SYMTUZA® (darunavir, cobicistat, emtricitabine, and tenofovir alafenamide
Safety Information of SYMTUZA – Gastrointestinal Adverse Effects

SUMMARY

- In the AMBER study, drug-related diarrhea and nausea were reported in 34 (9%) and 20 (6%) patients in the SYMTUZA arm from baseline to week 96, respectively.[1]
- In the DIAMOND study, diarrhea, nausea, and vomiting were reported in 13 (12%), 13 (12%), and 4 (4%) patients in the SYMTUZA arm from baseline to week 48, respectively.[2]
- In the EMERALD study, drug-related diarrhea and abdominal pain were reported in 17 (2%) and 11 (1%) patients in the SYMTUZA arm from baseline to week 96, respectively.[3]
- Post hoc analyses of the two phase 3 AMBER and EMERALD studies found that incidences of SYMTUZA-related gastrointestinal (GI) adverse events of interest (AEOIs) were low, tended to present within the first weeks of therapy, and rapidly decreased thereafter.[4]

CLINICAL DATA

Treatment-Naïve Patients

AMBER

The AMBER study was a phase 3, randomized, active-controlled, double-blind, noninferiority study to evaluate efficacy and safety of SYMTUZA vs darunavir/cobicistat (DRV/COBI) fixed dose combination co-administered with emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) in antiretroviral (ARV) treatment-naïve human immunodeficiency virus type 1 (HIV-1)-infected adults (N=725).[5]

Study Design/Methods

- Patients were stratified by screening viral load (VL; < / ≥100,000) and by screening CD4+ cell counts (< / ≥200 cells/mm^3) and then randomized to a single-tablet regimen (STR) of SYMTUZA (800 mg/150 mg/200 mg/10 mg) with matching DRV/COBI + FTC/TDF placebo or the active-control regimen of DRV/COBI + FTC/TDF with a matching SYMTUZA placebo.
- After week 48, patients continued to take their blinded study drug until the last subject had reached week 48 and treatment assignments were unblinded.
- After unblinding, all patients entered the open-label, single-group treatment phase with continued SYMTUZA use in the SYMTUZA group and switch to SYMTUZA in the control group up to week 96.
- A post-hoc analysis was conducted to assess the incidence, prevalence, and duration of GI AEOIs through week 96.[4]
    - GI AEOIs were defined using Medical Dictionary for Regulatory Activities (MedDRA) v21 preferred terms of diarrhea, nausea, abdominal discomfort, and flatulence.
    - Related GI AEOIs were those assessed by the investigator to be very likely, probably, or possibly related to study drug.
    - Duration was reported for SYMTUZA-related GI AEOIs through week 96 for patients whose AEs had start and stop dates.
    - Concomitant medications were evaluated based on the percentage of patients who received such a medication for the treatment of a GI AEOI through week 96.

Results

- Episodes of study drug-related diarrhea were mostly transient.[1]
- Two patients in the SYMTUZA arm and 1 in the control arm discontinued the study due to diarrhea before week 48, with no additional discontinuations occurring after week 48.

Study Drug-related GI AEs (All Grades; ≥5% SYMTUZA Arm Through Week 96)[1]

n (%)	SYMTUZA Arm			Control Arm	
	SYMTUZA (Baseline-Week 48) (n=362)	SYMTUZA (Week 48-Week 96) (n=335)	SYMTUZA (Baseline-Week 96) (n=362)	DRV/COBI + TDF/FTC (Baseline-Switch) (n=363)	SYMTUZA (Switch-Week 96)[a] (n=295)
Diarrhea	33 (9)	2 (1)	34 (9)	42 (12)	1 (<1)
Nausea	20 (6)	0	20 (6)	36 (10)	3 (1)

Abbreviations: AE, adverse event; DRV/COBI, darunavir/cobicistat; GI, gastrointestinal; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.
[a]Respectively, 2.5%, 41.3%, and 36.4% of patients randomized to the control arm switched to SYMTUZA at week 60, week 72, and week 84.

- In the post-hoc subanalysis, through week 48, 14% of patients receiving SYMTUZA and 19% of patients receiving DRV/COBI + TDF/FTC experienced a study drug-related AEOI.[4]
  - All GI AEOIs were grade 1 or 2 and no serious AEs were reported.
- The incidence of SYMTUZA-related GI AEOIs was low and tended to present early in the study and rapidly decrease thereafter.
  - The incidence of SYMTUZA-related diarrhea and nausea was 5% for each during week 1 and decreased to ≤1% after week 2.
  - The prevalence of SYMTUZA-related diarrhea decreased to <5% starting at week 2, and the prevalence of SYMTUZA-related nausea decreased to <3% by week 2 and <1% by week 5.
  - One case of SYMTUZA-related abdominal discomfort was reported (week 1), and the incidence of SYMTUZA-related flatulence was <1% through week 96.
- Ten (3%) patients required treatment with a concomitant medication for a SYMTUZA-related GI AEOI during the study period.
- Through week 96, there were 62 GI AEOI events (out of 76 total) in which the duration could be calculated, and results were skewed towards shorter durations. The median duration was 16.5 days.

DIAMOND

The DIAMOND study was a phase 3, single-arm, open-label, multicenter study to evaluate the safety and efficacy of SYMTUZA in newly diagnosed, HIV-1 infected, treatment-naïve patients in a rapid initiation model of care over 48 weeks (N=109).[2]

Study Design/Methods

- Eligible patients were enrolled and started on SYMTUZA once daily (QD) as soon as within 24 hours of the screening/baseline visit and before results of the baseline safety and resistance laboratory tests were available.

Results

- There were no discontinuations due to GI adverse events (AEs) through week 48.[2]

Most Common GI Adverse Drug Reactions (≥2% of Patients) Through Week 48[2]

n (%)	SYMTUZA (N=109)	
	Any Grade	≥Grade 2
Diarrhea	13 (12)	2 (2)
Nausea	13 (12)	2 (2)
Vomiting	4 (4)	0

Abbreviations: GI, gastrointestinal.

Treatment-Experienced Patients

EMERALD

The EMERALD study was a phase 3, randomized, active-controlled, open-label noninferiority study to evaluate the efficacy, safety, and tolerability of switching to SYMTUZA vs continuing the current regimen consisting of a boosted protease inhibitor (bPI) combined with TDF/FTC in virologically-suppressed, HIV-1-infected adults (N=1141).[6]

Study Design/Methods

- Patients were stratified according to bPI (darunavir/ritonavir [DRV/r] or DRV/COBI QD, atazanavir/ritonavir [ATV/r] or atazanavir/cobicistat [ATV/COBI] QD, or lopinavir/ritonavir [LPV/r] twice daily [BID]) and then randomized 2:1 to switch to SYMTUZA or to continue their bPI regimen.
- At week 52, patients in the SYMTUZA arm could continue on current therapy and patients in the control arm could switch to SYMTUZA in an extension phase until week 96.
- A post-hoc analysis was conducted to assess the incidence, prevalence, and duration of GI AEOIs through week 96.[4]
    - GI AEOIs were defined using MedDRA v21 preferred terms of diarrhea, nausea, abdominal discomfort, and flatulence.
    - Related GI AEOIs were those assessed by the investigator to be very likely, probably, or possibly related to study drug.
    - Duration was reported for SYMTUZA-related GI AEOIs through week 96 for patients whose AEs had start and stop dates.
    - The percentage of patients who received concomitant medication for the treatment of a GI AEOI was also assessed.

Results

- Through week 96, GI AE-related discontinuations included abdominal pain, diarrhea, gastroesophageal reflux disease, and pancreatitis in the SYMTUZA arm (n=1 each), and diarrhea, nausea, and vomiting in the SYMTUZA late switch arm (n=1 each).[3]

Study Drug-related GI AEs (All Grades; ≥1% in Either Arm) Through Week 96[3]

n (%)	SYMTUZA Arm			Late Switch Arm	
	SYMTUZA (Baseline-Week 48) (n=763)	SYMTUZA (Week 48-Week 96) (n=728)	SYMTUZA (Baseline-Week 96) (n=763)	bPI + TDF/FTC (Baseline-Week 52) (n=378)	SYMTUZA[a] (Week 52-Week 96) (n=352)
Diarrhea	16 (2)	1 (<1)	17 (2)	2 (1)	4 (1)
Abdominal pain	11 (1)	0	11 (1)	0	0

Abbreviations: AE, adverse event; bPI, boosted protease inhibitor; GI, gastrointestinal; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.
[a]Comprising 44 weeks of SYMTUZA exposure (ie, from the switch to SYMTUZA at week 52).

- In the post-hoc subanalysis, through week 48, 3% of patients receiving SYMTUZA and 1% of patients in the control arm experienced a study drug-related AEOI.[4]
    - All were grade 1 or 2 in severity, and none were serious.
- The incidence of study drug-related GI AEOIs was low and tended to present within the first week and rapidly decrease thereafter.
    - The incidence of SYMTUZA-related diarrhea and nausea was 2% and <1%, respectively, during week 1 and decreased to ≤0.1% after week 2.
    - The prevalence of SYMTUZA-related diarrhea and nausea was each <1% starting at week 2.

    - One case of SYMTUZA-related abdominal discomfort was reported (week 1), and the incidence of SYMTUZA-related flatulence was 0.4% at week 1 and <0.1% thereafter.
- Six (<1%) patients required treatment with concomitant medication for a SYMTUZA-related GI AEOI during the study period.
- Through week 96, there were 28 AEOI events (out of 32 total) for which the duration could be calculated, and results were skewed towards shorter durations. The median duration was 8.5 days.

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 26 February 2025. Data from company-sponsored studies were summarized.

REFERENCES

1. Orkin C, Eron JJ, Rockstroh J, et al. Week 96 results of a phase 3 trial of darunavir/cobicistat/emtricitabine/tenofovir alafenamide in treatment-naive HIV-1 patients. *AIDS*. 2020;34(5):707-718.

2. Huhn G, Crofoot G, Ramgopal M, et al. Darunavir/cobicistat/emtricitabine/tenofovir alafenamide in a rapid-initiation model of care for HIV-1 infection: primary analysis of the DIAMOND study. *Clin Infect Dis*. 2020;71(12):3110-3117.

3. Eron JJ, Orkin C, Cunningham D, et al. Week 96 efficacy and safety results of the phase 3, randomized EMERALD trial to evaluate switching from boosted-protease inhibitors plus emtricitabine/tenofovir disoproxil fumarate regimens to the once daily, single-tablet regimen of darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) in treatment-experienced, virologically-suppressed adults living with HIV-1. *Antiviral Res*. 2019;170:104543.

4. Dunn K, Baugh B, Bejou N, et al. Low incidence and brief duration of gastrointestinal adverse events with darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) over 96 weeks: post hoc analyses of AMBER and EMERALD. *J Int Assoc Provid AIDS Care*. 2022;21:23259582221088200.

5. Eron JJ, Orkin C, Gallant J, et al. A week-48 randomized phase-3 trial of darunavir/cobicistat/emtricitabine/tenofovir alafenamide in treatment-naive HIV-1 patients. *AIDS*. 2018;32(11):1431-1442.

6. Orkin C, Molina JM, Negredo E, et al. Efficacy and safety of switching from boosted protease inhibitors plus emtricitabine and tenofovir disoproxil fumarate regimens to single-tablet darunavir, cobicistat, emtricitabine, and tenofovir alafenamide at 48 weeks in adults with virologically suppressed HIV-1 (EMERALD): a phase 3, randomised, non-inferiority trial. *Lancet HIV*. 2018;5(1):e23-e34.