¹, S. Dutta¹**¹AbbVie, Cilinical Pharmacology and Pharmacometrics, North Chicago, USA*

Background: Dasabuvir is an HCV NS5B non-nucleoside polymerase inhibitor that is given with ombitasvir, paritaprevir (identified by AbbVie and Enanta) and ritonavir as combination therapy with and without ribavirin for the treatment of hepatitis C virus (HCV) infection. The objectives were to characterize dasabuvir pharmacokinetics and to identify subject-specific covariates that affect dasabuvir exposures.

Materials & Methods: Pharmacokinetic data were obtained from a Phase 1 single-dose, crossover study in healthy volunteers (N=59). Subjects received dasabuvir at 250 mg and 500 mg doses as part of therapeutic and supratherapeutic combination regimens of ombitasvir + paritaprevir + ritonavir + dasabuvir. A dasabuvir population pharmacokinetic model was built using non-linear mixed-effects modeling approach (NONMEM 7.2) with First Order Conditional Estimation with interaction (FOCE-I) estimation method. Covariates (age, sex, race, body weight, body surface area, and body mass index) were tested on apparent clearance (CL/F) and central volume of distribution (Vc/F). Model development was guided by diagnostic plots, likelihood ratio tests, and prior knowledge of dasabuvir pharmacokinetics. Final model evaluation was done by bootstrap analysis and visual predictive checks.

Results: Dasabuvir plasma concentrations were optimally characterized by a two-compartment model with first-order elimination and absorption with a lag time. Only body weight was identified as a significant covariate on CL/F. Mean (standard error of estimate) dasabuvir

pharmacokinetic parameter estimates were: CL/F (for a 75 kg subject) = 20.9 (1.2) L/h; Vc/F = 54.2 (6.7) L; peripheral volume of distribution (Vp/F) = 308 (61) L; intercompartmental clearance (Q/F) = 10.9 (0.8) L/h; absorption rate constant (k_a) = 0.204 (0.011) h⁻¹; absorption lag time (t_{lag}) = 0.909 (0.011) h.

Conclusions: The pharmacokinetic model adequately described the observations over the entire dasabuvir plasma concentration range. This model can be used to conduct simulations or to evaluate the dasabuvir exposure-response relationship.

Conflict of interest: AbbVie contributed to the study design, research, and interpretation of data, writing, reviewing, and approving the publication. All authors are AbbVie employees and may hold AbbVie stocks or options.

Abstract: 39*PK/PD modeling***Population Pharmacokinetics of Paritaprevir, Ombitasvir and Ritonavir in Japanese Subjects with HCV Genotype 1b infection***S. Gopalakrishnan¹, A. Polepally², S. Mensing¹, R. Menon², A. Khatri²**¹AbbVie Deutschland GmbH & Co KG, Clinical Pharmacology and Pharmacometrics, Ludwigshafen am Rhein, Germany; ²AbbVie Inc., Clinical Pharmacology and Pharmacometrics, North Chicago IL, USA*

Background: In Japan, about 2 million individuals are infected with Hepatitis C virus (HCV). Only 1% to 2.5% of HCV-infected Japanese patients carry sub-genotype 1a, and 70% of infection is due to sub-genotype 1b (GT1b). The all-oral interferon (IFN)-free, 2 direct acting antiviral (2D) regimen of paritaprevir/r (NS3/4A protease inhibitor identified by AbbVie and Enanta, coadministered with ritonavir, a pharmacokinetic enhancer) + ombitasvir (NS5A inhibitor) ± ribavirin is being evaluated in HCV GT1b/2-infected Japanese subjects. The

objective of these analyses was to characterize the population pharmacokinetics (PopPK) of paritaprevir, ombitasvir and ritonavir, and to identify the patient-specific covariates affecting their exposures.

Materials & methods: Pharmacokinetic data from a Phase 3 study (N = 257) were used for the analysis. In this study, HCV GT1b-infected subjects received ombitasvir/paritaprevir/r 25/150/100 mg QD for 12 weeks. PopPK model building and parameter estimation was performed using first-order conditional estimation with interaction (FOCE-I) method in NONMEM 7.3. Patient-specific covariates (age, sex, body weight, body mass index, body surface area, creatinine clearance [CrCL], and presence of cirrhosis [CRHS]) were tested for their effect on PopPK model parameters (clearance [CL/F] or volume of distribution [V/F]). Model development was guided by goodness-of-fit plots, likelihood ratio tests, and prior knowledge of DAA pharmacokinetics. Model evaluation was done by bootstrap analysis and visual predictive checks (VPCs).

Results: The pharmacokinetics of paritaprevir, ombitasvir and ritonavir were adequately described by a one-compartment model with first-order absorption and elimination. Presence of cirrhosis was a statistically significant covariate on CL/F of paritaprevir. The population estimates for CL/F and V/F were 1090 L/day and 459 L respectively. On average, subjects with cirrhosis were estimated to have approximately 95% to 145% higher paritaprevir exposures than those without cirrhosis.

Sex, CrCL and CRHS were statistically significant covariates on CL/F of ombitasvir. The population estimate of CL/F (for a male non-cirrhotic subject with the CrCL of 77 mL/min) and V/F were 639 L/day and 261 L, respectively. On average, female subjects were estimated to have approximately 58% to 81% higher ombitasvir exposures than male subjects and subjects with cirrhosis were estimated to have 19% to 24% lower ombitasvir exposures than those without cirrhosis.

Only CRHS was a statistically significant covariate on CL/F of ritonavir. The population estimates for CL/F and V/F were 905 L/day and 475 L, respectively. On average, subjects with cirrhosis were estimated to have approximately

58% to 68% higher ritonavir exposures than those without cirrhosis.

Bootstrap analyses indicated robust parameter estimation in all models and VPCs reflected good predictive performance.

Conclusions: The observed pharmacokinetic data for all drugs was well-described by the PopPK analysis. The results of the population pharmacokinetic analyses suggest that presence of cirrhosis was a significant predictor of higher exposures (paritaprevir and ritonavir) or lower exposures (ombitasvir) compared to the average population. However, these changes did not adversely affect the safety or efficacy and are not clinically relevant; no dose adjustment is recommended in these populations. Estimated covariate effects were generally consistent between Japanese and Western subjects.

Conflict of interest: AbbVie contributed to the study design, research, and interpretation of data, writing, reviewing, and approving the publication. All authors are AbbVie employees and may hold AbbVie stocks or options.

Abstract: 40

PK/PD modeling

Population pharmacokinetic modeling of tenofovir alafenamide following administration of elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide

F. Jin¹, J. Custodio¹, L. Gibiansky², W. Garner³, B. Kearney¹, J. Zack¹

¹Gilead Sciences, Clinical Pharmacology, Foster City, USA;

²QuantPharm LLC, Quantitative Pharmacology, North Potomac, USA; ³Gilead Sciences, Biometrics, Foster City, USA

Background: Tenofovir alafenamide (TAF), a novel prodrug of tenofovir (TFV), is a nucleotide analog that inhibits HIV-1 reverse transcription and is currently under regulatory review for the treatment of HIV-1 infection as a component of the elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (EVG/COBI/FTC/TAF (150/150/200/10 mg); E/C/F/TAF) single tablet regimen (STR). The objective of this analysis was to develop a population pharmacokinetic model for TAF and its metabolite TFV, and to evaluate the impact of covariates on their PK, following administration of E/C/F/TAF STR.

Materials & Methods: Data from 3 phase I studies in healthy volunteers (n=79) and 6 phase II/III studies in patients with HIV-1 infection (n=1543) were included in this analysis where TAF was given as a single tablet regimen containing E/C/F/TAF. Data were analyzed using NONMEM 7.3 with first order conditional estimation allowing for interaction (FOCE-I). Stepwise forward addition followed by backward elimination was implemented in the covariate (age, gender, race, body weight, body surface area, body mass index, creatinine clearance, and disease status) model building process to develop final PopPK model. Various model assessment methods were used to evaluate the model performance.

Results: Both TAF and TFV plasma PK were best described by two-compartment models with absorption lag time and sequential zero- and first-order absorption. Extensive covariate analyses did not identify any covariates that had a statistically significant influence on TAF PK. The population median estimated TAF apparent clearance and central volume of distribution for a typical HIV patient were 56.3 L/hr and 10.3 L, respectively. As expected, due to renal elimination of the metabolite TFV, the main covariate that influenced the PK of TFV was creatinine clearance. Other statistically significant covariates retained in the final model were HIV status (HIV-infected patient versus healthy subject), sex, and race (black versus nonblack). The population median estimated TFV apparent clearance and central volume of distribution for a typical HIV patient were 30.2 L/hr and 1600 L, respectively. Differences in TFV exposure between subjects due to statistically significant covariates were less than 2-fold. Since the systemic TFV exposures following E/C/F/TAF

STR were substantially lower compared to TDF (300 mg)-containing regimens, these differences were not considered clinically meaningful.

Conclusions: Following administration of E/C/F/TAF STR, the PK of both TAF and its metabolite TFV were adequately described by a two-compartment model with absorption lag time and sequential zero- and first-order absorption. No statistically significant covariates were identified for TAF PK. The influences of statistically significant covariates on TFV exposure were not considered to be clinically meaningful.

Conflict of interest: Employees/contracted by and shareholders of Gilead Sciences.

Abstract: 41

PK/PD modeling

Modeling of Maraviroc Pharmacokinetics in HIV-1 Infected Patients Co-Infected with Hepatitis B and/or Hepatitis C

M. Vourvahis¹, B. Weatherley², L. McFadyen²

¹Pfizer Inc, Clinical Pharmacology, New York NY, USA;

²Pfizer Inc, Pharmacometrics, Sandwich, United Kingdom

Background: Little data exists on the maraviroc (MVC) pharmacokinetics (PK) in HIV-infected patients co-infected with hepatitis. The present analysis uses a semi-physiological MVC PK model to estimate MVC exposures following the addition of MVC to optimized background therapy (OBT) in HIV-infected patients co-infected with HBV and/or HCV who had undetectable HIV-1 RNA for ≥ 3 months prior to study entry. An exploratory analysis was also conducted to assess the effect of MVC exposures on liver function tests, Enhanced Liver Fibrosis (ELF) test and Hepatic Elastography (FSCN).

Materials and Methods: MVC PK samples were taken pre-dose, 2 and 4 hours post-dose at Weeks 4 and pre-dose and 2 hours post-dose at Week 48. Nonlinear mixed effects modeling (NONMEM®) was used to apply a model with 2 absorption and 4 disposition compartments with different absorption rate constants and lag times on both depot compartments, a general GI first pass effect, a renal clearance and a nonlinear absorption component. In this analysis the model was updated to account for additional OBT treatments (CYP3A4 inducers) so that the model can be applied to all MVC dosing scenarios. Change from baseline to Week 48 for ELF test, hepatic elastography, ALT, AST, alkaline phosphatase (ALK) and bilirubin (BIL) was assessed for exploratory analysis. FSCN was assessed only at sites that have Fibroscan™ equipment.

Results: 70 subjects were assigned to the MVC plus OBT group and 67 to the placebo plus OBT group. Three subjects in the MVC group were excluded as PK data were not available. There were 283 observed MVC concentrations. The estimated median MVC average (C_{avg}) and maximum (C_{max}) concentrations were 270 ng/mL and 566 ng/mL, respectively. Of the 67 subjects in the MVC group, 31 subjects received MVC 150 mg BID with a potent CYP3A4 inhibitor (C_{avg} : 262 ng/mL; C_{max} : 496 ng/mL), 28 subjects received MVC 600 mg BID with a potent CYP3A4 inducer (C_{avg} : 309 ng/mL; C_{max} : 915 ng/mL), and 8 subjects received MVC 300 mg BID without a potent CYP3A4 inhibitor and/or inducer (C_{avg} : 166 ng/mL; C_{max} : 258 ng/mL).

There was no apparent relationship between change from baseline in ELF, ALK, ALT, AST and BIL versus MVC C_{avg} . There was an apparent trend of greater decrease in FSCN from baseline with increasing MVC C_{avg} ($p=0.087$).

Conclusions: The *post hoc* Bayesian PK parameter estimates provided reasonable individual PK profiles suitable for exposure-response analysis. MVC exposures were comparable to the exposures observed in the registrational studies when MVC was co-administered with a potent CYP3A4 inhibitor or without a potent CYP3A4 inhibitor and/or inducer although MVC 600 mg BID dose with potent CYP3A4 inducers was not studied in Phase 3. Graphical exposure-response analysis of PD endpoints showed no apparent exposure

relationships with MVC C_{avg} . However, although not statistically significant, a trend was seen for a greater decrease in FSCN from baseline with increasing MVC exposures.

Conflict of interest: Employee of Pfizer Inc, and hold stock/stock options in Pfizer Inc.

Abstract: 42

PK/PD modeling

Revisiting the Population Pharmacokinetics of Maraviroc in the MERIT study with the Inclusion of CYP3A4/CYP3A5 and SLCO1B1 Genotype Covariates

P.L.S. Chan¹, M. Vourvahis², B. Weatherley¹, A. Clark³, L. McFadyen¹

¹Pfizer Inc, Pharmacometrics, Sandwich, United Kingdom;

²Pfizer Inc, Clinical Pharmacology, New York NY, USA; ³ViiV Healthcare, London, United Kingdom

Background: The population pharmacokinetics of maraviroc (sparse PK) in treatment-naïve subjects in the MERIT study receiving maraviroc 300 mg QD and BID with zidovudine/lamivudine were reported in 2008. This analysis showed that taking maraviroc with food reduced AUC by 11% ($p<0.001$) and that Blacks+others had a 17.5% greater AUC than Whites+Asians ($p<0.05$). Female gender and greater age (predicting greater AUC) although significant on the likelihood ratio test (LRT) ($p<0.05$) were not significant using bootstrap confidence intervals for the covariate effect. These covariate effects were not deemed likely to cause safety or efficacy issues with the 300 mg BID dose.

Responding to a recent report that the CYP3A5*1/*1 wild-type genotype (common in Blacks) leads to lower concentrations, the population PK analysis was repeated with the addition of 3 genotypes to the covariate pool: CYP3A5 (No *1, One *1 or *1/*1 alleles),

CYP3A4/CYP3A5 cluster and SLCO1B1 (No *15, *1A/*15 or *1B/*5, *1B/*15 or *5/*15, *15/*15).

Materials and Methods: NONMEM 5.1.1 was used to re-analyze PK data from 494 subjects treated with maraviroc after removal of 18 subjects with no available genotype data/samples. The same structural model, a 2- compartment semi-mechanistic model with some fixed parameters from phase 1/2a, was used as in the 2008 analysis. Extraction ratio was estimated and the genotype covariates were tested on this parameter in addition to the original covariates. The original analysis pooling of race was re-tested. A manual forwards procedure was utilized for testing covariates ($p < 0.05$, objective function value change (OFV) of 3.84 with 1 degree of freedom for LRT) with the covariate giving the highest OFV change taken into the next forward round. A final backwards elimination procedure ($p < 0.05$) was then applied to exclude non-significant covariates from the final forward model.

Results: Results were similar to those found in 2008. Taking maraviroc with food had the most significant effect in reducing AUC ($p < 0.001$). Of the demographic covariates, race was again significant with Blacks+others having 6.15% reduction in extraction ratio vs Whites+Asians, females having 5.4% reduction in extraction ratio. Age was no longer significant on backwards deletion.

Only SLCO1B1 genotype (3 categories) showed statistical significance. Subjects with SLCO1B1*15/*15 ($n=6$) and those with SLCO1B1*1A/*15 or SLCO1B1*1B/*5 ($n=67$) were predicted to have decreased extraction ratio of 20.7% and 6.89 % respectively vs combined No SLCO1B1*15, $n=390$ or (*1B/*15 or *5/*15) $n=31$. CYP3A5 genotype alone was never significant in either the univariate analysis with the base food model or any further forward rounds. CYP3A4/CYP3A5 cluster was significant in the univariate analysis ($p < 0.05$) on the food base model but once race was accounted for in the model this covariate was no longer significant.

Conclusion: As in 2008, food and race were the most significant covariates with food reducing exposure and Black+other race increasing exposure compared with Whites+Asians. The only significant genotype covariate was SLCO1B1. CYP3A5 genotype alone or CYP3A4/CYP3A5 genotype cluster in the

multivariate population PK analysis did not account for PK variability in the MERIT study.

Conflict of interest: Employee of Pfizer Inc, and hold stock/stock options in Pfizer Inc.

Abstract: 43

PK/PD modeling

Aging Effects as Covariates in the Population Pharmacokinetics (PK) of Emtricitabine (FTC) and Its Intracellular Metabolite in HIV+ Subjects

J.W. Collins¹, C.R. Trezza¹, H.M. Prince², M.L. Cottrell¹, C. Sykes¹, N. White¹, S. Malone¹, R. Wang¹, C. Torrice³, N.E. Sharpless³, K.B. Patterson², A. Forrest⁴, A.D.M. Kashuba¹, J.B. Dumond¹

¹University of North Carolina at Chapel Hill, UNC Eshelman School of Pharmacy, Chapel Hill NC, USA; ²University of North Carolina at Chapel Hill, School of Medicine, Chapel Hill NC, USA; ³University of North Carolina at Chapel Hill, Lineberger Comprehensive Cancer Center, Chapel Hill NC, USA; ⁴State University of New York University at Buffalo, School of Pharmacy and Pharmaceutical Sciences, Buffalo NY, USA

Background: Despite wide clinical use of FTC for both treatment and prevention, intracellular PK of emtricitabine triphosphate (FTC-tp) has not been well-described. A steady-state population PK model was developed in HIV+ subjects describing disposition of both parent (FTC) and metabolite (FTC-tp). As aging and inflammation may play roles in disposition, subjects underwent frailty phenotyping, measurement of plasma cytokine concentrations, and p16^{INK4a} expression analysis. Expression of the tumor suppression gene p16^{INK4a} is a biomarker of cellular aging and senescence.

Materials & Methods: Plasma and peripheral blood mononuclear cell (PBMC) samples were collected at multiple time points in subjects receiving tenofovir/FTC with efavirenz or atazanavir/ritonavir. Concentrations were determined with validated LC-MS/MS methods. Population PK modeling was performed using the SAEM INTERACTION estimation method with simulated annealing in NONMEM 7.3 (ICON plc, Hanover, MD). Pre, post and graphical displays of data were performed using R (r-project.org). Covariates tested included sex, race, regimen duration, age, CrCL, frailty phenotype, and p16^{INK4a} expression. Model discrimination was accomplished using Akaike's Information Criterion, and the likelihood ratio test was used with forward addition/backward elimination ($\alpha = 0.05, 0.01$) to determine covariate effects.

Results: 91 subjects (females=30, atazanavir/ritonavir =31) ranged in age from 22-73yr (median = 49yr). Mean \pm SD body mass index (BMI) was 28 \pm 5 kg/m² and creatinine clearance (CrCL) was 114 \pm 36 mL/min. 32 Caucasians and 53 African Americans were included. 12 subjects provided 11 samples at a single visit (intensively sampled group), while the remainder contributed 4 samples over 1-3 visits. FTC disposition was best described by a 2-compartment model with first-order absorption and elimination, with fractional amount of total FTC clearance going to form FTC-tp metabolite. FTC-tp was described as a 1-compartment model with first order elimination. A proportional error model was used for both parent and metabolite. Parameter estimates for FTC were comparable to literature estimates. The estimated fraction of FTC converted to FTC-tp was 1.8%, and FTC-tp CL was estimated to be 0.0334 L/hr with both estimates conditioned on a fixed compartmental volume of 1 liter. Inter-individual variability was estimated for FTC CL/F (34.8% CV), central volume (Vc/F) (76.7% CV), and FTC-tp CL (52.2% CV). Significant covariates in the final model include CrCL on FTC CL/F, age on FTC Vc/F, and p16^{INK4a} expression on FTC-tp CL. This latter relationship showed that increase in p16^{INK4a} exponentially increased intracellular clearance. Goodness of fit plots and visual predictive checks indicate the model fits the FTC/FTC-tp data well.

Conclusions: Our model describes the disposition of both FTC and FTC-tp in HIV+ individuals, and could be used to link viral

dynamic modeling to metabolite disposition. Consistent with previous FTC models, CrCL was found to be a significant covariate on clearance of FTC. The potential relationship between central volume and chronologic age is a new finding from previous models. The potential relationship between FTC-tp clearance and p16^{INK4a} expression warrants further study to understand the mechanism between senescence and phosphorylation.

No conflict of interest

Abstract: 44

PK-PD of Drug Efficacy and Toxicity

Simultaneous Assessment of Changes in T-cell Activation and Endogenous dNTP Pools in Adults Receiving TDF/FTC

X. Chen¹, J.R. Castillo-Mancilla², A.L. Meditz³, S.M. Seifert¹, S. MaWhinney⁴, L.R. Bushman¹, P.L. Anderson¹

¹University of Colorado Anschutz Medical Campus, Department of Pharmaceutical Sciences, Aurora, USA;

²University of Colorado Anschutz Medical Campus, Division of Infectious Diseases, Aurora, USA; ³Boulder Community Hospital, Beacon Center for Infectious Disease, Boulder, USA; ⁴University of Colorado Anschutz Medical Campus, Department of Biostatistics and Bioinformatics, Aurora, USA

Introduction: Reduced immune activation during tenofovir disoproxil fumarate-emtricitabine (TDF/FTC) therapy in HIV-negative individuals and patients receiving antiviral therapy has been reported. In addition, endogenous deoxynucleotides (dNTP), which are associated with immune activation, are perturbed during TDF/FTC therapy. The objective of this study was to characterize the time course of immune activation and dNTP changes in HIV-negative and HIV-positive individuals.

Materials & Methods: Participants were enrolled in a pharmacokinetic study of daily TDF/FTC therapy for 30 days. Peripheral blood mononuclear cells (PBMC) were collected at

baseline, and days 1, 3, 7, 20, and 30 during dosing for dNTP pool analysis, which included TTP, dCTP, dGTP, and dATP quantification, with validated LC-MS/MS methodology. Immune activation was determined at baseline and days 3, 7, 20, and 30 by measuring %HLA-DR/CD38 co-expression on CD4 and CD8 T-cells using flow cytometry. Data were log transformed and analyzed with mixed model linear regression using SAS 9.4®. The nadir of changes was estimated with piecewise regression, selected by model goodness of fit (AIC).

Results: 40 individuals (19 HIV-positive) participated, of whom 34 subjects completed all study visits; two HIV-negative and four HIV-positive subjects stopped early. 279 PBMC samples were analyzed. Model estimation showed, at baseline in HIV-positive vs HIV-negative individuals, CD4 T-cell activation was 3.7 (95% CI 2.9, 4.6; $p < 0.0001$) fold higher, and CD8 T-cell activation was 9.8 (95% CI 7.1, 13; $p < 0.0001$) fold higher. CD4 T-cell activation nadir was reached at day 5 with a 21% (95% CI 1.7%, 34%; $p = 0.03$) reduction, then stabilized. In stratified analysis, this was only significant in the HIV-positive population. CD8 T-cell activation declined steadily to -26% (95% CI -36%, -12%; $p = 0.0007$) at day 30. In stratified analysis, this effect was significant in both populations ($P < 0.04$). The pyrimidines, TTP and dCTP were reduced by 37% (95% CI 26%, 46%; $p < 0.0001$) and 20% (95% CI 11%, 28%; $p < 0.0001$) from baseline to approximately 36 hours, after that no significant change was detected ($p > 0.16$). dGTP decreased by 19% (95% CI 8.9%, 27%; $p = 0.0004$) at approximately 36 hours, then increased between 36 hours and day 30 by 9.6% (95% CI 0.6%, 19%; $p = 0.04$). dATP was 13% (95% CI 0.6%, 27%; $p = 0.04$) higher in HIV-positive subjects at baseline, and decreased 14% (95% CI 4.8%, 21%; $p = 0.003$) by 2.9 days into therapy, then stabilized. In stratified analyses, initial purine (dATP and dGTP) changes were more pronounced in HIV-negative group.

Conclusions: TDF/FTC therapy was associated with changes in T-cell activation and dNTP pool levels, in both HIV-negative (as reported previously) and HIV-positive individuals. This work indicates that the nadir occurs within a few days of therapy in both dNTP and CD4 T-cell activation, whereas CD8 activation declined steadily. Future work is needed to evaluate

clinical implications and mechanisms for these findings, and to further probe differences between HIV-negative vs HIV-positive individuals.

No conflict of interest

Abstract: 45

PK-PD of Drug Efficacy and Toxicity

Evaluation of the Effect of GS-5816, a Pangenotypic HCV NS5A Inhibitor, on the QT/QTc Interval in Healthy Subjects

E. Mogalian¹, D. Brainard², J. Denning², G. Shen³, J. Cuvin⁴, A. Mathias⁵

¹Gilead Sciences, Clinical Pharmacology, San Francisco California, USA; ²Gilead Sciences, Clinical Research, Foster City California, USA; ³Gilead Sciences, Biostatistics, Foster City California, USA; ⁴Gilead Sciences, Clinical Operations, Foster City California, USA; ⁵Gilead Sciences, Clinical Pharmacology, Foster City California, USA

Background: GS-5816, a potent pangenotypic HCV NS5A inhibitor, is in clinical development for the treatment of genotype 1-6 chronic HCV infection in combination with sofosbuvir (SOF). In vitro, GS-5816 did not display significant inhibition of hERG channel activity ($IC_{50} > 30 \mu M$), 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 therapeutic and supratherapeutic doses of GS-5816 on QTc interval.

Methods: Healthy volunteers (N=48) were enrolled into one of 8 treatment sequences and received a single dose of GS-5816 100 mg (therapeutic exposure), GS-5816 500 mg (supratherapeutic exposure), and GS-5816 placebo in a randomized, blinded fashion, and a single dose of open-label moxifloxacin (positive control). GS-5816, placebo, and moxifloxacin treatments were followed by a 6-day washout. Triplicate time-matched ECGs were collected at baseline and following each treatment. Serial

plasma samples for GS-5816 concentration analysis were collected over 96-hours following each treatment. Change from baseline in QTc for GS-5816 or moxifloxacin vs placebo was determined using the Fridericia correction formula (QTcF, primary) and population correction formulation (QTcN, secondary). Pharmacokinetics (PK) and exposure-QT relationships (PK/PD) were evaluated. Safety was monitored throughout the study.

Results: Forty-nine subjects were enrolled into the study; one subject withdrew consent 4 hours after receiving study drug and was replaced by a subject who completed the study. Forty-eight subjects completed the study and were included in the PK, PD, and PK/PD analyses. Study treatments were well tolerated. The percentage of subjects with treatment-emergent AEs following administration of placebo, GS-5816 100 mg, GS-5816 500 mg, and moxifloxacin was similar at 14.6%, 24.5%, 18.8%, and 20.8%, respectively. All AEs were Grade 1 or Grade 2 in severity. GS-5816 AUC and C_{max} were approximately 4.4-fold and 3.1-fold higher, respectively, following administration of a 500 mg supratherapeutic dose, relative to GS-5816 exposure following administration of SOF plus GS-5816 100 mg in Phase 2 clinical studies in HCV infected patients. The lower bound of the 2-sided 96.67% CI for the mean difference in QTcF and QTcN for moxifloxacin vs placebo was > 5 msec at 2.5, 3, 4 and 4 hours post-dose, establishing assay sensitivity. Following therapeutic and supratherapeutic GS-5816 dosing, the upper bound of the 2-sided 90% CIs for the mean difference in time-matched baseline-corrected QTc between GS-5816 vs placebo was < 10 msec at all time points using the primary (Fridericia) or secondary (population) correction method. Categorical analyses did not demonstrate effects of GS-5816 on QTc intervals. The relationships between GS-5816 plasma concentrations and QTc intervals did not reveal an association using QTcF or QTcN methods.

Conclusion: The results from this study met the ICH E14 definition of a negative 'thorough QT/QTc study' and demonstrate that GS-5816 is not expected to prolong QTc interval in healthy adults.

Conflict of interest: Employees of Gilead Sciences, Inc.

Abstract: 46

PK-PD of Drug Efficacy and Toxicity

No Clinically Relevant Effect of Beclabuvir on the QTcF Interval in Healthy Subjects

I. Savant Landry¹, K. Sims¹, Y. Ding¹, E. Chung¹, H. Bing¹, J. Pursley¹, M. AbuTarif¹

¹Bristol-Myers Squibb, Clinical Pharmacology, Princeton NJ, USA

Background: Clinically significant delays in cardiac repolarization have been observed with some non-antiarrhythmic medications. Thus, electrocardiographic assessment represents an important safety evaluation for new drugs in development. Beclabuvir (BCV) is a potent, selective non-nucleoside hepatitis C virus (HCV) NS5B polymerase inhibitor currently in phase 3 development as part of an all-oral, direct acting antiviral combination with daclatasvir (pangenotypic NS5A inhibitor) and asunaprevir (NS3 protease inhibitor) for the treatment of HCV infection. Neither supratherapeutic daclatasvir nor asunaprevir have demonstrated clinically relevant effects on the Fridericia-corrected QT interval (QTcF). The effect of BCV on QTcF and other electrocardiographic parameters were assessed in this thorough QT/QTc trial.

Materials & Methods: This was a randomized, double-blind, positive and placebo-controlled, 3-period, 3-treatment, crossover study in healthy subjects (N=60). Subjects were randomized to receive three, 3-day treatments (Treatments A-C) in one of six treatment sequences. Treatment A was BCV 600mg QD for 2 days then 900mg on day 3. Treatment B was moxifloxacin (MOX; positive control) given on day 3 only. Treatment C was placebo for 3 days. BCV and placebo were blinded; MOX was open-label. All treatments were administered fasted, with a 7-day washout between each period. The BCV dose was selected to achieve at least a 5-fold greater C_{max} exposure in healthy subjects compared to therapeutic dosing of 75mg BID in HCV-infected patients. Triplicate electrocardiogram measurements were obtained via Holter monitor

at selected time points on Day -1 and Day 3 of each treatment period, and parameters including heart rate, QT, QTcF, QRS, PR intervals, and changes in waveform morphology were extracted. The effects of BCV dosing on the difference from placebo in time-matched change from baseline in QTcF ($\Delta\Delta\text{QTcF}$) and other electrocardiographic endpoints were assessed using linear mixed-effect models. Clinically relevant changes in QTcF were assumed if the upper bound of the 90% confidence interval (CI) for the estimated $\Delta\Delta\text{QTcF}$ at any post-dose measurement exceeded 10 msec. Pharmacokinetic samples for plasma concentrations of BCV, its active major metabolite BMS-794712, and a minor inactive metabolite BMS-948158, were taken at selected time points up to 72 hours post-dose on Day 3 of each treatment period, and assayed by liquid chromatography with tandem mass spectrometry. Subject safety was assessed by 12-lead electrocardiograms, laboratory testing, vital signs and investigator clinical assessments.

Results: Fifty-eight patients (97%) completed the study. BCV C_{max} (geometric mean 13865ng/mL) was 9-fold greater than the therapeutic exposure and the major metabolite (BMS-794712) C_{max} (geometric mean 3607ng/mL) was 10-fold greater. No clinically relevant QTcF prolongations were observed following 3-day administration of BCV; 90% CI upper-bounds for all post-dose measurements in $\Delta\Delta\text{QTcF}$ were <10msec. BCV did not have a clinically relevant effect on heart rate, QRS or PR intervals, or waveform morphology. No concentration-response trend was noted in a random coefficient regression model examining $\Delta\Delta\text{QTcF}$ versus BCV and metabolite concentrations. BCV was generally well tolerated in this population.

Conclusions: BCV does not cause a prolongation of QTcF when administered at doses yielding C_{max} for parent and major metabolite 9–10-fold above those observed at clinically relevant doses.

Conflict of interest: Employee of BMS

Abstract: 47

Therapeutic Drug Monitoring

First experience with proficiency testing of rilpivirine in The International Quality Control Program for Measurement of Antiretroviral Drugs in Serum

D. Burger¹, K. Robijns², R. Aarnoutse³, D. Touw⁴

¹RadboudUMC, 864 Dept. of Clinical Pharmacy, Nijmegen, The Netherlands; ²KKGT, Pharmacy, The Hague, The Netherlands; ³Radboud UMC, Pharmacy, Nijmegen, The Netherlands; ⁴UMCG, Pharmacy, Groningen, The Netherlands

Background: Rilpivirine is the latest non-nucleoside reverse transcriptase inhibitor that has been licensed for treatment of HIV-infection. Its pharmacokinetic properties (food- and pH-dependent absorption, large interpatient variability in pharmacokinetics, small therapeutic range and established concentration-effect relationships) make rilpivirine an attractive candidate for therapeutic drug monitoring. Rilpivirine was added to The International Quality Control Program for Measurement of Antiretroviral Drugs in Serum (KKGT) in 2014. The objective of this exploratory analysis is to present the first experience with rilpivirine in the Program.

Materials & Methods: Blank human serum samples spiked with either subtherapeutic (0.029 & 0.048 mg/L) or therapeutic (0.210 & 0.105 mg/L) concentrations of rilpivirine were shipped to participants in two rounds. Any reported concentration deviating more than 20% was considered to be inadequate. This was intended to be an exploratory analysis, so no statistical tests were performed.

Results: Twelve laboratories participated in both rounds of the Program (one in the 2nd round only) making a total of 46 results. Laboratories were located in The Netherlands (n=3), Germany (n=3), Canada, UK, USA, Italy, Switzerland and China

(n=1 each). Eight laboratories used LC-MS/MS techniques, the other four HPLC/UPLC-UV. Out of the 46 results, 33 (72%) were within the 20% limits for acceptance. The 13 results outside this boundary varied from 26.3 – 795% and 5 results were reported as being below the lower limit of quantification (LLOQ) of the assay. Out of the 30 samples analysed with LC-MS/MS, 24 (80%) were reported adequately vs. 9 of the 16 samples (56%) with HPL/UPLCC-UV. There was a trend suggesting that the participants performed better in analyzing therapeutic rilpivirine concentrations (>0.100 mg/L) than subtherapeutic rilpivirine concentrations (< 0.050 mg/L): 78.3 vs. 65.2%.

Conclusion: Analogous to our previous experience with TDM of antiretroviral agents, there is a significant proportion of laboratories that have to improve their methods for analyzing rilpivirine. Participation in the program alerted laboratories to previously undetected problems, showing the utility of this ongoing quality control program.

No conflict of interest

Abstract: 48

Therapeutic Drug Monitoring

What interest of unbound fraction in atazanavir therapeutic drug monitoring?

D. Metsu¹, P. Seraisol¹, P. Delobel², C. Cinq-Frais³, L. Cuzin⁴, J. Izopet⁵, E. Chatelut⁶, P. Gandia¹

¹CHU Toulouse - Purpan, Laboratoire de Pharmacocinétique et Toxicologie, Toulouse Cedex 9, France; ²CHU Toulouse - Purpan, Service des Maladies Infectieuses, Toulouse Cedex 9, France; ³CHU Toulouse - Purpan, Laboratoire de Biochimie, Toulouse Cedex 9, France; ⁴CHU Toulouse - Purpan, COREVIH Midi-Pyrénées-Limousin, Toulouse Cedex 9, France; ⁵CHU Toulouse - Purpan, Laboratoire de Virologie, Toulouse Cedex 9, France; ⁶Institut Universitaire du Cancer de Toulouse - Oncopôle, Laboratoire de Pharmacologie, Toulouse Cedex 9, France

Background: Beyond total concentration (C_t), unbound concentration (C_u) and fraction ($f_u = C_u/C_t$) could be useful to improve Therapeutic Drug Monitoring (TDM) of Protease Inhibitors (PI). Objectives were to explore (i) f_u , C_u and C_t variability of Atazanavir (ATV) and (ii) correlations between ATV unbound form (f_u , C_u) and biological markers (plasma proteins, viral load, hyperbilirubinemia).

Materials & Methods: Variability of C_u and the corresponding f_u was explored in 43 patients treated with ATV for an average of 25.4 months. C_u was determined by coupling ultrafiltration and liquid-chromatography. As ATV is highly bound to alpha-1-acid glycoprotein (AAG), the correlation between f_u and AAG was explored. Viral load was monitored to evaluate patients' virologic response, while total and unconjugated bilirubinemia were used as biomarkers of ATV toxicity. As the vast majority of ATV blood samples (n= 29) were collected far from the trough sampling time, corresponding total trough concentrations were estimated combining two published population pharmacokinetic models [1,2] Based on the fact that (i) ATV presents a high correlation between unbound and total concentrations for total concentrations ranging from 168 to 2940 µg/L with a constant f_u [3] and (ii) all our patients presented measured total concentrations included in this dosing interval, we determined for each estimated trough total concentration the corresponding trough unbound concentration applying the formula $C_u = C_t \cdot f_u$. Spearman and Mann-Whitney tests were applied. All the statistical tests were two-sided and considered as significant for a p-value less than 0.05.

Results: f_u , trough C_u and trough C_t medians were 3.8% (InterQuartileRange (IQR) 2.8 – 4.5), 37.9 µg/L (IQR 20.6 – 94.9) and 628.6 µg/L (IQR 362.7 – 1078.1) and showed high variability. f_u was independent of AAG values ($\rho = -0.06$, $p=0.67$), ranging from 0.30 to 1.89 g/L, while a good relationship was found between total and unbound concentration ($\rho = 0.72$, $p<0.001$). f_u ($p = 0.65$), trough C_u ($p=0.21$) and trough C_t ($p=0.19$) were not significantly different between patients with or without virologic failure. Each case of total hyperbilirubinemia was associated to unconjugated hyperbilirubinemia. Only 1 patient (2%) already had unconjugated hyperbilirubinemia before starting the ATV regimen. A trend between unconjugated bilirubin

and trough C_t ($\rho = 0.32$, $p = 0.045$) but not for trough C_u ($\rho = 0.22$, $p = 0.17$) was observed.

Conclusion: AAG level didn't explain f_u and neither total nor unbound concentrations fully explained hyperbilirubinemia. Given the strong correlation between C_u and C_t , ATV trough C_u does not appear to be more relevant than C_t for TDM.

[1]. Schipani A, Dickinson L, Boffito M, et al. Simultaneous population pharmacokinetic modelling of atazanavir and ritonavir in HIV- infected adults and assessment of different dose reduction strategies. *J Acquir Immune Defic Syndr* 2013;62:60-6.

[2]. Dickinson L, Boffito M, Back D, et al. Population pharmacokinetics of ritonavir-boosted atazanavir in HIV-infected patients and healthy volunteers. *J Antimicrob Chemother* 2009;63:1233-43.

[3] Fayet A, Béguin A, de Tejada BM, et al. Determination of unbound antiretroviral drug concentrations by a modified ultrafiltration method reveals high variability in the free fraction. *Ther Drug Monit* 2008;3:511-22.

Conflict of interest: Janssen-Cilag : IWCPHT inscription and travel from France to USA.

Abstract: 49

Therapeutic Drug Monitoring

Darunavir unbound fraction: association with viral load in hiv patients.

D. Metsu¹, P. Gandia¹, P. Delobel², P. Seraisol¹, F. Saint-Marcoux³, P. Marquet³, J. Izopet⁴, E. Chatelut⁵, J.B. Woillard³

¹CHU Toulouse - Purpan, Laboratoire de Pharmacocinétique et Toxicologie, Toulouse Cedex 9, France; ²CHU Toulouse - Purpan, Service des Maladies Infectieuses, Toulouse Cedex 9, France; ³CHU Limoges, Laboratoire de Pharmacologie Toxicologie et Pharmacovigilance, Limoges, France; ⁴CHU Toulouse - Purpan, Laboratoire de Virologie, Toulouse Cedex 9, France; ⁵Institut Universitaire du Cancer de Toulouse - Oncopôle, Laboratoire de Pharmacologie, Toulouse Cedex 9, France

Background: In previous study [1], virologic failure was not always related to Darunavir (DRV) total plasma concentration (C_t). It may be useful to associate the unbound plasma concentrations (C_u) representing the pharmacological active form, to the C_t to improve DRV therapeutic drug monitoring (TDM). Our objectives were (i) to develop a model to estimate trough C_u and (ii) to investigate relationships between pharmacokinetic exposure and viral load.

Material and Methods: Sixty-eight DRV C_t and C_u were collected in 57 patients during a drug interdose and measured by liquid chromatography. Unbound fraction (f_u) was calculated as $f_u = C_u / C_t$. A one compartment pharmacokinetic population model (POPPK) allowing C_u estimation was developed using the non-parametric NPAG algorithm in Pmetrics®. Relationships between dichotomized viral load ($> \text{or} < 20$ copies/mL) and pharmacodynamics/pharmacokinetics were investigated using logistic regression.

Results: Samples were collected at pharmacokinetic steady state, at (mean \pm SD) 18.9 ± 13.6 months after drug initiation. Trough C_u and C_t were (median [Inter Quartile Range IQR]) 89.9 [42.3 - 125.5] $\mu\text{g/L}$ and 2435.6 [1414.0 - 3730.0] $\mu\text{g/L}$ respectively and f_u was 3.4 [2.7 - 4.3] %. The POPPK model estimates adequately trough C_u (relative bias= 2.33%, RMSE= 17%). f_u was associated with an increased risk of positive viral load (per unit increase OR[Confidence Interval 95%]= 1.91 [1.07 - 3.4]; $p = 0.0282$), while no significant association was found between C_t and virologic failure (OR = 1.04 [0.82 ; 1.31]; $p=0.751$). C_u adjusted on both C_t and distribution volume was associated with increased viral load (per unit increase OR= 1.02 [1.01 - 1.03]; $p = 0.0309$). A statistical interaction between C_u and DRV clearance (Cl), explaining the relationship between C_u and viral load, was investigated and was significant ($p = 0.0325$). Indeed, linear regression showed an inverse relationship between C_u and the Cl ($C_u = 4.7 - 46.53 \cdot \text{Ln}(\text{Cl})$; $r^2 = 0.61$; $p = 1,7 \cdot 10^{-11}$).

Conclusion: Our model allowed accurate DRV C_u estimation. However, a prospective study on a larger population is required to use f_u and C_u in DRV TDM as a complement of trough C_t during virologic failure.

[1] Pellegrin I et al. Virological response to darunavir/ritonavir-based regimens in antiretroviral-experienced patients (PREDIZISTA study). *Antivir Ther.* 2008;13(2):271-9.

Conflict of interest: Janssen Cilag : IWCPHT inscription and travel from France to USA

Abstract: 50

Therapeutic Drug Monitoring

Low darunavir concentrations in patients receiving Stribild (elvitegravir / cobicistat / emtricitabine / tenofovir disoproxil fumarate) and darunavir once daily

F. Ricard¹, A. Wong¹, B. Lebouché², R. Therrien³, M.J. Lachance⁴, M. Munoz⁵, D. Thibeault⁶, N.L. Sheehan⁷

¹McGill University Health Centre, Chronic Viral Illness Service and Pharmacy Department, Montreal, Canada;

²McGill University Health Centre and McGill University, Chronic Viral Illness Service and Department of Family Medicine, Montreal, Canada; ³Hôpital Hôtel-Dieu Centre hospitalier de l'Université de Montréal, UHRESS, Montreal, Canada;

⁴Centre Hospitalier Universitaire de Sherbrooke, Pharmacy Department, Sherbrooke, Canada; ⁵Hôpital Notre-Dame Centre Hospitalier de l'Université de Montréal and Clinique Médicale l'Actuel, UHRESS, Montréal, Canada;

⁶McGill University Health Centre, Biochemistry Department, Montréal, Canada; ⁷McGill University Health Centre and Université de Montréal, Chronic Viral Illness Service and Pharmacy Department and Faculty of Pharmacy, Montréal, Canada

Background: Stribild™ (elvitegravir (EVG)/ cobicistat (COBI)/ emtricitabine/ tenofovir disoproxil fumarate) is indicated for the treatment of antiretroviral (ARV)-naïve HIV-infected patients and as per the product monograph should not be combined with other ARVs. An off-label ARV regimen of darunavir (DRV) and Stribild is of interest for treatment simplification in patients with multiresistant virus, though lower DRV concentrations have been documented and clinical data is lacking.

Materials & Methods : The objective of this retrospective case series is to present the DRV concentrations and virologic response of treatment-experienced HIV-1-infected subjects receiving DRV 800 mg and Stribild once daily. Subjects were identified if they had DRV therapeutic drug monitoring (TDM) done at least once while on this regimen. DRV concentrations were measured by a validated LC-MS/MS assay. When a sample was collected more than 10 hours post-dose, the DRV trough concentration (C_{trough}) was extrapolated using the mean DRV elimination half-life (7.57h with DRV 800mg/EVG 150mg/COBI 150mg daily). When subjects had viruses with DRV-specific mutations, a genotypic inhibitory quotient (GIQ) of 2.15 mg/L/mutation was targeted; otherwise, the C_{trough} target was empirically chosen as 3 times the protein-adjusted wild-type IC₅₀ (0.055 mg/L). Descriptive statistics are presented.

Results : Eight (8) subjects were included (median number of ARV regimens 9, past virologic failure to protease inhibitors 87.5%). Only one patient had viruses with darunavir-specific mutations (33F). At time of first TDM on DRV/Stribild, 87.5% of subjects had an undetectable viral load. All subjects reported 100% adherence. A total of 23 samples were available when subjects received DRV 800 mg/Stribild daily (mean time post-dose 17.5 hours). TDM performed during the absorption phase showed optimal absorption. Considering all TDM samples in the elimination phase, the median C_{trough} was 0.273 (IQR: 0.164-0.501) mg/L, 80% lower than the historical population median of 1.36 mg/L with DRV/ritonavir (RTV) 800/100 mg daily. Indeed, in two subjects with TDM results while on DRV/RTV daily before the switch to Stribild, the DRV C_{trough} decreased by 25 and 83% with Stribild, respectively. The GIQ value for the one subject with DRV-specific mutations was 0.34 mg/L/mutation. Overall, 52.6% of the results were subtherapeutic. Dose adjustments in two subjects to DRV 1200 mg daily provided no improvement in DRV C_{trough}. One subject was switched to DRV 600 mg BID / Stribild daily (am) with an additional COBI 150 mg dose (pm) and reached a therapeutic GIQ of 5.37 mg/L/mutation. 87.5% of subjects still have an undetectable viral load, though 3 subjects have shown viral blips while on the regimen.

Conclusions : DRV combined to Stribild provides lower than expected DRV Ctrough values, however most subjects still have an undetectable viral load. One hypothesis is that DRV and EVG are inducing COBI metabolism, causing insufficient CYP3A4 inhibition between 12 and 24 hours post-dose. Though previous studies have shown no relationship between DRV Ctrough and virologic response in patients with viruses without DRV-specific mutations, the viral blips shown in this study indicate that low DRV concentrations might hinder durability of virologic suppression.

Conflict of interest: Gilead (unrestricted research grant)

Abstract: 51

Drug Drug Interactions

Steady-State Pharmacokinetics of Daclatasvir, Asunaprevir, and Beclabuvir in Treatment-Naive Patients Infected with HCV Genotype 1

B. He¹, K. Sims², E. Chung¹, W.L. Luo², J. Pursley², M. Wind-Rotolo², F. LaCreta², R. Bertz¹, M. AbuTarif²

¹Bristol-Myers Squibb, Research and Development, Hopewell NJ, USA; ²Bristol-Myers Squibb, Research and Development, Lawrenceville NJ, USA

Background: Daclatasvir 30mg (DCV; NS5A inhibitor), asunaprevir 200mg (ASV; NS3 inhibitor), and beclabuvir 75mg (BCV; non-nucleoside NS5B inhibitor), administered twice daily (BID) in combination (DCV+ASV+BCV) is currently in phase 3 development for the treatment of HCV infection. DCV+ASV+BCV administered for 12 weeks achieved ≥92% sustained virologic response (SVR) rate in HCV genotype (GT) 1-infected treatment-naive patients, including those with compensated cirrhosis, in an open-label, multiple-dose study (AI443014); a similar SVR rate was observed in patients receiving DCV+ASV+BCV containing BCV 150mg BID. The pharmacokinetics of DCV, ASV, BCV and its active metabolite BMS-794712

following dosing of DCV+ASV+BCV containing BCV 75mg or 150mg BID are presented.

Materials & Methods: Patients (age, ≥18 years; BMI, 18–35 kg/m²; >10% with biopsy-confirmed compensated [Child-Pugh A] cirrhosis) infected with HCV GT1 received DCV+ASV+BCV containing BCV 75mg (n=80) or 150mg BID (n=86) for 12 weeks. Blood samples (0–12 h) were collected post-AM dose on days 1 and 14 from the first 20 non-cirrhotic patients and all cirrhotic patients for PK analysis by LC-MS/MS; non-compartmental PK parameters were calculated and summarized by descriptive statistics. Comparisons of DCV and ASV PK with PK data from Study AI447011 (DCV+ASV administered in combination to HCV-infected patients), and comparison of BCV and BMS-794712 PK with PK data from Study AI443012 (BCV + pegIFNα/RBV; HCV-infected patients) were performed.

Results: Steady-state DCV and ASV exposures during the 0-12 hour dosing interval (AUC_{TAU}) were similar in combination with BCV 75mg or 150mg BID. AUC_{TAU} as ng·hr/mL (CV%) for DCV were 6220 (40) with BCV 75mg and 5790 (31.2) with BCV 150mg; corresponding AUC_{TAU} for ASV were 1550 (130) and 1430 (158). DCV and ASV exposures with BCV were also similar to steady-state exposures of DCV (6568 (47)) and ASV (1528 (106)) in a prior clinical study (AI447011) of DCV+ASV without BCV. BCV exposure was ~1.6-fold higher following the DCV+ASV+BCV dose containing BCV 150mg BID (14600 (29.3)), compared with DCV+ASV+BCV containing BCV 75mg BID (8710 (40.2)). BCV exposure was generally lower (75mg BID, 17%; 150mg BID, 24%) on Day 14 vs Day 1 and is suggestive of weak to moderate metabolic auto-induction, as observed in prior studies. Similar results were observed for BMS-794712. Both DCV+ASV+BCV regimens were generally well tolerated.

Conclusions: No clinically significant changes in steady-state DCV and ASV exposures were observed when combined with BCV (75 or 150mg dose) in the DCV+ASV+BCV regimen.

No conflict of interest

Abstract: 52*Drug Drug Interactions***Effect of Comedications on Paritaprevir, Ritonavir, Ombitasvir, Dasabuvir and Ribavirin Pharmacokinetics**

A.R. Polepally¹, P. Badri¹, E.P. Coakley², A. Parikh¹, L. Rodrigues-Jr², B.A. Da Silva-Tillmann³, S. Mensing⁴, T.J. Podsadecki², W.M. Awni¹, S. Dutta¹, R.M. Menon¹

¹Abbvie, Clinical Pharmacology and Pharmacometrics, North Chicago, USA; ²Abbvie, Infectious Disease Development, North Chicago, USA; ³Abbvie, Global Pharmacovigilance, North Chicago, USA; ⁴Abbvie, Clinical Pharmacology and Pharmacometrics, Ludwigshafen, Germany

Background: The 3 direct acting antiviral combination (3D) of paritaprevir/r (NS3/4A protease inhibitor identified by Abbvie and Enanta dosed with ritonavir [RTV]), ombitasvir (NS5A inhibitor) and dasabuvir (NS5B polymerase inhibitor) ± ribavirin has completed 6 Phase 3 trials in >2300 hepatitis C virus (HCV) genotype 1 infected subjects. Subjects continued their standard comedications while receiving the 3D ± RBV regimen. The effects of comedications in the Phase 3 trials were examined.

Materials & Methods: In the 6 Phase 3 trials (N > 2300), comedications were managed using prespecified rules with/without dose adjustments. The effect of comedications on 3D ± RBV was evaluated by comparing the population pharmacokinetic model-predicted DAA, RTV & RBV AUC in the presence/absence of comedications. Earlier studies suggested that up to 50% reduction/100% increase in exposures did not impact the 3D regimen efficacy/safety and are therefore not clinically relevant. Interactions that resulted in changes in AUCs outside this range were examined in population pharmacokinetic models.

Results: Greater than 1200 comedications belonging to 15 drug classes (non-opioid analgesics, antihypertensives, antidepressants, proton pump inhibitors, antihistamines, opioids, hormone replacement therapies, steroids,

anti-infectives, antidiabetics, antiepileptics, statins and lipid lowering agents, antipsychotics, hormonal contraceptives, PDE5 inhibitors) and/or 19 enzyme (CYP 3A4/5/7, 2C8, 2D6, 1A2, 2C9, 2C19, 2B6, and UGTs)/transporter (P-gp, MRP2, BCRP, OATP1B1 and OATP 1B3) inhibitor and/or inducer categories were used concomitantly in Phase 3 trials. Approximately 1500 subjects (65%) in Phase 3 trials received 2 or more concomitant medications from multiple drug classes/categories. The 3D ± RBV regimen was well tolerated with a low rate of study drug discontinuation due to adverse events (~1%) and few serious adverse events. No comedication class/category had a clinically meaningful effect on ombitasvir, dasabuvir, RTV or RBV exposures. Opioids, antipsychotics, antiepileptics, antidiabetics and hormone replacement therapies had an apparent effect (AUC ratio ≤ 0.5 or ≥ 2.0) on paritaprevir exposure. Subsequent assessment in population pharmacokinetic model that accounts for multiple sources of variability indicated only opioids and antidiabetics increased paritaprevir exposures by up to 55%, which was not clinically relevant.

Conclusions: Greater than 1200 concomitant medications were administered with/without dose adjustment in Phase 3 trials with the 3D ± RBV regimen. No dose adjustment is necessary for the 3D ± RBV regimen and no safety/ efficacy issues are anticipated due to changes in DAA, RTV or RBV exposures. Based on these findings by extrapolation no dose adjustment is required for the 2D (ombitasvir/paritaprevir/r) ± RBV regimen.

Conflict of interest: AbbVie contributed to the study design, research, and interpretation of data, writing, reviewing, and approving the publication. All authors are AbbVie employees and may hold AbbVie stocks or options.

Abstract: 53*Drug Drug Interactions***Pharmacokinetic Drug-Drug Interaction Study Between Raltegravir and Citalopram in Healthy Volunteers.**

M. Blonk¹, C. Langemeijer², A. Colbers¹, K. Hoogtanders³, R. van Schaik⁴, B. Schouwenberg⁵, D. Burger¹

¹Radboud university medical center, Pharmacy, Nijmegen, The Netherlands; ²Radboud University Nijmegen, Biomedical Sciences, Nijmegen, The Netherlands; ³Maastricht University Medical Centre, Clinical Pharmacy and Toxicology, Maastricht, The Netherlands; ⁴Erasmus University Medical Centre, Clinical Chemistry, Rotterdam, The Netherlands; ⁵Radboud university medical center, Pharmacology and Toxicology, Nijmegen, The Netherlands

Background: Depression is the most common mental health disorder among HIV-infected patients. Recognizing and treating depression is important in order to improve quality of life and health outcomes in those living with HIV. A complicating factor in the concomitant use of antiretroviral agents and antidepressive agents, such as selective serotonin reuptake inhibitors (SSRIs), is the occurrence of drug-drug interactions. We investigated the two-way pharmacokinetic drug-drug interaction and tolerability of concomitant administration of the SSRI citalopram and the HIV-1 integrase strand transfer inhibitor raltegravir in healthy volunteers.

Materials & Methods: This was an open-label, cross-over, two-period phase I trial in 24 healthy volunteers. Subjects received the following treatments until steady-state plasma concentrations: citalopram 20 mg once daily for two weeks followed by citalopram 20 mg once daily with raltegravir 400 mg twice daily for 5 days and after a washout period raltegravir 400 mg twice daily for 5 days. Intensive steady-state 12- and 24-hour pharmacokinetic (PK) blood sampling was performed. PK parameters (AUC_{0-24h} , C_{max} , C_{12h}) were determined by non-compartmental analysis for raltegravir, citalopram and its principal metabolite desmethylcitalopram. Geometric mean ratios (GMRs) of the test

treatment [combination raltegravir + citalopram] versus the reference treatment [raltegravir or citalopram alone] and 90% confidence intervals (CIs) were calculated using a mixed-effects bioequivalence module (WinNonlin/Phoenix 6.3). CYP2C19 genotyping was performed because it plays an important role in the extent of N-demethylation of citalopram to desmethylcitalopram. Citalopram metabolite-to-parent ratios (mean \pm SD) of AUC_{0-24h} were calculated when citalopram was administered alone versus concomitant raltegravir use per CYP2C19 genotype subgroup (poor, intermediate and extensive metabolizers, respectively PM, IM and EM).

Results: Twenty-four healthy volunteers (13 males) were enrolled. Twenty-two subjects completed the trial, two subjects withdrew consent. Median (range) age and BMI were 47 (18-53) years and 24.8 (20.9-29.3) kg/m². No serious adverse events and clinically relevant changes in cardiovascular safety parameters (ECG recordings) were observed. GMR (90% CI) of raltegravir PK parameters were: 0.77 (0.50-1.19) for AUC_{0-12h} ; 0.64 (0.38-1.09) for C_{max} and 1.03 (0.71-1.50) for C_{12h} . Raltegravir PK showed extensive intra- and inter-subject variability consistent with known PK profile of raltegravir. Raltegravir C_{12h} , the most important PK parameter to evaluate with respect to virological efficacy, did not change with concomitant citalopram use. GMR (90% CI) of citalopram and desmethylcitalopram PK parameters were: 1.00 (0.98-1.03) and 0.99 (0.88-1.12) for AUC_{0-24h} ; 0.98 (0.95-1.01) and 0.97 (0.86-1.09) for C_{max} ; 1.03 (1.00-1.07) and 1.04 (0.92-1.18) for C_{24h} . Mean (\pm SD) AUC_{0-24h} citalopram metabolite-to-parent ratios for the reference versus the test treatment were 0.22 versus 0.21 for CYP2C19 PM (n=1), 0.25 (\pm 0.054) versus 0.25 (\pm 0.060) for CYP2C19 IM (n=7) and 0.39 (\pm 0.065) versus 0.39 (\pm 0.066) for CYP2C19 EM (n=14). Within each subgroup the metabolite-to-parent ratio, which is the most specific measure for metabolic enzyme activity, was not influenced by concomitant raltegravir use.

Conclusions: Raltegravir does not influence the pharmacokinetics of citalopram and its principal metabolite desmethylcitalopram. Co-administration of citalopram did not change the pharmacokinetics of raltegravir in a clinically meaningful way. The combination was well

tolerated and can be administered without dose adjustments.

Conflict of interest: This study was supported by the Investigator Initiated Study Program of Merck (#50404).

Abstract: 54

Drug Drug Interactions

An evaluation of doravirine pharmacokinetics when switching from efavirenz to doravirine treatment

K.L. Yee¹, R.I. Sanchez¹, P. Auger², R. Liu³, I. Triantafyllou⁴, C. Tomek², M. Iwamoto⁵, S. Khalilieh⁶

¹Merck & Co., Pharmacokinetics Pharmacodynamics and Drug Metabolism, Kenilworth, USA; ²Celerion, Lincoln, USA; ³Merck & Co, BARDS, Kenilworth, USA; ⁴Merck & Co, ESD Operations, Kenilworth, USA; ⁵Merck & Co., Clinical Research, Kenilworth, USA; ⁶Merck & Co., Clinical Pharmacology, Kenilworth, USA

Background: Doravirine is a novel non-nucleoside reverse transcriptase inhibitor (NNRTI) being developed for treatment of human immunodeficiency virus-1 (HIV-1) infection. In a Phase 2 trial comparing doravirine with efavirenz, both in combination with TRUVADA™, doravirine was efficacious in treating anti-retroviral therapy (ART)-naïve HIV-1 infected patients at doses from 25 mg to 200 mg per day over 48 weeks. The clinical dose of doravirine is projected to be 100 mg once-daily (QD). To support a Phase 2 study in which HIV-infected subjects will switch from efavirenz-based to doravirine-based treatment, a study was conducted to assess the impact on doravirine pharmacokinetics of switching from efavirenz to doravirine in healthy volunteers. Since doravirine is primarily metabolized by CYP3A4, efavirenz is a moderate CYP3A4 inducer, and doravirine exposure is reduced when co-administered with rifampin, a strong CYP3A4 inducer, some transient reduction in doravirine exposure is anticipated following a switch from efavirenz.

Materials & Methods: This was an open-label, fixed-sequence study in healthy males (n=17) and females (n=3). In Period 1, subjects received 100 mg doravirine QD for 5 days followed by a 7-day washout. In Period 2, subjects received 600 mg efavirenz QD for 14 days. In Period 3, subjects received 100 mg doravirine QD for 14 days, with no washout between Periods 2 and 3. Doravirine concentrations were determined on Day 1, at steady state, and at trough before and after efavirenz treatment. Efavirenz concentrations were determined daily following the cessation of efavirenz administration. Safety evaluations were performed throughout the study. The pharmacokinetics of doravirine on Day 1 and at steady state in Periods 1 and 3 were natural log (ln)-transformed and analyzed with a linear mixed-effects model with a fixed-effect term for period. The geometric mean ratios (Period 3/Period 1) and 90% confidence intervals (CI) were generated from the model. The doravirine C24 geometric mean and 90% CI on Days 1-14 of Period 3 were calculated based on ln-transformed values with a linear mixed-effects model with day and subject as categorical fixed and random effects, respectively. In Period 3, efavirenz concentrations on Days 1-15 were analyzed in a similar fashion, excluding slow metabolizers (CYP2B6*6/*6).

Results: On Day 1 following cessation of efavirenz treatment, doravirine AUC, C_{max}, and C₂₄ were reduced by approximately 60%, 35%, and 85%, respectively, relative to those observed prior to efavirenz treatment. Doravirine C₂₄ values increased steadily through Day 15 following cessation of efavirenz treatment. By Day 14, the reductions in doravirine AUC, C_{max}, and C₂₄ were 32%, 14%, and 50%, respectively, relative to values without efavirenz pretreatment. Efavirenz geometric least-square mean concentrations decreased steadily from 3180 ng/mL on Day 1 to 95.7 ng/mL on Day 15 following cessation of efavirenz dosing. The administration of doravirine and efavirenz was generally well tolerated in healthy subjects.

Conclusions: Doravirine exposure is transiently decreased when doravirine treatment is initiated immediately following cessation of efavirenz therapy. The clinical relevance of this transient interaction will be further evaluated in a Phase 2 study switching virologically-suppressed HIV-

infected patients on combination ART from efavirenz to doravirine.

Conflict of interest: Employee of Merck & Co.

Abstract: 55

Drug Drug Interactions

Drug Interactions with Direct Acting Antiviral Combination of Paritaprevir/ritonavir + Ombitasvir

P. Badri¹, S. Dutta¹, H. Wang², T. Podsadecki³, A. Polepally¹, E. Coakley³, A. Khatri¹, J. Zha¹, Y. Chiu², W. Awni¹, R. Menon¹

¹AbbVie, Clinical Pharmacology and Pharmacometrics, North Chicago, USA; ²AbbVie, Biometrics, North Chicago, USA;

³AbbVie, Clinical Infectious Diseases, North Chicago, USA

Background: The 2 direct acting antiviral (2D) combination of paritaprevir /r (nonstructural 3/4A [NS3/4A] protease inhibitor identified by AbbVie and Enanta dosed with ritonavir) and ombitasvir (NS5A inhibitor) ± ribavirin is being evaluated in HCV subgenotype 1b and genotype 4 infected subjects. Drug-drug interaction (DDI) studies were conducted in healthy volunteers to guide dosing recommendations for 11 medications when coadministered with the 2D regimen.

Materials & Methods: DDIs of the 2D regimen with ketoconazole (CYP3A + P-gp inhibitor), pravastatin (OATP1B1/B3 substrate), rosuvastatin (OATP1B1/B3 + BCRP substrate), digoxin (P-gp substrate), warfarin (CYP2C9 substrate) and omeprazole (CYP2C19 substrate) were evaluated in healthy volunteers for potential mechanism based interactions. Additionally, DDIs with 5 medications (duloxetine, escitalopram, methadone, buprenorphine and naloxone) were evaluated to inform co-administration in patients. One sequence crossover design studies (N=12 for each study) and central value ratios (90% confidence intervals) for C_{max} and AUC were used

to examine the potential for DDIs (11 concomitant medications in 8 studies).

Results: Clinically significant change (C_{max} and AUC) was not observed in warfarin, duloxetine, escitalopram, methadone or naloxone exposures when coadministered with the 2D regimen. Buprenorphine exposures increased up to 51%, however, there were no significant changes in pharmacodynamic measurements (pupil diameter, opioid withdrawal scale score, or desire for drug questionnaire score) when buprenorphine/naloxone was administered with the 2D regimen. Omeprazole exposures decreased by 50% while ketoconazole, digoxin, pravastatin and rosuvastatin exposures increased up to 105%, 58%, 76% and 161%, respectively. These concomitant medications did not have a clinically significant effect on paritaprevir, ritonavir, or ombitasvir exposures. Co-administration of the 2D regimen with these concomitant medications was generally safe and well tolerated by the subjects in these studies.

Conclusions: Warfarin (with routine clinical monitoring), duloxetine, escitalopram, methadone, buprenorphine and naloxone can be co-administered with the 2D regimen without dose adjustment. When co-administered with the 2D regimen, higher dose of omeprazole can be used (if clinically indicated), ketoconazole dose should be limited to < 200 mg/day, digoxin dose should be reduced by 30-50% with therapeutic drug monitoring and statin (pravastatin and rosuvastatin) doses should be reduced by 50%. No dose adjustment is necessary for the 2D regimen when co-administered with any of the 11 evaluated medications.

Conflict of interest: AbbVie contributed to the study design, research, and interpretation of data, writing, reviewing, and approving the publication. All authors are AbbVie employees and may hold AbbVie stocks or options.

Abstract: 56*Drug Drug Interactions***Drug Interactions between Hepatoprotective Agents Ursodeoxycholic Acid or Glycyrrhizin and Ombitasvir/Paritaprevir/Ritonavir in Healthy Japanese Subjects**

J. Zha¹, P. Badri¹, B. Ding¹, N. Uchiyama², K. Alves³, R. Redman³, S. Dutta¹, R.M. Menon¹

¹AbbVie, Clinical Pharmacology and Pharmacometrics, North Chicago IL, USA; ²AbbVie GK, ADME/PK, Tokyo, Japan

³AbbVie, Infectious Disease Development, North Chicago IL, USA

Background: The 2 direct-acting antiviral combination (2D) of ombitasvir (NS5A inhibitor, OBV) and paritaprevir/r (NS3/4A protease inhibitor identified by Abbvie and Enanta dosed with ritonavir, PTV/r) is being developed for the treatment of chronic HCV infection in Japan. Ursodeoxycholic acid (UDCA) and glycyrrhizin (GCR) are hepatoprotective agents widely used in Japan for the improvement of liver function in patients with chronic liver disease. A drug-drug interaction (DDI) study was conducted in healthy Japanese subjects to guide dosing recommendations for UDCA and GCR when coadministered with the 2D regimen.

Materials & Methods: This was a Phase 1, multiple-dose, open-label study to evaluate the pharmacokinetics, safety, and tolerability of the 2D regimen (OBV/PTV/r 25/150/100 mg orally once daily) and UDCA or GCR when given alone and in combination. Twenty-four healthy Japanese subjects were enrolled in 2 independent arms. DDIs between the 2D regimen (Days 3-18) and UDCA (50 mg orally 3 times daily [TID, alone on Days 1-2, and in combination on Days 17-18]) were evaluated in Arm 1. DDIs between the 2D regimen (Days 10-25) and GCR (80 mg intravenously once daily, alone on Days 1-2, and in combination on Days 24-25) were evaluated in Arm 2. Intensive PK sampling was performed for study drugs when administered

alone and during coadministration and parameters estimated by noncompartmental analyses. Safety was evaluated through assessment of adverse events, vital signs, ECG and clinical laboratory tests. An ethics committee approved the research.

The DDIs (ratios of central values and their 90% confidence intervals) were assessed by comparing exposures from coadministration of 2D regimen and UDCA or GCR versus 2D regimen or UDCA or GCR alone, using repeated measures analyses of natural logarithms of C_{max} and AUC.

Results: When multiple doses of the 2D regimen were co-administered with multiple oral doses of UDCA, steady-state exposures (C_{max} and AUC) of OBV, PTV and ritonavir were similar ($\leq 9\%$ change in central values) to the exposures from the 2D regimen administered alone. Coadministration of TID oral dosing of UDCA with the 2D regimen had little to no effect on UDCA C_{max} or AUC ($\leq 20\%$ change) compared to UDCA administered alone. When multiple doses of the 2D regimen were coadministered with daily IV dosing of GCR, steady-state exposures of OBV, PTV and ritonavir were not affected ($\leq 9\%$ change). Co-administration of daily IV dosing of GCR with the 2D regimen had no effect ($< 1\%$ change) on GCR C_{max} but increased GCR AUC by 49%.

The safety profile of the 2D regimen coadministered with UDCA in Arm 1 and with GCR in Arm 2 in this study was comparable to that of the 2D regimen administered alone.

Conclusions: No dose adjustment is needed for the 2D regimen when administered with UDCA or GCR. No dose adjustment is needed for UDCA when it is administered with the 2D regimen. No dose adjustment for GCR is needed when coadministered with the 2D regimen; however, clinical monitoring of the patients is recommended because of the approximately 50% higher GCR AUC in central values.

Conflict of interest: AbbVie contributed to the study design, research, and interpretation of data, writing, reviewing, and approving the publication. All authors are AbbVie employees and may hold AbbVie stocks or options.

Abstract: 57*Drug Drug Interactions***Drug-Drug Interactions of Ombitasvir/Paritaprevir/r plus Dasabuvir with Dolutegravir or Abacavir plus Lamivudine**

A. Khatri¹, R. Trinh², W. Zhao³, T. Podsadecki², R. Menon¹

¹AbbVie, Clinical Pharmacology and Pharmacometrics, North Chicago Illinois, USA; ²AbbVie, Infectious Disease Clinical Development, North Chicago Illinois, USA; ³AbbVie, Biometrics, North Chicago Illinois, USA

Background: The all-oral IFN-free 3 direct acting antiviral (DAA) combination (3D) of paritaprevir/r (NS3/4A inhibitor identified by AbbVie and Enanta, dosed with ritonavir), ombitasvir (NS5A inhibitor) and dasabuvir (NS5B polymerase inhibitor) ± ribavirin (RBV) has been approved by the FDA and the EMA for treatment of HCV genotype 1 infected patients including patients with HIV-1 coinfection. The TURQUOISE-I study evaluated the 3D regimen with RBV in GT 1 HCV/HIV-1 co-infected subjects on atazanavir- or raltegravir-based antiretroviral therapy (ART) with sustained virologic response rates of 90-94% observed. This study evaluated the pharmacokinetic (PK) and safety profiles of coadministration of the 3D regimen with dolutegravir in Arm 1 and abacavir plus lamivudine in Arm 2 to enable evaluation of the 3D regimen in subjects on dolutegravir or abacavir plus lamivudine.

Materials & Methods: This Phase 1, open-label, multiple-dose, 2-period, non-fasting study enrolled 24 healthy subjects (12 subjects/arm). In Period 1, subjects received dolutegravir for 7 days (Arm 1) or abacavir plus lamivudine for 4 days (Arm 2). In Period 2, subjects received the 3D regimen for 14 days (Study Days 1-14) followed by co-administration of the 3D regimen with dolutegravir (Arm 1) or abacavir plus lamivudine (Arm 2) for 10 days (Study Days 15 - 24). Period 1 and 2 were separated by 7 and 5 days of washout in Arm 1 and 2, respectively. Doses of study drugs were: ombitasvir/paritaprevir /r/ 25/150/100 mg QD, dasabuvir 250 mg BID, dolutegravir 50 mg QD, abacavir 600 mg QD and

lamivudine 300 mg QD. Intensive PK assessment was performed on Study Day 7 in Period 1 of Arm 1 (dolutegravir), Study Day 4 in Period 1 of Arm 2 (abacavir and lamivudine) and Days 14 (3D regimen) and 24 (3D regimen with dolutegravir or abacavir plus lamivudine) in Period 2. The effect of the DAAs on dolutegravir or abacavir and lamivudine PK and vice versa was assessed by a repeated-measures analysis using SAS. Safety was evaluated through assessment of adverse events (AEs), vital signs, ECGs and clinical laboratory tests.

Results: During co-administration with the 3D regimen, dolutegravir exposures (C_{max} , AUC and C_{trough}) at steady state were 22% to 38% higher, abacavir exposures were up to 13% lower and lamivudine C_{max} and AUC were up to 22% lower and C_{trough} was 29% higher. DAA and ritonavir exposures were up to 18% lower, except for up to 34% decrease in paritaprevir and ritonavir C_{trough} during co-administration with dolutegravir or abacavir plus lamivudine. All AEs reported were mild in severity. No clinically significant vital signs, ECGs or laboratory measurements were observed during the study.

Conclusions: The co-administration of dolutegravir or abacavir plus lamivudine with the 3D regimen was well tolerated by the 24 healthy subjects for 10 days. No dose adjustment is recommended for the 3D regimen, dolutegravir or abacavir and lamivudine during co- administration.

Conflict of interest: AbbVie contributed to the study design, research, and interpretation of data, writing, reviewing, and approving the publication. All authors are AbbVie employees and may hold AbbVie stocks or options.

Abstract: 58*Drug Drug Interactions***Effect of Ketoconazole on the Pharmacokinetics of Doravirine (MK-1439), a Novel Non-Nucleoside Reverse Transcriptase Inhibitor for the Treatment of HIV-1 Infection**

M.S. Anderson¹, C. Chung¹, E. Tetteh², K.L. Yee², Y. Guo³, S. Rasmussen⁴, J.A. Wagner⁵, J.R. Butters⁵

¹Merck & Co. Inc., Clinical Pharmacology and Experimental Therapeutics, Kenilworth NJ, USA; ²Merck & Co. Inc., Pharmacokinetics Pharmacodynamics and Drug Metabolism, Kenilworth NJ, USA; ³Merck & Co. Inc., Early Clinical Development Statistics, Kenilworth NJ, USA; ⁴Celerion, Clinical Research, Lincoln NE, USA; ⁵Merck & Co. Inc., Clinical Pharmacology and Clinical Therapeutics, Kenilworth NJ, USA

Background: Doravirine is a novel, potent, HIV-1 non-nucleoside reverse transcriptase inhibitor that is primarily metabolized by oxidation via CYP3A4 and is a P-glycoprotein (P-gp) substrate in vitro. Thus, doravirine may be affected by CYP3A4 inhibitors or inducers. Ketoconazole is a strong inhibitor of CYP3A and the P-gp transporter. The objective of this study was to assess the effect of ketoconazole on the pharmacokinetics of doravirine at the 100 mg dose.

Materials & Methods: This was an open-label, 2-period, fixed sequence trial to assess the effect of multiple doses of ketoconazole on the single-dose plasma pharmacokinetic profile of doravirine. In Period 1, subjects received a single oral dose of 100 mg doravirine. In Period 2, subjects received oral doses of 400 mg ketoconazole QD for 10 days, with co-administration of a single oral dose of 100 mg doravirine on Day 2 with a 7 day washout between periods. Healthy male (n=8) and female (n=2) subjects were enrolled. Safety evaluations were performed throughout the study. Plasma samples for analysis of doravirine pharmacokinetics were collected over 72 hours postdose in Period 1 and over 216 hours

postdose in Period 2. Pharmacokinetic parameters were natural log transformed and analyzed with a linear mixed effects model with treatment as fixed effect and an unstructured covariance matrix.

Results: There were no serious clinical or laboratory adverse experiences (AEs). There were no discontinuations due to a study drug related AE. One subject experienced 2 episodes of mild papular rash which were considered related to doravirine only. Overall, 6 subjects reported a total of 18 adverse experiences, 13 of which were considered drug-related (6 related to doravirine only, 5 related to ketoconazole only, and 2 related to both doravirine and ketoconazole). All reported AEs were judged as mild in intensity and transient. The geometric mean ratio (GMR) (90% confidence interval) for (doravirine + ketoconazole/ doravirine) was 3.06 (2.85, 3.29) for $AUC_{0-\infty}$, 1.25 (1.05, 1.49) for C_{max} , and 2.75 (2.54, 2.98) for C_{24hr} . Geometric mean apparent terminal half-life increased from 15.23 hours with doravirine alone to 32.37 hours in the presence of ketoconazole, consistent with a decrease in clearance due to inhibition of CYP3A4 metabolism.

Conclusions: Multiple dosing of ketoconazole increases the plasma $AUC_{0-\infty}$ of doravirine, primarily by reducing the rate of CYP3A-mediated clearance. The minimal increase in C_{max} suggests that P-gp inhibition does not impact the absorption of doravirine. These changes are likely not clinically meaningful based on available safety data to date and the lack of exposure-response relationship for efficacy or safety up to a dose of 200 mg in a Phase 2 study. Co-administration of doravirine and ketoconazole was generally well tolerated. The 100 mg dose was subsequently selected for evaluation in Phase 3 studies where the use of strong CYP3A inhibitors is permitted.

Conflict of interest: Employee of Merck & Co., Inc.

Abstract: 59*Drug Drug Interactions***A 2-Way Steady State PK Interaction Study of Doravirine (MK-1439) and Dolutegravir**

M.S. Anderson¹, S. Khalilieh¹, K.L. Yee², R. Liu³, M.L. Rizk², V. Shah⁴, A. Hussaini⁵, I. Song⁶, L. Ross⁷, J.R. Butters¹

¹Merck & Co. Inc., Clinical Pharmacology and Experimental Therapeutics, Kenilworth NJ, USA; ²Merck & Co. Inc., Pharmacokinetics Pharmacodynamics and Drug Metabolism, Kenilworth NJ, USA; ³Merck & Co. Inc., Early Clinical Development Statistics, Kenilworth NJ, USA; ⁴Merck & Co. Inc., Early Stage Development Operations, Kenilworth NJ, USA; ⁵Parexel, EP Research Physicians, Baltimore MD, USA; ⁶GlaxoSmithKlein, Clinical Pharmacology Modeling & Simulation, Research Triangle Park NC, USA; ⁷ViiV HealthCare Inc., Medical Affairs, Research Triangle Park NC, USA

Background: Doravirine is a novel, potent, HIV-1 non-nucleoside reverse transcriptase inhibitor that is primarily metabolized by oxidation via CYP3A4. Thus, doravirine may be affected by CYP3A4 inhibitors or inducers, but has demonstrated no inhibitory or inductive potential on CYPs, suggesting a low propensity to be a perpetrator of clinically meaningful drug interactions. Dolutegravir (DTG) is an HIV-1 integrase strand transfer inhibitor that is primarily metabolized via UGT1A1 with some contribution from CYP3A, and is not an inhibitor or inducer of cytochrome-P450 metabolism. The objective of this study was to assess the 2-way PK interaction of doravirine and DTG at steady state.

Materials & Methods: This was an open-label, 3-period, fixed sequence trial designed to evaluate the steady state pharmacokinetics, safety, and tolerability of DTG 50 mg QD alone for 7 days (Period 1), doravirine 200 mg QD alone for 7 days (Period 2) and DTG 50 mg + 200 mg doravirine co-administered QD for 7 days (Period 3). There was a 7 day washout between Periods 1 and 2 but no washout between Periods 2 and 3. Healthy male (n=6) and female (n=6) subjects were enrolled. Safety evaluations were performed throughout the study. Plasma samples for doravirine and for DTG pharmacokinetics were

collected on Days 5 (predose), 6 (predose), and 7 of each treatment period.

Results: One subject was discontinued due to a protocol violation prior to the doravirine + DTG coadministration period. There were no serious clinical or laboratory adverse experiences (AEs). Five transient AEs were reported by 4 subjects of constipation (2), myalgia, musculoskeletal stiffness, and follicular conjunctivitis, none of which were considered related to doravirine or DTG. All reported AEs were judged as mild in intensity. The geometric mean ratio (GMR) (90% confidence interval [CI]) for (doravirine + DTG/ doravirine) was 1.00 (0.89, 1.12) for AUC_{0-24hr}, 1.06 (0.88, 1.28) for C_{max}, and 0.98 (0.88, 1.09) for C_{24hr}. The GMR (90% CI) for (doravirine + DTG/ DTG) was 1.36 (1.15, 1.62) for AUC_{0-24hr}, 1.43 (1.20, 1.71) for C_{max}, and 1.27 (1.06, 1.53) for C_{24hr}.

Conclusions: Multiple dosing of doravirine and DTG is generally well tolerated and exhibits a PK profile supportive of coadministration. DTG 50 mg at steady state did not alter the PK of coadministered 200 mg doravirine. Steady state doravirine 200 mg increased DTG AUC_{0-24hr}, C_{max} and C_{24hr} ~36, 43, and 27%, respectively, but not to a clinically meaningful degree.

Conflict of interest: Employee of Merck & Co., Inc.

Abstract: 60*Drug Drug Interactions***Effect of Doravirine (MK-1439) on the Pharmacokinetics of an Oral Contraceptive (Ethinyl Estradiol [EE] and Levonorgestrel [LNG])**

M.S. Anderson¹, D. Kaufman¹, P. Castronuovo¹, E. Tetteh², K.A. Lai², R. Liu³, D.R. Armas⁴, J.A. Wagner¹, J.R. Butters¹

¹Merck & Co. Inc., Clinical Pharmacology and Experimental Therapeutics, Kenilworth NJ, USA; ²Merck & Co. Inc., Pharmacokinetics Pharmacodynamics and Drug Metabolism, Kenilworth NJ, USA; ³Merck & Co. Inc., Early Clinical Development Statistics, Kenilworth NJ, USA; ⁴Celerion, Early Clinical Research, Tempe AZ, USA

Background: Doravirine is a novel, potent, HIV-1 non-nucleoside reverse transcriptase inhibitor that is primarily metabolized by oxidation via CYP3A4, but has demonstrated no inhibitory or inductive potential on CYPs both in vitro and in clinical studies, and has shown no interaction with enzymes involved in the metabolism of either EE or LNG. The objective of this study was to assess the effect of 100 mg doravirine, the Phase 3 clinical dose, on the plasma pharmacokinetics of an oral contraceptive containing EE and LNG.

Materials & Methods: This was an open-label, 2-period, fixed sequence trial to assess the effect of multiple doses of doravirine on the single-dose pharmacokinetics of a monophasic combination of EE/LNG (Nordette®-28) in healthy female subjects. In Period 1, subjects received a single oral dose of 0.03 mg EE/0.15 mg LNG. In Period 2, subjects received 100 mg doravirine once daily for 17 consecutive days, with a single oral dose of 0.03 mg EE/0.15 mg LNG co-administered with doravirine on Day 14. There was a washout of at least 7 days between dosing in Period 1 and Period 2. Twenty healthy postmenopausal or oophorectomized adult female subjects were enrolled. Safety evaluations were performed throughout the study. Plasma samples for determination of EE and LNG concentrations were obtained for up to 96 hours postdose in each period. The pharmacokinetic parameters of EE and LNG were natural log-transformed and analyzed using a linear mixed-effects model with treatment as fixed effect and an unstructured covariance matrix.

Results: There were no serious clinical or laboratory adverse experiences (AEs). There was one discontinuation due to an AE judged not related to any study drug. Overall, 12 subjects reported a total of 27 postdose clinical AEs, 3 of which were considered drug-related (2 related to doravirine alone [mild erythematous rash, oral

herpes] and 1 related to both doravirine and Nordette®-28 [nervousness]) as well as 1 laboratory AE, judged related to doravirine and Nordette®-28 (red blood cells in urine). All reported AEs were judged to be mild or moderate in intensity and were transient. The geometric mean ratio (GMR) (90% confidence interval [CI]) for EE (Nordette®-28 + doravirine/ Nordette®-28) was 0.98 (0.94, 1.03) for AUC_{0-∞}, and 0.83 (0.80, 0.87) for C_{max}; the GMR and 90% CI for LNG (Nordette®-28 + doravirine/ Nordette®-28) was 1.21 (1.14, 1.28) for AUC_{0-∞}, and 0.96 (0.88, 1.05) for C_{max}.

Conclusions: Multiple dosing of doravirine does not alter the plasma pharmacokinetics of EE or of LNG to a clinically meaningful extent. Coadministration of doravirine and a single dose of an oral contraceptive was generally well tolerated. Consequently, there are no restrictions on the use of oral contraceptives in Phase 3 trials of doravirine.

Conflict of interest: Employee of Merck & Co., Inc.

Abstract: 61

Drug Drug Interactions

Utility of Informatics Resource to Identify Future HIV-HCV Drug-Drug Interaction Studies

C.J. Bednasz¹, S.S. Sithole¹, H.R. Hamilton¹, Q. Ma¹, F. Liguicota¹, F.S. Kaufman¹, R. DiFrancesco¹, G.D. Morse¹

¹University at Buffalo, Translational Pharmacology Research Core, Buffalo NY, USA

Background: The AIDS Clinical Trials Group Precautionary and Prohibited Medications Database (PPMD) is a resource for ACTG researchers to aid in protocol development and subject enrollment. The PPMD includes drug-drug interaction data presented at scientific conferences, among other sources, to provide a consolidated resource for new pharmacokinetic (PK) data obtained from early clinical drug development studies. The PPMD uses a format

with designations of PK interaction status as 'precautionary', 'prohibited', or 'no interaction/no action necessary'. The architecture of the PPMD may also provide an opportunity to analyze and identify gaps in drug-drug interactions studies during drug development as well as identify healthy volunteer versus patient studies. This analysis investigated drug-drug interaction data for 2nd generation direct acting antivirals (DAAs) for hepatitis C virus (HCV) infection in co-infected HIV patients.

Materials & Methods: The PPMD was queried for drug interaction data submitted between 2010-2015 involving the HCV DAAs paritaprevir/ritonavir, ombitasvir and dasabuvir (collectively known as 3D) and daclatasvir, asunaprevir and beclabuvir to identify potential interactions with medications commonly taken by HIV/HCV co-infected patients. Categories included opioid addiction, lipid management, bacterial and fungal infections, depression, cardiovascular disease, and contraception. Drug interaction entries within these categories were documented for each DAA regimen and individual DAA components.

Results: All of the interactions reported with the 3D regimen (n=14) were identified in studies administering all of the three HCV DAAs. For daclatasvir, asunaprevir and beclabuvir, none of the interactions reported (n=16) contained all 3 DAAs, and one study contained 2 DAAs (digoxin vs daclatasvir and asunaprevir). Daclatasvir had studies reported within all 7 categories, and the combination 3D was studied with drugs from 6 of the 7 categories (no studies with antibacterials). Buprenorphine and methadone were studied independently with daclatasvir and asunaprevir. In addition to opioid addiction treatments, asunaprevir was studied with cardiovascular and antidepressant category treatments. No studies of beclabuvir with evaluated drug interaction categories were noted.

Conclusions: DAA combinations are often used in HCV patients receiving multiple concomitant drugs. The combined DAAs likely have different mechanisms of drug interaction, including effects on drug metabolizing enzymes and membrane transporters. When these DAAs are combined their interaction mechanisms may create a 'net' effect on the observed PK of concomitant drugs. By increasing the functionality of the PPMD, the database may be a resource to determine

recently reported drug interactions and assess 'gaps' that may be used to prioritize additional drug-drug interaction studies.

No conflict of interest

Abstract: 62

Drug Drug Interactions

Development of Lopinavir and Darunavir Physiologically-Based Pharmacokinetic Models Incorporating the Pharmacokinetic Effects of Ritonavir

C. Wagner¹, P. Zhao¹, V. Arya¹, C. Mullick², K. Struble², S. Au¹

¹Food and Drug Administration, Office of Clinical Pharmacology, Silver Spring MD, USA; ²Food and Drug Administration, Office of Antimicrobial Products, Silver Spring MD, USA

Background: The overall goal of the project is to apply Physiologically-Based Pharmacokinetic (PBPK) Modeling to determine the impact of the combination of intrinsic and extrinsic factors on the systemic exposure of antiretroviral medications in HIV-1 infected patients. As part of the project, substrate models were developed for two antiretroviral medications: lopinavir (LPV) and darunavir (DRV). Ritonavir (RTV), a CYP3A inhibitor, is coadministered with LPV and DRV to increase systemic exposures (hereafter referred to as LPV/RTV and DRV/RTV, respectively).

Materials & Methods: All simulations were performed using Simcyp v13.2 (Sheffield, UK). Initial model development was focused on simulating the concentration-time profiles of DRV and LPV administered without RTV. The PBPK models were built using physicochemical properties, in vitro parameters, and clinical data (e.g., absorption rate constant and volume of distribution) and were further optimized according to observed oral (LPV) and intravenous (DRV) clearance. In order to predict the effect of RTV on LPV and DRV exposure, a RTV model, which has previously been refined by the Simcyp software developer, was used. RTV effects on DRV or LPV exposure with the recommended once or twice daily dosing regimens were simulated.

Results: The PBPK models predicted the observed LPV and DRV exposure in the absence of RTV within 2-fold of the observed data. In the case of LPV/RTV, the coupled LPV-RTV PBPK model predicted LPV pharmacokinetics for 800 mg/200 mg once daily and 400 mg/100 mg twice daily within 2-fold of the observed data. In the case of DRV/RTV, the coupled DRV-RTV PBPK model overpredicted the observed DRV pharmacokinetics for both dosing regimens (800 mg/100 mg once daily and 600 mg/100 mg twice daily) more than 10-fold. Further refinement of the DRV PBPK model included decreasing the fraction metabolized (fm) by CYP3A, which was adjusted based on ketoconazole-DRV drug-drug interaction data, and yielded exposure predictions within 2-fold of the observed data.

Conclusion: We demonstrated the feasibility of using PBPK models to describe the concentration-time profiles of DRV and LPV when administered without RTV and to predict the effect of RTV on LPV and DRV exposure. These models can be used to predict drug-drug interactions between LPV/RTV or DRV/RTV and other medications.

No conflict of interest

Abstract: 63

Drug Drug Interactions

No Pharmacokinetic Interaction Between HCV Inhibitors Grazoprevir/Elbasvir with Rilpivirine

W.W. Yeh¹, H.P. Feng², P. Auger³, Z. Guo⁴, D. Stypinski³, J. Bredja⁵, P. Jumes⁶, B. Cook⁷, W.L. Marshall¹, M. Iwamoto⁸, J. Butters¹

¹Merck & Co. Inc., Clinical Pharmacology Experimental Therapeutics, Boston, USA; ²Merck & Co. Inc., Quantitative Pharmacokinetics and Pharmacometrics, West Point, USA; ³Celerion, Pharmacokinetics, Lincoln, USA; ⁴Merck & Co. Inc., Biostatistics, Upper Gwynedd, USA; ⁵Celerion, Statistics, Lincoln, USA; ⁶Merck & Co. Inc., Early Stage Operations, Boston, USA; ⁷Celerion, Clinical, Lincoln, USA; ⁸Merck & Co. Inc., Clinical Pharmacology Experimental Therapeutics, Rahway, USA

Background: Grazoprevir (GZR, MK-5172) is a once-daily (QD) inhibitor of the hepatitis C virus (HCV) NS3/4A protease and elbasvir (EBR, MK-8742) is a QD inhibitor of the HCV NS5A that are being developed as a fixed-dose combination therapy for treatment of HCV infection in mono- and HCV/human immunodeficiency virus (HIV)-coinfected patients. This study evaluated the safety and potential drug-drug interaction (DDI) when GZR and EBR are coadministered with rilpivirine (RPV), a HIV-1 non-nucleoside reverse transcriptase inhibitor in healthy subjects.

Materials & Methods: This was an open-label, 3-period, fixed-sequence study in 20 healthy adult males and females. Since GZR in HCV-infected patients demonstrates ~2-fold higher exposure compared to healthy subjects, a 200 mg dose of GZR in healthy subjects was used in this study to match the exposure of a 100 mg dose (the intended clinical dose) in HCV-infected patients. In Period 1, 200 mg GZR + 50 mg EBR were coadministered once daily (QD) from Days 1 to 8. In Period 2, 25 mg RPV was administered QD from Days 1 to 11. In Period 3, 200 mg GZR + 50 mg EBR were coadministered with 25 mg RPV QD from Days 1 to 9. There was a 9-day washout between Periods 1 and 2, but no washout

between Period 2 and 3. Pharmacokinetic (PK) parameters were determined for RPV on Days 11 of Period 2 and 9 of Period 3, and for GZR and EBR on Days 8 of Period 1 and 9 of Period 3. Safety assessments included electrocardiograms, vital signs, clinical laboratory tests, physical examination, and adverse event monitoring.

Results: Coadministration with GZR, EBR, and RPV did not have a clinically meaningful effect on GZR PK with AUC₀₋₂₄, C_{max}, and C₂₄ geometric mean ratios (GMR)s [90% confidence intervals (CIs)] of 0.98 [0.89, 1.07], 0.97 [0.83, 1.14], and 1.00 [0.93, 1.07], respectively. Coadministration with GZR, EBR, and RPV did not have a clinically meaningful effect on EBR PK with AUC₀₋₂₄, C_{max}, and C₂₄ GMRs [90% CIs] of 1.07 [1.00, 1.15], 1.07 [0.99, 1.16], and 1.04 [0.98, 1.11], respectively. Coadministration with GZR, EBR, and RPV did not have a clinically meaningful effect on RPV PK with AUC₀₋₂₄, C_{max}, and C₂₄ GMRs [90% CIs] of 1.13 [1.07, 1.20], 1.07 [0.97, 1.17], and 1.16 [1.09, 1.23], respectively. Coadministration of GZR + EBR with RPV was generally well tolerated in the healthy subjects.

Conclusions: Coadministration of GZR + EBR with RPV had no clinically meaningful effect on the PK of RPV, GZR, or EBR, demonstrating that these drugs can be coadministered in HIV/HCV co-infected patients without need for dose adjustments.

Conflict of interest: I am an employee of Merck & Co., Inc.

Abstract: 64

Drug Drug Interactions

Influence of nevirapine administration on the pharmacokinetics of dolutegravir in HIV-1 infected patients

E. Dailly¹, C. Allavena², M. Grégoire¹, V. Reliquet², H. Hernando¹, E. Billaud², R. Bouquie¹, S. Bouchez², G. Deslandes¹, N. Hall², P. Joliet¹, F. Raffi²

¹Nantes University Hospital, clinical pharmacology, Nantes, France; ²Nantes University Hospital, infectious diseases, Nantes, France

Background: The metabolic pathways of dolutegravir (DTG) and nevirapine (NVP) suggest a potential pharmacokinetic interaction between these drugs. The objective of this study is to investigate the influence of NVP administration on the pharmacokinetics of DTG in HIV-1 infected patients after repeated administrations of DTG and NVP (ClinicalTrials.gov, number NCT02067767).

Material & Methods: This was an open-label study. DTG (administered as a 50 mg once daily in the morning with standardized breakfast) was added for 5 days to the stable antiretroviral regimen [abacavir/lamivudine (ABC/3TC) 600/300 mg qd fixed dose + NVP 400 mg/day] in 10 adult patients. After discontinuation of NVP, the combination of DTG + ABC/3TC was continued. Blood samples were collected at H0 (pre-dose), H1, H2, H4, H6, H8, H10, H24 post-dose 5 days after adding DTG to NVP + ABC/3TC regimen and 2 weeks after discontinuation of NVP. The pharmacokinetic parameters of DTG were calculated by a non compartmental analysis. The log transformed values of pharmacokinetic parameters of DTG were compared between periods with and without NVP co-administration using a paired t-test.

Results : DTG pharmacokinetic parameters (mean ± standard deviation) were significantly ($p < 0.05$) decreased [area under the plasma concentration–time curve from when the dose is administered until the end of the dosing interval $56\,683 \pm 14\,235$ vs $45\,836 \pm 12\,528$ µg/l x h (- 19 %), plasma concentration at the end of the dosing interval 836 ± 439 vs 551 ± 276 mg/l (- 34%), terminal half-life 9.5 ± 2.3 vs 8.1 ± 1.4 h (-15%)] and increased [apparent oral clearance 0.94 ± 0.25 vs 1.16 ± 0.28 l/h (+23%)] by the co-administration of NVP. Tolerance of the combination was good with no clinical or laboratory adverse events, and no serious adverse events were reported.

Conclusion: The decrease of DTG exposure in combination with NVP suggests DTG metabolism is induced by NVP and DTG therapeutic drug

monitoring may be useful if a regimen combined NVP and DTG is required.

Conflict of interest: This study was an investigator-initiated trial and was supported by a grant from Viiv Healthcare

Abstract: 65

Drug Drug Interactions

Raltegravir pharmacokinetics in patients on daclatasvir/asunaprevir (ANRS HC 30)

A. Barrail-Tran¹, C. Vincent², V. Furlan³, H. Paniez², E. Billaud⁴, I. Rosa⁵, M. Simony⁶, J.M. Molina⁷, A.M. Taburet⁸, L. Piroth⁹

¹University Paris Sud Hospital Bicêtre, Clinical Pharmacy UMR 1184, Le Kremlin Bicêtre, France; ²INSERM, SC10-US019, Villejuif, France; ³Hospital Bicêtre, Clinical Pharmacy, Le Kremlin Bicêtre, France; ⁴University Hospital Nantes, Clinical immunology laboratory, Nantes, France; ⁵Centre Hospitalier Intercommunal, Hepatology, Creteil, France; ⁶INSERM, ANRS, Paris, France; ⁷Hospital Saint Louis University Paris Diderot, Department of infectious diseases, Paris, France; ⁸Hospital Bicêtre, Clinical Pharmacy UMR 1184, Le Kremlin Bicêtre, France; ⁹CHU, Department of infectious diseases, Lyon, France

Background: This study was designed to assess raltegravir pharmacokinetics (PK) in HIV/HCV co-infected patients receiving hepatitis C treatment (hepC) with asunaprevir (ASV), daclatasvir (DCV), pegylated interferon-ribavirin (PR) in the ANRS HC 30 QuadriH study.

Materials & Methods: Twenty patients included in the QuadriH trial receiving a raltegravir-based antiretroviral therapy were asked to participate in this PK study. Patients were on raltegravir 400 mg bid with tenofovir DF and either emtricitabine (n=18) or abacavir (n=1) or emtricitabine+enfuvirtide (n=1). They received a 4-week lead-in phase of PR, followed by a 24-week quadruple therapy combining ASV (100mg bid), DCV (60 mg qd), and PR. Blood samples were drawn before (D0) and 4 weeks after quadruple therapy initiation (week 8). Drugs were administered with a light continental breakfast in the morning. ASV, DCV and raltegravir plasma

levels were assayed by validated LC/MS/MS assay. Pharmacokinetic parameters were estimated by a model independent method. Results are expressed as median and range in parenthesis. Geometric mean ratios (GMR) of pharmacokinetic parameters with and without HCV treatment and 90% confidence interval (CI) were generated.

Results: Patients' characteristics were: 18 males, age: 49 (37-59) years, weight 74 (54-83) kg, baseline HCV viral load 6.1 (5.0-7.4) log₁₀ IU/mL, CD4⁺ T-cell count: 849 (362-1994)/mm³ and 19 patients had HIV-RNA below 50 copies/mL. Among the 20 patients, 7 had Child A liver cirrhosis. Ratios for C_{max} and AUC_{last} of raltegravir on and off hepatitis C treatment were 1.04 (0.87-1.23) and 0.94 (0.78-1.14) respectively and were close to one and to 90% CI close to the 0.80-1.25 bioequivalence range. The raltegravir C₀ was lower on hepatitis C treatment than at week 0: 359 ng/mL (46-1126) versus 232 ng/mL (32-1853) respectively, but the difference was not statistically significant. In addition no HIV breakthrough was observed. Raltegravir C_{max} and AUC in patients without or with cirrhosis on day 0 were the following: 2247 (492-7536) ng/mL and 7059 (1677-21523) ng.h/mL in patients without cirrhosis and 2002 (208-4338) ng/mL and 10171 (814-14568) ng.h/mL in patients with cirrhosis respectively.

C_{max} and AUC of ASV and DCV measured on week 8 were 305 (106-1100) ng/mL, 1025 (602-3436) ng.h/mL and 1140 (444-2880) ng/mL and 12008 (6026-32500) ng.h/mL respectively and were not affected by cirrhosis.

No severe adverse event occurred during this study.

Conclusions: Raltegravir PK parameters remained unchanged when combined with DCV/ASV/PR. Daclatasvir and asunaprevir PK parameters remained also unchanged when associated with raltegravir. Raltegravir, DCV, ASV PK parameters were similar in patients with or without cirrhosis. These data suggest that in HIV-HCV coinfecting patients, there is no clinically significant drug drug interaction between asunaprevir/daclatasvir and raltegravir. Asunaprevir and daclatasvir could be administered safely with raltegravir.

No conflict of interest

Abstract: 66*Drug Drug Interactions***An in vitro assessment of the interaction between rifampicin and darunavir/ritonavir using primary human hepatocytes**

O. Roberts¹, D. Back¹, S. Khoo¹, A. Owen¹, M. Siccardi¹

¹University of Liverpool, Department of Molecular and Clinical Pharmacology, Liverpool, United Kingdom

Background: The treatment of tuberculosis (TB) and HIV in co-infected patients is complex, and therapeutic options are limited by drug-drug interactions (DDIs). Rifampicin (RIF) is a potent inducer of certain key metabolic enzymes, and can have a detrimental effect on antiretroviral bioavailability, clearance and efficacy. The aim of this study was to investigate the potential interaction between ritonavir (RTV)-boosted darunavir (DRV/r) and RIF using a hepatocyte-based *in vitro* approach.

Materials & Methods: Primary cryopreserved human hepatocytes were plated on collagen-coated 96-well cell culture plates, and were overlaid with Geltrex™. Hepatocyte cultures were incubated with 10 µM RIF alone, or together with a range of concentrations of RTV (0.01–10 µM) in Williams' Medium E incubation medium. Drugs were replenished at 24-hour intervals for three days. At 72 hours post initial incubation, cells were treated with 10 µM RIF alone, or together with various concentrations of RTV in combination with 5 µM DRV for 60 minutes. DRV was extracted from the incubation medium, and DRV concentrations quantified using HPLC-UV. Each experimental condition was assessed in triplicate. Apparent intrinsic clearance (CL_{int.app}) of DRV was calculated, and expressed as the mean ± SD (µl/min/1 × 10⁶ hepatocytes) of a total of six biological replicates, using cells obtained from two separate donors.

Results: Under control conditions, CL_{int.app} of DRV was 12.4 ± 3.1 µl/min, whereas incubation with 10 µM RIF increased the CL_{int.app} of DRV to 22.9 ± 1.7 µl/min (84.2 ± 14.0% increase compared to control levels). Inclusion of 1 µM

RTV was sufficient to overcome the effect of 10 µM RIF (CL_{int.app} = 10.4 ± 2.2 µl/min; a decrease of 15.9 ± 18 % compared to control). RTV concentrations were inversely associated with DRV CL_{int.app}, with 5 µM RTV resulting in a CL_{int.app} of DRV = 9.2 ± 2.5 µl/min (decrease of 25.8 ± 20.3% compared to control) and 10 µM RTV resulting in a DRV CL_{int.app} of 6.2 ± 2.3 µl/min (decrease of 50.2 ± 18.3 % compared to control), respectively.

Conclusions: Primary cryopreserved human hepatocytes were successfully utilised as valuable *in vitro* model for the investigation of complex DDIs. RIF increases the intrinsic clearance of DRV by primary cryopreserved human hepatocytes, an effect that can be overcome by RTV. In addition, the RTV-mediated attenuation of RIF-enhanced DRV intrinsic clearance appears to occur in a concentration-dependent manner. These results provide data to inform pharmacokinetic modelling for the identification of dose optimisation strategies in patients concomitantly receiving antiretrovirals and anti-TB drugs.

No conflict of interest

Abstract: 67*Drug Drug Interactions***HIV-1 Attachment Inhibitor Prodrug BMS-663068: Assessment of Interactions with Raltegravir in Treatment-Experienced HIV-1-Infected Subjects**

I. Landry¹, D.C. Cui², J. Wang³, M. Lataillade⁴, D.W. Boulton⁵

¹Bristol-Myers Squibb, Clinical Pharmacology and Pharmacometrics Virology, Princeton, USA; ²ICON Clinical Research, Pharmacokinetics Pharmacodynamics Modeling & Simulation Early Phase, Hanover, USA; ³Bristol-Myers Squibb, Analytical and Bioanalytical Development, Princeton, USA; ⁴Bristol-Myers Squibb, Research and Development Virology, Wallingford, USA; ⁵AstraZeneca LP, Quantitative Clinical Pharmacology, Gaithersburg, USA

Background: BMS-663068 is a prodrug of BMS-626529, a first-in-class attachment inhibitor that binds directly to HIV-1 gp120, preventing initial viral attachment and subsequent entry into host CD4+ T cells. Raltegravir (RAL), metabolized to RAL-glucuronide by UGT1A1, is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults. It is likely that BMS-663068 will be coadministered with RAL so potential drug–drug interactions (DDI) were investigated by evaluating the pharmacokinetics of BMS-626529 and RAL in treatment-experienced, HIV-1-infected subjects.

Materials & Methods: Study A1438011 is an ongoing Phase 2b, randomized, active-controlled, blinded-to BMS-663068 dose, multiple-dose trial evaluating the safety and efficacy of BMS-663068. In the primary study, treatment-experienced, HIV-1-infected subjects (n=254) were randomized 1:1:1:1:1 to five treatment groups: four BMS-663068 groups (600mg once daily [QD], 1200mg QD, 400mg twice daily [BID], or 800mg BID) and a reference group (ritonavir-boosted atazanavir 300/100mg QD), each with RAL 400mg BID + tenofovir disoproxil fumarate (TDF) 300mg QD. A previous clinical pharmacology study found no clinically relevant DDI between BMS-626529 and TDF, so in the present study a fixed backbone of RAL+TDF was used. An optional 7-day BMS-663068 monotherapy substudy preceded the primary study. Blood samples taken on Day 7 and at Week 2 were used to measure BMS-626529 plasma concentrations, and at Week 2 only to measure RAL concentrations. PK parameters were derived using non-compartmental methods. Geometric mean ratios and 90% confidence intervals (CI) were calculated for BMS-626529 and RAL from log-transformed C_{max} , AUC_{tau} and C_{tau} using a linear mixed-effect model. RAL PK was compared informally to historical data. Safety was monitored throughout the study.

Results: 251 subjects were treated in the primary study (monotherapy substudy data available for 29 subjects [$n \leq 10$ per BMS-663068 group]). At BMS-663068 doses 600mg QD, 1200mg QD 400mg BID and 800mg BID, the geometric mean (coefficient of variance; CV%) of BMS-626529 C_{max} was 1480ng/mL (44%), 4220ng/mL (49%), 1400ng/mL (44%), and 3290ng/mL (42%), respectively. Geometric mean (CV%) of AUC_{tau} was 14784ng.h/mL (50%), 29611ng.h/mL (63%), 8923ng.h/mL (36%), and 20905ng.h/mL (46%),

respectively. Geometric mean of BMS-626529 C_{tau} was 99.3ng/mL (165%), 127ng/mL (128%), 284ng/mL (87%), and 603ng/mL (59%), respectively. Compared with administration of BMS-663068 alone, coadministration of all BMS-663068 doses with RAL+TDF had little effect on BMS-626529 C_{max} , AUC_{tau} or C_{tau} (except an ≈ 2 -fold increase in C_{tau} at 600mg QD and 400mg BID, likely due to small sample size).

RAL PK parameters were highly variable following coadministration with BMS-663068+TDF; geometric mean RAL C_{max} ranged from 2120 to 3370ng/mL, AUC_{tau} , 8776 to 14983 ng.h/mL, and C_{tau} , 149 to 259ng/mL across all BMS-663068 doses. The variable RAL (CV% 49–77%) exposures were consistent with those from other studies in HIV-infected subjects. The modest differences in RAL PK parameters across BMS-663068 doses were consistent with *in vitro* data suggesting that BMS-626529 does not inhibit UGT1A1 and hence does not meaningfully affect RAL systemic exposure. All study drugs were generally safe and well tolerated.

Conclusions: There were no clinically relevant DDI between BMS-626529 and RAL over a wide range of BMS-663068 doses.

Conflict of interest: Ishani Landry, Jian Wang and Max Lataillade are BMS employees and BMS shareholders. David Boulton was an employee of BMS at the time the work was performed and is a BMS shareholder. Dapeng Cui has no financial relationships to disclose.

Abstract: 68

Drug Drug Interactions

The experience with drug-drug interaction studies between antiviral medications and oral contraceptives.

I. Younis¹, R. Ayala², V. Arya¹

¹US Food and Drug Administration, Office of Clinical Pharmacology Office of Translational Sciences CDER, Silver Spring, USA; ²US Food and Drug Administration, Office of Scientific Investigations, Silver Spring, USA

Background: Drug-drug interaction (DDI) studies between antiviral medications (AVs) and oral contraceptives (OCs) are frequently conducted to establish knowledge about safe and effective use of OCs in women receiving HIV or HCV treatment. The aim of this work was to construct a database of DDI trials that evaluate the effect of AVs on OCs to understand the major design features of these trials

Materials & Methods: Design features and results of OC-AV DDI trials were collected from drug labels and clinical pharmacology reviews available at drugs@fda. The database contains information regarding trial design (number of menstrual cycles evaluated, population, type of OC used) and results (pharmacokinetic parameters, pharmacodynamic markers, and clinical recommendations in AV medication labels).

Results: Thirty percent of the DDI studies with oral contraceptive submitted to 341 NDAs of NMEs approved between 2000 and 2014 were with antiviral medications. Among all antivirals approved, a total of 27 DDI studies with oral contraceptives were conducted. Most of these trials were open-label with a fixed sequence design (n=22, 82%). Only five trials used a double-blind cross-over design. Most trials were conducted within one 28-day ovulatory cycle (n=10, 37%), followed by three ovulatory cycles (n=9, 33%), and two ovulatory cycles (n=8, 30%). OCs were administered in multiple doses in the majority of trials (n=23, 85%). Most trials enrolled healthy women (n=26, 96%); of which one study recruited postmenopausal women and another study recruited surgically sterilized women. Only one study enrolled HIV-1 infected women. The participating volunteers were receiving stable doses of OCs prior to enrolling in 12 trials (44%). The median number of women in a trial was 20 (mean =24) with a range of 12 to 52. Norethindrone/ ethinyl estradiol (EE) combination was the most commonly used OC (n=16, 55%) followed by norgestimate/EE (n=9, 31%). The primary objective of all trials was to evaluate the changes in the exposure of OC components upon the co-administration of AVs. Pharmacodynamic evaluation (LSH and FSH measurement) was performed in 10 trials (37%) of which progesterone levels were quantified in 7 trials. Two antiviral drugs (atazanavir and boceprevir) had DDI studies with two different OCs. Labeling

recommendations were based on exposure changes in 25 cases (92.5%) and safety observations in the trial informed labeling recommendations in two cases.

Conclusions: A wide variety of AV-OC DDI trials have been performed and were used to provide clinical recommendations regarding the co-administration of AVs and OCs in the respective AV labels. The primary objective of these trials was to assess the changes in OC exposures when co-administered with AVs to inform dosing recommendations upon co-administration. There is no preferred study design and the answer to the exposure question can be achieved utilizing any design while taking into consideration other aspects such as safety considerations and logistical issues such as synchronization.

No conflict of interest

Abstract: 69

Drug Drug Interactions

Lessons learned from drug-drug interaction studies between antiviral medications and methadone

I. Younis¹, E. Lakotal²

¹US Food and Drug Administration, Office of Clinical Pharmacology Office of Translational Sciences CDER, Silver Spring, USA; ²State University of New York at Buffalo, School of Pharmacy, Buffalo, USA

Background: Methadone is a racemic mixture of R- methadone (R) and S- methadone (S) primarily metabolized by CYP3A4 (R=S), CYP2B6 (S>R), and CYP2C19 (R>S). Due to the frequent co-administration of methadone and antiviral medications formal methadone drug-drug interaction (DDI) studies are often performed during antiviral medications development. Our objective was to summarize lessons learned from the overall experience with Antiviral medications-methadone DDI studies.

Materials & Methods: Drug labels for new molecular entities (NMEs) approved between 2000-2013, in addition to labels for all antiviral medications approved prior to the end of 2013, were surveyed for methadone co-administration recommendations. Results from methadone DDI studies (changes in AUC and C_{max}), labeling recommendations, and CYP inhibition or induction potential of the antiviral medications were collected.

Results: Of the 309 NMEs surveyed, 13 had methadone DDI studies of which 12 (92%) were with antiviral medications. Of the 31 antiviral medications approved, 25 (81%) antiviral medications had methadone DDI studies and 27 (87%) antiviral medication labels contain clinical recommendations for the co-administration of the respective antiviral medications and methadone. The clinical recommendations in these 27 labels fell into three categories as follows: no methadone dose adjustment (59%), methadone dose may need to be increased (33%), methadone dose may need to be decreased (8%). There were no definitive recommendations regarding the amount by which doses should be altered. When methadone was administered with moderate and strong CYP3A4 inhibitors, methadone AUC decreased. Of the DDI studies which collected data on both R-methadone and S-methadone, the antiviral medications consistently impacted S-methadone to a greater extent than R-methadone, suggesting higher involvement of CYP2B6 in the interactions than CYP3A4. A majority of the interactions could be explained by the antiviral medications ability to inhibit or induce CYP2B6.

Conclusions: Methadone disposition appears to be more sensitive to the inhibition or induction of CYP2B6 than inhibition or induction of CYP3A4. Because the clinical recommendations regarding the co-administration of methadone and antiviral medications falls into one of three categories and are based on the direction rather than amount of the interaction; labeling can potentially be achieved using reliable and valid prediction methods, such as IVIVE and PBPK, that can predict the direction of methadone exposure changes when co-administered with antiviral medications.

No conflict of interest

Abstract: 70

Drug Drug Interactions

Correlation between efavirenz and levonorgestrel plasma concentrations during a drug-drug interaction study

K.K. Scarsi¹, K.M. Darin², S. Nakalema³, D.J. Back⁴, P. Byakika-Kibwika⁵, L. Else⁴, S. Dilly-Penchala⁴, C. Merry⁶, S.E. Cohn⁷, M. Lamorde³

¹University of Nebraska Medical Center, College of Pharmacy, Omaha, USA; ²Northwestern University Feinberg School of Medicine, Center for Global Health, Chicago, USA; ³Makerere University, Infectious Diseases Institute, Kampala, Uganda; ⁴University of Liverpool, Department of Molecular and Clinical Pharmacology, Liverpool, United Kingdom; ⁵Makerere University, Department of Medicine, Kampala, Uganda; ⁶Trinity College Dublin, Department of Pharmacology and Therapeutics, Dublin, Ireland; ⁷Northwestern University Feinberg School of Medicine, Division of Infectious Diseases, Chicago, USA

Background: Recently we reported a clinically significant drug-drug interaction between the levonorgestrel (LNG) subdermal contraceptive implant and efavirenz (EFV)-containing antiretroviral therapy (ART). In women receiving EFV 600mg, the LNG area under the concentration time curve was reduced 48%, and three (15%) unintended pregnancies among 20 women were observed within 48-weeks of combined use. With the emerging use of EFV 400mg daily, it is unknown if this EFV dose reduction will influence the magnitude of EFV-related drug-drug interactions. Although reducing the daily dose of EFV from 600mg to 400mg decreases the geometric mean (GM) EFV C_{12h} by 27%, the inter-individual variability remains high (90% confidence interval: 0.55-0.97). Therefore, we sought to evaluate if high EFV concentrations influenced the extent of the observed LNG-EFV drug-drug interaction in our cohort.

Materials & Methods: A 2-rod (75mg/rod) LNG implant was inserted at entry in 20 participants on tenofovir/emtricitabine/efavirenz. Blood was collected 12-14 hours post-EFV dose at screening, entry and at 1, 4, 12, 24, 36, and 48

weeks after entry for assessment of both LNG and EFV plasma concentrations. Nine subjects did not complete the week 48 visit due to early closure of the EFV study arm following unintended pregnancy outcomes. Plasma LNG and EFV concentrations were analyzed by a validated LC-MS/MS and HPLC method, respectively. Associations between LNG and EFV concentrations at each time point were assessed by Pearson's correlation (r) and with linear regression analysis ($p < 0.05$ significant). Suboptimal LNG exposure was defined as any concentration that fell below the highest concentration at which a pregnancy was observed in our cohort (303 pg/mL). Data are presented as median (range).

Results: All women were Black African, 31 (24-40) years of age, and weighed 59.5 (45-88) kg at entry. Subjects had received EFV for 10 (5-66) months prior to entry, all with an undetectable HIV-RNA and CD4+ count of 534 (284-853) cells/mm³. The median EFV C_{12-14h} over the 48-week study period was 2.3 (0.1-20.0) mcg/mL. LNG was inversely correlated with EFV concentrations by bivariate analysis ($r = -0.42$; $p < 0.001$). The correlation persisted when low EFV concentrations consistent with medication non-adherence (< 1 mcg/mL, $n = 10$ individual concentrations in 6 subjects) were removed from the analysis ($r = -0.40$; $p < 0.001$). LNG remained inversely correlated with efavirenz concentrations after adjustment for other covariates, including age, weight, and study visit ($\beta = -36$ pg/mL; $p = 0.012$). 15 women (75%) had suboptimal LNG exposure; of these women, only 7 (46.7%) had an EFV concentration > 3 mcg/mL ($p = 1.0$).

Conclusions: In our cohort, LNG concentrations were inversely related to EFV concentrations (for every 1 mcg/mL increase in EFV, LNG decreased 36 pg/mL). Nonetheless, suboptimal LNG exposure was common in women receiving EFV, even in those with EFV concentrations within the expected therapeutic range (1-3 mcg/mL). In the absence of formal pharmacokinetic data, these results suggest that if a 33% lower dose of EFV were used, a clinically significant drug-drug interaction between EFV and the LNG implant remains likely.

No conflict of interest

Abstract: 71

Drug Drug Interactions

Drug Interactions between anti-HCV Antivirals Ledipasvir/Sofosbuvir and Integrase Strand Transfer Inhibitor-Based Regimens

K. Garrison¹, J. Custodio¹, P. Pang², M. Das², F. Cheng³, G. Ma³, A. Mathias¹

¹Gilead Sciences, Clinical Pharmacology, Foster City, USA;

²Gilead Sciences, Clinical Research, Foster City, USA;

³Gilead Sciences, Biometrics, Foster City, USA

Background: Use of some anti-HCV agents with HIV antiretrovirals (ARVs) may be complicated by drug-drug interactions (DDIs). A fixed-dose combination tablet composed of the NS5A inhibitor ledipasvir (LDV) 90 mg and NS5B inhibitor sofosbuvir (SOF) 400 mg is indicated for the treatment of chronic hepatitis C genotype 1 infection in adults. We conducted two Phase 1 studies in healthy volunteers to evaluate potential DDIs between LDV/SOF and integrase strand transfer inhibitor based regimens: elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (E/C/F/TAF) or dolutegravir (DTG) plus emtricitabine/tenofovir DF (FTC/TDF; TVD).

Materials & Methods: These were multiple-dose, randomized, cross-over DDI studies. Study 1 subjects (N=30) received LDV/SOF, E/C/F/TAF (150 mg/150 mg/200 mg/10 mg) and LDV/SOF plus E/C/F/TAF. Study 2 subjects (N=30) received LDV/SOF, DTG (50 mg) +FTC/TDF (200 mg/300 mg) and LDV/SOF plus DTG+FTC/TDF. All study treatments were administered once daily with food for 10 days.

LDV, SOF, GS-331007 (predominant circulating metabolite of SOF), and ARV plasma concentrations were analyzed and PK parameters were calculated. 90% CIs for the geometric least squares means ratios% (combination vs. alone) for analytes' AUC_{tau}, C_{max} and C_{tau} were estimated by linear mixed effect model and compared to lack of PK alteration

boundaries of 70-143%. Safety assessments were conducted during the study.

Results: All subjects (Study 1) and 29/30 subjects (Study 2) completed the study. Study treatments were generally well tolerated. All adverse events (AE) in Study 1 were Grade 1 except for 2 occurrences of constipation (Grade 2) in subjects receiving LDV/SOF+E/C/F/TAF. Occurrences of AEs were comparable across treatments; most common AEs were GI disorders including diarrhea and nausea. The majority of Study 2 AEs were Grade 1; the most commonly reported AEs were nausea, headache and constipation. One Study 2 subject discontinued LDV/SOF+ DTG+TVD treatment due to Grade 2 ALT/AST increases; LFTs normalized 14 days after treatment cessation. No Grade 3 or 4 AEs were observed in either study. LDV exposure parameters (AUC_{tau} , C_{max} and C_{tau}) were ~ 65% to 93% higher with E/C/F/TAF. Higher SOF AUC_{tau} (~47%) and C_{max} (~28%), and higher GS-331007 AUC_{tau} (~48%) and C_{tau} (~66%) were observed on coadministration; there was no alteration in GS-331007 C_{max} (90% CIs within 70-143%). EVG C_{tau} was increased by ~46% and COBI AUC_{tau} and C_{tau} were increased by ~53% and ~225%, respectively, with LDV/SOF. The higher COBI exposure following coadministration is not considered clinically relevant based on the totality of data from Phase 2/3 studies showing no association between higher COBI exposure and the incidence of common AEs or renal function parameters. No changes in FTC, TAF or TFV PK were observed.

LDV/SOF PK was unaffected by DTG+TVD. There were also no alterations in the PK of DTG or FTC with LDV/SOF. TFV PK parameters were ~61% to 115% higher on coadministration. Increases in TFV exposure are comparable to those observed following administration of LDV/SOF with NNRTI-based regimens efavirenz+TVD or rilpivirine+TVD.

Conclusions: Study treatments were generally well tolerated. LDV/SOF may be administered with E/C/F/TAF or DTG+TVD. Appropriate monitoring for TFV-associated AEs is advised during coadministration of LDV/SOF with DTG+TVD.

Conflict of interest: Authors are employees and shareholders of Gilead Sciences.

Abstract: 72

Drug Drug Interactions

Metabolism and Excretion of Pangenotypic HCV NS5A Inhibitor GS-5816 in Humans

E. Mogalian¹, C. Yang², L.M. Stamm³, G. Shen⁴, M. Hernandez⁵, A. Mathias⁶

¹Gilead Sciences, Clinical Pharmacology, Foster City California, USA; ²Gilead Sciences, Drug Metabolism and Pharmacokinetics, Foster City California, USA; ³Gilead Sciences, Clinical Research, Foster City CA, USA; ⁴Gilead Sciences, Biostatistics, Foster City CA, USA; ⁵Gilead Sciences, Clinical Operations, Foster City CA, USA; ⁶Gilead Sciences, Clinical Pharmacology, Foster City CA, USA

Background: GS-5816, a potent pangenotypic HCV NS5A inhibitor, is in clinical development for the treatment of genotype 1-6 chronic HCV infection in combination with sofosbuvir (SOF). Preclinical data suggest that GS-5816 is primarily excreted as parent and metabolites in the feces. The present study was conducted to understand the metabolic and excretory pathways of GS-5816 in humans.

Materials & Methods: Healthy male volunteers (N=8) were administered a single oral dose of an ethanolic solution of 100 mg GS-5816 containing 100 μ Ci [¹⁴C]-labeled GS-5816 in a capsule after completing a standardized meal. Blood, urine, and feces samples were collected until prespecified standard criteria for collection of administered radiolabeled material were met. All samples were analyzed for total radioactivity, pooled plasma and excreta samples were subject to HPLC radioprofiling, and plasma samples were subject to HPLC-MS/MS analyses. Quantification of GS-5816 was performed using a synthetic standard, and previously identified metabolites were quantified based on HPLC profiles of radioactivity. Safety was assessed by routine clinical and laboratory monitoring throughout the study.

Results: Eight subjects enrolled, received study drug, and completed the study. In general GS-5816 was well tolerated. Four of the 8 enrolled subjects reported adverse events (AEs), all were mild in severity. None of the AEs were considered related to study drug. No laboratory abnormalities occurred. Total mean recovery of radioactivity in excreta was $95 \pm 5\%$ (SD) of the radioactive dose, primarily in feces (94%) with minimal excretion in the urine (0.4%). The predominant circulating species in plasma was GS-5816 (~99% of total radioactivity AUC). The whole blood to plasma ratio of total radioactivity ranged from 0.52-0.67 indicating exclusion of total radioactivity from erythrocytes. In all subjects, blood and plasma radioactivity were undetectable following the 12 and 24 hour time points, respectively. GS-5816 was the major species detected in the feces (77% of dose) with hydroxy-GS-5816-1 (M18) and desmethyl-GS-5816 (M19) accounting for 5.9% and 3.0% of the dose, respectively. Two additional unidentified components in the feces accounted for a mean of 2.8% and 0.5% of the dose, respectively.

Conclusions: GS-5816 was not subject to significant metabolism and accounted for ~99% of systemic exposure. GS-5816 was primarily excreted into feces as parent (~77% of dose) and minor metabolites. Renal excretion exists as a minor elimination pathway (~0.4% of dose). A single dose of GS-5816 with [^{14}C]-GS-5816 was generally safe and well tolerated.

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

Abstract: 73

Drug Drug Interactions

Evaluation of the drug interaction potential between elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide and sertraline

J. Custodio¹, S. West², M. Das³, A. Nichols⁴, B. Kearney¹, J. Zack¹

¹Gilead Sciences, Clinical Pharmacology, Foster City, USA;

²Gilead Sciences, Biometrics, Foster City, USA; ³Gilead Sciences, Clinical Research, Foster City, USA; ⁴Gilead Sciences, Clinical Operations, Foster City, USA

Background:

Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (EVG/COBI/FTC/TAF (150/150/200/10 mg); E/C/F/TAF) is a single tablet regimen (STR) under regulatory review for treatment of HIV. Sertraline (SER; Zoloft[®]), a selective serotonin reuptake inhibitor (SSRI), is a commonly prescribed coadministered medication in the HIV-infected population for treatment of disorders including but not limited to major depressive disorder. SER is eliminated by multiple CYP450 enzymes including CYP2D6, CYP2C9, CYP2B6, CYP2C19 and CYP3A4 (contribution of each enzyme estimated at 35, 29, 14, 13 and 9%, respectively). COBI, a pharmacokinetic (PK) enhancer, is an inhibitor of CYP3A (major) and CYP2D6 (minor). This study evaluated the PK and drug interaction potential between EVG, COBI, FTC, TAF and SER when coadministered as E/C/F/TAF + SER.

Materials & Methods: This was an open label, three period, single center study. Healthy subjects (n=20) received the following treatments in a fixed sequence manner: SER 50 mg on Day 1; E/C/F/TAF on Days 2-13; E/C/F/TAF + SER on Day 14. PK assessments were performed on final day of each treatment period (Days 1, 13 and 14). Statistical comparisons of EVG, COBI, FTC, TAF, TFV and SER exposures were made using geometric mean ratios (GMR) and associated 90% confidence interval (CI) bounds of 70-143% (>90% power to conclude no-effect), with E/C/F/TAF + SER serving as the test treatment (Day 14) and E/C/F/TAF or SER administered alone serving as the reference treatment (Day 13 or 1, respectively).

Results: Nineteen of the 20 enrolled subjects completed the study; one subject prematurely discontinued after withdrawing consent. All study treatments were generally well tolerated and no Grade 2, 3 or 4 adverse events were observed. Following coadministration of E/C/F/TAF + SER, relative to SER alone, the 90% CIs about the

GMRs of the PK parameters of SER were within the protocol defined no-effect boundary (GMR (90% CI) AUC_{inf} : 93.3 (77.0, 113) and C_{max} : 114 (93.7, 138)), indicating a lack of an effect of E/C/F/TAF on the CYP-mediated elimination of SER. Additionally and as expected due to the limited liability of SER as a perpetrator of DDI, following coadministration of E/C/F/TAF + SER, relative to E/C/F/TAF alone, the 90% CIs about the GMRs of the PK parameters of EVG, COBI, FTC, TAF, and TFV were within the protocol defined no-effect boundary (GMR (90% CI) EVG AUC_{tau} : 93.5 (89.5, 97.8); COBI AUC_{tau} : 99.9 (97.0, 103); FTC AUC_{tau} : 84.4 (81.1, 87.7); TAF AUC_{last} : 95.6 (89.2, 103); and TFV AUC_{tau} : 102 (100, 104)).

Conclusions: All study treatments were generally well tolerated. No clinically relevant changes in the PK of SER or any components of the E/C/F/TAF STR were observed upon coadministration with E/C/F/TAF +SER, relative to E/C/F/TAF or SER administered alone. No dose adjustment is required upon coadministration of these agents.

Conflict of interest: Authors are employees and shareholders of Gilead Sciences.

Abstract: 74

Drug Drug Interactions

Pharmacokinetics of simeprevir with TMC647055/ritonavir with/without ribavirin or with/without JNJ-56914845 in genotype 1 HCV-infected patients

T.N. Kakuda¹, T. Kirsilä², A. Vandevoorde³, P. Van Remoortere⁴, R. Verloes⁵

¹Janssen Research & Development, Clinical Pharmacology, Titusville, USA; ²Janssen Infectious Diseases BVBA, Biostatistics, Beerse, Belgium; ³Janssen Infectious Diseases BVBA, Project Management, Beerse, Belgium; ⁴Janssen Research & Development, Clinical Development, Titusville, USA; ⁵Janssen Research & Development BVBA, Medical, Beerse, Belgium

Background: Simeprevir is a once-daily (QD) hepatitis C virus (HCV) NS3/4A protease inhibitor, TMC647055 is a non-nucleoside HCV polymerase inhibitor and JNJ-56914845 is an NS5A replication complex inhibitor. The pharmacokinetic interaction between these drugs was previously evaluated in healthy volunteers. A Phase IIa, open-label study (NCT01724086) assessed the combination of simeprevir+TMC647055/ritonavir±ribavirin or ±JNJ-56914845 in chronic HCV genotype 1-infected treatment-naïve patients and prior relapsers. Ritonavir was included in the regimen to counteract TMC647055 auto-induction of CYP3A and simeprevir dosed 75mg QD to adjust for the interaction with ritonavir. Rich pharmacokinetic data from the study are presented.

Materials & Methods: The study comprised four 12-week treatment panels: simeprevir 75mg QD + TMC647055/ritonavir 450mg/30mg QD with ribavirin 1000–1200mg/day (Panel 1 [n=10; genotype 1a] and Panel 2-Arm 1 [n=12; genotype 1b]) or without ribavirin (Panel 2-Arm 2 [n=9; genotype 1b]); simeprevir 75mg QD + TMC647055/ritonavir 600mg/50mg QD with ribavirin 1000–1200mg/day (Panel 3-Arm 1 [n=7; genotype 1a] or without ribavirin (Panel 3-Arm 2 [n=8; genotype 1b]); or simeprevir 75mg QD + TMC647055/ritonavir 450mg/30mg QD with JNJ-56914845 30mg QD (Panel 4-Arm 1 [n=22; genotype 1] or 60mg QD (Panel 4-Arm 2 [n=22; genotype 1a/1b]). Serial blood samples were taken over 24 hours (pre-dose, 1, 2, 3, 4, 5, 6, 8, 10, 12 and 24 hours post-dose) at Week 4 from all patients. Plasma concentrations of simeprevir, TMC647055, ritonavir and JNJ-56914845 were obtained using validated LC-MS/MS methods. Pharmacokinetic parameters were calculated using non-compartmental analysis (Phoenix WinNonlin 6.2.1).

Results: Administration of simeprevir 75mg QD in combination with TMC647055/ritonavir resulted in simeprevir exposure in the range observed with simeprevir dosed at 150mg QD. Simeprevir exposure was increased when co-administered with high-dose TMC647055/ritonavir (600/50mg vs 450/30mg) (Panel 3-Arm 1 vs Panel 1: maximum plasma concentration (C_{max}) 5,989 vs 3,043 ng/mL, area under the curve (AUC) 91,627 vs 40,064 ng.h/mL; Panel 3-Arm 2 vs Panel 2-Arm 2: C_{max} 8,966 vs 4,583 ng/mL, AUC 127,318 vs

67,437 ng.h/mL). A more than dose-proportional increase in TMC647055 exposure occurred following co-administration of TMC647055/ritonavir 600mg/50mg QD vs 450mg/30mg QD, both with simeprevir 75mg QD (Panel 3-Arm 2 vs Panel 2-Arm 2: C_{max} 36,288 vs 13,936 ng/mL; AUC: 273,964 vs 112,769 ng.h/mL). Increase in exposure to JNJ-56914845 60mg vs 30mg QD was dose proportional when co-administered with simeprevir 75mg + TMC647055/ritonavir 450mg/30mg QD (Panel 4-Arm 2 vs Panel 4-Arm 1: C_{max} 821 vs 389 ng/mL, AUC 7,747 vs 3,358 ng.h/mL). Co-administration of high-dose JNJ-56914845 60mg QD with simeprevir 75mg QD + TMC647055/ritonavir 450mg/30mg QD increased simeprevir exposure (Panel 4-Arm 2 vs Panel 2-Arm 2: C_{max} 5,419 vs 4,583 ng/mL; AUC 80,893 vs 67,437 ng.h/mL) but had minimal effect on TMC647055 and ritonavir exposure. No deaths, serious adverse events (AEs), Grade 4 AEs or AEs leading to discontinuation occurred.

Conclusions: High exposure to TMC647055 was achieved in combination with ritonavir. Dose adjustment of simeprevir to 75mg QD is recommended when co-administered with TMC647055/ritonavir±JNJ-56914845. Co-administration of simeprevir+TMC647055/ritonavir±ribavirin or ±JNJ-56914845 was safe and well tolerated.

Conflict of interest: Employee and stock holder of Johnson & Johnson

Abstract: 75

Drug Drug Interactions

Dolutegravir drug interaction with DRV/r or ATV/r: impact on its pharmacokinetic?

M.P. Le¹, J.B. Pain¹, A. Desnoyer¹, D. Descamps², C. Katlama³, V. Calvez⁴, Y. Yazdanpanah⁵, G. Peytavin¹

¹Hôpital Bichat-Claude Bernard, Clinical Pharmacokinetic, Paris, France; ²Hôpital Bichat-Claude Bernard, Virology, Paris, France; ³Hôpital Pitié-Salpêtrière, Infectious Diseases, Paris, France; ⁴Hôpital Pitié-Salpêtrière, Virology, Paris,

France; ⁵Hôpital Bichat-Claude Bernard, Infectious Diseases, Paris, France

Background: Dolutegravir (DTG) is a potent HIV integrase strand transfer inhibitor (INSTI) approved in association with other antiretroviral drugs. The daily dose mainly depends on patients' INSTI history and the risk of cross-resistance to INSTI (documented or clinically suspected). Its metabolism is mainly processed by UGT1A1, however DTG is also a substrate of UGT1A3, UGT1A9, CYP3A4, Pgp, and BCRP. These pathways highlight potential drug-drug interaction (DDI) with other antiretroviral drugs. The objective of this study was to compare DTG trough concentrations, C24h or C12h regarding its dose regimen (QD or BID), associated with ATV/r or DRV/r or without any of PI/r or NNRTI.

Materials & Methods: Multicenter and observational study conducted on HIV-infected patients receiving DTG 50mg QD or BID in association with ATV/r (300/100mg QD) or DRV/r (800/100mg QD or 600/100mg BID). Patients with other PI/r or NNRTI were excluded. From these patients, 5 groups were represented according to the ARV regimen: among patients receiving DTG 50mg QD, a reference group without any PI/r or NNRTI (REFQD), a group with DRV/r 800/100mg QD (DRVQD) and a group with ATV/r 300/100mg QD (ATVQD); among patients receiving DTG 50mg BID, a reference group without any PI/r or NNRTI (REFBID) and a group with DRV/r 600/100mg BID (DRVBID). Plasma concentrations of DTG, DRV, ATV and RTV were determined with UPLC-MS/MS, 12hr or 24hr post-dose. Limits of quantification (LOQ) were determined as 5ng/mL (DTG and DRV) and 10ng/mL (ATV). DTG C24h and C12h were interpreted regarding an efficacy threshold of 1000ng/mL (Sailing Study). All results are expressed as median (IQR25-75%). Non-parametric Mann-Whitney and Spearman's correlation tests were performed for statistical analysis.

Results: Overall, 91 patients were recruited. [73% men, age 49yr (43-56)]. Among patients receiving DTG 50mg QD, DTG C24h was 1,831ng/mL (1,324-2,788; CV=69%; n=16) in REFQD, with 4 patients <1,000ng/mL; 3,442ng/mL (2,310-3,718; CV=37%; n=14) in ATVQD, with none <1000ng/mL, and 759ng/mL

(325-1,432; CV=61%; n=16) in DRVQD, with 10 patients <1,000ng/mL. ATV C24h was 582ng/mL (309-1,015; CV=96% n=14); DRV C24h was 1,501ng/mL (1,134-2,257; CV=61%; n=16). DTG C24h was significantly lower in DRVQD than in REFQD (-61%; $p<0.01$), however, DTG C24h was significantly higher in ATVQD than in REFQD (+43%; $p<0.01$).

Among patients receiving DTG 50mg BID, DTG C12h was 4,438ng/mL (2,593-5,647; CV=58%; n=10) in REFBID, with none <1,000ng/mL and 2,277ng/mL (1,332-3,439; CV=73%; n=35) in DRV BID, with 6 <1,000ng/mL; DRV C12h was 2,951ng/mL (1,795-4,171; CV=54%; n=35). DTG C12h was significantly lower in DRV BID than in REFBID (-45%; $p<0.05$).

Moreover, pooled DTG C24h and C12h were correlated with RTV C24h and C12h when associated to DRV ($r=0.745$; $p=1.29$).

Conclusion: In these patient's settings, our results are consistent with a favourable interaction between DTG and ATV/r, allowing higher DTG C24h. Surprisingly, in both dose regimen (QD and BID), a DDI between DRV/r and DTG was reported with a significant decrease of DTG C24h and C12h. A higher ratio of patients with inadequate DTG C24h&C12h was reported in DRVQD than in DRV BID (63% vs 17%) suggesting that DTG 50mg QD+DRV/r 800/100mg QD should be reserved to maintenance strategy instead of induction treatment.

No conflict of interest

Abstract: 76

Drug Drug Interactions

Which dose of daclatasvir should be used with darunavir/ritonavir 800/100mg once-daily containing regimen in hiv/hcv co-infected patients?

A. Desnoyer¹, M.P. L  1, E. Belissa¹, J.B. Pain¹, A. Gervais², J. Chas³, M.A. Valantin⁴, P. Perr  ⁵, D. Salmon-C  ron⁶, S. Dominguez⁷, L. Larrouy⁸, Y. Yazdanpanah², G. Peytavin¹

¹H  pital Bichat-Claude Bernard, Pharmacotoxicology Department, Paris, France; ²H  pital Bichat-Claude Bernard, Infectious Diseases & Tropical Department, Paris, France; ³H  pital Tenon, Infectious Diseases & Tropical Department, Paris, France; ⁴H  pital Piti  -Salp  tri  re, Infectious Diseases & Tropical Department, Paris, France; ⁵CHD Vend  e, Internal Medicine Department, La Roche sur Yon, France; ⁶H  pital Cochin, Internal Medicine Department, Paris, France; ⁷H  pital Henri Mondor, Clinical Immunology Department, Cr  teil, France; ⁸H  pital Bichat-Claude Bernard, Virology Department, Paris, France

Background: Daclatasvir (DCV, NS5A inhibitor) is a one of the Direct Acting Anti-HCV (DAAs) favorably used in association in HIV/HCV+ infected patients. The approved dose of DCV is 60mg once daily (QD), which could be reduced to 30mg QD when co-administered with strong inhibitors of CYP3A4, such as ritonavir (RTV)-boosted protease inhibitors (PI/r). However, darunavir (DRV) also presents induction properties that might not be completely compensated by RTV inhibition when administered QD. The objective is to determine the adequate daily dose of DCV in HIV/HCV+ patients receiving DRV/r QD.

Materials & Methods: Multicentre, prospective and observational study. Inclusion criteria: HIV/HCV+ patients receiving DCV 30mg (group 30mg) or 60mg (group 60mg) with DRV/r QD, controlled HIV-infection on stable maintenance ARV therapy (plasma HIV-RNA<50c/mL), F3-F4 fibrosis stage, null or partial responders to previous anti-HCV treatment (including telaprevir/boceprevir) and eGFR>30mL/min. 58 patients are included. Determinations of steady-state plasma concentrations 24h post-dose (C24h) were performed with UPLC-MS/MS. DCV C24h was compared to a control group of HIV/HCV+ patients receiving DCV 60 mg QD and raltegravir or dolutegravir containing regimen as antiretroviral without any other drug interactions as with non nucleoside reverse transcriptase inhibitors or PI/r (reference group). All results are expressed as median (IQR25-75%). Non-parametric Mann-Whitney tests were used for statistical analysis.

Results: 58 patients were enrolled: 53 yrs (50-56), 43 men, 40 Caucasians, 6 South Americans & 12 Africans. Demographic parameters were similar between each group. In pooled groups with DRV/r,

DCV C24h was 159ng/mL (91-336; CV=100%; n=38 samples). In the reference group DCV C24h was 202ng/mL (106-407; CV=108%; n=81). DCV C24h were similar between group 60mg [175ng/mL (129-384; CV=92%; n=26)] and reference group ($p=0.865$). Whereas, DCV C24h was significantly lower in group 30mg [98ng/mL (78-165; CV=79%; n=12)] compared to group 60mg ($p=0.018$) and to the reference group ($p=0.015$).

Conclusions: In our cohort of HIV/HCV+ co-infected patients receiving DCV and DRV/r 800/100mg QD, DCV C24h was higher in patients receiving DCV 60mg than those receiving 30mg. Moreover, DCV C24h obtained after 60 mg was close to those of the reference group, suggesting that a DCV dosing adjustment to 60 mg QD might be proposed when associated to DRV/r 800/100 mg QD to counteract the persisting inducer effect of DRV on DCV metabolism despite RTV boosting.

No conflict of interest

Abstract: 77

Drug Drug Interactions

Lack of clinically significant interaction between the levonorgestrel implant and nevirapine-based antiretroviral therapy

K.M. Darin¹, S. Nakalema², L. Else³, P. Byakika-Kibwika⁴, D.J. Back³, S. Dilly-Penchala³, S.E. Cohn⁵, C. Merry⁶, M. Lamorde², K.K. Scarsi⁷

¹Northwestern University Feinberg School of Medicine, Center for Global Health, Chicago, USA; ²Makerere University, Infectious Diseases Institute, Kampala, Uganda; ³University of Liverpool, Department of Molecular and Clinical Pharmacology, Liverpool, United Kingdom; ⁴Makerere University, Department of Medicine, Kampala, Uganda; ⁵Northwestern University Feinberg School of Medicine, Division of Infectious Diseases, Chicago, USA; ⁶Trinity College Dublin, Department of Pharmacology and

Therapeutics, Dublin, Ireland; ⁷University of Nebraska Medical Center, College of Pharmacy, Omaha, USA

Background: The levonorgestrel (LNG) subdermal implant is a highly efficacious form of long-acting, reversible contraception. Combined use of LNG with some antiretroviral therapy (ART) regimens is complicated due to drug-drug interactions mediated by cytochrome P450 3A induction, the isoenzyme responsible for LNG metabolism. We recently reported that among HIV-infected women using the LNG implant with efavirenz-based ART, LNG serum concentrations were reduced by 45-57% over 48 weeks and 3 (15%) unintended pregnancies occurred. In contrast, LNG concentrations increased by over 30% in women receiving nevirapine-based ART over 24 weeks. To assess this unexpected finding over a longer duration, herein we report the final, 48-week results of the LNG implant combined with nevirapine-based ART.

Materials & Methods: A longitudinal, parallel group study compared LNG pharmacokinetics in HIV-infected women who were receiving nevirapine-based ART (NVP group, n=20) to those not yet eligible for ART (control group, n=17). After providing informed consent, a two-rod (75 mg/rod) LNG implant was placed subdermally at study entry. Blood samples for pharmacokinetic analysis were obtained at study entry, then at weeks 1, 4, 12, 24, 36, and 48 post-implant insertion; a urine pregnancy test and adherence assessment were also performed. LNG concentrations were analyzed by validated LC-MS/MS methods with an assay calibration range of 50-1500 pg/mL. Pharmacokinetic data were reported as geometric mean ratio (GMR) with 90% confidence intervals (CI). Secondly, the relationship between baseline weight and LNG concentration was assessed by Pearson's correlation. Demographic data were analyzed with a T-test or chi-square. LNG exposure (AUC₀₋₄₈) was normalized for body weight using the formula: .

Results: All subjects were HIV-infected Ugandan women with a mean age of 31 years. At baseline, women in the control group weighed significantly more than those in the NVP group (73 versus 63 kg, $p=0.03$). All subjects in the NVP group had an undetectable HIV RNA and had received nevirapine-based ART for a median (range)

duration of 30.5 (4-105) months prior to enrollment. The GMR (90%CI) of LNG concentrations for NVP to control groups were: week 1: 1.28 (1.19, 1.43); week 4: 1.30 (1.26, 1.36); week 12: 1.32 (1.25, 1.42); week 24: 1.35 (1.29, 1.43); week 36: 1.06 (1.03, 1.09); and week 48: 1.14 (1.14, 1.16). LNG concentration was significantly correlated with baseline weight ($r=-0.279$, $p=0.001$). The unadjusted LNG AUC_{0-48wk} GMR [1.24 (1.23, 1.25)] decreased to 1.09 (1.04, 1.16) after normalizing for weight. No pregnancies occurred in either the NVP or control group during the study period.

Conclusions: Over 48-weeks, LNG concentrations were 6-35% higher in women using a LNG implant in combination with nevirapine-based ART. This difference is explained in part by the higher baseline weight observed in the control group and is unlikely to have clinical significance. These findings are particularly important given the significant reduction in LNG exposure and high rate of unintended pregnancies that we observed among women receiving efavirenz-based ART. In contrast, these data suggest nevirapine-based ART is an alternative option for women who desire a LNG implant for contraception.

Previous presentation: Preliminary pharmacokinetic data through week 24 were presented at the 2014 Glasgow HIV Drug Therapy conference.

No conflict of interest

Abstract: 78

Drug Drug Interactions

Effect of daclatasvir with asunaprevir and beclabuvir on the pharmacokinetics of an oral contraceptive containing ethinyl estradiol and norethindrone acetate in women

R. Adamczyk¹, S. Lubin¹, M. Hesney¹, M. Stonier¹, M. Abu Tarif¹

¹Bristol-Myers Squibb, Research and Development, Princeton NJ, USA

Background: This open-label, 2-cycle study in healthy women of childbearing potential assessed the effects of the all-oral, daclatasvir (DCV)-TRIO regimen – a fixed-dose combination of the pangenotypic, NS5A inhibitor DCV (30 mg), the NS3 protease inhibitor asunaprevir (ASV, 200 mg) and the non-nucleoside NS5B inhibitor beclabuvir (BCV, 75mg) – on the pharmacokinetics of norethindrone (NE) and ethinyl estradiol (EE) after dosing with a combined oral contraceptive containing NE acetate/EE.

Materials & Methods: Female subjects (age 18–40 years; BMI 18–32 kg/m²; N=22) received once-daily NE acetate/EE 1000/20 µg (low dose) during Cycle 1 (days 1–21) and once-daily NE acetate/EE 1500/30 µg (high dose) during Cycle 2 (days 29–49); DCV-TRIO + additional single-agent BCV 75 mg (to achieve BCV exposures comparable to those seen in HCV-infected individuals) were administered twice daily during the second half of Cycle 2 (days 39–49). Serial pharmacokinetic samples were collected on Day 21 of both cycles. Based on previous data with the individual agents, some reduction in EE exposure was anticipated. Therefore, the impact of DCV-TRIO+BCV coadministration with NE acetate/EE was assessed by comparing low dose NE acetate/EE administered alone (Cycle 1) with high dose NE acetate/EE administered with DCV-TRIO+BCV (primary objective). Geometric Mean Ratios (GMR, Cycle 2/Cycle 1) and 90% confidence intervals (CI) for NE and EE C_{max} and AUC_{tau} were estimated using a linear mixed-effect model. Clinical equivalence was established if the 90% CIs were within the pre-specified boundaries of 0.8–1.875. Secondary objectives included assessment of GMR (Cycle 2/Cycle 1) for dose-normalized pharmacokinetic parameters of NE and EE and assessment of safety and tolerability.

Results: Following coadministration of high-dose NE acetate/EE and DCV-TRIO+BCV, the C_{max} and AUC_{tau} of NE and EE were within the clinical equivalence boundaries when compared to exposure with low-dose NE acetate/EE alone (for NE C_{max} GMR 1.187 [90% CI 1.064, 1.325], AUC_{tau} GMR 1.403 [90% CI 1.247, 1.579]; for EE C_{max} GMR 1.638 [90% CI 1.518, 1.768], AUC_{tau} GMR 1.268 [90% CI 1.190, 1.351]). When dose-

normalization was applied, compared with administration of NE acetate/EE alone, coadministration of DCV-TRIO+BCV and NE acetate/EE resulted in an approximate 21% reduction of NE C_{max} (GMR 0.792 [90% CI 0.709, 0.883]), with comparable NE AUC_{tau} (GMR 0.936 [90% CI 0.832, 1.053]); and, an approximate 16% reduction of EE AUC_{tau} (GMR 0.845 [90% CI 0.793, 0.901]), with comparable EE C_{max} (1.092 [90% CI 1.012, 1.178]). Overall, adverse events (AEs) were reported by 14 subjects (63.6%); most were mild with 2 subjects (9.1%) reporting moderate AEs (headache and hypertension, not considered related to study drug). No subjects discontinued due to an AE.

Conclusion: Coadministration of DCV-TRIO+BCV with high-dose NE acetate/EE was generally well tolerated, and provided NE and EE exposures that were within the range where the safety and efficacy of the OC have been previously established. Therefore, it is expected that co-administration of high-dose NE acetate/EE with DCV-TRIO in HCV-infected individuals will be well tolerated and provide effective contraception.

No conflict of interest

Abstract: 79

Drug Drug Interactions

Evaluation of Drug Interactions between Dolutegravir and Daclatasvir in Healthy Subjects

L. Song¹, F. Jerva², J. Zong¹, M. Choukour³, B. Wynne⁴, A. Buchanan⁴, T. Eley⁵, S.P. Huang⁶, L. Ross⁷

¹GSK, CPMS, Research Triangle Park, USA; ²GSK, CPSSO, Research Triangle Park, USA; ³Parexel, Clinical Statistics, Tampa, USA; ⁴GSK, MD ID, Research Triangle Park, USA; ⁵BMS, Clinical Pharmacology, Princeton, USA; ⁶BMS, Clinical Statistics, Princeton, USA; ⁷ViiV Healthcare, Clinical Science, Research Triangle Park, USA

Background: People with HIV infection are often co-infected with viral hepatitis. Dolutegravir (DTG) is an HIV integrase strand transfer inhibitor

approved for use in combination with other antiretrovirals for the treatment of HIV-1 infection in adults and adolescents. Daclatasvir (DCV) is a highly selective NS5A replication complex inhibitor approved for the treatment of HCV infection in the EU and Japan. DTG is metabolized primarily through UGT1A1 with a minor component (~10%) via cytochrome P450 (CYP)3A4 and is a substrate of p-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). *In vitro*, DTG demonstrates minimal or no direct inhibition of CYP isozymes and P-gp, and is not an inducer of CYP3A4. DCV is a substrate of CYP3A4 and P-gp and an inhibitor of P-gp and BCRP. As DTG and DCV are likely concomitantly administered in patients co-infected with HIV and HCV, the objective of this study was to assess the potential for drug interactions between DTG and DCV.

Materials & Methods: This was a single-center, open-label, three-period, crossover study in healthy adult subjects. Eligible subjects were randomized into one of two sequences (n=6 in each sequence). Subjects received DTG 50 mg q24h (Treatment A) or DCV 60 mg q24h (Treatment B) for 5 days in Period 1; DCV 60 mg q24h (Treatment B) or DTG 50 mg q24h (Treatment A) for 5 days in Period 2; and DTG 50 mg + DCV 60 mg q24h for 5 days in Period 3 (Treatment C). There was a washout period of at least seven days between Period 1 and Period 2 but no washout between Period 2 and Period 3. All doses of study drug were taken under fasting conditions. Serial plasma PK samples and safety assessments were obtained throughout the study. Noncompartmental PK analysis was performed and geometric least squares (GLS) mean ratios and 90% confidence intervals (CI) were generated by the mixed effect model for within-subject treatment comparisons.

Results: All 12 subjects completed the study as planned. The GLS mean ratios (90% CI) of DCV $AUC(0-\tau)$, C_{max} , and C_t were 0.978 (0.831, 1.15), 1.03 (0.843, 1.25), and 1.06 (0.876, 1.29), respectively, when DCV was administered with DTG compared to DCV administered alone. Co-administration of DTG with DCV increased DTG $AUC(0-\tau)$, C_{max} , and C_t by approximately 33%, 29%, and 45%, respectively, compared to DTG administered alone. No Grade 2 or higher adverse events (AE), deaths or serious AEs were reported during the study. The most frequently

reported AEs were headache (n=3). No clinically significant changes in hematology or clinical chemistry values were observed.

Conclusions: Co-administration of DCV increased DTG plasma exposures that remain in the range observed in clinical trials with HIV-infected patients and do not confer significant safety risks. DCV exposures did not change. Co-administration of DTG and DCV was well tolerated in this study. Therefore DTG and DCV can be co-administered without dose adjustment.

Conflict of interest: Employee of GSK

Abstract: 80

Drug Drug Interactions

Assessment of drug-drug interactions between daclatasvir and darunavir/ritonavir or lopinavir/ritonavir

Y. Gandhi¹, R. Adamczyk¹, R. Wang¹, M. Stonier¹, H. Kandoussi¹, M. Hesney¹, Z. Liu¹, P. Ackerman¹, T. Garimella¹, T. Eley¹

¹Bristol-Myers Squibb, Research and Development, Princeton, USA

Background: Well-tolerated, short-course oral HCV regimens may improve patient uptake of HCV treatment in HIV-HCV coinfection; thus drug-drug interactions (DDIs) between direct-acting HCV antivirals and combination antiretroviral therapy (cART) merit evaluation. Daclatasvir (DCV) is a potent pangenotypic HCV NS5A inhibitor previously evaluated with peginterferon-ribavirin or sofosbuvir in HIV-HCV coinfecting patients. DCV is a substrate of CYP3A4, and the standard daily dose of 60 mg DCV was reduced to 30 mg for patients in coinfection studies taking ritonavir-boosted protease inhibitors (PI/r) due to a 2-fold increase in DCV AUC_{tau} observed in a DDI study with atazanavir/ritonavir (ATV/r). Steady-state DDIs between DCV and darunavir/ritonavir (DRV/r) or lopinavir/ritonavir (LPV/r) were assessed.

Materials & Methods: PI/r effects on DCV PK were assessed in an open-label, nonrandomized interaction study (A1444-093) in healthy volunteers, who received 60 mg DCV QD for 4 days then 30 mg DCV QD (Days 5–14) with DRV/r 800/100 mg QD (group A; N=14) or LPV/r 400/100 mg BID (group B; N=14). Serial PK samples were collected up to 24 hours post-dose on Days 4 (DCV alone) and 14. Plasma DCV was measured by a validated LC-MS/MS assay. Ratios of geometric means (GMR) and 90% confidence intervals (CI) with vs. without PI/r were derived for observed and dose-normalized DCV AUC_{tau} and C_{max} using linear mixed-effects models. DCV effects on PI/r were investigated using similar methods in an exploratory subanalysis of study A1444-043, whereby coinfecting patients receiving DRV/r (N=11) or LPV/r (N=5) in stable cART underwent serial PK sampling for DRV or LPV before, and two weeks after, initiating DCV (30 mg) with peginterferon-ribavirin.

Results: In A1444-093, observed AUC_{tau} for DCV 30 mg with DRV/r or LPV/r was lower than for DCV 60 mg taken alone (GMR 0.70 [0.66–0.75] and 0.58 [0.54–0.62], respectively) and observed C_{max} was lower by 62% and 66%, respectively. With both DRV/r and LPV/r, dose-normalized increases in DCV AUC_{tau} (GMR 1.41 [1.32–1.50] and 1.15 [1.07–1.24], respectively) and reductions in C_{max} (23% and 33% lower, respectively) were observed. There were no deaths or serious adverse events; all adverse events (AEs) resolved by study end. Four subjects discontinued for AEs during PI/r + DCV treatment (3 skin eruptions [2 group A, 1 group B] and 1 ECG PR prolongation [group A]); 1 subject (group B) withdrew consent. In the A1444-043 substudy, no significant effect of DCV on DRV or LPV exposure was observed (C_{max} GMR 0.97 [0.80–1.17] and 1.22 [1.06–1.41]; AUC_{tau} GMR 0.90 [0.73–1.11] and 1.15 [0.77–1.72], and C_{min} GMR 0.98 [0.67–1.44] and 1.54 [0.46–5.07], respectively). CIs were wide for LPV due to sample size. DCV parameters were largely comparable to historical data.

Conclusions: Increases in dose-normalized DCV exposure with DRV/r (41%) and LPV/r (15%) are less than previously observed with ATV/r, and DCV has no significant effect on PI/r exposure. Collectively, these data suggest that no dose adjustments are required, and 60 mg daily is the

optimal DCV dose, when DCV is coadministered with DRV/r or LPV/r.

Conflict of interest: Employee and stock holder of Bristol-Myers Squibb

Abstract: 81

Drug Drug Interactions

The Effect of Daclatasvir, Asunaprevir, and Beclabuvir on the Pharmacokinetics of Selective Serotonin Reuptake Inhibitors In Healthy Subjects

X. Tao¹, K. Sims¹, M. Hesney¹, M. Stonier¹, J. Pursley¹, A. Griffies¹, R. Bhatnagar², C. Smith², J. Huang², M. AbuTarif¹

¹Bristol-Myers Squibb, Research and Development, Princeton NJ, USA; ²PPD, Research, Wilmington NC, USA

Background: Psychiatric illness, including depression, is common in patients with chronic hepatitis C virus (HCV) infection; selective serotonin reuptake inhibitors, e.g. escitalopram (ESC) and sertraline (SER) are treatment options for depression. DCV-TRIO, an all-oral fixed-dose combination of daclatasvir (DCV; pangenotypic NS5A inhibitor), asunaprevir (ASV; NS3 protease inhibitor), and beclabuvir (BCV; non-nucleoside NS5B inhibitor) is currently in phase 3 development for the treatment of HCV. This study investigated the drug-drug interaction (DDI) potential between DCV-TRIO and ESC or SER. ESC and SER are metabolised by CYP3A4 (CYP3A4 is weakly induced by ASV/BCV) and CYP2C19 (CYP2C19 is moderately induced by DCV-TRIO).

Materials & Methods: Healthy subjects (age, 25-55 years; BMI, 18.0-32.0 kg/m²) received oral ESC 10 mg QD (Cohort 1) or SER 50 mg QD (Cohort 2) on Study Days 1-7 and Days 23-29, respectively; all subjects received DCV-TRIO (DCV 30 mg; ASV 200 mg; BCV, 75 mg) BID + BCV 75 mg BID (to adjust for exposure differences between healthy and HCV-infected subjects) on Days 13-29. Blood samples for

pharmacokinetic analyses of ESC / SER (predose-24h Days 7/29), and DCV-TRIO components and the BCV major circulating metabolite, BMS-794712 (predose-12h Days 22 and 29), were collected. Geometric mean ratios (GMR) and 90 % confidence intervals (CI) for analyte area under the plasma concentration time curve in one dosing interval (AUC_{TAU}) and maximum plasma concentrations (C_{MAX}; to be presented) were calculated. No-effect boundary limits for ESC and SER (0.7-1.7), DCV (0.75-1.5), and ASV (0.5-2.0) were set by literature/clinical data review.

Results: All subjects enrolled in Cohort 1 (N=18; mean age, 41.1 years) and Cohort 2 (N=23; mean age, 37.9 years) completed the study and were included in the analyses. Co-administration with DCV-TRIO + BCV 75 mg BID resulted in decreases in exposure of ESC (AUC_{TAU} GMR [90%CI], 0.65 [0.61, 0.69]) and SER (AUC_{TAU} GMR [90%CI], 0.62 [0.60, 0.65]) below the no-effect boundary, versus ESC or SER administration alone. Co-administration with ESC did not affect exposure (AUC_{TAU}) of DCV-TRIO components or BMS-794712, relative to administration of DCV-TRIO + BCV 75 mg BID alone; AUC_{TAU} GMRs (90% CIs) were close to 1 and within the no-effect limits: DCV, 1.00 (0.93, 1.09); ASV, 0.92 (0.85, 1.00); BCV, 0.96 (0.91, 1.02); BMS-794712, 0.93 (0.89, 0.98). Similarly, SER did not affect exposure (AUC_{TAU}) of DCV-TRIO components or BMS-794712; AUC_{TAU} GMRs (90% CIs) were close to 1 and within the no-effect limits: DCV, 0.96 (0.93, 0.98); ASV, 1.02 (0.92, 1.13); BCV, 0.94 [0.92, 0.97]; BMS-794712, 0.92 (0.89, 0.95). Similar results for C_{MAX} were observed. DCV-TRIO + BCV 75 mg BID, with or without ESC or SER was generally well tolerated.

Conclusions: Co-administration of DCV-TRIO (plus BCV 75 mg BID) with ESC or SER results in a decrease in ESC (AUC_{TAU}, 35%) and SER (AUC_{TAU}, 38%) exposures, relative to ESC or SER administration alone; DCV-TRIO and BMS-794712 exposures were unaffected. No *a priori* ESC or SER dose-adjustments are recommended during co-administration with DCV-TRIO; however, monitoring recommendations in the ESC and SER package inserts should be followed.

Conflict of interest: Employee of Bristol-Myers Squibb

Abstract: 82*Drug Drug Interactions***Lack of Effect of Oral Cabotegravir on the Pharmacokinetics of a Levonorgestrel/Ethinyl Estradiol Containing Oral Contraceptive in Healthy Adult Females**

C. Trezza¹, S.L. Ford², E. Gould³, Y. Lou⁴, C. Huang⁵, G. Bowers⁶, A. Buchanan¹

¹GlaxoSmithKline, Infectious Diseases Medicines Discovery and Development, Research Triangle Park, USA;

²GlaxoSmithKline, Clinical Pharmacology Modeling and Simulation, Research Triangle Park, USA; ³GlaxoSmithKline, Project Clinical Platforms and Sciences, Research Triangle Park, USA; ⁴GlaxoSmithKline, Clinical Statistics, Research Triangle Park, USA; ⁵PAREXEL International, Clinical Statistics, Carmel, USA; ⁶GlaxoSmithKline, Drug Metabolism and Pharmacokinetics, Research Triangle Park, USA

Background: Cabotegravir (CAB) is an investigational integrase inhibitor in development as both an oral tablet and a long-acting injectable for HIV-1 treatment and pre-exposure prophylaxis indications. As both a treatment and prevention modality, CAB is expected to be co-administered with oral contraceptives (OC) in HIV-infected and uninfected women. Drug interactions that result in sub-therapeutic concentrations of the estrogen or progestin components of OC may lead to contraceptive failure. Although *in vitro* data suggest that the potential for a significant interaction is minimal, this clinical study aimed to demonstrate the lack of effect of CAB on the pharmacokinetics (PK) of a levonorgestrel (LNG) and ethinyl estradiol (EE) containing OC.

Materials & Methods: This was an open-label, fixed-sequence crossover study in healthy adult female subjects. The study consisted of two consecutive treatment periods that spanned a single menstrual cycle. Subjects received Microgynon® (LNG 0.15 mg/EE 0.03mg) once daily on Days 1-10 followed by serial PK sampling of LNG and EE on Day 10. Subjects then received oral CAB 30mg once daily in combination with

Microgynon on Days 11-21 and underwent serial PK sampling of LNG, EE, and CAB on Day 21. Safety assessments were evaluated throughout the study. Plasma LNG/EE/CAB concentrations were determined by high-performance liquid chromatography-tandem mass spectrometry. Preliminary PK parameters generated using non-compartmental analysis were compared using a mixed effects model to estimate geometric least squares (GLS) mean ratios with 90% confidence intervals (CI) for the differences between test (LNG/EE + CAB) and reference (LNG/EE alone) treatments. Lack of effect was to be confirmed if the 90% CIs for AUC(0- τ) and C_{max} GLS mean ratios for both LNG and EE were within 0.8 and 1.25.

Results: Twenty female subjects (age 18-39 years) were enrolled, and 19 completed the study. One subject was withdrawn due to an adverse event (AE) unrelated to study medications. The PK profile of LNG/EE was unaffected by CAB. The GLS mean ratios (90% CI) for LNG AUC(0- τ) and C_{max} were 1.11 (1.06-1.16) and 1.05 (0.96-1.15), respectively, following LNG + CAB relative to LNG alone. The GLS mean ratios (90% CI) for AUC(0- τ) and C_{max} of EE were 1.05 (0.98-1.13) and 0.92 (0.83-1.03), respectively, following co-administration of EE + CAB relative to EE alone. Steady state CAB PK parameters were comparable to historical data. All AEs were mild to moderate in intensity and no serious AEs were reported. No clinically significant trends in laboratory abnormalities, vital signs, or ECG values were observed.

Conclusions: The combination of CAB and LNG/EE was well-tolerated in healthy volunteers. Repeat doses of oral CAB had no effect on the pharmacokinetics of LNG and EE. The results suggest that CAB can be administered in combination with LNG/EE OCs without clinically significant drug-drug interactions.

Conflict of interest: I was a post-doctoral fellow on assignment at GlaxoSmithKline at the time this abstract was submitted

16th International Workshop on Clinical Pharmacology of HIV & Hepatitis Therapy

26 – 28 May 2015, Washington, DC, USA

Author Index

Author	Abstract Title	Abst #	Page #
Abutarif, M.	The Effect of Daclatasvir, Asunaprevir, and Beclabuvir on the Pharmacokinetics of Selective Serotonin Reuptake Inhibitors In Healthy Subjects	81	83
Adamczyk, R.	Effect of daclatasvir with asunaprevir and beclabuvir on the pharmacokinetics of an oral contraceptive containing ethinyl estradiol and norethindrone acetate in women	78	80
Anderson, M.	Effect of Ketoconazole on the Pharmacokinetics of Doravirine (MK-1439), a Novel Non-Nucleoside Reverse Transcriptase Inhibitor for the Treatment of HIV-1 Infection	58	62
Anderson, M.	A 2-Way Steady State PK Interaction Study of Doravirine (MK-1439) and Dolutegravir	59	63
Anderson, M.	Effect of Doravirine (MK-1439) on the Pharmacokinetics of an Oral Contraceptive (Ethinyl Estradiol [EE] and Levonorgestrel [LNG])	60	63
Badri, P.	Drug Interactions with Direct Acting Antiviral Combination of Paritaprevir/ritonavir + Ombitasvir	55	59
Barrail-Tran, A.	Genetics of nevirapine metabolite kinetics at steady state in HIV-infected Cambodians (ANRS12154 study)	37	42
Barrail-Tran, A.	Raltegravir pharmacokinetics in patients on daclatasvir/asunaprevir (ANRS HC 30)	65	68
Bednasz, C.	Utility of Informatics Resource to Identify Future HIV-HCV Drug-Drug Interaction Studies	61	64
Blonk, M.	Pharmacokinetic Drug-Drug Interaction Study Between Raltegravir and Citalopram in Healthy Volunteers.	53	57
Brown, K.	Pharmacokinetics (PK) of Etravirine (ETR) in HIV-1-Infected Pregnant Women	29	34
Burger, D.	First experience with proficiency testing of rilpivirine in The International Quality Control Program for Measurement of Antiretroviral Drugs in Serum	47	51
Chen, X.	Simultaneous Assessment of Changes in T-cell Activation and Endogenous dNTP Pools in Adults Receiving TDF/FTC	44	48
Colbers, A.	Ritonavir Pharmacokinetics during Pregnancy and Postpartum	27	32
Colbers, A.	A Comparison of the Pharmacokinetics of Rilpivirine during Pregnancy and Postpartum	28	33
Collins, J.	Aging Effects as Covariates in the Population Pharmacokinetics (PK) of Emtricitabine (FTC) and Its Intracellular Metabolite in HIV+ Subjects	43	47
Crauwels, H.	Model-Based Pediatric Dosing of Ritonavir-Boosted Darunavir: An Alternative to WHO Guidelines	15	17
Crauwels, H.	Rilpivirine Population Pharmacokinetic Modeling in Antiretroviral-Naïve HIV-1-infected adolescents in PAINT	33	38
Custodio, J.	The pharmacokinetics of tenofovir and tenofovir diphosphate following administration of tenofovir alafenamide versus tenofovir disoproxil fumarate	6	8
Custodio, J.	Population pharmacokinetic modeling of tenofovir alafenamide following administration of elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide	40	44
Custodio, J.	Evaluation of the drug interaction potential between elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide and sertraline	73	75
Darin, K.	Lack of clinically significant interaction between the levonorgestrel implant and nevirapine-based antiretroviral therapy	77	79
Desnoyer, A.	Sofosbuvir in haemodialysis: 400 mg daily or only the day of hemodialysis?	19	21
Desnoyer, A.	Which dose of daclatasvir should be used with darunavir/ritonavir 800/100mg once-daily containing regimen in hiv/hcv co-infected patients?	76	78
Di Francesco, R.	Factors Influencing Antiretroviral Quantitation in HIV-HCV Co-Infection	20	25

Author	Abstract Title	Abst #	Page #
Dickinson, L.	Prediction of Intracellular (IC) Tenofovir Diphosphate (TFV-DP) and Emtricitabine Triphosphate (FTC-TP) Concentrations Following Drug Intake Cessation	10	12
Dumond, J.	Association of a Senescence Biomarker with Intracellular Nucleotide Metabolite and Endogenous Nucleotide Exposures in HIV+ Subjects Receiving Tenofovir/Emtricitabine	30	35
Eley, T.	Assessment of drug-drug interactions between daclatasvir and darunavir/ritonavir or lopinavir/ritonavir	80	82
Elliot, E.	Pharmacokinetics (PK) of once-daily dolutegravir (DTG) and elvitegravir/cobicistat (EVG/COBI) following drug cessation	13	15
Garrison, K.	Drug Interactions between anti-HCV Antivirals Ledipasvir/Sofosbuvir and Integrase Strand Transfer Inhibitor-Based Regimens	71	73
Giguère, P.	Microboosting of atazanavir 300 mg with 50 mg versus 100mg of ritonavir daily in HIV-infected patients	7	9
Gopalakrishnan, M.	Population Pharmacokinetics of Paritaprevir, Ombitasvir and Ritonavir in Japanese Subjects with HCV Genotype 1b infection	39	43
Grégoire, M.	Influence of nevirapine administration on the pharmacokinetics of dolutegravir in HIV-1 infected patients	64	67
He, B.	Steady-State Pharmacokinetics of Daclatasvir, Asunaprevir, and Beclabuvir in Treatment-Naive Patients Infected with HCV Genotype 1	51	55
Kakuda, T.	Pharmacokinetics of simeprevir with TMC647055/ritonavir with/without ribavirin or with/without JNJ-56914845 in genotype 1 HCV-infected patients	74	76
Khalilieh, S.	Administration of a Supratherapeutic Dose of Doravirine Does Not Result in a Clinically Meaningful Increase in QTcP	21	26
Khalilieh, S.	Moderate Hepatic Impairment does not affect Doravirine Pharmacokinetics	24	29
Khatr, A.	Drug-Drug Interactions of Ombitasvir/Paritaprevir/r plus Dasabuvir with Dolutegravir or Abacavir plus Lamivudine	57	61
Kirby, B.	Evaluation of PK/PD Relationships between Ribavirin and Sustained Virologic Response in HCV-Genotype 3 Infected Subjects in the Sovaldi® Phase 3 Program	2	4
Kosloski, M.	Bioequivalence Assessment of Ribavirin Tablets: A Randomized, Single-Dose, Open-Label, Two-Period Crossover Study in Healthy Volunteers	23	28
Landry, I.	HIV-1 Attachment Inhibitor Prodrug BMS-663068: Assessment of Interactions with Raltegravir in Treatment-Experienced HIV-1-Infected Subjects	67	69
Langness, J.	Readying HIV/HCV Coinfected Patients for HCV Treatment: Occurrence and Management of Antiviral Interactions	18	20
Le, M.P.	Dolutegravir drug interaction with DRV/r or ATV/r: impact on its pharmacokinetic?	75	77
Lee, S.	Disulfiram Reactivates Latent HIV Infection in a Dose-Dependent Manner	11	13
Metsu, D.	What interest of unbound fraction in atazanavir therapeutic drug monitoring?	48	52
Metsu, D.	Darunavir unbound fraction: association with viral load in hiv patients.	49	53
Mogalian, E.	Evaluation of the Effect of GS-5816, a Pangenotypic HCV NS5A Inhibitor, on the QT/QTc Interval in Healthy Subjects	45	49
Mogalian, E.	Metabolism and Excretion of Pangenotypic HCV NS5A Inhibitor GS-5816 in Humans	72	74
Moltó, J.	Physiologically based pharmacokinetic model to predict drug-drug interaction in patients receiving antiretroviral and antineoplastic therapies	4	6
Moltó, J.	Population pharmacokinetic analysis of darunavir/ritonavir in HIV-infected pregnant women	26	31

Author	Abstract Title	Abst #	Page #
Moss, D.	Modelling the inhibition of transporters and enzyme for increased tenofovir bioavailability	22	27
Polepally, A.	Drug-Drug Interactions of Commonly Used Medications with Direct Acting Antiviral HCV Combination Therapy of Paritaprevir/r, Ombitasvir and Dasabuvir	16	18
Polepally, A.	Pharmacokinetics of Dasabuvir when Administered with Ombitasvir, Paritaprevir and Ritonavir in Healthy Volunteers	38	43
Polepally, A.	Effect of Comedications on Paritaprevir, Ritonavir, Ombitasvir, Dasabuvir and Ribavirin Pharmacokinetics	52	56
Rakhmanina, N.	Pharmacokinetics of efavirenz and 8-hydroxymetabolites in pre-pubertal children and adolescents with HIV infection.	31	36
Rakhmanina, N.	Week 24 data from a Phase 3 clinical trial of E/C/F/TAF in HIV-infected adolescents	36	41
Roberts, O.	An in vitro assessment of the interaction between rifampicin and darunavir/ritonavir using primary human hepatocytes	66	69
Rower, J.	Pharmacokinetics of GS-331007 Triphosphate in Red Blood Cells in HCV-infected Subjects Receiving Sofosbuvir plus Ribavirin in the SPARE trial	8	10
Savant Landry, I.	HIV-1 Attachment Inhibitor Prodrug BMS-663068: Exposure-Response Modeling in Predicting QTcF Interval Prolongation for Quantitative Dose Selection for the Phase 3 Program	9	11
Savant Landry, I.	No Clinically Relevant Effect of Beclabuvir on the QTcF Interval in Healthy Subjects	46	50
Scarsi, K.	Correlation between efavirenz and levonorgestrel plasma concentrations during a drug-drug interaction study	70	72
Schalkwijk, S.	A Comparison of the Pharmacokinetics of Abacavir during Pregnancy and Postpartum	32	37
Schalkwijk, S.	First human data on placental transfer of dolutegravir using an ex vivo perfusion model	34	39
Sheehan, N.	Evaluating Concentrations of Antiretrovirals : Atazanavir, Darunavir and Tenofovir in Subjects with HIV and Type 2 Diabetes Mellitus - a Pilot Study	35	40
Sheehan, N.	Low darunavir concentrations in patients receiving Stribild (elvitegravir / cobicistat / emtricitabine / tenofovir disoproxil fumarate) and darunavir once daily	50	54
Song, I.H.	Pharmacokinetic-Pharmacodynamic Modeling and Simulation of the Virologic Response of Dolutegravir in HIV-Infected Patients with Integrase Inhibitor Resistant Virus	14	16
Song, I.H.	Evaluation of Drug Interactions between Dolutegravir and Daclatasvir in Healthy Subjects	79	
Tafoya, E.	Population viral kinetic modeling: SVR prediction in HCV GT-3 cirrhotic patients with 24 weeks of Daclatasvir + Sofosbuvir administration	3	5
Trezza, C.	Lack of Effect of Oral Cabotegravir on the Pharmacokinetics of a Levonorgestrel/Ethinyl Estradiol Containing Oral Contraceptive in Healthy Adult Females	82	84
Vourvahis, M.	CYP3A5*1 Allele Not Associated with Lower Maraviroc Exposures in the Phase 2b/3 MERIT Study	12	14
Vourvahis, M.	Modeling of Maraviroc Pharmacokinetics in HIV-1 Infected Patients Co-Infected with Hepatitis B and/or Hepatitis C	41	45
Vourvahis, M.	Revisiting the Population Pharmacokinetics of Maraviroc in the MERIT study with the Inclusion of CYP3A4/CYP3A5 and SLCO1B1 Genotype Covariates	42	46
Wagner, C.	Development of Lopinavir and Darunavir Physiologically-Based Pharmacokinetic Models Incorporating the Pharmacokinetic Effects of Ritonavir	62	65
Yee, K.L.	Doravirine Efficacy Exposure-Response Analysis at Week 48 and Implications	5	7
Yee, K.L.	An evaluation of doravirine pharmacokinetics when switching from efavirenz to doravirine treatment	54	58

Author	Abstract Title	Abst #	Page #
Yeh, W.	Coadministration of HCV Protease Inhibitor Grazoprevir With HCV NS5A Inhibitor Elbasvir Has No Effect On Pravastatin But Increases Rosuvastatin Exposure In Healthy Subjects	17	19
Yeh, W.	No Pharmacokinetic Interaction Between HCV Inhibitors Grazoprevir/Elbasvir with Rilpivirine	63	66
Younis, I.	Sensitivity of liver function classification systems for exposure changes	1	3
Younis, I.	The experience with drug-drug interaction studies between antiviral medications and oral contraceptives.	68	70
Younis, I.	Lessons learned from drug-drug interaction studies between antiviral medications and methadone	69	71
Zha, J.	Effect of Food on Bioavailability of Ombitasvir/Paritaprevir/Ritonavir (OBV/PTV/r) Coformulated Tablets in Healthy Japanese Subjects	25	30
Zha, J.	Drug Interactions between Hepatoprotective Agents Ursodeoxycholic Acid or Glycyrrhizin and Ombitasvir/Paritaprevir/Ritonavir in Healthy Japanese Subjects	56	60