SYMTUZA® (darunavir, cobicistat, emtricitabine, and tenofovir alafenamide)
SYMTUZA - DEFINE Study

SUMMARY

- The DEFINE study is a multicenter, randomized, open-label, parallel assignment phase 4 study to evaluate the effect of switching to SYMTUZA in virologically suppressed adults with HIV-1 who have experienced ≥10% increase in body weight within a 36-month period on an integrase strand transfer inhibitor (INSTI) + tenofovir alafenamide/emtricitabine (TAF/FTC; NCT04442737).[1,2]
    - Participants were randomized to switch immediately to SYMTUZA once daily for 48 weeks or to remain on their current regimen for 24 weeks, after which they will switch to SYMTUZA for an additional 24 weeks.
    - The primary endpoint was the percent change in body weight from baseline at week 24.
- At week 24, in the intention to treat (ITT) population, there was no significant difference in percent change in body weight from baseline between participants in the SYMTUZA arm (0.63 [-0.44, 1.70]) and control arm (-0.24 [-1.35, 0.87]).[2]
- At week 24, percent change in body weight from baseline was consistent among various subgroups (BMI≥30 kg/m^2, gender, and race) in both study arms.[2]
- A post-hoc analysis evaluated changes in body weight by antiretroviral (ARV) treatment baseline characteristics, including the length of INSTI exposure, how quickly the initial weight was gained after an INSTI was started, and how recently the weight gain took place prior to enrollment in the study.[3]
    - The likelihood of gaining ≥3% body weight was 31% in patients on INSTIs <24 months vs 10% in patients on INSTIs for ≥24 months.
- The most frequently reported adverse events (AEs) in the SYMTUZA arm were COVID-19 (11%), diarrhea (6%), nausea (6%), and hypertension (2%).[2]
- For additional information on this study, please visit clinicaltrials.gov.

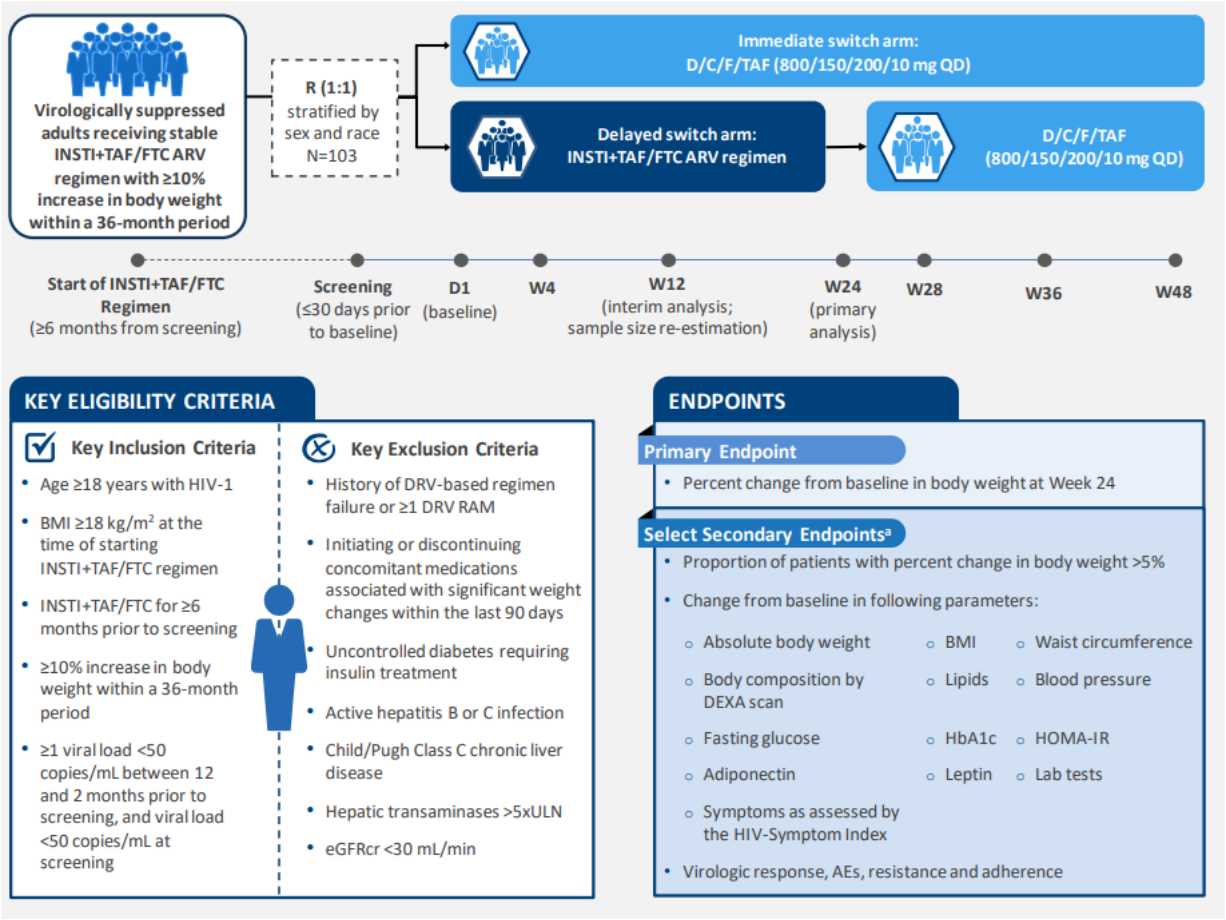
CLINICAL DATA

DEFINE STUDY

The DEFINE study is a multicenter, randomized, open-label, parallel assignment phase 4 study conducted in virologically suppressed adults with HIV-1 who have experienced ≥10% increase in body weight within a 36-month period on an INSTI + TAF/FTC to determine if a switch to SYMTUZA results in a change in body weight (N=103).[1,2]

Study Design/Methods

SYMTUZA - DEFINE Study[1,2]



Abbreviations: AEs, adverse events; ARV, antiretroviral; BMI, body mass index; D/C/F/TAF, darunavir/cobicistat/emtricitabine/tenofovir alafenamide; DEXA, dual-energy X-ray absorptiometry; D, day; DRV, darunavir; eGFRcr, creatinine-based estimated glomerular filtration rate; HbA1c, hemoglobin A1C; HIV-1, human immunodeficiency virus type 1; HOMA-IR, homeostatic model assessment of insulin resistance; INSTI, integrase strand transfer inhibitor; TAF/FTC, tenofovir alafenamide/emtricitabine; QD, once daily; R, randomized; RAM, resistance-associated mutation, ULN, upper limit of normal; w, week.
[a]All endpoints are assessed at weeks 24 and 48.

Results

Baseline Characteristics

- A total of 103 participants (n=53 SYMTUZA; n=50 INSTI + TAF/FTC) were randomized and included in the ITT population. Of these participants, 30% were female and 61% were black.[2]
- Greater than 90% of participants were still in the study at 24 weeks.[2]

Baseline Demographics and Characteristics (ITT Set)[2,3]

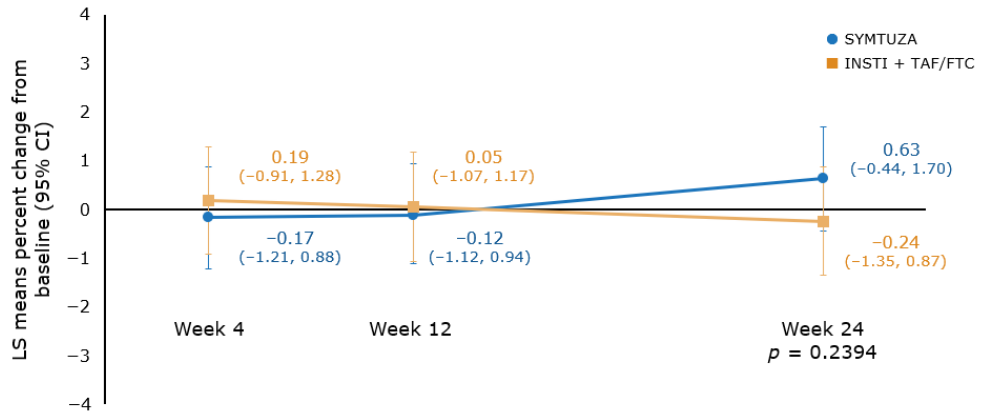
	SYMTUZA (n=53)	INSTI +TAF/FTC (n=50)	Total (N=103)
Age, years, median (range)	42.0 (22, 73)	49.0 (22, 69)	45.0 (22, 73)
BMI, kg/m^2, median (range)	31.4 (22, 61)	34.7 (22, 58)	32.7 (22, 61)
Body weight, kg, median (range)	94.5 (69, 188)	102.9 (70, 188)	100.2 (69, 188)
Hispanic or Latino ethnicity, n (%)	6 (11)	10 (20)	16 (16)
Percent weight gained on current regimen at baseline, median (range)*	12.8 (−4, 56)	15.7 (−15, 86)	14.2 (−15, 86)
Type of INSTI regimen at baseline, n (%)†			
EVG/c/TAF/FTC	5 (9)	7 (14)	12 (12)
DTG + TAF/FTC	4 (8)	4 (8)	8 (8)
BIC/TAF/FTC	44 (83)	39 (78)	83 (81)
Baseline CD4+, cells/mm^3, median (range)	696.0 (205, 1543)	622.5 (153, 2059)	680.0 (153, 2059)
Length of current INSTI exposure, n (%)			
<24 months	20 (38)	17 (34)	37 (36)
≥24 months	33 (62)	33 (66)	66 (64)
Time from starting current INSTI to initial weight gain, n (%)			
n	51**	50	101
≤12 months	19 (37)	26 (52)	45 (45)
>12 months	32 (63)	24 (48)	56 (55)
Time from initial weight gain to randomization, n (%)			
n	51**	50	101
≤12 months	31 (61)	26 (52)	57 (56)
>12 months	20 (39)	24 (48)	44 (44)

Abbreviations: BIC/TAF/FTC, bictegravir/tenofovir alafenamide/emtricitabine; BMI, body mass index; DTG, dolutegravir; EVG/c/TAF/FTC, elvitegravir/cobicistat/tenofovir alafenamide/emtricitabine; INSTI, integrase strand transfer inhibitor; ITT, intention-to-treat; TAF/FTC, tenofovir alafenamide/emtricitabine
*One participant in the SYMTUZA arm did not have available data. †Percentages may not sum to 100% due to rounding. **Two participants with breaks in their current INSTI regimen prior to randomization were excluded.

Weight and Body Composition

- At week 24, there was no significant difference in percent change in body weight from baseline between participants in the SYMTUZA arm (0.63 [-0.44, 1.70]) and control arm (TAF/FTC) (-0.24 [-1.35, 0.87]).[2]

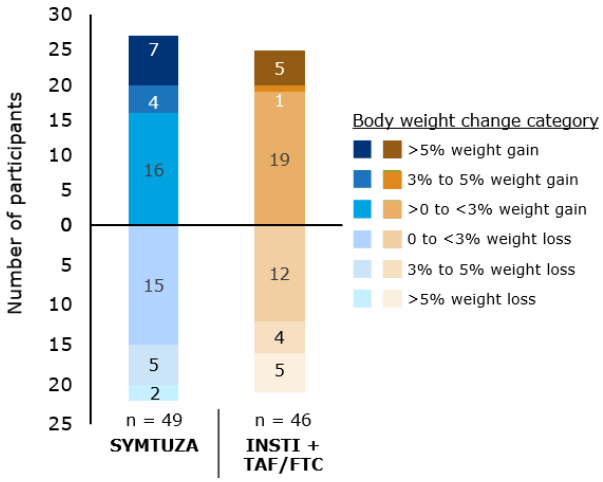
Percent Change from Baseline Body Weight Over Time (primary endpoint, ITT set)*[2]



*LS means percent changes in body weight were calculated in the ITT set of randomized participants who had received ≥1 dose of the study drug using a MMRM, in which visits were repeated measures. Participants in the ITT set with baseline records and ≥1 postbaseline record were included. **Abbreviations**: CI, confidence interval; INSTI, integrase strand transfer inhibitor; ITT, intention-to-treat; LS, least squares; MMRM, mixed model for repeated measures; TAF/FTC, tenofovir alafenamide/emtricitabine.

- At week 24, of the 49 participants in the SYMTUZA arm, 31 had body weight changes of ≤±3% (See Figure: Body Weight Category Changes at Week 24 (ITT set)).[2]
- Additionally, most participants remained within baseline BMI and waist circumference categories.[2]

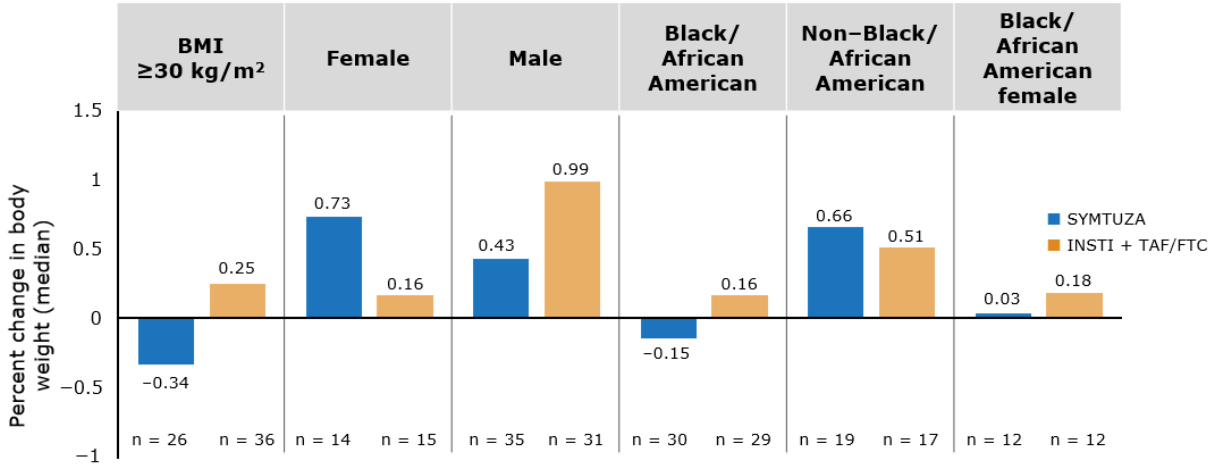
Body Weight Category Changes at Week 24 (ITT set)[2]



Abbreviations: BMI, body mass index/; INSTI, integrase strand transfer inhibitor; ITT, intention-to-treat; TAF/FTC, tenofovir alafenamide/emtricitabine.

- At week 24, percent change in body weight from baseline was consistent among various subgroups (BMI ≥30 kg/m^2, gender, and race).[2]

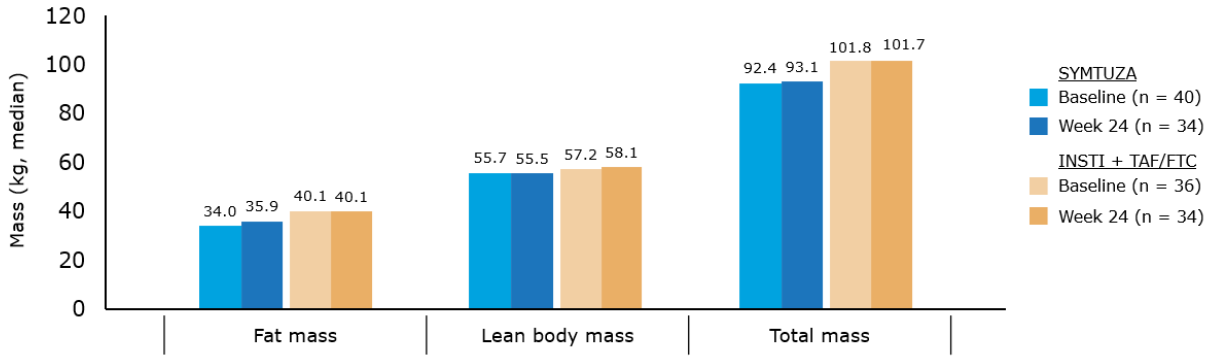
Percent Change from Baseline in Body Weight at Week 24 (ITT set)[2]



BMI, body mass index; INSTI, integrase strand transfer inhibitor; ITT, intention-to-treat; TAF/FTC, tenofovir alafenamide/emtricitabine.

- A post-hoc analysis evaluated changes in body weight by antiretroviral (ARV) treatment baseline characteristics, including the length of INSTI exposure, how quickly the initial weight was gained after an INSTI was started, and how recently the weight gain took place prior to enrollment in the study.[3]
  - Patients on INSTIs for <24 months experienced 1.5% weight gain in both the SYMTUZA (n=20) and control (n=15) arms, while patients on INSTIs for ≥24 months experienced weight loss (SYMTUZA -0.27% [n=29]; control -0.23% [n=31]).
    - Regardless of treatment arm, the likelihood of gaining ≥3% body weight was 31% in patients on INSTIs <24 months vs 10% in patients on INSTIs for ≥24 months.
  - Patients who gained weight within 12 months of INSTI initiation continued to gain weight during the study (SYMTUZA 1.57% [n=18], control 1.0% [n=22]), while patients whose initial weight gain took longer either maintained their weight (SYMTUZA 0.12% [n=29]) or experienced weight loss (control -1.36% [n=24]) by week 24.
  - Minimal differences in weight change from baseline were seen in patients who were enrolled in the study <12 months after their initial weight gain and those who were enrolled later.
  - At week 24, regardless of treatment arm, the baseline factors more commonly seen in patients who lost ≥3% body weight included:
    - Higher baseline CD4+ cell count, lower baseline body weight, longer exposure to INSTIs and TAF (assessed independently of each other), lower levels of education, lower percentage body weight gain at baseline, and slower baseline weight gain after starting an INSTI.
- Body composition by dual x-ray absorptiometry (DEXA) was stable from baseline to week 24 across both study arms (See Figure: Body Composition by DEXA at Baseline and Week 24 (ITT set)).[2]
  - DEXA measurements of appendicular and visceral fat indicated minimal changes in both study arms.

Body Composition by DEXA at Baseline and Week 24 (ITT set)[2]

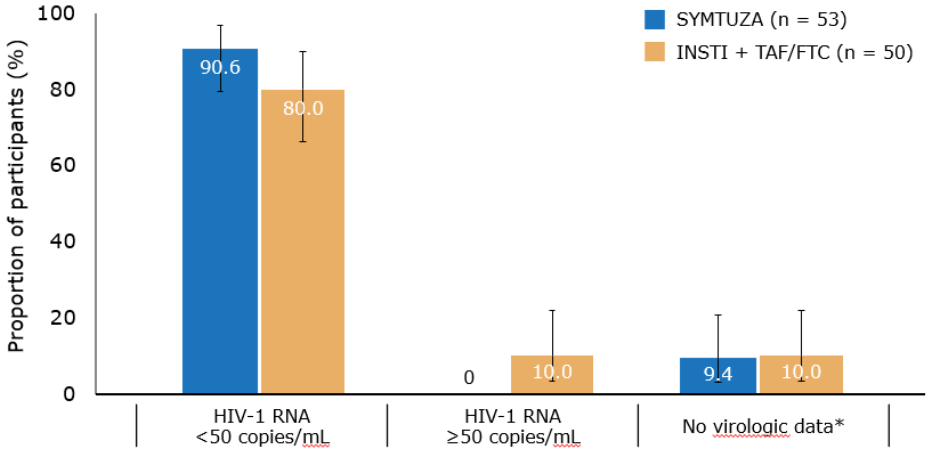


DEXA, dual x-ray absorptiometry; INSTI, integrase strand transfer inhibitor; ITT, intention-to-treat; TAF/FTC, tenofovir alafenamide/emtricitabine.

Efficacy

- At week 24, viral suppression (VL<50 copies/mL; FDA snapshot analysis) was maintained in 90.6% of participants in the SYMTUZA arm compared to 80% of participants in the control arm (See Figure: Virologic Response at Week 24 by FDA Snapshot Approach (ITT set)).[2]
  - Virologic failure occurred in 0 participants in the SYMTUZA arm compared to 5 participants in the control arm.
  - CD4+ cell counts were stable over time and similar in both study arms.

Virologic Response at Week 24 by FDA Snapshot Approach (ITT set)[2]



Error bars show 95% CI. *In the SYMTUZA arm, 2 (4%) participants discontinued due to AE/death, 2 (4%) participants discontinued due to other reasons with the last available HIV-1 RNA <50 copies/mL (or missing), and 1 (2%) participant had missing data during the window but was on-study; in the INSTI + TAF/FTC arm, 1 (2%), 2 (4%), and 2 (4%) participants were in these categories, respectively. AE, adverse event; CI, confidence interval; FDA, US Food and Drug Administration; HIV-1, human immunodeficiency virus–1; INSTI, integrase strand transfer inhibitor; ITT, intention-to-treat; TAF/FTC, tenofovir alafenamide/emtricitabine.

Safety

- Safety data through week 24 is reported in Table: Most Frequently Reported AEs and AEs of Interest by Preferred Term (Safety Analysis Set).[2]

- The most frequently reported AEs in the SYMTUZA arm were COVID-19 (11%), diarrhea (6%), nausea (6%), and hypertension (2%).[2]
- At week 24, gastrointestinal AEs occurred in 17% of participants in the SYMTUZA arm compared to 16% in the control arm.[2]
- In the SYMTUZA arm, there were increases from baseline to week 24 in the median total cholesterol (179 mg/dL to 211 mg/dL) and the median low density lipoprotein cholesterol (LDL-C; 108 mg/dL to 133 mg/dL).[2]

Most Frequently Reported AEs and AEs of Interest by Preferred Term (Safety Analysis Set)[2]

	SYMTUZA (n=53)		INSTI+TAF/FTC (n=50)	
	Overall	**Related**	**Overall**	**Related**
Participants with ≥1 AE, n (%)	30 (57)	6 (11)	31 (62)	3 (6)
Most frequently reported AEs,* n (%)				
COVID-19	6 (11)	0	2 (4)	0
Diarrhea	3 (6)	3 (6)	4 (8)	3 (6)
Nausea	3 (6)	3 (6)	3 (6)	2 (4)
Hypertension	1 (2)	0	6 (12)	0
Proteinuria	0	0	3 (6)	0
AEs of interest, n (%)				
Lipid abnormalities	3 (6)	0	3 (6)	0
Bone	2 (4)	0	2 (4)	0
Hyperglycemia	1 (2)	0	3 (6)	0
Hepatotoxicity	1 (2)	1 (2)	2 (4)	0
Rash	1 (2)	1 (2)	1 (2)	0
Renal toxicity	0	0	3 (6)	0
Ocular (for posterior uveitis)	0	0	0	0

*Occurring in >5% of participants in either study arm, regardless of relatedness to the study drug.
AE, adverse event; INSTI, integrase strand transfer inhibitor; TAF/FTC, tenofovir alafenamide/emtricitabine

LITERATURE SEARCH

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

REFERENCES

1. Janssen Scientific Affairs, LLC. A study of darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) evaluated as a fixed dose combination regimen in participants switching from an integrase inhibitor who have experienced rapid weight gain (DEFINE). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [accessed 14 May 2021]. NLM Identifier: NCT04442737. Available from: https://www.clinicaltrials.gov/ct2/show/NCT04442737?term=DEFINE+Janssen&;cond=HIV.

2. Short W, Ramgopal M, Hagins D, et al. A prospective, randomized trial to assess a protease inhibitor–based regimen switch strategy to manage integrase inhibitor–related weight gain. Oral presentation presented at: 12th International AIDS Society Conference on HIV Science (IAS); July 23-26, 2023; Brisbane, Australia.

3. Short W, Ramgopal M, Hagins D, et al. A prospective, randomized trial to assess a protease inhibitor-based regimen switch strategy to manage integrase inhibitor-related

weight gain: post hoc analyses. Oral Presentation presented at: ID Week; October 11-15, 2023; Boston, MA.