Impact of the bioavailability of darunavir, cobicitat, entecitabine and tenofovir alafenamide, the first protease inhibitor-based complete HIV-1 regimen (DCFTAF)

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Abstract

Keywords: DCFTAF, darunavir, cobicitat, entecitabine and tenofovir alafenamide, HIV-1 regimen, bioavailability, pharmacokinetic interactions, study design and treatments

Introduction

Darunavir, a single-tablet, complete HIV-1 regimen has been shown to improve treatment adherence, patient satisfaction, and virologic outcomes compared with multi-tablet regimens.1,2 DCFTAF is the first protease inhibitor (PI)-based, single-tablet, complete HIV-1 regimen, for which bioavailability data is available.3 This regimen combines darunavir (DRV, D 800mg) with the pharmacoenhancer, ritonavir-boosted cobicistat (COBI, 150mg) and the first protease inhibitor-based complete HIV-1 regimen, tenofovir alafenamide (TAF), forming a PI/PI complex. This study assessed the comparative bioavailability of each active agent as a single oral dose of DCFTAF under fed or fasted conditions, and after 24 hours following a single oral dose of DCFTAF under fed or fasted conditions.4

Methods

Study design and treatments

- A Phase 1, open-label, randomized, single-center, crossover study in HIV-negative, healthy adult participants.
- In two treatment arms, participants received a single oral dose of DCFTAF under fasted conditions on day 0 or 23 or after a standardized high-fat breakfast consumed within a washout period of at least 7 days in between each treatment occasion.
- The mean plasma concentrations of DRV, COBI, FTC and TAF were assessed over time following intake of a single dose of DCFTAF under fasted and fed conditions.
- The study protocol and amendments were reviewed and approved by an Independent Ethics Committee. The trial was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines and applicable regulatory requirements. All participants provided written informed consent.
- PK parameters determined for each of the component drugs included: time to maximum concentration (Cmax), area under the concentration-time curve extrapolated to infinity (AUCinf), and aurorea (Clast), for TAF, COBI, FTC and DRV, respectively.

Pharmacokinetic (PK) and safety evaluations

- Blood samples were taken pre-dose and at 0.5, 1, 1.5, 2, 2.5, 4, 6, 8, 12, 24, 30, 48, and 72 hours after PK/day.
- The PK profile of the component drugs were determined up to 12 hours for DRV and COBI, 48 hours for FTC and 12 hours for TAF.
- Plasma concentrations of DRV, COBI, FTC and TAF were determined using validated high-performance liquid chromatography-mass spectrometry analytes.
- The lower limit of quantification was 0.05 ng/mL for DRV, COBI, FTC and TAF, respectively.
- PK parameters were determined using non-compartmental analysis (NCA; version 1.4.0.0220, Phoenix, Santa Clara, CA, USA).
- The PK parameters for each of the components included time to maximum plasma concentration (tmax), terminal elimination half-life (t1/2), exposure at time of dosing (AUCinf), maximum plasma concentration (Cmax) and area under the concentration-time curve (AUC0–t).
- The Cmax and AUCinf values were normalized to dose and expressed in ng/mL h/mL for DRV, COBI and FTC and ng/mL for TAF.
- Laboratory abnormalities were mostly grade 1 or 2. No consistent or clinically relevant changes in blood chemistry or hematology were observed.

Results

Table 1: DRV, COBI, FTC and TAF PK parameters and statistical analyses following administration of a single dose of DCFTAF under fed (standardized high-fat breakfast) or fasted conditions

<table>
<thead>
<tr>
<th>Component</th>
<th>Fed (standardized high-fat breakfast)</th>
<th>Fasted</th>
<th>Ratio (%)</th>
<th>90% CI (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRV</td>
<td>6.7 (4.0–11.2)</td>
<td>1.3 (1.1–1.5)</td>
<td>50 (42–60)</td>
<td></td>
</tr>
<tr>
<td>COBI</td>
<td>6.6 (5.2–8.3)</td>
<td>1.4 (1.2–1.7)</td>
<td>81 (69–93)</td>
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<tr>
<td>FTC</td>
<td>1.2 (0.9–1.5)</td>
<td>1.3 (1.1–1.5)</td>
<td>95 (85–101)</td>
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<tr>
<td>TAF</td>
<td>6.3 (5.2–7.6)</td>
<td>1.1 (1.0–1.2)</td>
<td>110 (95–125)</td>
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Safety and tolerability

- All AEs were grade 1 or 2 in intensity, with no grade 3 or 4 events reported.
- The most common AEs (observed in >2 volunteers during any treatment phase) were:
  - 125.99 (112.85–140.65) for nausea,
  - 107 (65.2) for diarrhea,
  - 10.8 (1.2) for increased creatinine.
- The incidence of AEs by preferred term was generally comparable under fasted and fed conditions.
- Similarly, exposure to COBI was 16% to 30% lower under fasted versus fed conditions.
- The least square (LS) means of natural logarithm-transformed Cmax, AUC0–t, and AUCinf for DRV were 26% higher in fasted compared with fed conditions, while AUCinf was 32% lower in fasted conditions.
- For TAF, the Cmax and AUC0–t values were 76% and 47%, respectively, lower under fasted versus fed conditions.
- In the ongoing Phase III AMBER and EMERALD trials in HIV-1-infected adults, DCFTAF as compared to remaining on a PI boosted with low-dose ritonavir or COBI, a regimen comprising a DRV/COBI FDC with FTC/TDF FDC in approximately 1100 virologically suppressed, HIV-1-infected patients.

Acknowledgements and disclosures

This study was sponsored by Janssen Pharmaceuticals.

References


4. Accurate determination not possible for more than 50% of participants; interpret with caution; §§ the food effect was observed on following administration of DCFTAF

5. Abbreviations: DCFTAF = darunavir (800mg)/cobicitat (150mg)/entecitabine (200mg)/tenofovir alafenamide (10mg); FTC/TDF = emtricitabine (200mg)/tenofovir disoproxil fumarate (300mg); TAF = tenofovir alafenamide; GRC = geometric mean ratio; CI = confidence interval; AUC0–t = area under the concentration-time curve extrapolated to time of last quantifiable concentration; AUCinf = area under the concentration-time curve extrapolated to infinity; CV = coefficient of variation; Cmax = maximum concentration; tmax = time to maximum concentration; t1/2 = elimination half-life; 80–125% = ratio within the 80% to 125% boundaries of no effect

Table 1: DRV, COBI, FTC and TAF PK parameters and statistical analyses following administration of a single dose of DCFTAF under fed (standardized high-fat breakfast) or fasted conditions

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For DRV, the Cmax following administration of DCFTAF were 8% higher in fasted conditions, while the AUC24 was 12% lower in fasted compared with fed conditions (Table 3). The AUCinf of DRV was comparable to fasted and fed conditions, with the 80–125% limits within the 80–125% boundaries of no effect.

For FTC, the Cmax following administration of DCFTAF were 2% lower in fasted conditions, while the AUC0–t values were 12% lower in fasted conditions.

For TAF, the Cmax following administration of DCFTAF were 2% lower in fasted conditions, while the AUC0–t values were 12% lower in fasted conditions.