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 subsequently administered.
- Currently, there is no information about crushing the fixed-dose combination of elvitegravir/cobicistat/ric行硫酸/tenofovir (E/C/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/T is not recommended.

A possible PK interaction between elvitegravir (EVG) and diet 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 combination between EVG and calcium.

Objectives:
- To assess the bioequivalence of single dose E/C/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/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, A(BC); B(AC); CAB; CBA.
- A Standardized breakfast (350Cal) followed by E/C/T (whole tablet).
- B Standardized breakfast (350Cal) followed by crushed and suspended E/C/T.
- C 350 ml of drip feed (35CalNut). Suspension followed by a whole tablet and a standardized dose of drip feed followed by a crushed and suspended tablet.

Pharmacokinetics
- Mean concentration-time curves for EVG and COBI, for all treatments, are shown in Figure 1.
- Mean concentration-time curves for FTP 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 FT and EVG were calculated 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.

3. RESULTS
- No serious adverse events were reported. A total number of 9 adverse events was reported, all but one grade 1 severity. Seven subjects reported bad taste after intake of the crushed trial medication (E/C/T), which was judged to be definitely related to the trial medication. Two additional adverse events (diarrhea and elevated alanamys) were judged to be probably related to the trial medication.

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

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Dose</th>
<th>E/C/T (Mean) (90% CI)</th>
<th>E/C/T (Mean) (90% CI)</th>
<th>E/C/T (Mean) (90% CI)</th>
<th>E/C/T (Mean) (90% CI)</th>
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<tbody>
<tr>
<td>Emtricitabine</td>
<td>0.5</td>
<td>5.0 (4.5)</td>
<td>5.0 (4.5)</td>
<td>5.0 (4.5)</td>
<td>5.0 (4.5)</td>
</tr>
<tr>
<td>T1/2 (h)</td>
<td>6.2</td>
<td>6.0 (5.8)</td>
<td>6.2 (6.0)</td>
<td>6.2 (6.0)</td>
<td>6.2 (6.0)</td>
</tr>
<tr>
<td>FT conc. (mg/L)</td>
<td>17.12</td>
<td>17.12 (16.60-17.64)</td>
<td>17.12 (16.60-17.64)</td>
<td>17.12 (16.60-17.64)</td>
<td>17.12 (16.60-17.64)</td>
</tr>
<tr>
<td>Cobicistat conc. (mg/L)</td>
<td>6.02</td>
<td>6.02 (5.60-6.44)</td>
<td>6.02 (5.60-6.44)</td>
<td>6.02 (5.60-6.44)</td>
<td>6.02 (5.60-6.44)</td>
</tr>
<tr>
<td>T1/2 (h)</td>
<td>6.24</td>
<td>6.24 (5.88-6.60)</td>
<td>6.24 (5.88-6.60)</td>
<td>6.24 (5.88-6.60)</td>
<td>6.24 (5.88-6.60)</td>
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4. CONCLUSIONS
- ALCUs within the bioequivalence ranges for all compounds. For Cobicistat, the 90% CI were just outside the bioequivalence range, but this was considered not clinically relevant. E/C/T can be crushed and suspended with drip feed.
- Single dose E/C/T was well tolerated by the healthy volunteers.