**SYMTUZA® (darunavir, cobicistat, emtricitabine, and tenofovir alafenamide)**
**Splitting/Crushing of SYMTUZA**

## SUMMARY

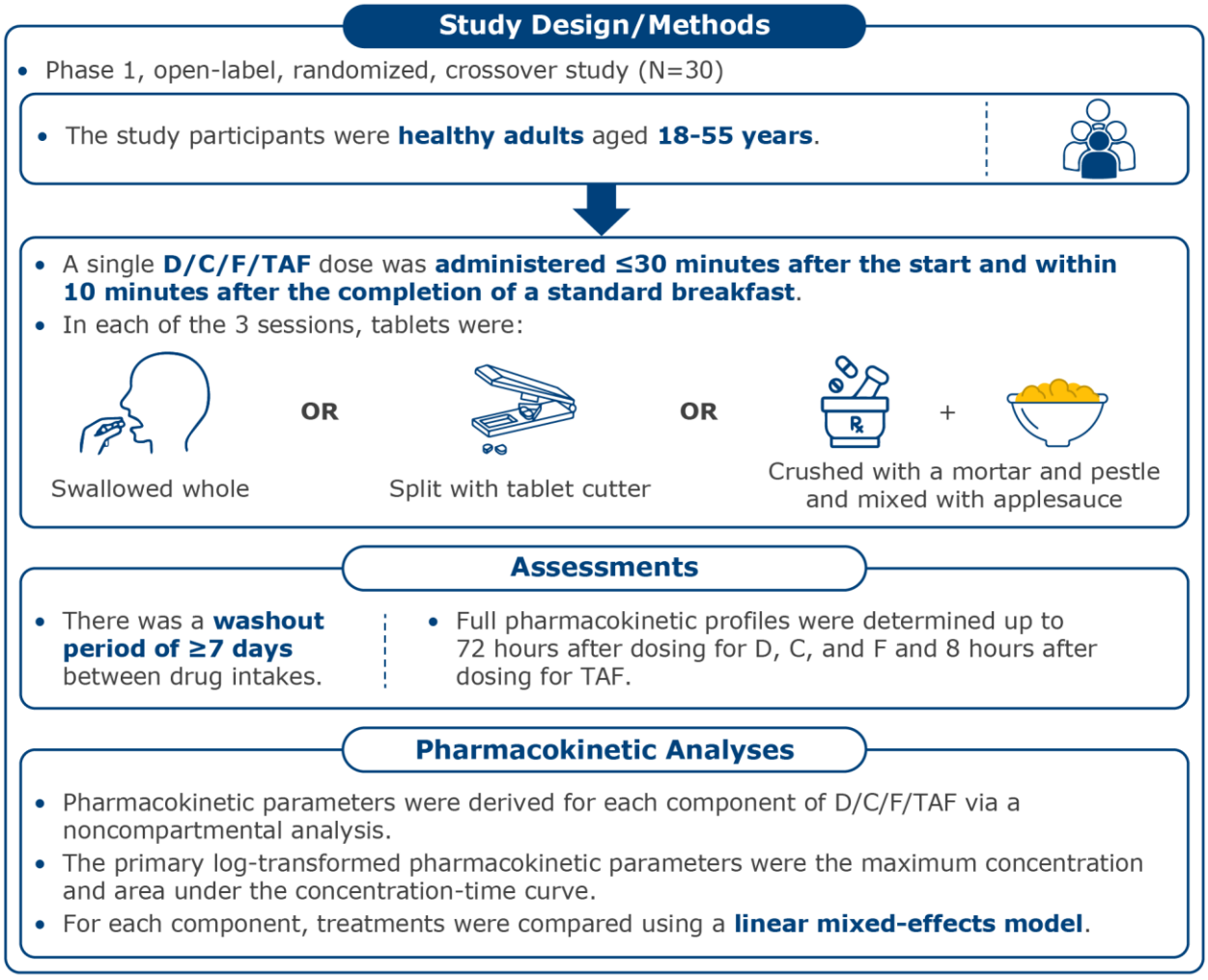

- For patients who are unable to swallow the whole tablet, SYMTUZA may be split into two pieces using a tablet-cutter.[1]
- The bioavailability of the components of SYMTUZA were not affected when administered orally as a split tablet compared to administration as a tablet swallowed whole.[1]
- When administered as a crushed tablet, there was no relevant impact on the bioavailability of darunavir, cobicistat, and emtricitabine, however, there was a decrease (~20%) in the bioavailability of tenofovir alafenamide. Crushing is not recommended.[1]


## CLINICAL STUDIES

### Phase 1 Study

**Brown et al (2019)**[1] assessed the relative bioavailability of SYMTUZA components after oral administration as a split or crushed tablet versus swallowed as a whole tablet. The study design and methods are depicted in the Figure: Phase 1 Study Design/Methods.

**Phase 1 Study Design/Methods**[1]




**Abbreviations:** C, cobicistat; D, darunavir; F, emtricitabine; TAF, tenofovir alafenamide.

### *Results*

- A total of 18 men (60%) and 12 women (40%) were enrolled in the study. At screening, the mean±standard deviation age was 36.7±11.0 years, and most participants were white (26 [87%]) and Hispanic or Latino (25 [83%]).
- There was no relevant impact on the bioavailability of SYMTUZA components when administered as a split versus whole tablet, as depicted in Table: Whole Tablet Versus Split Tablet.
- When administered as a crushed tablet, there was no relevant impact on the bioavailability of darunavir, cobicistat, and emtricitabine, however, there was a decrease (~20%) in the bioavailability of tenofovir alafenamide.

**Whole Tablet Versus Split Tablet**[1]

| | Darunavir | | Cobicistat | | Emtricitabine | | Tenofovir alafenamide | |
|---|---|---|---|---|---|---|---|---|
| | **Whole tablet** | **Split tablet** | **Whole tablet** | **Split tablet** | **Whole tablet** | **Split tablet** | **Whole tablet** | **Split tablet** |
| n[a] | 30 | 30 | 30 | 30 | 30[b] | 30[c] | 30 | 30[d] |
| **Parameter, mean (SD)** | | | | | | | | |
| $C_{max}$ (ng/mL) | 8437 (1674) | 8963 (2366) | 931 (231) | 985 (241) | 1915 (565) | 1892 (537) | 163 (71.6) | 155 (90.4) |
| $t_{max}$[e] (hours) | 4.0 (1.0-8.0) | 4.0 (1.5-6.0) | 4.0 (1.0-5.0) | 3.6 (1.5-6.0) | 2.0 (0.8-4.0) | 2.5 (0.8-5.0) | 1.3 (0.3-2.5) | 1.0 (0.3-2.5) |
| $AUC_{last}$ (ng·hour/mL) | 116,139 (38,309) | 123,917 (53,827) | 7785 (3433) | 8297 (4076) | 11,830 (2737) | 11,742 (2728) | 155 (43.2) | 153 (51.3) |
| $AUC_{\infty}$ (ng·hour/mL) | 116,422 (38,652) | 124,469 (54,875) | 7883 (3497) | 8391 (4144) | 11,975 (2,806) | 12,202 (2,809) | 156 (43.2) | 156 (52.1) |
| $t_{1/2term}$ (hours) | 5.5 (2.3) | 5.3 (2.0) | 3.8 (1.0) | 3.8 (1.0) | 16.7 (4.3) | 16.2 (3.4) | 0.4 (0.1) | 0.4 (0.2) |
| **LS means ratio (90% CI), %** | | | | | | | | |
| $C_{max}$ | 105 (100-110) | | 106 (101-110) | | 100 (93-109) | | 89 (75-107) | |
| $AUC_{last}$ | 103 (97-109) | | 105 (99-110) | | 99 (95-103) | | 97 (90-105) | |
| $AUC_{\infty}$ | 103 (98-109) | | 104 (99-110) | | 99 (94-104) | | 98 (90-106) | |

**Abbreviations:** $AUC_{\infty}$, area under the plasma concentration-time curve from time 0 extrapolated to infinity; $AUC_{last}$, area under the plasma concentration-time curve from time 0 to the last measurable concentration; CI, confidence interval; $C_{max}$, maximum concentration; LS, least squares; SD, standard deviation; $t_{1/2term}$, terminal elimination half-life; $t_{max}$, time to reach maximum plasma concentration.
[a]All exclusions were related to a coefficient of determination <0.90 for the pharmacokinetic parameter estimation.
[b]n=29 for $AUC_{\infty}$ and $t_{1/2term}$.
[c]n=26 for $AUC_{\infty}$ and $t_{1/2term}$.
[d]n=28 for $AUC_{\infty}$ and $t_{1/2term}$.
[e]$t_{max}$ is reported as median (range).

**Whole Tablet Versus Crushed Tablet**[1]

| | Darunavir | | Cobicistat | | Emtricitabine | | Tenofovir alafenamide | |
|---|---|---|---|---|---|---|---|---|
| | **Whole tablet** | **Crushed tablet** | **Whole tablet** | **Crushed tablet** | **Whole tablet** | **Crushed tablet** | **Whole tablet** | **Crushed tablet** |
| n[a] | 30 | 29 | 30 | 29 | 30[b] | 29[c] | 30 | 29 |
| **Parameter, mean (SD)** | | | | | | | | |
| $C_{max}$ (ng/mL) | 8437 (1674) | 9484 (1867) | 931 (231) | 937 (242) | 1915 (565) | 1599 (472) | 163 (71.6) | 121 (69.9) |
| $t_{max}$[d] (hours) | 4.0 (1.0-8.0) | 3.0 (1.5-5.0) | 4.0 (1.0-5.0) | 3.0 (2.0-6.0) | 2.0 (0.8-4.0) | 2.0 (1.0-4.0) | 1.3 (0.3-2.5) | 0.6 (0.3-2.0) |
| $AUC_{last}$ (ng·hour/mL) | 116,139 (38,309) | 130,532 (48,649) | 7785 (3433) | 8062 (3786) | 11,830 (2737) | 11,013 (2690) | 155 (43.2) | 126 (37.5) |
| $AUC_{\infty}$ (ng·hour/mL) | 116,422 (38,652) | 130,940 (49,458) | 7883 (3497) | 8180 (3898) | 11,975 (2,806) | 10,956 (2682) | 156 (43.2) | 128 (37.4) |
| $t_{1/2term}$ (hours) | 5.5 (2.3) | 5.0 (1.7) | 3.8 (1.0) | 3.8 (1.3) | 16.7 (4.3) | 16.0 (3.7) | 0.4 (0.1) | 0.5 (0.2) |
| **LS means ratio (90% CI), %** | | | | | | | | |
| $C_{max}$ | 113 (108-119) | | 100 (96-104) | | 83 (77-90) | | 71 (59-86) | |
| $AUC_{last}$ | 111 (105-118) | | 101 (96-107) | | 92 (88-96) | | 81 (75-88) | |
| $AUC_{\infty}$ | 111 (105-118) | | 101 (96-107) | | 93 (88-97) | | 82 (75-88) | |

**Abbreviations:** $AUC_{\infty}$, area under the plasma concentration-time curve from time 0 extrapolated to infinity; $AUC_{last}$, area under the plasma concentration-time curve from time 0 to the last measurable concentration; CI, confidence interval; $C_{max}$, maximum concentration; LS, least squares; SD, standard deviation; $t_{1/2term}$, terminal elimination half-life; $t_{max}$, time to reach maximum plasma concentration.
[a]All exclusions were related to a coefficient of determination <0.90 for the pharmacokinetic parameter estimation.
[b]n=29 for $AUC_{\infty}$ and $t_{1/2term}$.
[c]n=27 for $AUC_{\infty}$ and $t_{1/2term}$.
[d]$t_{max}$ is reported as median (range).

- All adverse events were grade 1 or 2, aside from one adverse event which was grade 4 (increased lipase, which was considered possibly related to drug).
- The most frequent adverse events across all treatments were nausea (40%), headache (30%), and vomiting (17%).
- The incidence of adverse events was generally comparable between treatments.

**Safety**[1]

| Parameter, n (%) | Whole tablet (n=30) | Split tablet (n=30) | Crushed tablet (n=29) | All treatments (n=30) |
|---|---|---|---|---|
| ≥1 AE | 14 (47) | 15 (50) | 10 (34) | 22 (73) |
| ≥1 grade 3 or 4 AE | 1 (3)[a] | 0 | 0 | 1 (3)[a] |
| ≥1 serious AE | 0 | 0 | 0 | 0 |
| Death | 0 | 0 | 0 | 0 |
| ≥1 AE for which study drug was permanently stopped | 1 (3)[a] | 0 | 0 | 1 (3)[a] |
| ≥1 AE possibly related to any study drug | 12 (40) | 15 (50) | 9 (31) | 22 (73) |

| Parameter, n (%) | Whole tablet (n=30) | Split tablet (n=30) | Crushed tablet (n=29) | All treatments (n=30) |
|---|---|---|---|---|
| Most common AEs[b] | | | | |
| Nausea | 4 (13) | 6 (20) | 5 (17) | 12 (40) |
| Headache | 5 (17) | 3 (10) | 2 (7) | 9 (30) |
| Vomiting | 3 (10) | 2 (7) | 0 | 5 (17) |

**Abbreviation:** AE, adverse event.
[a]One participant prematurely discontinued study drug because of an AE (increased lipase), which was grade 4 in severity and considered to be possibly related to the study drug. It was deemed nonserious by the investigator.
[b]By preferred term and occurring in ≥15% of participants (all-treatments population).

## LITERATURE SEARCH

A literature search of MEDLINE®, EMBASE®, BIOSIS Previews®, and DERWENT® (and/or other resources, including internal/external databases) was conducted on 18 April 2023.

## REFERENCES

1. Brown K, Thomas D, McKenney K, et al. Impact of splitting or crushing on the relative bioavailability of the darunavir/cobicistat/emtricitabine/tenofovir alafenamide single-tablet regimen. *Clin Pharmacol Drug Dev*. 2019;8(4):541-548.