Relative bioavailability of dolutegravir (DTG) and emtricitabine/tenofovir alafenamide fumarate (F/TAF) administered as paediatric tablet formulations in healthy volunteers

Bevers L.A.H.¹, Kamphuis A.E.M.¹, van der Wekken-Pas L.C.¹, Leisegang R.², Lewis L.³, Burger D.M.¹, Colbers A.¹

¹Department of Pharmacy, Radboud Institute for Medical Innovations (RIMI), Radboud University Medical Center, Nijmegen, the Netherlands
²Clinical Pharmacology, Paediatric Centre of Excellence, Gilead Sciences, Dublin, Ireland
³Clinical and Regulatory Affairs, Product Development and Regulatory Affairs team, Clinton Health Access Initiative (CHAI)

Introduction

• In the EDCTP2-funded UNIVERSAL project (RIA2019PD-2882) a paediatric fixed dose combination (FDC) product containing dolutegravir/emtricitabine/tenofovir alafenamide (DTG/FTC/TAF) will be developed.

• The pharmacokinetic data on the combination of DTG dispersible tablets (DT) and F/TAF for oral suspension (TOS) are currently lacking.

We undertook a relative bioavailability (RBA) study in HIV-negative volunteers to investigate a potential pharmacokinetic effect when paediatric DTG DT (30 mg dose) and F/TAF TOS (180/22.5 mg dose) are taken together.

Material and Methods

• An open label, single-center, single-dose, 3-period, randomized, cross-over trial in 16 HIV-negative volunteers.

• Reference A: Single dose of 3 X 60/7.5 mg (180/22.5 mg) F/TAF TOS.
• Reference B: Single dose of 6 X 5 mg (30 mg) DTG DT.
• Test C: Single dose of 180/22.5 mg F/TAF TOS plus 30 mg DTG DT.

• Randomized treatment sequences: ABC; ACB; BCA; BAC; CAB; CBA.

• Blood samples were collected at time = 0, 0.17, 0.33, 0.5, 0.75, 1.0, 1.5, 2.5, 3, 4, 6, 8, 10, 12, 24 and 48 hours post-dose.

• Pharmacokinetic parameters were determined using a non-compartmental analysis in Phoenix/WinNonlin version 8.4.

• We applied the statistical method used in bioequivalence studies (ANOVA on log-transformed PK parameters with fixed effects: treatment, period, sequence and subject within sequence) to investigate the presence of a relevant pharmacokinetic interaction between two treatments.

• Pre-defined criteria: if after a single dose the 90% CIs of the GLSM ratios (Test/Reference) of AUC and Cmax of each compound is within 0.70 and 1.43, there is no clinically relevant pharmacokinetic interaction.

Results

• In total, 15 participants were included. The median age of these included subjects (6 female / 9 male) was 27.0 (IQR 21.0-31.0) years with a median BMI of 25.1 (IQR 21.6-26.0) kg/m².

Discussion and Conclusion

• We observed no relevant pharmacokinetic interaction for DTG in this study, however individual ratios for Cmax showed a trend above 1. There might be a small increase in the absorption of DTG when combined with FTC/TAF TOS.

• For TAF the GLSM ratio was outside the pre-defined criteria, but with half of the individual ratios above and half below 1, we don’t see a trend. Moreover, we rely on TDF exposure over TAF because of TAF being a pro-drug and no relevant interaction was found for TFDV.

• We found no relevant pharmacokinetic interaction for FTC.

These data will inform on the dose ratio and dose selection for a paediatric DTG/FTC/TAF FDC to be developed in the UNIVERSAL project.