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Bioequivalence of a Paediatric Fixed-dose Combination Tablet Darunavir/Cobicistat/Emtricitabine/Tenofovir Alafenamide Compared With Coadministration of the Separate Agents in Healthy Adults

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Introduction

- D/C/F/TAF 800/150/200/10 mg is a once-daily FDC ARV therapy for HIV-1 infection[1]
- The efficacy, safety, and high genetic barrier to resistance of D/C/F/TAF 800/150/200/10 mg were demonstrated in phase 3 trials that included both treatment-naïve and treatment-experienced, virologically suppressed adult patients with HIV-1[2-5]
- D/C/F/TAF 800/150/200/10 mg is approved in Europe and the United States for the treatment of HIV-1 infection in adults and paediatric patients (aged ≥12 years in Europe) weighing ≥40 kg[1,6]
- A paediatric formulation of D/C/F/TAF at doses of 675/150/200/10 mg is under development as an FDC tablet with a score line to allow for administration as a whole or split tablet

Objective

- To evaluate the bioequivalence of a D/C/F/TAF paediatric formulation (675/150/200/10 mg) administered as an FDC tablet versus coadministration of separate commercial formulations in healthy adults under fed conditions

Methods

Study Design

- TMC114FD2HTX1007 (ClinicalTrials.gov Identifier: NCT04661397) was a phase 1, randomised, open-label, 2-treatment, 2-sequence, 4-period, replicate crossover study conducted in healthy adults aged 18 to 55 years
- The study consisted of 3 phases: a screening phase of ~4 weeks (Days –28 to –1); an open-label treatment phase consisting of 4 single-dose treatment periods of 4 days each (Days 1-4), each separated by a washout period of ≥7 days between dosing (starting on Day 1); and an end-of-study/follow-up assessment phase (7-10 days after final dosing)
- Participants received 1 of the following treatments in each of the 4 treatment periods, under fed conditions:
  - Treatment A (test): a single oral dose of D/C/F/TAF 675/150/200/10 mg FDC
  - Treatment B (reference): oral DRV 600 mg and 75 mg, COBI 150 mg, and FTC/TAF 200/10 mg FDC
- Participants were randomised to 1 of 2 treatment sequence groups: A-B-B-A and B-A-A-B
- As TAF C_{max} is highly variable (ie, $\%CV_{intraindividual}$ >30%), a traditional 2-way crossover design applying conventional bioequivalence limits (ie, 80.00%-125.00%) would require a high sample size to achieve sufficient power
  - Therefore, a replicate crossover design was utilised in accordance with regulatory guidelines[7] to allow for widening of TAF C_{max} bioequivalence limits and hence reduce unnecessary exposure of participants to D/C/F/TAF
  - This design allows intraindividual comparisons, with each participant acting as their own control, and a smaller sample size

Assessments

- The key PK parameters assessed were C_{max}, t_{max}, AUC_{last}, AUC_{inf}, and $t_{1/2}$
- Plasma samples of DRV, COBI, FTC, and TAF were analysed using a validated bioanalytical method involving liquid chromatography for separation and tandem mass spectrometry
- Safety and tolerability were monitored throughout the study

Data Analyses

- A minimum of 28 participants was estimated to yield ≥90% power to establish bioequivalence at a 5% significance level, assuming the test and reference treatment geometric means differed by ≤5%
- The randomised analysis set included all participants who were randomised in the study
- Descriptive statistics were calculated for each treatment for plasma concentrations and derived PK parameters of DRV, COBI, FTC, and TAF at each applicable time point for all participants with ≥1 PK concentration and/or ≥1 evaluable PK parameter
- Inferential statistics analyses were conducted in participants who completed all treatment periods and for whom an evaluable PK parameter could be obtained in all treatment periods
- To meet bioequivalence criteria, 90% CIs of the GMRs for DRV and FTC C_{max} and AUC_{last}, TAF AUC_{last}, and the GMR for TAF C_{max} needed to fall within 80.00% to 125.00% (inclusive). The 90% CI of the GMR for TAF C_{max} needed to fall within the widened bioequivalence limits calculated per regulatory guidelines[7]
- All participants who were enrolled and received ≥1 dose of the study intervention were included in the safety and tolerability analysis

Results

Participants

- In total, 37 participants were enrolled and 32 completed the study (n = 16 per treatment sequence)
- Of the participants enrolled, 64.9% were male, 91.9% were White, and the median age was 26.0 years (**Table 1**)

Table 1. Demographic and baseline characteristics (randomised analysis set)

Parameter	Treatment sequence: A-B-B-A n = 19	Treatment sequence: B-A-A-B n = 18	Total N = 37
Age, median (range), years	26.0 (18-54)	27.5 (19-55)	26.0 (18-55)
Sex, n (%)			
Male	11 (57.9)	13 (72.2)	24 (64.9)
Female	8 (42.1)	5 (27.8)	13 (35.1)
Race, n (%)			
White	17 (89.5)	17 (94.4)	34 (91.9)
Multiple	1 (5.3)	1 (5.6)	2 (5.4)
Asian	1 (5.3)	0	1 (2.7)
Ethnicity, n (%)			
Not Hispanic or Latino	18 (94.7)	18 (100)	36 (97.3)
Hispanic or Latino	1 (5.3)	0	1 (2.7)
BMI, median (range), kg/m^2	25.2 (19.3-28.2)	24.8 (20.0-29.9)	25.1 (19.3-29.9)

PK Results

- Individual PK parameters for DRV, COBI, FTC, and TAF with descriptive statistics are provided in **Table 2**

Table 2. PK parameter results for DRV, COBI, FTC, and TAF after oral administration of a paediatric formulation of D/C/F/TAF 675/150/200/10 mg FDC versus coadministration of the separate commercial agents (PK data analysis)

Parameter, mean (SD)*	D/C/F/TAF (test) n = 69†,‡	DRV + COBI + FTC/TAF (reference) n = 68†,§
DRV		
C_{max}, ng/mL	6,363 (1,449)	6,426 (1,277)
t_{max}, h	3.00 (1.00-8.00)	3.00 (1.00-8.00)
AUC_{last}, ng·h/mL	74,698 (23,915)	72,380 (22,435)
AUC_{inf}, ng·h/mL	74,891 (23,974)	72,564 (22,502)
$t_{1/2}$, h	5.5 (1.6)	5.6 (2.4)
COBI		
C_{max}, ng/mL	842 (206)	898 (202)
t_{max}, h	3.00 (1.00-8.00)	3.00 (1.00-8.00)
AUC_{last}, ng·h/mL	6,160 (2,116)	6,366 (2,113)
AUC_{inf}, ng·h/mL	6,276 (2,169)	6,476 (2,190)
$t_{1/2}$, h	3.7 (0.6)	3.7 (0.7)
FTC		
C_{max}, ng/mL	1,806 (385)	1,835 (366)
t_{max}, h	2.00 (0.50-5.00)	1.50 (0.50-5.00)
AUC_{last}, ng·h/mL	9,967 (1,854)	9,995 (1,802)
AUC_{inf}, ng·h/mL	10,174 (1,900)	10,199 (1,791)
$t_{1/2}$, h	16.8 (3.9)	16.3 (4.6)
TAF		
C_{max}, ng/mL	144 (86.8)	134 (78.8)
t_{max}, h	1.00 (0.25-4.00)	0.89 (0.25-4.00)
AUC_{last}, ng·h/mL	124 (36.7)	113 (44.1)
AUC_{inf}, ng·h/mL	127 (38.4)	116 (43.8)
$t_{1/2}$, h	0.4 (0.2)	0.4 (0.2)

*Except t_{max} = median (range).
†n = the total number of observations (number of individual values per PK parameter).
‡FTC: n = 66 for AUC_{inf} and $t_{1/2}$; TAF: n = 59 for AUC_{inf} and $t_{1/2}$.
§FTC: n = 64 for AUC_{inf} and $t_{1/2}$; TAF: n = 60 for AUC_{inf} and $t_{1/2}$.

- The C_{max} and AUCs for DRV, COBI, FTC, and TAF were comparable for test and reference treatments (**Table 3**)
- As the 90% CIs of the GMRs of C_{max} and AUCs were contained within the predefined 80.00% to 125.00% bioequivalence limits for DRV, COBI, FTC, and TAF, the test and reference treatments were considered bioequivalent

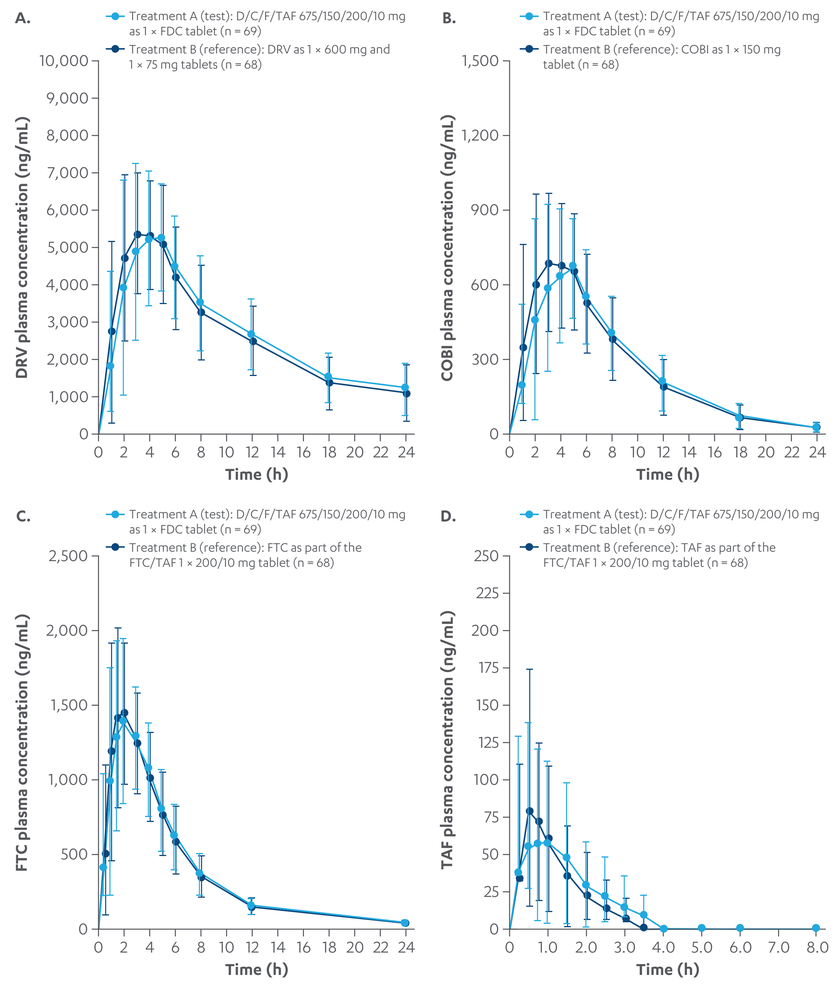
Table 3. Statistical analysis summary of DRV, COBI, FTC, and TAF after oral administration of a paediatric formulation of D/C/F/TAF 675/150/200/10 mg FDC versus coadministration of the separate commercial agents (PK data analysis)

Parameter*	D/C/F/TAF (test) n	DRV + COBI + FTC/TAF (reference) n	GMR (%)	90% CI (%)	Intraindividual CV (%) of test	Intraindividual CV (%) of reference
DRV						
C_{max}, ng/mL	32	32	98.06	94.10-102.18	13.2	10.3
AUC_{last}, ng·h/mL	32	32	102.74	98.11-107.60	9.5	9.6
AUC_{inf}, ng·h/mL	32	32	102.73	98.10-107.58	9.5	9.5
COBI						
C_{max}, ng/mL	32	32	93.67	89.63-97.90	14.5	14.2
AUC_{last}, ng·h/mL	32	32	97.45	93.18-101.91	10.7	11.0
AUC_{inf}, ng·h/mL	32	32	97.68	93.44-102.10	10.7	10.9
FTC						
C_{max}, ng/mL	32	32	98.64	93.66-103.89	17.6	17.6
AUC_{last}, ng·h/mL	32	32	100.60	98.83-102.40	5.8	6.3
AUC_{inf}, ng·h/mL	25	25	101.26	99.31-103.24	5.9	5.7
TAF						
C_{max}, ng/mL	32	32	105.23	90.86-121.87	49.3	56.9
AUC_{last}, ng·h/mL	32	32	113.41	106.82-120.41	14.8	23.1
AUC_{inf}, ng·h/mL	19	19	115.01	107.31-123.25	14.9	20.8

*Log-transformed PK parameters were analysed by mixed-model analysis of variance, with period, treatment, and treatment sequence as fixed effects and participant within-sequence as a random effect; the results were back-transformed using antilogarithm.

- The mean plasma concentration-time profiles for DRV, COBI, FTC, and TAF were similar following administration of the test treatment compared with the reference treatment (**Figure 1**)

Figure 1. Mean (SD) plasma concentration-time profiles of (A) DRV, (B) COBI, (C) FTC, and (D) TAF after oral administration of a paediatric formulation of D/C/F/TAF 675/150/200/10 mg FDC versus coadministration of the separate commercial agents (PK data analysis)



Safety

- Of the 37 participants who received treatment, 32 (86.5%) experienced ≥1 TEAE (**Table 4**)
- Overall, 20/36 (55.6%) participants experienced a TEAE after the test treatment and 26/36 (72.2%) after the reference treatment
- The most frequently reported TEAEs were nausea (40.5%), catheter site–related reaction (32.4%), headache (21.6%), decreased appetite (16.2%), fatigue (13.5%), abdominal discomfort (10.8%), and diarrhoea (10.8%)
- Eleven of 37 (29.7%) participants experienced TEAEs considered related to the study intervention (7 after the test treatment and 7 after the reference treatment)
- One participant experienced renal colic of grade 1 severity after administration of the reference treatment; the event was considered not related to the study intervention but led to study discontinuation
- No grade 3/4 TEAEs, serious AEs, or deaths were reported

Table 4. Summary of AEs (safety analysis set)

Parameter	D/C/F/TAF (test) n = 36	DRV + COBI + FTC/TAF (reference) n = 36	Overall N = 37
AE, n (%)*			
Any AE	20 (55.6)	26 (72.2)	32 (86.5)
Most common AEs (≥10% of participants)			
Nausea	8 (22.2)	13 (36.1)	15 (40.5)
Catheter site–related reaction	6 (16.7)	7 (19.4)	12 (32.4)
Headache	6 (16.7)	5 (13.9)	8 (21.6)
Decreased appetite	4 (11.1)	2 (5.6)	6 (16.2)
Fatigue	4 (11.1)	3 (8.3)	5 (13.5)
Abdominal discomfort	3 (8.3)	2 (5.6)	4 (10.8)
Diarrhoea	2 (5.6)	3 (8.3)	4 (10.8)

*Participants were counted only once for any given event, regardless of the number of times they actually experienced the event. Percentages were calculated with corresponding safety count in the respective treatment as the denominator.

Key Findings

- The C_{max}, AUC_{last}, and AUC_{inf} obtained for DRV, COBI, FTC, and TAF were similar after administration of D/C/F/TAF 675/150/200/10 mg as an FDC tablet (test) compared with coadministration of the separate commercial formulations (reference)
- The 90% CIs of the GMRs for C_{max} and AUCs for DRV, COBI, FTC, and TAF fell within predefined bioequivalence limits (80.00%-125.00%); therefore, both test and reference treatments were considered bioequivalent
- Both treatments were considered safe, and no new safety findings were identified

Conclusion

- Administration of D/C/F/TAF 675/150/200/10 mg as an FDC tablet to healthy adults under fed conditions was bioequivalent to coadministration of the separate commercial formulations

Abbreviations

AE, adverse event; ARV, antiretroviral; AUC_{inf}, area under the plasma concentration-time curve from time zero to infinity; AUC_{last}, area under the plasma concentration-time curve from time zero to the last measurable concentration; BMI, body mass index; CI, confidence interval; C_{max}, maximum plasma concentration; COBI, cobicistat; CV, coefficient of variation; $CV_{intraindividual}$, intraindividual coefficient of variation; D/C/F/TAF, darunavir/cobicistat/emtricitabine/tenofovir alafenamide; DRV, darunavir; FDC, fixed-dose combination; FTC, emtricitabine; GMR, geometric mean ratio; HIV-1, human immunodeficiency virus–1; PK, pharmacokinetic; SD, standard deviation; $t_{1/2}$, elimination half-life; TAF, tenofovir alafenamide; TEAE, treatment-emergent adverse event; t_{max}, time to maximum plasma concentration.

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