Development of a protease inhibitor-based single-tablet complete HIV-1 regimen of darunavir/cobicistat/emtricitabine/tenofovir alafenamide (DCFTAF)

Bryan Baugh¹, Erika Van Landuyt², Simon Vanveggel², Herta Crauwels², Elisabeth Dammers², Anja Hijzen², Erkki Lathouwers², Magda Opsomer²

¹Janssen Research & Development LLC, Raritan, NJ, USA; ²Janssen Pharmaceutica NV, Beerse, Belgium
DCFTAF
The first single-tablet regimen containing a boosted PI

- DCFTAF is an HIV-1 regimen in clinical development that combines darunavir (DRV, D, 800mg), with cobicistat (COBI, C, 150mg), emtricitabine (FTC, F, 200mg), and tenofovir alafenamide (TAF, 10mg)\(^1\)
  
  - Boosted DRV 800mg has demonstrated a high and durable virologic response, with a high genetic barrier to the development of resistance, in various patient populations\(^2\)–\(^4\)

  - TAF, a novel prodrug of tenofovir (TFV), provides comparable efficacy to tenofovir disoproxil fumarate (TDF) at one-tenth the dose, resulting in a ~90% lower TFV plasma concentration and fewer adverse effects, particularly renal and bone\(^1,5\)–\(^7\)

- Current treatment guidelines recommend DRV, boosted with ritonavir or COBI, combined with other antiretroviral (ARV) drugs, for HIV-1-infected treatment-naïve patients\(^8\)


ART-naïve, HIV-1-infected adults (N=153) randomized 2:1 to each arm:

DCFTAF vs DRV + COBI + FTC/TDF

- Non-inferior virologic efficacy at Week 24 (FDA snapshot analysis; primary endpoint)
- Difference in virologic response rates at Week 48 was primarily due to a higher rate of discontinuations for reasons other than virologic failure or AEs in the DCFTAF arm 16 (15.5%) vs 3 (6.0%) patients, respectively†
- No treatment-emergent phenotypic resistance to any of the compounds

*GS-US-299-0102 (NCT01565850)
†Weighted difference in response rates (95% CI)
‡Main reason for these discontinuations was loss to follow-up (10/16 vs 1/3 patients)
ART=antiretroviral treatment; AE=adverse event
ITT=intent-to-treat

## Exploratory Phase II study: safety of DCFTAF

<table>
<thead>
<tr>
<th>Incidence, n (%)</th>
<th>DCFTAF N=103</th>
<th>DRV + COBI + FTC/TDF N=50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>95 (92)</td>
<td>47 (94)</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>5 (5)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Grade 3 or 4 AEs</td>
<td>7 (7)</td>
<td>4 (8)</td>
</tr>
<tr>
<td>AEs leading to discontinuation</td>
<td>2* (2)</td>
<td>2† (4)</td>
</tr>
<tr>
<td>Most common AEs‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>22 (21)</td>
<td>13 (26)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>16 (16)</td>
<td>7 (14)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>14 (14)</td>
<td>9 (18)</td>
</tr>
<tr>
<td>Nausea</td>
<td>13 (13)</td>
<td>5 (10)</td>
</tr>
<tr>
<td>Rash</td>
<td>12 (12)</td>
<td>4 (8)</td>
</tr>
</tbody>
</table>

*DCFTAF: Rash and substance dependence; †DRV + COBI + FTC/TDF: Worsening of diarrhea and proximal renal tubulopathy; ‡Occurring in ≥10% of patients in DCFTAF group

- **Mean change in serum creatinine at Week 48**
  - DCFTAF: + 0.06 mg/dL
  - DRV + COBI + FTC/TDF: + 0.09 mg/dL  
    \[(p=0.053)\]
- **Decreases in hip and spine BMD were smaller in the TAF vs in the TDF group**
An update on the ongoing DCFTAF development program is presented.
DCFTAF BA food effect
Study design* and baseline demographics

- Phase I, open-label, randomized, two-period, single-center, crossover study in 24 HIV-negative, healthy adult participants

<table>
<thead>
<tr>
<th>Session 1</th>
<th>At least 7 days washout*</th>
<th>Session 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group 1</strong>&lt;br&gt;(N=12)</td>
<td>Single oral dose of DCFTAF under fasted conditions (test)</td>
<td>→</td>
</tr>
<tr>
<td><strong>Group 2</strong>&lt;br&gt;(N=12)</td>
<td>Single oral dose of DCFTAF after a standardized high-fat breakfast (reference)</td>
<td>→</td>
</tr>
</tbody>
</table>

* Day 1 of a treatment session is the first day of the washout period

- PK profiles component drugs evaluated over 24 hours; PK parameters determined using non-compartmental analysis
  - Treatment comparison evaluated using GMRs with 90% CIs

- Half of participants were female and all were white of median (range) age 35 (18–54) years and body mass index 23.7 (19.8–29.5) kg/m²

---

*TMC114FD2HTX1002 (NCT02475135)
GMR=geometric mean ratio; CI=confidence interval

2. Crauwels H et al. HIV Drug Therapy, Glasgow 2016. Poster 310
## DCFTAF BA food effect

### PK parameters statistical analysis

<table>
<thead>
<tr>
<th>GMR, % (90% CI)</th>
<th>DRV</th>
<th>COBI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fasted (test)</td>
<td>Fed (high fat) (reference)</td>
</tr>
<tr>
<td>n‡</td>
<td>23 vs 24</td>
<td>23 vs 24</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>54.99 (46.73–64.71)</td>
<td>76.96 (55.70–106.33)</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;last&lt;/sub&gt;</td>
<td>65.65 (56.76–75.92)</td>
<td>70.90 (51.13–98.30)</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;inf&lt;/sub&gt;</td>
<td>70.25† (59.49–82.95)</td>
<td>84.39‡ (68.52–103.95)</td>
</tr>
</tbody>
</table>

‡test vs reference; †n=20 for test and reference; ‡n=22 for test; C<sub>max</sub>=maximum plasma concentration, AUC=area under the plasma concentration-time curve from time of administration up to the last timepoint with a measurable concentration post-dose (AUC<sub>last</sub>) and extrapolated to infinity (AUC<sub>inf</sub>)

2. Crauwels H et al. HIV Drug Therapy, Glasgow 2016. Poster 310
## DCFTAF BA food effect
### PK parameters statistical analysis, safety and tolerability

<table>
<thead>
<tr>
<th>GMR, % (90% CI)</th>
<th>FTC</th>
<th>TAF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fasted (test)</td>
<td>Fed (high fat) (reference)</td>
</tr>
<tr>
<td>n(^\dagger)</td>
<td>24 vs 24</td>
<td>24 vs 24</td>
</tr>
<tr>
<td>C(_{\text{max}})</td>
<td>125.99 (112.85–140.65)</td>
<td>182.29 (140.50–236.50)</td>
</tr>
<tr>
<td>AUC(_{\text{last}})</td>
<td>100.12 (96.29–104.10)</td>
<td>89.54 (81.20–98.72)</td>
</tr>
<tr>
<td>AUC(_{\text{inf}})</td>
<td>–</td>
<td>80.38 (^\ddagger) (73.04–88.45)</td>
</tr>
</tbody>
</table>

*test vs reference; \(^\ddagger\) n=21 for test and n=16 for reference

- Administration of DCFTAF was generally well tolerated under both fed and fasted conditions, and no new safety issues were identified

---

2. Crauwels H et al. HIV Drug Therapy, Glasgow 2016. Poster 310
Phase III trial in ART-naïve patients

Double-blind, randomized, multicenter, parallel-group, non-inferiority study

**Objective:** Evaluate the efficacy and safety of DCFTAF vs D/C + F/TDF in HIV-1-infected, ART-naïve adults

**Primary endpoint:** Proportion of participants with plasma HIV-1 RNA <50 c/mL at Week 48 using the FDA Snapshot algorithm for the ITT population

- Non-inferiority margin: -10% NI
- Week 48 data to support NDA/MAA submissions with ongoing observation through Week 96 followed by roll over in extension phase until DCFTAF tablet becomes available

*Will be conducted when all patients have completed Week 48 assessments

Phase III trial in virologically suppressed patients

Open-label, randomized, multicenter, parallel-group, non-inferiority study

Objective: Evaluate the efficacy and safety of switching to DCFTAF vs continuing the current regimen of a bPI + FTC/TDF in ART-experienced*, virologically-suppressed†, HIV-1-infected adults

Primary endpoint: Proportion of patients with virologic rebound (confirmed HIV-1 RNA ≥50 c/mL or premature discontinuations, with a last single HIV-1 RNA ≥50 c/mL) through Week 48

• Non-inferiority margin: -4% NI

• Week 48 data to support NDA/MAA submissions followed by extension phase with DCFTAF through Week 96 or beyond, until DCFTAF tablet becomes available

Screening phase

Randomization 2:1
N=1149

≤30 days prior to baseline

Treatment phase

DCFTAF

Continue bPI + F/TDF

Baseline

Interim analysis‡

Extension phase

DCFTAF

Week 48
Primary endpoint‡

Roll-over phase

DCFTAF

Week 96

*Previous ART virologic failure allowed.
*Absence of history of failure on DRV treatment and absence of DRV RAMs, if historical genotype available
†At least one HIV RNA <50c/mL between 12–2 months before screening visit (HIV RNA <50c/mL) (single viral load blip allowed if re-suppressed)
‡Will be conducted when all patients have completed assessments
bPI=protease inhibitor boosted with low-dose ritonavir or COBI

Summary

- DCFTAF is a single-tablet regimen containing a boosted PI and TAF in clinical development
- A prior Phase II study with DCFTAF showed good antiviral activity and safety
- DCFTAF is currently in Phase III development
  - Phase III AMBER and EMERALD trials in HIV-1-infected adults are fully recruited and ongoing
  - Treatment-naive HIV-infected adults and switch population
  - 48-week primary endpoint
- Consistent with prescribing recommendations for other DRV formulations,¹ it is recommended that the DCFTAF FDC tablet be taken with food
  - Following administration of DCFTAF in fasted conditions, the DRV exposure (AUC, C_{max}) decreased by 30–45% compared with in fed conditions, consistent with what has been previously reported for DRV/r² or DRV/COBI³
  - Differences in exposure to COBI, FTC and TAF in fed versus fasted conditions were not considered to be clinically relevant
  - The food effect for DRV was previously shown to be similar for different types of food¹
  - Administration of DCFTAF was generally well tolerated under both fed and fasted conditions, and no new safety issues were identified

¹ PREZISTA® (darunavir). Full Prescribing Information. June 2016
Acknowledgements and disclosures

• We would like to thank
  – The study participants and site staff for their participation and support during the Janssen-sponsored studies included in this presentation
  – The Janssen team members from the bioanalysis department, in particular Vera Hillewaert for the DCFTAF BA food effect study; Jiri Letal who was the DCFTAF BA food effect study statistician; and Janssen Research & Development team members, in particular Maria Blanca Hadacek, Katia Boven, Kimberley Brown, Julia Sugumar and Eric Y. Wong for their input into this poster

• All authors are full-time employees of Janssen and potential stockholders of Johnson & Johnson

• Medical writing support was provided by Ian Woolveridge from Zoetic Science, Macclesfield, UK, an Ashfield Company. Support for medical writing assistance was provided by Janssen Pharmaceuticals

• The DCFTAF food effect data have been presented previously:
  – Crauwels et al. 21st IAC 2016. Abstract and poster THPEB064
  – HIV Drug Therapy, Glasgow 2016. Abstract and poster P310