Abstract # 431

Pharmacokinetics of Crushed Elvitegravir Combination Tablet Given with Drip Feed

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1. BACKGROUND

- If HIV-patients are unconscious or cannot swallow tablets for other reasons, antiretroviral medication is often crushed and solved prior to administration.
- Currently, there is no information about crushing the fixed-dose combination of elvitegravir/cobicistat/emtricitabine/tenofovir (E/C/E/T). Crushing can influence pharmacokinetics (PK) leading to altered drug exposure, possibly leading to treatment failure, development of resistance or toxicity. Therefore, crushing of E/C/E/T is not recommended.
- A possible PK interaction between elvitegravir (EVG) and drip feed is expected, based on the interaction between EVG and antacids. No interaction occurs between other pH-increasing drugs (omeprazole) and EVG, therefore the interaction is most likely caused by complexation between EVG and cations.

Objectives:

- To assess the bioequivalence of single dose E/C/E/T after administration of standardized breakfast followed by a whole tablet and a crushed and suspended tablet.
- To assess the bioequivalence of single dose E/C/E/T after administration of a standardized breakfast followed by a whole tablet and a standardized dose of drip feed followed by a crushed and suspended tablet.

2. METHODS

- This was an open label, 3-period, randomized, cross-over, trial in 24 healthy volunteers.
- The 24 subjects were divided into one of the following treatment sequences: ABC; ACB; BCA; BAC; CAB; CBA
- A Standardized breakfast (350kCal) followed by E/C/E/T (whole tablet).
- B Standardized breakfast (350kCal) followed by crushed and suspended E/C/E/T.
- C 350 mL of drip feed (350kCal, Nutrison®) followed by crushed and suspended E/C/E/T.

- The tablet was crushed using a tablet crusher.
- Between the different treatment periods a wash-out period of 7 days was scheduled. Blood samples for PK assessment were collected during a 32-hour period for elvitegravir (EVG), cobicistat (COBI), emtricitabine (FTC) and tenofovir (TFV) after medication intake on Day 1, 8 and 15.
- Blood samples were collected up to 32 hours after observed intake of the study medication at the following time points: t=0 (pre-dose), 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 10, 12, 24 and 32 hours post ingestion.

2. METHODS (continued)

- EVG and COBI plasma concentrations were analyzed by use of a (combined) validated ultrahigh-pressure liquid chromatography (UPLC) method with a lower limit of quantification of 0.05 mg/L for EVG and 0.03 mg/L for COBI. TFV plasma concentrations were analyzed by use of a validated high-pressure liquid chromatography (HPLC) method with a lower limit of quantification of 0.015 mg/L. FTC plasma concentrations were analyzed by use of a validated high-pressure liquid chromatography (HPLC) method with a lower limit of quantification of 0.03 mg/L.
- Pharmacokinetic parameters were determined using a non-compartmental analysis in Phoenix/WinNonlin version 6.3.
- Geometric means ratios (GMRs) and 90% confidence intervals (CI) of $AUC_{0\text{-}32h}$ and C_{max} of all analytes were calculated for the comparison: B versus A and C versus A.
- This trial is registered at ClinicalTrials.gov, number NCT02325934.

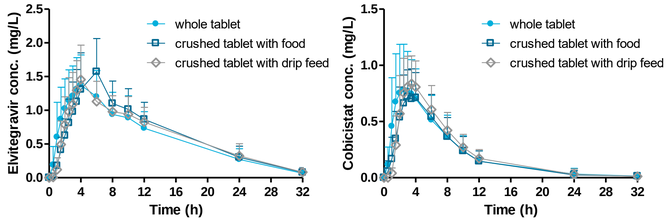
3. RESULTS

- Twenty-four healthy volunteers, of which 12 males and 12 females, were included in the study (23 Caucasian, 1 mixed race). All subjects completed the trial.
- Median (range) age and Body Mass Index were 37 (20-54) years and 24 (19-29) kg/m^2, respectively.

Pharmacokinetics

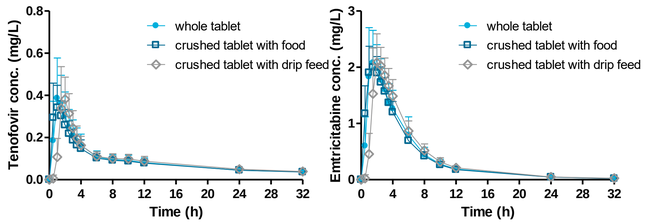
- Mean concentration-time curves for EVG and COBI, for all treatments, are shown in Figure 1.
- Mean concentration-time curves for TFV and FTC, for all treatments, are shown in Figure 2.
- PK parameters per treatment (GM & CV%) and the comparison of the crushed tablet with breakfast versus whole tablet (B versus A) are depicted in Table 1.
- PK parameters per treatment (GM & CV%) and the comparison of the crushed tablet with drip feed versus whole tablet (C versus A) are depicted in Table 2.

Figure 1: Mean EVG and COBI concentrations after a single oral dose E/C/E/T



3. RESULTS (continued)

Figure 2: Mean TFV and FTC concentrations after a single oral dose E/C/E/T



Safety

- No serious adverse events were reported. A total number of 89 adverse events was reported, of maximally grade 2 severity. Seven subjects reported bad taste after intake of the crushed trial medication (E/C/E/T), which was judged to be definitely related to the trial medication. Two additional adverse events (diarrhea and elevated amylase) were judged to be probably related to the trial medication.

Table 1: PK parameters crushed tablet with food versus whole tablet

	Crushed & food	Whole tablet	GMR (90% CI)
Elvitegravir			
$AUC_{0\text{-}32}$ (h*mg/L)	18.83 (30)	17.27 (37)	109.0 (99-120)
$AUC_{0\text{-}inf}$ (h*mg/L)	19.56 (32)	17.84 (38)	109.6 (100-120)
C_{max} (mg/L)	1.62 (31)	1.40 (32)	115.8 (105-127)
T_{max} (h)	6.00 (3.00-6.28)	3.75 (1.00-6.03)	
$T_{1/2}$ (h)	5.68 (32)	5.76 (28)	
Cobicistat			
$AUC_{0\text{-}32}$ (h*mg/L)	5.26 (43)	5.88 (39)	89.4 (82-97)
$AUC_{0\text{-}inf}$ (h*mg/L)	5.35 (42)	5.98 (38)	89.4 (82-97)
C_{max} (mg/L)	0.73 (29)	0.87 (37)	83.3 (76-91)
T_{max} (h)	3.25 (2.00-4.00)	2.25 (1.00-6.00)	
$T_{1/2}$ (h)	3.76 (25)	4.15 (24)	
Tenofovir			
$AUC_{0\text{-}32}$ (h*mg/L)	2.67 (24)	2.76 (27)	96.7 (91-103)
$AUC_{0\text{-}inf}$ (h*mg/L)	3.59 (24)	3.61 (31)	99.5 (92-107)
C_{max} (mg/L)	0.37 (29)	0.45 (35)	81.0 (71-92)
T_{max} (h)	1.00 (0.50-2.00)	1.28 (0.53-3.00)	
$T_{1/2}$ (h)	17.23 (22)	15.98 (29)	
Emtricitabine			
$AUC_{0\text{-}32}$ (h*mg/L)	11.47 (15)	11.58 (17.97)	99.1 (95-103)
$AUC_{0\text{-}inf}$ (h*mg/L)	11.69 (15)	11.79 (18.20)	99.1 (95-103)
C_{max} (mg/L)	2.07 (15.70)	2.30 (22.18)	89.9 (83-97)
T_{max} (h)	1.50 (0.97-2.50)	1.51(1.00-3.50)	
$T_{1/2}$ (h)	6.30 (18.62)	6.24 (18.88)	

Geometric mean + CV%, or median (range) for T_{max}

3. RESULTS (continued)

Table 2: PK parameters crushed tablet with drip feed versus whole tablet

	Crushed & drip feed	Whole tablet	GMR (90% CI)
Elvitegravir			
$AUC_{0\text{-}32}$ (h*mg/L)	18.02 (31)	17.27 (37)	104.3 (95-114)
$AUC_{0\text{-}inf}$ (h*mg/L)	18.85 (32)	17.84 (38)	105.6 (96-116)
C_{max} (mg/L)	1.47 (31)	1.40 (32)	104.5 (95-115)
T_{max} (h)	4.00 (1.52-10.00)	3.75 (1.00-6.03)	
$T_{1/2}$ (h)	6.10 (36)	5.76 (28)	
Cobicistat			
$AUC_{0\text{-}32}$ (h*mg/L)	6.02 (34)	5.88 (39)	102.4 (94-111)
$AUC_{0\text{-}inf}$ (h*mg/L)	6.11 (34)	5.98 (38)	102.2 (94-111)
C_{max} (mg/L)	0.88 (27)	0.87 (37)	100.9 (92-111)
T_{max} (h)	3.00 (2.00-6.00)	2.25 (1.00-6.00)	
$T_{1/2}$ (h)	3.77 (22)	4.15 (24)	
Tenofovir			
$AUC_{0\text{-}32}$ (h*mg/L)	2.78 (22)	2.76 (27)	100.7 (95-107)
$AUC_{0\text{-}inf}$ (h*mg/L)	3.77 (23)	3.61 (31)	104.6 (97-113)
C_{max} (mg/L)	0.43 (27)	0.45 (35)	94.2 (83-107)
T_{max} (h)	1.76 (1.50-2.50)	1.28 (0.53-3.00)	
$T_{1/2}$ (h)	17.12 (24)	15.98 (29)	
Emtricitabine			
$AUC_{0\text{-}32}$ (h*mg/L)	11.65 (15)	11.58 (17.97)	100.6 (97-105)
$AUC_{0\text{-}inf}$ (h*mg/L)	11.88 (15)	11.79 (18.20)	100.8 (97-105)
C_{max} (mg/L)	2.25 (15.07)	2.30 (22.18)	97.6 (91-105)
T_{max} (h)	2.00 (1.50-3.53)	1.51(1.00-3.50)	
$T_{1/2}$ (h)	6.15 (17.92)	6.24 (18.88)	

Geometric mean + CV%, or median (range) for T_{max}

Discussion

- EVG C_{max} after a single crushed tablet taken with a standardized breakfast was higher compared to the C_{max} of the whole tablet taken with a standardized breakfast, whereas the TFV C_{max} was lower in the same situation. These small deviations in C_{max} were judged to be not clinically relevant, as they fall within the normal variation in EVG or TFV exposure.

4. CONCLUSIONS

- AUCs fell within the bioequivalence ranges for all compounds. For C_{max} the 90% CI were just outside the bioequivalence range, but this was considered not clinically relevant. E/C/E/T can be crushed and suspended and given with drip feed.
- Single dose E/C/E/T was well tolerated by the healthy volunteers.

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