**SYMTUZA® (darunavir, cobicistat, emtricitabine, and tenofovir alafenamide)**
**Pharmacokinetics of SYMTUZA - Food Effect**

## SUMMARY

- A study conducted in healthy subjects which assessed the impact of food on the single-dose pharmacokinetics (PK) of the components of SYMTUZA found a food effect for darunavir (DRV), whereas differences in exposure to cobicistat (COBI), emtricitabine (FTC), and tenofovir alafenamide (TAF) in fasted versus fed conditions were not considered to be clinically relevant.[1]
- 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.[1]

## CLINICAL STUDIES

### Phase 1 Study-Impact of Food

**Crauwels et al (2019)**[1] 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.
  - The standard high-fat breakfast (928 kCal; 56 g fat) consisted of 2 eggs fried in butter, 2 strips of bacon, 2 slices of white bread with butter, 1 croissant with 1 slice of cheese, and 240 mL (8 oz) of whole milk (or its equivalent).
- 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 D/C/F/TAF 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**[1]

| 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) |

| 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] |
| $t_{max}$, 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*

- Adverse events (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)**[1] 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.
    - The standard regular breakfast (533 kCal; 21 g fat) consisted of 4 slices of bread, 2 slices of ham and/or cheese, butter, fruit preserve, and 2 cups (up to 480 mL) of decaffeinated coffee or tea with milk and/or sugar (or its equivalent).
- 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 $t_{max}$ 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)**[1]

| 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] |
| $t_{max}$, 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] | - |

| Parameter, mean (SD)[a] | SYMTUZA (test) N=94 | Separate agents (reference) N=96 | GMR (90.14% CI),[b] % |
|---|---|---|---|
| $AUC_{last}$, 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.

## 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.

## REFERENCES

1. Crauwels HM, Baugh B, Landuyt EV, et al. Bioequivalence of the once-daily single-tablet regimen of darunavir, cobicistat, emtricitabine, and tenofovir alafenamide compared to combined intake of the separate agents and the effect of food on bioavailability. *Clin Pharmacol Drug Dev*. 2019;8(4):480-491.