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

SUMMARY

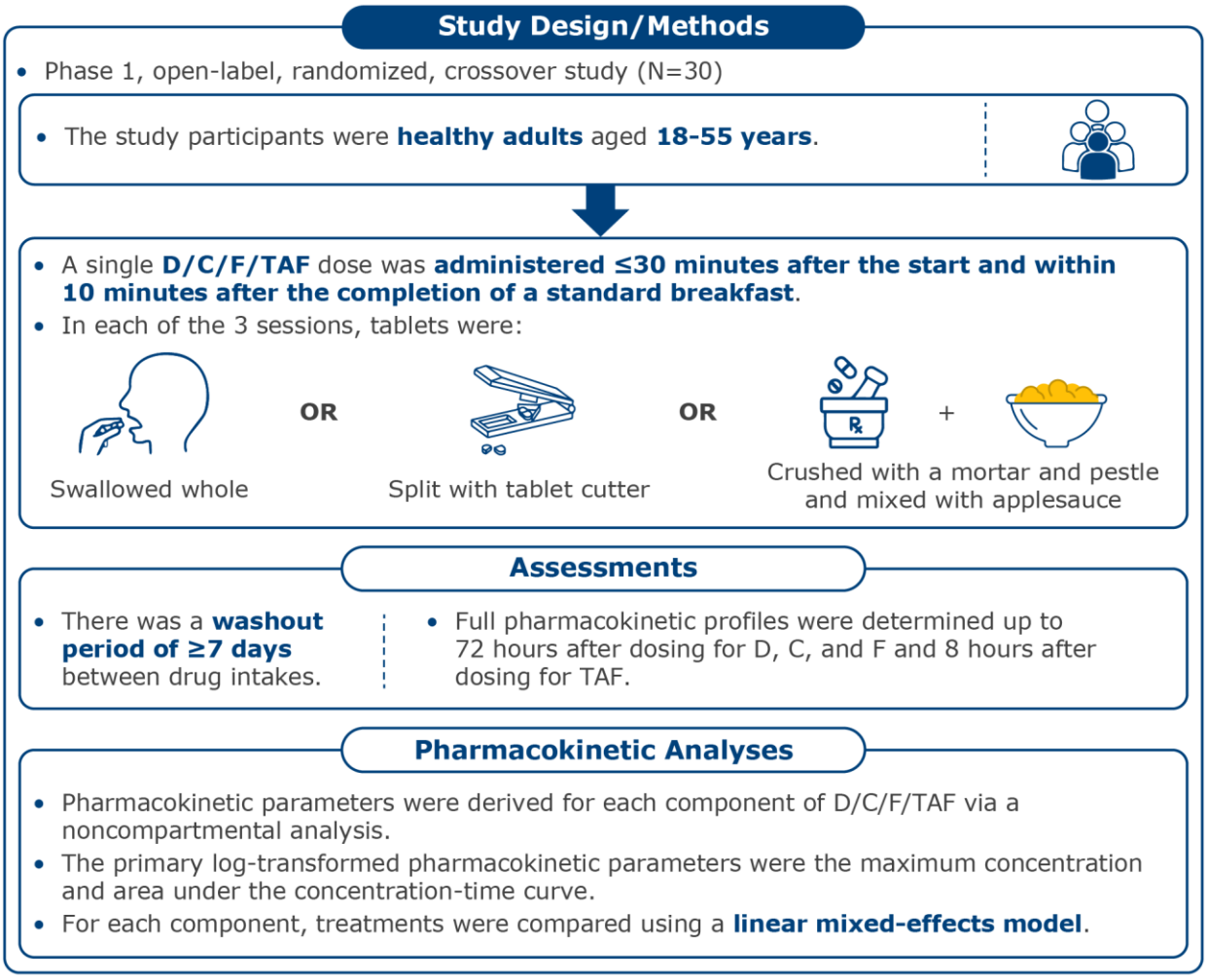
- For patients who are unable to swallow the whole tablet, SYMTUZA may be split into two pieces using a tablet-cutter.[1]
- The bioavailability of the components of SYMTUZA were not affected when administered orally as a split tablet compared to administration as a tablet swallowed whole.[1]
- When administered 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.[2]
- An additional citation identified during a literature search have been included in the REFERENCES section for your review.[3]

CLINICAL STUDIES

Phase 1 Study

Brown et al (2019)[2] 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[2]



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[2]

	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_{∞} (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, n% (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_{∞}	103 (98-109)		104 (99-110)		99 (94-104)		98 (90-106)	

Abbreviations: AUC_{∞}, 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_{∞} and $t_{1/2term}$.
[c]n=26 for AUC_{∞} and $t_{1/2term}$.
[d]n=28 for AUC_{∞} and $t_{1/2term}$.
[e]t_{max} is reported as median (range).

Whole Tablet Versus Crushed Tablet[2]

	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_{∞} (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, n% (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_{∞}	111 (105-118)		101 (96-107)		93 (88-97)		82 (75-88)	

Abbreviations: AUC_{∞}, 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_{∞} and $t_{1/2term}$.
[c]n=27 for AUC_{∞} 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[2]

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 Drug File (and/or other resources, including internal/external databases) pertaining to this topic was conducted on 09 April 2025.

REFERENCES

1. SYMTUZA (darunavir, cobicistat, emtricitabine, and tenofovir alafenamide) [Prescribing Information]. Titusville, NJ: Janssen Pharmaceuticals, Inc; https://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/SYMTUZA-pi.pdf.

2. 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.

3. Van Hemelryck S, Van Landuyt E, Hufkens V, et al. Assessment of swallowability and acceptability of scored darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) fixed-dose combination (FDC) tablets in HIV-1–infected children aged ≥6 to <12 years, using matching placebo tablets: a randomized study. *Antivir Ther*. 2024;29(2):13596535241248282.