EVG/COBI/FTC/TAF TABLETS DISSOLVED IN TAP WATER NEAR BIOEQUIVALENT WITH WHOLE TABLETS

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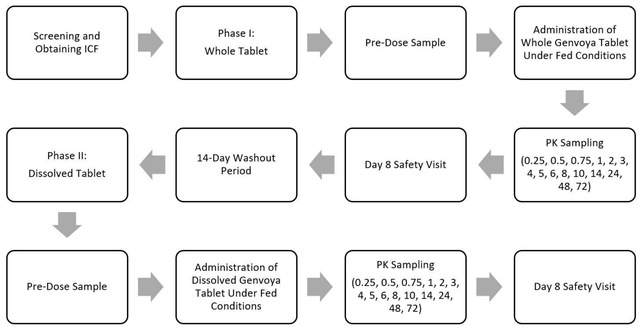
BACKGROUND

- Single pill fixed dose antiretroviral (ARV) HIV treatment regimens improve adherence.[1,2]
- Despite the availability of several single dose regimens, many PWH struggle with swallowing pills, affecting adherence.[2,3]
- Some patients crush or dissolve their tablets.[2,4]
- Concerns exist over the bioavailability of the dissolved tablets with potential impact on plasma drug concentrations and antiviral effect.
- While some case studies show maintenance of viral suppression in patients crushing and dissolving their ARV medications, further PK assessment is a necessary step to confirm bioequivalence (BE).[5-8]
- Elvitegravir [EVG]/Cobicistat [COBI]/ Emtricitabine [FTC]/ Tenofovir Alafenamide [TAF]) is a widely used single pill fixed dose ARV combination; therefore, we wanted to assess its BE when dissolved in tap water.

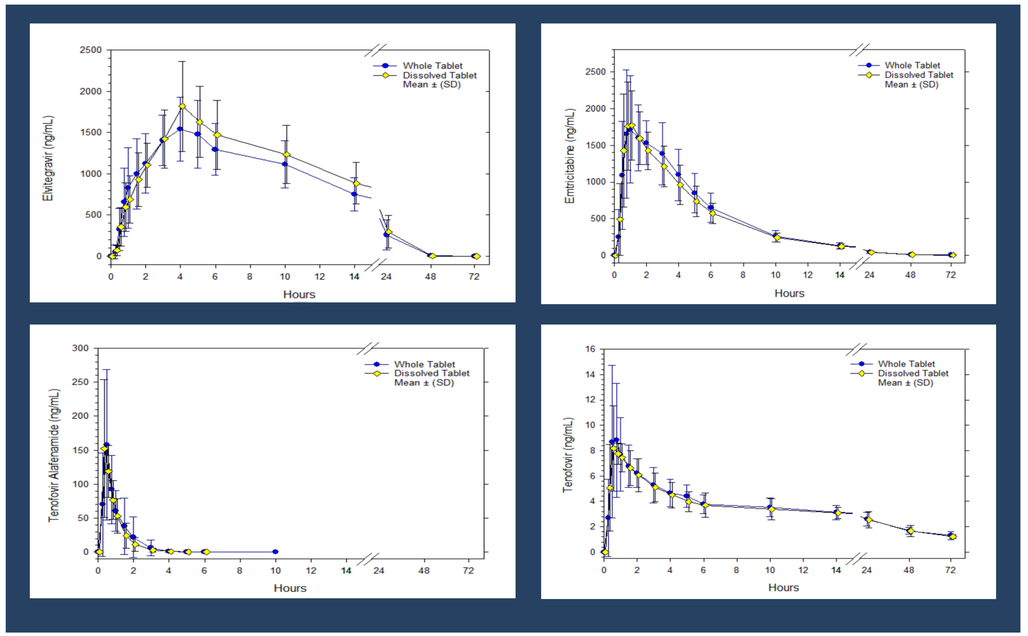
HYPOTHESIS

- Dissolved fixed dose EVG/COBI/FTC/TAF combination tablets will be bioequivalent to whole tablets.

METHODS



- Phase 4, fixed order, open label comparison study
- EVG/COBI/FTC/TAF (Genvoya) tablets dissolved in 120 mL tap H_2O at room temperature for <5 minutes, then taken orally.
- After dosing, 120 mL tap H_2O added to cup to capture residual drug, then taken orally.
- Plasma samples analyzed for each ARV using validated liquid chromatographic-tandem mass spectrometry.



RESULTS

- 12 adult, healthy, and HIV negative research participants were enrolled.
- 8 were females and 4 were males. 7 were black and 5 were white.
- No complaints of taste from the dissolved tablet were reported by the participants

PK Parameter (Units)	Whole Tablet Mean (SD)	Dissolved Tablet Mean (SD)	Geometric Mean Ratio (90% Confidence Interval)	Bioequivalence[8] (YES/NO)
Elvitegravir (EVG)				
T_{max} [a] (h)	3.9 (1.0,5.1)	4.0 (3.0,9.8)		
C_{max} (ng/mL)	1650 (371)	1946 (545)	0.85 (0.74, 0.97)	NO
AUC_{inf} (ng.h/mL)	24219 (6074)	26948 (5955)	0.89 (0.82, 0.96)	YES
Emtricitabine (FTC)				
T_{max} (h)	0.98 (0.67,3.0)	0.95 (0.52,2.9)		
C_{max} (ng/mL)	2095 (445)	1968 (481)	1.07 (0.92, 1.24)	YES
AUC_{inf} (ng.h/mL)	11603 (2296)	10969 (1818)	1.05 (1.00, 1.11)	YES
Tenofovir Alafenamide (TAF)				
T_{max} (h)	0.51 (0.32,1.6)	0.28 (0.23,0.77)		
C_{max} (ng/mL)	186 (80)	171 (73)	1.09 (0.81, 1.46)	NO
AUC_{inf} (ng.h/mL)	145 (64)	128 (48)	1.09 (0.93, 1.26)	NO
Tenofovir (TFV)				
T_{max} (h)	0.77 (0.42,3.0)	0.68 (0.25,1.5)		
C_{max} (ng/mL)	11 (4.1)	9.5 (2.3)	1.09 (0.91, 1.30)	NO
AUC_{inf} (ng.h/mL)	253 (47)	241 (46)	1.05 (0.96, 1.15)	YES

[a]T_{max} median (interquartile range); [8]FDA Bioequivalence Guidance

RESULTS (CONTINUED)

- FTC met the FDA BE standards.
- EVG concentrations were higher when dissolved
  - C_{max} 17% and AUC_{inf} 11% higher.
- TAF and TFV concentrations were lower when dissolved.
  - TAF, C_{max} 7% and AUC_{inf} 11% lower
  - TFV, C_{max} 11% and AUC_{inf} 4% lower.

CONCLUSIONS

- Our hypothesis of bioequivalence was not supported
- Since statistical BE criteria were not met, we evaluated the deviations for clinically significant reductions in ARV concentration that might impact ARV efficacy.
- FTC met BE criteria and EVG was slightly higher with tablet dissolution; so, these should not be of concern.
- Regarding TAF, our judgement is that the failure to meet BE criteria is not clinically significant:
  - TAF AUC_{inf} GMR upper 90% confidence bound by only 1% (whole TAF concentration greater than dissolved)
  - TAF C_{max}, while above the upper BE boundary by 21% (lower TAF peaks with dissolved tablets), C_{max} is a less important measure of therapeutic effect
  - The above small differences in one of two NRTI backbone drugs, in combination with increased potent EVG concentrations, are considered very minor
  - Our expectation, though not evaluated, is that adherence improvements resulting from tablet dissolution for those who struggle swallowing tablets, may offset the minor PK differences.
- ***Not all components of EVG/COBI/FTC/TAF met bioequivalence when dissolved in tap water compared to whole tablets, but no therapeutic difference is expected.***

ACKNOWLEDGMENT

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REFERENCES

1. Sax PE, et al. (2012). Adherence to Antiretroviral Treatment and Correlation with Risk of Hospitalization among Commercially Insured HIV Patients in the United States. PLoS ONE, 7(2), e31591.
2. Cohen CJ, et al. (2013). Association between daily antiretroviral pill burden and treatment adherence, hospitalisation risk, and other healthcare utilisation and costs in a US medicaid population with HIV. BMJ Open, 3(8), e003028.
3. Dorman RM, et al. (2019). Understanding HIV-Related Pill Aversion as a Distinct Barrier to Medication Adherence. Behavioral medicine (Washington, D.C.), 45(4), 294–303.
4. Swindells S, et al. (2011). The Critical Need for Alternative Antiretroviral Formulations, and Obstacles to Their Development. The Journal of Infectious Diseases, 204(5), 669–674.
5. Roa PE, Bazzi R. (2021). Crushed bictegravir/emtricitabine/tenofovir alafenamide in a human immunodeficiency virus-positive patient with pancreatic cancer. International Journal of STD & AIDS, 33(1), 97–98.
6. Fulco PP, Ayala-Sims VA. (2014). Sustained virological response after taking crushed elvitegravir–cobicistat–emtricitabine–tenofovir tablets. American Journal of Health-System Pharmacy, 71(10), 784–786.
7. Buscemi L. (2016). Virological suppression after use of crushed tenofovir–emtricitabine and dolutegravir tablets in a patient with HIV infection. American Journal of Health-System Pharmacy, 73(15), 1125–1126.
8. Guidance for Industry Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs - General Considerations DRAFT GUIDANCE. (2014).