SYMTUZA® (darunavir, cobicistat, emtricitabine, and tenofovir alafenamide)
Pharmacokinetics of SYMTUZA

SUMMARY

- In a pharmacokinetic (PK) analysis in HIV-1-infected patients receiving SYMTUZA single-tablet regimen (STR) in the AMBER and EMERALD studies, population PK models described the darunavir (DRV) and tenofovir alafenamide (TAF) PK and associated variability. Efficacy and safety were found to be consistent across a range of DRV and TAF exposures.[1]
- A study conducted in healthy subjects which assessed the impact of food on the single-dose PK of the components of SYMTUZA found a food effect for DRV following administration of SYMTUZA, whereas differences in exposure to cobicistat (COBI), emtricitabine (FTC), and TAF in fasted versus fed conditions were not considered to be clinically relevant.[2]
- A study conducted in healthy subjects found that the SYMTUZA tablet was bioequivalent to the combined administration of the separate agents DRV 800 mg, FTC/TAF 200/10 mg fixed-dose combination (FDC), and COBI 150 mg.[2]
- In a study which compared the efficacy and safety of SYMTUZA with that of DRV + COBI + FTC/tenofovir disoproxil fumarate (TDF) in treatment-naïve HIV-1-infected patients, systemic exposure to tenofovir (TFV) was over 90% lower and intracellular concentrations of TFV diphosphate (active moiety of TFV) were 6.5-fold higher in the TAF group versus the TDF group.[3]

BACKGROUND

The selection of the TAF dose (10 or 25 mg) in an STR is dependent upon if the coadministered third agent (in the case of SYMTUZA, COBI-boosted DRV) has a clinically significant effect on TAF exposure. This ensures that patients have a TAF systemic exposure that is within the range of reference exposure achieved with TAF 25 mg.[4] PK enhancers, such as COBI, substantially increase TAF exposure by inhibiting p-glycoprotein-mediated efflux of TAF.[5–9] Hence, the TAF 10 mg dose is utilized with COBI-boosted STRs, and the TAF 25 mg dose utilized with unboosted regimens.[4]

CLINICAL DATA

Phase 3 Study

Ackaert et al (2021)[1] characterized the PK of TAF and COBI-boosted DRV in the AMBER and EMERALD studies using a population PK modelling approach, and explored a relationship between exposure to DRV or TAF and efficacy and safety endpoints of interest.

Study Design/Methods

- Blood samples were collected at different times post-dose at weeks 2, 4, 8, 12, 24, and 48 from patients receiving SYMTUZA in AMBER and EMERALD to quantify plasma concentrations of DRV and COBI (AMBER, EMERALD) and TAF (AMBER only).
- For DRV, the existing population PK model based on historical data from healthy volunteers and HIV-infected patients was updated with data from AMBER and EMERALD.
- For TAF, the population PK model was developed using richly sampled phase 1/2 data and updated with sparsely sampled data from AMBER.

Results

Baseline Demographics

- For participants with PK data receiving SYMTUZA in the AMBER study, the median age was 35.6 years (range, 19-61 years) and 12% of participants were female. The median

(range) weight, creatinine clearance (CrCL), and alpha 1-acid glycoprotein (AAG) were 74.5 kg (48-140), 119 mL/min (74.5-257), and 80.4 mg/dL (47-169), respectively.
- For participants with PK data receiving SYMTUZA in the EMERALD study, the median age was 46 years (range 19-75 years) and 18% of participants were female. The median (range) weight, CrCL, and AAG were 77.8 kg (40.5-204), 104 mL/min (47.4-314), and 81 mg/dL (39.7-201), respectively.

Population PK Model for DRV

- For DRV, the population PK model consisted of a 2-compartment disposition model with sequential zero-order input into the depot compartment followed by first-order absorption.
- Estimated apparent oral clearance for DRV was 44.07 L/h and the apparent central volume of distribution was 88.2 L.
- Effects of total daily dose (TDD), AAG, and body weight (WT) were included in the model as they were shown to have a significant impact on DRV apparent clearance (CL/F):
  - $CL/F = 44.07*(1/(1 + 0.0304*AAG))*(TDD/1200)^{0.388}*(WT/70)^{0.307}$
  - This translates in a model-predicted decrease of 13% and 22.4% in mean area under the plasma concentration-time curve over the 24-hour dosing interval (AUC_{24h}) and trough (predose) plasma concentration (C_{0h}), respectively, between the 1st (67.8 kg) and 4th (87.5 kg) WT quartiles, which was not considered clinically relevant.
- DRV PK did not significantly vary by age, gender, or race.
- A summary of estimated individual DRV exposure metrics in HIV-1-infected patients using SYMTUZA is noted in Table: Across-Study Comparison of PK Parameter Estimates for DRV and TAF in HIV-1-Infected Patients

Population PK Model for TAF

- TAF PK were best described by a one-compartment disposition model with absorption described by a dual input (slow and fast pathway).
  - Absorption via the slow pathway was described by a first-order absorption rate constant.
  - Absorption via the fast pathway was described by a series of transit compartments following an absorption lag time.
- Because of the large variability in absorption between and within patients, a mixture model on the lag-time for the fast pathway was included.
- Estimated apparent oral clearance for TAF was 89.0 L/h and the apparent central volume of distribution was 36.3 L.
- Covariate effects of lean body mass (LBW) and AAG were included in the model as they were shown to have a significant impact on TAF CL/F:
  - $CL/F = 89.0*(LBW/55)^{0.70}*(AAG/68)^{-0.63}$
  - This translates in a model-predicted decrease of 29% in the mean AUC_{24h} between the 1st (47.6 kg) and 4th (62.7 kg) quartiles of LBW, and a decrease of 38% in the mean AUC_{24h} between the 4th (90 mg/dL) and 1st (60 mg/dL) quartiles of AAG.
  - Reductions in AUC_{24h} were not considered clinically relevant given the wide therapeutic window for TAF at the recommended dose.
- TAF PK did not significantly vary by age, gender, or race.
- A summary of estimated individual TAF exposure metrics in HIV-1-infected patients using SYMTUZA is noted in Table: Across-Study Comparison of PK Parameter Estimates for DRV and TAF in HIV-1-Infected Patients

Across-Study Comparison of PK Parameter Estimates for DRV and TAF in HIV-1-Infected Patients[1]

Parameter	DRV			TAF	
	SYMTUZA QD (ART-naïve)	SYMTUZA QD (ART-experienced)	DRV/COBI Single Agents 800/150 mg QD (ART-naïve and experienced[a])[b]	SYMTUZA QD (ART-naïve)	SYMTUZA QD (ART-naïve)
	Week 48 AMBER	Week 48 EMERALD	Week 24 GS-US-216-0130	Week 48 AMBER	Week 48 GS-US-299-0102
N	355	750	298	335	52
C_{0h}, ng/mL, Mean (SD), Median (range)	1899 (759) 1783 (418-5895)	1813 (859) 1679 (231-6757)	2150 (1320) 1980 (70-6530)	NA[c]	NA[c]
AUC_{24h} ng·h/mL Mean (SD), Median (range)	87,909 (20,232) 84,248 (40,697-188,760)	85,972 (22,413) 82,529 (41,920-209,490)	102,000 (33,100) 99,100 (31,700-218,000)	132 (41) 124 (71-400)	102 (51) 87 (38-296)

Abbreviations: ART, antiretroviral treatment; AUC_{24h}, area under the plasma concentration-time curve over the 24-hour dosing interval; C_{0h}, trough (predose) plasma concentration; COBI, cobicistat; DRV, darunavir; N, maximum number of patients with data; NA, not available; PK, pharmacokinetic; QD, once daily; SD, standard deviation; TAF, tenofovir alafenamide.
[a]3 patients with PK data were ART-experienced.
[b]Data from Kakuda et al (2014)[10] and Tashima et al (2014).[11]
[c]C_{0h} was not evaluated given the short half-life and 24-h dosing interval.

PK/Pharmacodynamic Relationships

- There were no apparent relationships (both graphically and via logistic regression; *P*>0.5) between the DRV or TAF PK and primary efficacy endpoints (virologic response in AMBER, protocol-defined virologic rebound in EMERALD).
- There were no apparent clinically relevant relationships between the DRV or TAF PK and the occurrence of adverse events (AE) of interest or treatment-emergent laboratory abnormalities.

Phase 1 Study – Impact of Food

Crauwels et al (2019)[2] assessed the impact of food on the single-dose PK of the components of SYMTUZA in healthy subjects (N=24).

Study Design/Methods

- Phase 1, single-dose, open-label, randomized, 2-period, single center, crossover study.
- In 2 treatment sessions, subjects received a single oral dose of SYMTUZA under fasted conditions or 30 minutes after a standard high-fat breakfast with a washout period of ≥7 days between each treatment session.
- PK profiles of the component drugs were determined up to 72 hours for DRV and COBI, 48 hours for FTC, and 12 hours for TAF.

Results

Patient Characteristics

- Twenty-four subjects completed the study; 12 males and 12 females; median (range) age 35 (18-54) years.

PK

- Effects of food on the bioavailability of the components of SYMTUZA are summarized in Table: DRV, COBI, FTC, and TAF PK Parameters and Statistical Analyses Following Administration of a Single Dose of SYMTUZA Under Fed (Standard High-Fat Breakfast) and Fasted Conditions.

DRV, COBI, FTC, and TAF PK Parameters and Statistical Analyses Following Administration of a Single Dose of SYMTUZA Under Fed (Standard High-Fat Breakfast) and Fasted Conditions[2]

PK parameter, mean (SD)[a]	DRV		COBI		FTC		TAF	
	Fasted (test) (n=23)[b]	Fed (high fat) (ref) (n=24)[b]	Fasted (test) (n=23)[c]	Fed (high fat) (ref) (n=24)	Fasted (test) (n=24)[d]	Fed (high fat) (ref) (n=24)[e]	Fasted (test) (n=24)[f]	Fed (high fat) (ref) (n=24)[d]
C_{max}, ng/mL	4089 (1846)	6629 (1543)	704 (368)	711 (164)	2247 (573)	1785 (486)	180 (90.6)	107 (65.2)
t_{max}, hours	3.00 (1.00-8.02)	5.00 (1.50-8.00)	3.00 (1.00-6.00)	5.00 (2.00-6.10)	1.00 (0.50-2.00)	2.00 (0.75-5.00)	0.50 (0.25-0.75)	0.88 (0.25-5.00)
AUC_{last}, ng·hour/mL	67,504 (35,642)	93,541 (39,730)	5771 (3206)	6168 (2260)	11,593 (2573)	11,499 (2055)	106 (44.7)	117 (51.5)
AUC_{inf}, ng·hour/mL	72,147 (36,009)	94,686 (40,882)	6136 (3064)	6258 (2268)	12,286 (2729)	10,029 (1079)[g]	109 (47.7)	125 (57.3)
$t_{1/2}$, hours	7.0 (2.3)	7.8 (3.5)	4.1 (0.9)	3.9 (0.6)	10.8 (1.2)	10.7 (1.2)[g]	0.3 (0.2)	0.5 (0.1)
Geometric mean ratio, % (90% CI)								
n[h]	23 vs 24		23 vs 24		24 vs 24		24 vs 24	
C_{max}	54.99 (46.73-64.71)		76.96 (55.70-106.33)		125.99 (112.85-140.65)		182.29 (140.50-236.50)	
AUC_{last}	65.65 (56.76-75.92)		70.90 (51.13-98.30)		100.12 (96.29-104.10)		89.54 (81.20-98.72)	
AUC_{inf}	70.25[i] (59.49-82.95)		84.39[j] (68.52-103.95)		-		80.38[k] (73.04-88.45)	

Abbreviations: AUC_{inf}, area under the plasma concentration-time curve from time of administration to infinity; AUC_{last}, area under the plasma concentration-time curve from time of administration up to the last time point with a measurable concentration post-dose; CI, confidence interval; C_{max}, maximum plasma concentration; COBI, cobicistat; DRV, darunavir; FTC, emtricitabine; ref, reference; PK, pharmacokinetic; SD, standard deviation; $t_{1/2}$, terminal half-life; TAF, tenofovir alafenamide; t_{max}, time to maximum plasma concentration; vs, versus.
[a]Except t_{max}=median (range).
[b]n=20.
[c]n=22.
[d]n=16.
[e]n=7.
[f]n=21 for AUC_{inf} and $t_{1/2}$.
[g]Accurate determination not possible for more than 50% of participants; interpret with caution.
[h]Test vs ref.
[i]n=20 for test and ref.
[j]n=22 for test.
[k]n=21 for test and n=16 for ref.

Safety

- AEs were observed in 9 (38%) and 10 (42%) subjects under fasted and fed conditions, respectively, following a single-dose administration of SYMTUZA.
- All AEs were grade 1 or 2.

- The most common AEs were headache (13% fasted versus 21% fed) and nausea (17% fasted versus 8% fed).
- Grade 2 AEs included irritable bowel syndrome (fasted), and nausea and headache (fed).
- One grade 3 laboratory abnormality (transient increase in LDL) was reported.

Phase 1 Study - Bioequivalence

In a separate study, **Crauwels et al (2019)**[2] assessed the bioequivalence of the SYMTUZA tablet compared to combined intake of the separate agents in healthy subjects (N=96).

Study Design/Methods

- Phase 1, open-label, randomized, 2-period, crossover study.
- In 2 treatment sessions, subjects received a single oral dose of the SYMTUZA tablet (test) or a single oral dose of DRV as one 800 mg tablet, FTC/TAF as one 200/10 mg FDC tablet, and COBI as one 150 mg tablet (as combined intake, reference), with a washout period of ≥7 days between each treatment session.
- Bioequivalence was assessed under fed conditions. Doses were administered within 5 minutes after standard regular breakfast.
- PK profiles of the component drugs were determined over 72 hours for DRV, COBI, and FTC, and over 8 hours for TAF.

Results

Patient Characteristics

- Ninety-six subjects completed the study; 52 males and 44 females; median (range) age 26.0 (18-55) years.
- PK data for DRV, COBI, and FTC (test treatment only) were excluded from the PK analysis of one subject who vomited on Day 1 of both treatment sessions (within 2 times the median maximum plasma concentration [t_{max}] for DRV, COBI, and FTC in one or both treatments).

PK

- Component drug PK parameters and statistical analysis are summarized in Table: PK Parameters and Statistical Analysis of DRV, COBI, FTC, and TAF Following Administration of a Single Oral Dose of SYMTUZA or a Single Oral Dose of the Separate Agents Under Fed Conditions (Standard Regular Breakfast).

PK Parameters and Statistical Analysis of DRV, COBI, FTC, and TAF Following Administration of a Single Oral Dose of SYMTUZA or a Single Oral Dose of the Separate Agents Under Fed Conditions (Standard Regular Breakfast)[2]

Parameter, mean (SD)[a]	SYMTUZA (test) N=94	Separate agents (reference) N=96	GMR (90.14% CI),[b] %
DRV			
C_{max}, ng/mL	7042 (1481)[c]	6620 (1429)[c]	106.73 (103.50-110.06)[c]
t_{max}, hours	4.00 (1.50-8.00)[c]	4.00 (2.00-12.00)[c]	-
AUC_{last}, ng·hour/mL	87200 (27385)[c]	84406 (29481)[c]	104.84 (100.87-108.97)[c]
AUC_{inf}, ng·hour/mL	87280 (28097)[d]	85210 (29581)[d]	103.74 (99.62-108.02)[d]
$t_{1/2}$, hours	5.9 (2.1)[d]	6.2 (2.7)[d]	-
COBI			
C_{max}, ng/mL	894 (254)[c]	881 (207)[c]	100.69 (96.80-104.73)[c]

Parameter, mean (SD)[a]	SYMTUZA (test) N=94	Separate agents (reference) N=96	GMR (90.14% CI),[b] %
t_{max}, hours	4.00 (1.50-6.00)[c]	4.00 (1.50-5.05)[c]	-
AUC_{last}, ng·hour/mL	6681 (2486)[c]	6763 (2436)[c]	98.77 (95.14-102.52)[c]
AUC_{inf}, ng·hour/mL	6785 (2518)[c]	6868 (2459)[c]	98.76 (95.15-102.52)[c]
$t_{1/2}$, hours	3.7 (0.7)[c]	3.7 (0.7)[c]	-
FTC			
C_{max}, ng/mL	2041 (481)[e]	2053 (469)[e]	99.32 (95.61-103.17)[e]
t_{max}, hours	2.00 (0.60-5.00)[e]	2.00 (0.50-5.00)[e]	-
AUC_{last}, ng·hour/mL	11722 (1959)[e]	11746 (1868)[e]	100.04 (98.46-101.66)[e]
AUC_{inf}, ng·hour/mL	11882 (2002)[f]	11927 (1935)[f]	100.13 (98.36-101.93)[f]
$t_{1/2}$, hours	16.5 (3.3)[f]	17.0 (3.4)[f]	-
TAF			
C_{max}, ng/mL	110 (54.1)	120 (74.0)	96.87 (88.95-105.50)
t_{max}, hours	1.50 (0.25-3.50)	1.01 (0.25-4.00)	-
AUC_{last}, ng·hour/mL	123 (42.0)	132 (58.1)	96.59 (91.72-101.73)
AUC_{inf}, ng·hour/mL	127 (39.4)[g]	141 (59.7)[g]	95.42 (90.62-100.48)[g]
$t_{1/2}$, hours	0.3 (0.1)[g]	0.3 (0.1)[g]	-

Abbreviations: AUC_{inf}, area under the plasma concentration-time curve from time of administration to infinity; AUC_{last}, area under the plasma concentration-time curve from time of administration up to the last time point with a measurable concentration post-dose; CI, confidence interval; C_{max}, maximum plasma concentration; COBI, cobicistat; DRV, darunavir; FTC, emtricitabine; GMR, geometric mean ratio; PK, pharmacokinetic; SD, standard deviation; $t_{1/2}$, terminal half-life; TAF, tenofovir alafenamide; t_{max}, time to maximum plasma concentration.
[a]Except t_{max}=median (range).
[b]As a result of a blinded (for treatment) sample size reestimation, to control the nominal type I error rate, an adjusted 90.14% CI was calculated as opposed to the traditional 90% CI. No additional participants were recruited beyond the originally planned number.
[c]n=93 test, n=95 reference.
[d]n=87 test, n=91 reference.
[e]n=93 test, n=96 reference.
[f]n=85 test, n=87 reference.
[g]n=79 test, n=78 reference.

Safety

- All AEs were grade 1.
- AEs were observed in 52/94 (55%) and 46/96 (48%) subjects following single-dose administration of SYMTUZA or the separate agents, respectively.
- The most common AEs were headache (14/94 [15%] with SYMTUZA versus 15/96 [16%] with separate agents) and nausea (17/94 [18%] versus 14/96 [15%], respectively).
- A total of 28 subjects (30%) experienced ≥1 AE that was considered possibly related to SYMTUZA by the investigator, most commonly nausea, headache, vomiting, abdominal pain, dizziness, somnolence, and diarrhea.
- Laboratory abnormalities were mostly grade 1 and not reported as AEs.
    - One patient had a transient grade 3 increase in lipase plus grade 2 increases in total amylase and pancreatic amylase following treatment with the separate agents on day 4, but values were within normal limits at all other time points.

Phase 2 Study

Mills et al (2015)[3] compared the efficacy and safety of the SYMTUZA STR to that of DRV + COBI (administered as single agents) + FTC/TDF in HIV-1 infected, treatment-naïve patients (N=153).

Study Design/Methods

- Phase 2, multicenter, randomized, double-blind, 48-week study.
- Patients were required to have an estimated glomerular filtration rate by Cockroft-Gault formula ($eGFR_{CG}$) ≥70 mL/min.
- Patients were stratified by baseline viral load (VL; ≤100,000 and >100,000) and race (black and non-black) and randomized 2:1 to receive an STR containing DRV 800 mg, COBI 150 mg, FTC 200 mg, and TAF 10 mg (TAF group), or a regimen consisting of DRV 400 mg x 2 + COBI 150 mg + FTC/TDF 200/300 mg tablets (TDF group).
- Each group also received matching placebos.
- Primary endpoint: VL <50 copies/mL at week 24 (FDA snapshot).
- Secondary endpoint: VL <50 copies/mL at week 48.

Results

Patient Characteristics

- Baseline characteristics were similar between groups.
- Patients were primarily male (92.8%), with a median age of 33 years, median baseline VL 4.7 log_{10} copies/mL, median CD4+ count 384 cells/mm^3, and median $eGFR_{CG}$ of 114.6 mL/min.
- VL was >100,000 in 19.6% of patients, and CD4+ count was <200 cells/mm^3 in 13.7%.
- Approximately 35% of patients were black, 65% non-black (60% white, 5% other).

PK

- An intensive PK analysis was conducted in a subset of 32 patients.
- Plasma exposures of DRV, COBI, and FTC are noted in Table: PK Parameters of DRV, COBI, and FTC.
- Systemic exposure to tenofovir was over 90% lower in the TAF group versus the TDF group (see Table: Plasma Tenofovir PK Parameters).
- Intracellular concentrations of tenofovir diphosphate (active moiety of tenofovir) were 6.5-fold higher in patients who received TAF than in patients who received TDF.

PK Parameters of DRV, COBI, and FTC[3]

Drug	AUC_{tau} (ng·hour/mL) Mean (%CV)	C_{max} (ng/mL) Mean (%CV)	C_{tau} (ng/mL) Mean (%CV)	T_{max} (hours) Median (Q1, Q3)	$T_{1/2}$ (hours) Median (Q1, Q3)
DRV	99301.8 (45.3)	8826.2 (33.3)	1651.0 (108.0)	3.00 (2.00, 4.00)	9.42 (6.31, 13.87)
COBI	8744.5 (43.9)	1128.7 (35.3)	30.5 (135.1)	3.03 (3.00, 4.00)	3.16 (2.77, 3.70)
FTC	11918.0 (35.9)	2056.4 (25.3)	93.1 (58.3)	1.52 (1.50, 2.00)	7.51 (6.40, 8.79)

Abbreviations: %CV, percent coefficient of variation; AUC_{tau}, area under the concentration versus time curve over the dosing interval; C_{max}, maximum plasma concentration; COBI, cobicistat; C_{tau}, minimum plasma concentration; DRV, darunavir; FTC, emtricitabine; PK, pharmacokinetic; Q, quartile; $T_{1/2}$, plasma half-life; T_{max}, time to maximum plasma concentration.

Plasma Tenofovir PK Parameters[3]

Parameter (Mean, %CV)[a]	TAF (n=21)	TDF (n=11)
AUC_{tau}, ng·hour/mL	339.0 (37.1)	3737.0 (26.8)
C_{max}, ng/mL	18.8 (37.6)	413.2 (28.3)
T_{max}, hours	2.0 (1.5, 3.1)	1.0 (1.0, 3.0)
C_{tau}, ng/mL	11.7 (39.3)	75.4 (30.9)
$t_{1/2}$, hours	43.8 (32.0, 59.2)	11.9 (11.4, 16.2)

Abbreviations: %CV, percent coefficient of variation; AUC_{tau}, area under the concentration versus time curve over the dosing interval; C_{max}, maximum plasma concentration; C_{tau}, minimum plasma concentration; PK, pharmacokinetic; Q, quartile; $t_{1/2}$, plasma half-life; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; T_{max}, time to maximum plasma concentration.
[a]Median (Q1, Q3) for T_{max} and $t_{1/2}$.

LITERATURE SEARCH

A literature search of MEDLINE®, EMBASE®, BIOSIS Previews®, and DERWENT® (and/or other resources, including internal/external databases) was conducted on 12 October 2023.

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