PREZCOBIX® (darunavir/cobicistat)
Use of PREZCOBIX in Combination with Descovy
(emtricitabine/tenofovir alafenamide)

SUMMARY

- A pharmacokinetic (PK) study found that systemic exposure to tenofovir (TFV) was 3.2-fold higher after coadministration of emtricitabine (FTC)/tenofovir alafenamide (TAF) with darunavir (DRV) 800 mg + cobicistat (COBI) 150 mg (administered separately). DRV and COBI exposures were unaffected.[1]
- A PK study in 24 healthy Japanese participants randomized into 3 treatment groups (consisting of: FTC/TAF with PREZCOBIX, FTC/TAF with DRV/ritonavir (r), and FTC/TAF alone) showed no clinically relevant PK differences for TAF, TFV, and FTC between Japanese and non-Japanese subjects based on historical data.[2]
- A retrospective, real-world study was conducted to evaluate the treatment patterns, including adherence and persistence, of treatment-naïve (n=308) and treatment-experienced (n=2325) patients infected with HIV-1 who were treated with the single-tablet regimen (STR) DRV/COBI/FTC/TAF or PREZCOBIX + FTC/TAF.[3]
    - The persistence rates were higher in patients treated with the STR than in patients treated with PREZCOBIX + FTC/TAF during the 6-months post-index.
    - During the 6 months post-index, the optimal adherence (proportion of days covered [PDC] ≥95%) rate was higher in patients treated with the STR (45.8%) than in those treated with PREZCOBIX + FTC/TAF (33.9%).
        - Patients treated with PREZCOBIX + FTC/TAF had a higher non-adherence (PDC <80%) rate than patients treated with the STR (46% vs 28%, respectively).

PK STUDIES

Custodio et al (2015)[1] evaluated the PK of DRV, COBI, FTC, TAF, and TFV following administration of DRV 800 mg + COBI 150 mg (administered as single agents) + FTC/TAF 200/25 mg vs FTC/TAF alone.

Study Design/Methods

- Open-label, crossover, two-cohort, multiple-dose study
- Cohort 1 (n=12, 6 males/6 females) received FTC/TAF for 12 days, followed by FTC/TAF + DRV + COBI for 10 days
- Cohort 2 (n=14, 9 males/5 females) received DRV + COBI for 10 days, followed by DRV + COBI + FTC/TAF for 12 days.
- Intensive PK sampling was conducted on the final day of each period in both cohorts and also after the first dose of each treatment in cohort 1 to compare single-dose and multiple-dose TAF PK with and without DRV + COBI.
- Intracellular concentrations of the parent compound (TFV) were not evaluated.
- Safety was also assessed.

Results

- TAF exposure was 63% higher following coadministration of a single dose of FTC/TAF with DRV + COBI vs a single dose of FTC/TAF alone; however, the effect was not sustained following multiple dosing (Geometric Mean Ratio [GMR] 97.6; 90% CI: 80.3-119).
- This was attributed to the conflicting effects on intestinal P-glycoprotein (P-gp) by COBI (inhibition) and DRV (induction after multiple dosing), which ultimately affects TAF absorption since TAF is a P-gp substrate.
- DRV and COBI exposures (area under the concentration-time curve [AUC]) were unaffected by coadministration of FTC/TAF.
    - DRV: GMR 99.1; 90% CI 91.5-107
    - COBI: GMR 109; 90% CI 103-115

- FTC exposure was increased after coadministration of DRV + COBI (GMR 124; 90% CI 117-131); however, this was not considered clinically relevant.
- Exposure to the TAF metabolite (TFV) was increased 3.2-fold during coadministration with DRV + COBI vs. FTC/TAF alone (see Table: TFV PK).

TFV PK[1]

PK Parameter, Mean (% CV)	FTC/TAF + DRV + COBI (n=11)	FTC/TAF (n=11)	GMR (90% CI)
AUC_{last} (ng·h/mL)	953 (20)	299 (30)	324 (302-347)
C_{max} (ng/mL)	57.4 (23)	18.3 (28)	316 (300-333)
C_{tau} (ng/mL)	33.7 (20)	10.8 (33)	321 (290-354)

Abbreviations: AUC_{last}, area under the concentration-time curve from t=0 to last time point; C_{max}, maximum serum concentration; CI, confidence interval; COBI, cobicistat; CV, coefficient of variation; DRV, darunavir; GMR, geometric mean ratio; PK, pharmacokinetics.

- Treatments were generally well tolerated, and all adverse events (AEs) were mild or moderate in severity.
- No grade 3-4 AEs or deaths were reported.

Yamada et al (2018)[2] evaluated pharmacokinetic differences for TAF, TFV, and FTC between Japanese and non-Japanese subjects using historical information.

Study Design/Methods

- Phase 1, randomized, open-label, single-dose, parallel-group study in healthy Japanese male subjects (ages 20 to 45) in a fed state.
- The 24 study subjects were randomized into 3 treatment groups with no obvious differences in age, height, body weight, and BMI observed between groups.
- Treatment A (n=8) received FTC/TAF 200/10 mg co-administered with DRV/r 800/100 mg.
- Treatment B (n=8) received FTC/TAF 200/10 mg co-administered with PREZCOBIX.
- Treatment C (n=8) received FTC/TAF 200/25 mg administered alone.
- Full PK profiles of TAF, TFV, and FTC were assessed from samples collected pre-dose and 0.25, 0.5, 0.75, 1, 1.5, 2 ,3, 4, 5, 8, 12, 24, 48, and 72 hours post-dose.
- Safety was also assessed from day 1 to day 4 of the study.

Results

- PK parameters between the 3 treatment groups were comparable except for differences observed in TAF exposure between treatment groups A or B and treatment group C.
- The mean exposure of TAF regarding C_{max} (125 – 154 ng/mL) and AUC_{inf} (119 – 179 ng·h/mL) for all 3 treatment groups was comparable to 3 phase 1 studies (n=79) and 6 phase 2/3 studies (n=1543) in non-Japanese patient with HIV-1 infection.
- TFV exposure in the study (range of mean AUC_{inf} 271 – 313 ng·h/mL) was consistent with the historical mean AUC_{tau} of 339 ng·h/mL in non-Japanese patients.
- FTC exposure in the study (range of mean AUC_{inf} 11353 – 11883 ng·h/mL) was consistent with the historical mean AUC_{tau} of 11918 in non-Japanese patients.
- A summary of TAF, TFV and FTC pharmacokinetic parameters are provided in Table: Summary of TAF, TFV, and FTC Pharmacokinetic Parameters.

Summary of TAF, TFV, and FTC Pharmacokinetic Parameters[2]

PK Parameter, Mean (SD)[a]	Treatment A FTC/TAF 200/10mg with DRV/r (n=8)	Treatment B FTC/TAF 200/10MG with PREZCOBIX (n=8)	Treatment C FTC/TAF 200/25mg (n=8)
TAF			
t_{max} (h)	1.00 (0.50-2.00)	1.50 (0.75-2.00)	1.50 (0.75-2.00)
C_{max} (ng/mL)	125 ± 62	148 ± 79	154 ± 69
AUC_{inf} (ng·h/mL)	119 ± 38[b]	140 ± 43[b]	179 ± 38[c]
AUC_{last} (ng·h/mL)	110 ± 33	123 ± 40	164 ± 46
$t_{1/2}$ (h)	0.32 ± 0.10 [b]	0.36 ± 0.20[b]	0.35 ± 0.04[c]
TFV			
t_{max} (h)	2.50 (1.50-4.00)	3.00 (1.00-4.00)	2.00 (1.50-4.00)
C_{max} (ng/mL)	8.2 ± 2.0	7.4 ± 1.4	7.9 ± 1.5
AUC_{inf} (ng·h/mL)	313 ± 35	271 ± 58	273 ± 46
AUC_{last} (ng·h/mL)	219 ± 40	182 ± 32	195 ± 32
$t_{1/2}$ (h)	43.2 ± 12.2	45.6 ± 7.4	40.0 ± 3.4
FTC			
t_{max} (h)	1.75 (1.00-4.00)	2.00 (1.00-3.00)	2.00 (1.00-3.00)
C_{max} (ng/mL)	2483 ± 348	2388 ± 668	2638 ± 635
AUC_{inf} (ng·h/mL)	11883 ± 780	11574 ± 1819[d]	11353 ± 729[d]
AUC_{last} (ng·h/mL)	11720 ± 774	11155 ± 1843	11418 ± 904
$t_{1/2}$ (h)	17.0 ± 3.2	13.9 ± 4.2[d]	13.9 ± 3.2[d]

Abbreviations: AUC_{inf}, area under the concentration-time curve from the time of dosing to infinity; AUC_{last}, area under the concentration-time curve from the time of dosing to the last quantifiable time point; C_{max}, maximum plasma concentration; DRV, darunavir; PK, pharmacokinetics; SD, standard deviation; $t_{1/2}$, half-life; t_{max}, time to reach C_{max}.
[a]Values are shown as mean ± SD except t_{max}, which is shown as median (range); [b]n = 5; [c]n = 6; [d]n = 7.

- All treatments were well tolerated, and no adverse events were reported in the study.

REAL-WORLD DATA

Adherence Study

This was a retrospective, longitudinal, real-world study conducted to evaluate the treatment patterns, including adherence and persistence, of treatment-naïve (n=308) and treatment-experienced (n=2325) patients infected with HIV-1 who were treated with the STR DRV/COBI/FTC/TAF or PREZCOBIX + FTC/TAF.[3]

Study Design/Methods

- Data from the Decision Resources Group's Real-World Data Repository from 07/17/2017 to 06/01/2019 were used for this analysis.
- Eligible patients were prescribed the STR DRV/COBI/FTC/TAF or a multi-tablet regimen of PREZCOBIX + FTC/TAF.
    - The date of initiation of antiretroviral therapy (ART) was considered the index date (on or after 07/17/2018).

- The pre-index period consisted of 12-months of continuous clinical activity prior to the index date.
- The post-index period was the time from the index date until the end of data availability or the end of continuous clinical activity.

- Treatment-experienced patients were excluded if they were not virologically suppressed during the 6 month pre-index period.
- Study measures: treatment patterns, including persistence and adherence, were assessed during the pre-index and over the post-index period.
  - Patients with no medication gap for >60 or >90 days during the first 6 months post-index were considered persistent. Those who were initiated on the multi-tablet regimen had to be taking both PREZCOBIX and FTC/TAF to be considered persistent.
  - Adherence was calculated for each using the PDC calculation:
    - STR: the sum of non-overlapping days of supply for the index regimen divided by 6 months.
    - PREZCOBIX + FTC/TAF: the sum of non-overlapping days during which patients had a simultaneous supply of PREZCOBIX and FTC/TAF divided by 6 months.
  - The PDC thresholds are listed below (PDC ≥90% was also reported):
    - PDC <80%: nonadherence
    - PDC ≥80% and <95%: suboptimal adherence
    - PDC ≥95%: optimal adherence

Results

Persistence

- A total of 1,026 patients had ≥6 months of continuous clinical activity post-index.
- The persistence rates were higher in patients treated with the STR than in patients treated with PREZCOBIX + FTC/TAF (See Table: Persistence Results During the 6-months Post-Index)

Persistence Results During the 6-months Post-Index[3]

Persistence	DRV/COBI/FTC/TAF (n=822)	PREZCOBIX + FTC/TAF (n=204)	All Patients (n=1,026)
Proportion of patients with no medication gap for >60 days, %	79.7	68.6	77.5
Proportion of patients with no medication gap for >90 days, %	85.9	75.0	83.7
Abbreviations: COBI, cobicistat; DRV, darunavir; FTC, emtricitabine; PDC, proportion of days covered; TAF, tenofovir alafenamide.			

Treatment Adherence

- A total of 867 patients had ≥6 months of continuous clinical activity post-index with ≥1 claim for ART during the 6 months pre- and post-index period.
  - In this cohort, 86% of patients (746/867) received the STR and 14% (121/867) received PREZCOBIX + FTC/TAF.
- During the 6 months post-index, the mean (median) PDC was 81% (93%) in the STR group and 73% (83%) in the PREZCOBIX + FTC/TAF group (see Table: Adherence Results During the 6-months Post-Index).
  - The optimal adherence (PDC ≥95%) rate was higher in patients treated with the STR (45.8%) than in those treated with PREZCOBIX + FTC/TAF (33.9%).
  - Patients treated with PREZCOBIX + FTC/TAF had a higher non-adherence (PDC <80%) rate than patients treated with the STR (46% vs 28%, respectively).

Adherence Results During the 6-months Post-Index[3]

Treatment Adherence	DRV/COBI/FTC/TAF (n=746)	PREZCOBIX + FTC/TAF (n=121)	All Patients (n=867)
PDC <80%	28.4	45.5	30.8
PDC ≥80% and <95%	25.7	20.7	25
PDC ≥95%	45.8	33.9	44.2
PDC ≥90%	57.8	44.6	55.9
Abbreviations: COBI, cobicistat; DRV, darunavir; FTC, emtricitabine; PDC, proportion of days covered; TAF, tenofovir alafenamide.			

Predictors of low adherence included:

- Aged 18 to 34 years (adjusted odds ratio [OR]: 2.36; *P*=0.017)
- Patients residing in the Northeast region of the United States (adjusted OR: 1.98; *P*<0.001)
- A higher Quan-Charlson comorbidity index score (adjusted OR: 1.32; *P*=0.012)
- Patients initiated on a multi-tablet regimen (adjusted OR: 1.69; *P*=0.022)
- Patients with a PDC <80% to any ART during the 6 months pre-index (adjusted OR: 2.56; *P*<0.001).

LITERATURE SEARCH

A literature search of MEDLINE®, EMBASE®, BIOSIS Previews®, and DERWENT® databases (and/or other resources, including internal/external databases) pertaining to this topic was conducted on 25 October 2023.

REFERENCES

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2. Yamada H, Yonemura T, Nemoto T, et al. Pharmacokinetics of Tenofovir Alafenamide, Tenofovir, and Emtricitabine Following Administration of Coformulated Emtricitabine/Tenofovir Alafenamide in Healthy Japanese Subjects. *Clin Pharm Drug Dev*. 2019;8(4):511-520.

3. Chow W, Donga P, Côté-Sergent A, et al. Treatment Patterns and Predictors of Adherence in HIV Patients Receiving Single- or Multiple-Tablet Darunavir, Cobicistat, Emtricitabine, and Tenofovir Alafenamide. *Patient Prefer Adher*. 2020;14:2315-2326.