**SYMTUZA® (darunavir, cobicistat, emtricitabine, and tenofovir alafenamide)**
**Safety Information of SYMTUZA – Neurologic/Psychiatric Adverse Effects**

## SUMMARY


- In the AMBER, DIAMOND, and EMERALD studies, the only neurologic or psychiatric adverse event (AE) reported in more than 5% of patients was headache.[1–3] Incidence of drug-related headache in each study was:
  - AMBER (week 96): 3.3%[1]
  - DIAMOND (week 48): 1.8%[2]
  - EMERALD (week 96): 1.4%[3]
- A subgroup analysis of the two phase 3 studies AMBER and EMERALD found that patients with baseline neuropsychiatric comorbidities (NPCs) did not experience higher rates of study-drug related AEs compared to those without baseline NPCs.[4]
- In the SYMTRI study, drug-related neuropsychiatric AEs were reported in 13 (9%) patients in the SYMTUZA arm and 32 (21%) patients in the dolutegravir (DTG)/lamivudine (3TC)/abacavir (ABC) arm (*P*=0.005).[5]
- In the DETOX study, at week 4, in patients who continued DTG/3TC/ABC, the Pittsburgh Sleep Quality Index (PSQI) score remained unchanged, whereas in patients who switched to SYMTUZA, the PSQI score significantly improved. At weeks 4 and 8, all patients who switched to SYMTUZA had significant improvements in the PSQI, Hospital Anxiety and Depression scale (HADS) scores, and neuropsychiatric symptoms scores.[6]


## 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 (DRV)/cobicistat (COBI) fixed dose combination co-administered with emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) in antiretroviral (ARV) treatment-naïve human immunodeficiency viruses (HIV)-1-infected adults (N=725).[7]

#### *Study Design/Methods*

- Patients were stratified by screening viral load (VL; < / ≥100,000) and by screening clusters of differentiation (CD)4+ cell counts (< / ≥200 cells/mm$^3$) and then randomized to a single-tablet regimen (STR) of SYMTUZA (DRV 800 mg, COBI 150 mg, emtricitabine FTC 200 mg, and tenofovir alafenamide [TAF] 10 mg) with matching DRV/COBI + FTC/TDF placebos 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 arm and switch to SYMTUZA in the control arm up to week 96.
- A subgroup analysis was conducted to assess the prevalence of preexisting NPCs and to compare outcomes in patients with and without baseline NPCs.[4]
  - NPCs were based on verbatim medical history terms and were defined as those within the Medical Dictionary for Regulatory Activities (MedDRA) v22 entire system organ classes of Nervous System Disorders or Psychiatric Disorders.
  - For psychiatric disorders, the terms sexual dysfunctions/disturbances, gender identity disorders, and eating disorders/disturbances were excluded.

***Results***

- At week 48, the only neurologic or psychiatric AE reported in more than 5% of patients was headache (n=47 [13.0%] in the SYMTUZA arm and n=32 [8.8%] in the control arm).
  - Of these, 12 cases (3.3%) and 6 cases (1.7%) were thought to be drug-related in the SYMTUZA and control arms, respectively.[8]
- Through week 96, the only neurologic or psychiatric AE reported in more than 5% of patients in the SYMTUZA arm was headache (n=54, 14.9%).[1]
  - No additional patients had drug-related headache between weeks 48-96.
- There were no drug-related neurologic/psychiatric AEs classified as serious and none leading to discontinuation of therapy.[1]
- There were 88/362 patients with baseline NPCs and 274/362 without baseline NPCs.[4]
  - Neurologic comorbidities were present in 38/88 (43%); the most common were headache (18/88; 20%) and migraine (5/88; 6%).
  - Psychiatric comorbidities were present in 56/88 (64%); the most common were depression (31/88; 35%), anxiety (16/88; 18%), sleep disorder (8/88; 9%), and insomnia (6/88; 7%).
- Through week 96, patients with vs without baseline NPCs reported a higher incidence of new or worsening neurologic and/or psychiatric AEs overall; however, the incidence of drug-related AEs did not differ between arms (Table: Summary of Neurologic and Psychiatric AEs in AMBER).[4]
- The specific neurologic and psychiatric study drug-related AEs reported are noted in Table: Study Drug-related Neurologic and Psychiatric AEs (Specific Terms) Through Week 96.

**Summary of Neurologic and Psychiatric AEs in AMBER**[4]

| AEs, n (%) | SYMTUZA (BL-Week 48) | | SYMTUZA (BL-Week 96) | | Control (BL-Week 48) | |
|---|---|---|---|---|---|---|
| | With BL NPCs (n=88) | Without BL NPCs (n=274) | With BL NPCs (n=88) | Without BL NPCs (n=274) | With BL NPCs (n=99) | Without BL NPCs (n=264) |
| Any neurologic[a] | 18 (20) | 47 (17) | 25 (28) | 50 (18) | 20 (20) | 28 (11) |
| Related | 4 (5) | 13 (5) | 4 (5) | 13 (5) | 5 (5) | 8 (3) |
| ≥Grade 2 | 0 | 2 (1) | 0 | 2 (1) | 3 (3) | 2 (1) |
| Any psychiatric[b] | 17 (19) | 26 (9) | 26 (30) | 33 (12) | 19 (19) | 18 (7) |
| Related | 1 (1) | 8 (3) | 1 (1) | 9 (3) | 1 (1) | 3 (1) |
| ≥Grade 2 | 0 | 1 (<1) | 0 | 1 (<1) | 0 | 1 (<1) |

**Abbreviations:** AE, adverse event; BL, baseline; NPC, neuropsychiatric comorbidity.
[a]System organ class of nervous system disorders.
[b]System organ class of psychiatric disorders.

**Study Drug-Related Neurologic and Psychiatric AEs (Specific Terms) Through Week 96**[4,a]

| SYMTUZA | | Control | |
|---|---|---|---|
| With Baseline NPCs (n=88) | Without Baseline NPCs (n=274) | With Baseline NPCs (n=99) | Without Baseline NPCs (n=264) |
| • Neurologic[b] (n=4)<br>○ Headache (n=1)<br>○ Dizziness exertional (n=1) | • Neurologic[b] (n=13)<br>○ Headache (n=11)<br>○ Dizziness (n=1) | • Neurologic[b] (n=5)<br>○ Headache (n=3)<br>○ Dizziness postural (n=1) | • Neurologic[b] (n=8)<br>○ Headache (n=3)<br>○ Dizziness (n=1)<br>○ Hypoesthesia (n=2) |

| SYMTUZA | | Control | |
|---|---|---|---|
| **With Baseline NPCs (n=88)** | **Without Baseline NPCs (n=274)** | **With Baseline NPCs (n=99)** | **Without Baseline NPCs (n=264)** |
| ○ Dizziness postural (n=1)<br>○ Disturbance in attention (n=1)<br>○ Dizziness (n=1)<br>○ Somnolence (n=1)<br>• Psychiatric[c] (n=1)<br>○ Listless (n=1)<br>○ Restlessness (n=1) | ○ Dizziness postural (n=1)<br>○ Somnolence (n=2)<br>• Psychiatric[c] (n=9)<br>○ Insomnia (n=5)<br>○ Depression (n=2)<br>○ Sleep disorder (n=1)<br>○ Abnormal dreams (n=2) | ○ Somnolence (n=1)<br>• Psychiatric[c] (n=1)<br>○ Insomnia (n=1) | ○ Somnolence (n=2)<br>• Psychiatric[c] (n=3)<br>○ Insomnia (n=1)<br>○ Abnormal dreams (n=1)<br>○ Mood altered (n=1) |

**Abbreviations:** AE, adverse event; NPC, neuropsychiatric comorbidity.
[a]The n values represent numbers of participants, not events. A single participant may have reported >1 neurologic or psychiatric study drug-related AE.
[b]System organ class of nervous system disorders.
[c]System organ class of psychiatric disorders.

**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).[9]

***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***

- At week 48, the only neurologic or psychiatric AE reported in more than 5% of patients was headache (n=10, 9.2%). Of these, 2 cases (1.8%) were thought to be drug-related.[2]
- At week 48, there were no drug-related neurologic/psychiatric AEs classified as serious and none leading to discontinuation of therapy.[2]

**SYMTRI**

The SYMTRI study was a randomized, parallel, open-label, multicenter, noninferiority study to compare 2 single-pill triple regimens based on SYMTUZA (protease inhibitor [PI]-based regimen) and DTG/3TC/ABC (second-generation integrase inhibitor regimen) in ARV-naïve patients with HIV-1.[5]

***Study Design/Methods***

- ARV-naïve patients with HIV-1 (aged ≥18 years) with plasma HIV-1 RNA levels ≥500 copies/mL were included.
- Patients were randomized 1:1 and stratified based on HIV-1 RNA (≤100,000 or >100,000 copies/mL) and CD4 counts (≤200 or >200 cells/mm$^3$) to receive fixed dose combinations of SYMTUZA or DTG/3TC/ABC (50/600/300 mg) orally (PO) QD.

### *Results*

- A total of 316 patients were randomized, of whom 158 were included in the SYMTUZA and DTG/3TC/ABC arms each. At least 1 dose of study treatment was received by 306 patients.
- Drug-related neuropsychiatric AE was reported in 13 (9%) patients in the SYMTUZA arm and 32 (21%) patients in the DTG/3TC/ABC arm (*P*=0.005).

## 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 FTC/TDF in virologically-suppressed, HIV-1-infected adults (N=1141).[10]

### *Study Design/Methods*

- Patients were stratified according to bPI (DRV/ritonavir [r] or DRV/COBI QD, atazanavir [ATV]/r or ATV/COBI QD, or 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 subgroup analysis was conducted to assess the prevalence of preexisting NPCs and to compare outcomes in patients with and without baseline NPCs.[4]
    - NPCs were based on verbatim medical history terms and were defined as those within the MedDRA v22 entire system organ classes of Nervous System Disorders or Psychiatric Disorders.
    - For psychiatric disorders, the terms sexual dysfunctions/disturbances, gender identity disorders, and eating disorders/disturbances were excluded.

### *Results*

- At week 48, the only neurologic or psychiatric AE reported in more than 5% of patients was headache (n=58 [7.6%] in the SYMTUZA arm and n=16 [4.2%] in the control arm).
    - Of these, 10 cases (1.3%) and 0 cases (0%) were thought to be drug-related in the SYMTUZA and control arms, respectively.[11]
- There was 1 neurologic AE leading to permanent discontinuation of therapy in each arm at week 48, both of which (headache in the SYMTUZA arm and tunnel vision in the control arm) were thought to be drug-related.[11]
- There were 2 psychiatric AEs leading to permanent discontinuation of therapy in the SYMTUZA arm at week 48, only 1 of which (depression/suicidal) was thought to be drug-related.[11]
- At week 96, the only neurologic or psychiatric AE reported in more than 5% of patients in the SYMTUZA arm was headache (n=79, 10.4%).[3]
    - Only one case of drug-related headache occurred after week 48.
- At week 96, there were no drug-related neurologic/psychiatric AEs classified as serious.[3]
- Between weeks 48-96, there were no additional neurologic/psychiatric AEs leading to permanent discontinuation of therapy in the SYMTUZA arm.[3]
- There were 294/763 patients with baseline NPCs and 469/763 without baseline NPCs.[4]
    - Neurological comorbidities were present in 125/294 (43%); the most common were headache (37/294, 13%), peripheral neuropathy (27/294; 9%), and migraine (17/294; 6%).

- Psychiatric comorbidities were present in 241/294 (82%); the most common were depression (126/294; 43%), insomnia (100/294, 34%), anxiety (81/294; 28%), and attention deficit/hyperactivity disorder (16/294; 5%).

- Overall, patients with vs without baseline NPCs reported a higher incidence of neurologic and psychiatric AEs; however, the incidence of drug-related AEs did not differ between arms (Table: Summary of Neurologic and Psychiatric AEs in EMERALD).[4]

**Summary of Neurologic and Psychiatric AEs in EMERALD**[4]

| AEs, n (%) | SYMTUZA (BL-Week 48) | | SYMTUZA (BL-Week 96) | | Control (BL-Week 48) | |
|---|---|---|---|---|---|---|
| | With BL NPCs (n=294) | Without BL NPCs (n=469) | With BL NPCs (n=294) | Without BL NPCs (n=469) | With BL NPCs (n=166) | Without BL NPCs (n=212) |
| Any neurological[a] | 52 (18) | 64 (14) | 73 (25) | 89 (19) | 17 (10) | 18 (8) |
| Related | 7 (2) | 15 (3) | 7 (2) | 16 (3) | 0 | 0 |
| ≥Grade 2 | 2 (1) | 4 (1) | 2 (1) | 5 (1) | 0 | 0 |
| Any psychiatric[b] | 36 (12) | 41 (9) | 54 (18) | 59 (13) | 25 (15) | 14 (7) |
| Related | 6 (2) | 8 (2) | 6 (2) | 8 (2) | 0 | 0 |
| ≥Grade 2 | 2 (1) | 3 (1) | 2 (1) | 4 (1) | 0 | 0 |

**Abbreviations:** AE, adverse event; BL, baseline; NPC, neuropsychiatric comorbidity.
[a]System organ class of nervous system disorders.
[b]System organ class of psychiatric disorders.

**Study Drug-Related Neurologic and Psychiatric AEs (Specific Terms) Through Week 96**[4,a]

| SYMTUZA | |
|---|---|
| **With Baseline NPCs (n=294)** | **Without Baseline NPCs (n=469)** |
| • Neurologic[b] (n=7)<br>○ Headache (n=3)<br>○ Postural dizziness (n=2)<br>○ Paresthesia (n=1)<br>○ Somnolence (n=1)<br>• Psychiatric[c] (n=6)<br>○ Sleep disorder (n=3)<br>○ Insomnia (n=2)<br>○ Euphoric mode (n=1)<br>○ Irritability (n=1) | • Neurologic[b] (n=16)<br>○ Headache (n=8)<br>○ Postural dizziness (n=3)<br>○ Carpal tunnel syndrome (n=1)<br>○ Hypoesthesia (n=1)<br>○ Paresthesia (n=1)<br>○ Syncope (n=1)<br>○ Dysgeusia (n=1)<br>• Psychiatric[c] (n=8)<br>○ Abnormal dreams (n=5)<br>○ Sleep disorder (n=2)<br>○ Depression (n=1)<br>○ Insomnia (n=1)<br>○ Suicidal depression (n=1)<br>○ Tearfulness (n=1) |

**Abbreviations:** AE, adverse event; NPC, neuropsychiatric comorbidity.
[a]The n values represent numbers of participants, not events. A single participant may have reported >1 neurologic or psychiatric study drug-related AE.
[b]System organ class of nervous system disorders.
[c]System organ class of psychiatric disorders.

## DETOX

DETOX was a randomized, open-label study that was conducted in 2 phases to evaluate whether switching from DTG/3TC/ABC to SYMTUZA could help in improving the quality of sleep, mood, and neuropsychiatric status in virologically-suppressed, HIV-infected adults.[6]

### *Study Design/Methods*

- Phase 1: Patients were randomized to switch at baseline from DTG/3TC/ABC to SYMTUZA (immediate switch arm) or to continue 4 weeks with DTG/3TC/ABC and then switch to SYMTUZA (deferred switch arm).
- Phase 2: Patients from both the arms completed 8 weeks of follow-up after switching to SYMTUZA.
- Patients with HIV who had no major neuropsychiatric comorbidities (major depression with psychotic symptoms or suicidal ideation, drug abuse/dependence, dementia, or psychosis), were receiving DTG/3TC/ABC for at least 4 weeks, had poor quality of sleep (PSQI score >5), and did not complain of insomnia, were included.
- At each study visit, patients completed 3 patient-reported outcome (PRO) questionnaires, which included PSQI score, HADS score, and a neuropsychiatric symptom score (defined as DETOX score).

### *Results*

- Compared with patients who continued 4 weeks with DTG/3TC/ABC and then switched to SYMTUZA, those who switched at baseline from DTG/3TC/ABC to SYMTUZA experienced significant improvements in the PSQI score (mean±standard deviation [SD] change, -3.3±11.4 vs -18.0±16.2; *P*<0.001), see Table: PSQI, HADS, and CNS Symptom Scores in the DTG/3TC/ABC and SYMTUZA Arms at Baseline and Week 4.
- Compared with patients who continued 4 weeks with DTG/3TC/ABC and then switched to SYMTUZA, those who switched at baseline from DTG/3TC/ABC to SYMTUZA experienced significant improvements in self-reported scores (DETOX changes; mean±SD, -1.3±8.6 vs -13.7±13.3; *P*<0.001 and HADS anxiety subscale changes; mean±SD, -1.9±15.6 vs -14±16.9; *P*=0.003) and no differences were observed in HADS depression subscale changes (mean±SD, 1.8±10.8 vs -5.8±11.1; *P*=0.041).

**PSQI, HADS, and CNS Symptom Scores in the DTG/3TC/ABC and SYMTUZA Arms at Baseline and Week 4**[6]

| Scores | Baseline | | Week 4 | | *P* value |
|---|---|---|---|---|---|
| | DTG/3TC/ABC | SYMTUZA | DTG/3TC/ABC | SYMTUZA | |
| PSQI | 36.5 | 38.2 | 35.5 | 26.7 | <0.001 |
| HADS anxiety subscale score | 39.1 | 36.8 | 36.8 | 23.3 | 0.003 |
| HADS depression subscale score | 27.8 | 22 | 24.1 | 15.2 | 0.203 |
| CNS symptoms score | 27.1 | 27.8 | 25.8 | 14.5 | <0.001 |

**Abbreviations**: 3TC, lamivudine; ABC, abacavir; CNS, central nervous system; DTG, dolutegravir; HADS, Hospital Anxiety and Depression scale; PSQI, Pittsburgh Sleep Quality Index.

- At week 8, after all the patients switched to SYMTUZA, progressive improvements were observed in the DETOX scores and HADS scores of anxiety and depression, see table: PSQI, HADS, and CNS Symptom Scores in All the Patients Who switched to SYMTUZA.

**PSQI, HADS, and CNS Symptom Scores in All the Patients Who Switched to SYMTUZA**[6]

| Mean±95% CI Scores | Baseline | Week 4 | Week 8 |
|---|---|---|---|
| PSQI | 36.9±1.3 | 27.5±1.6 | 21.8±1.5 |
| HADS anxiety score | 36.8±2.3 | 26.0±2.1 | 22.3±2.1 |
| HADS depression scale | 23.0±2.0 | 17.0±1.8 | 16.0±1.8 |
| CNS symptoms score | 26.9±2.0 | 13.7±1.5 | 9.5±1.2 |

**Abbreviations**: CI, confidence interval; CNS, central nervous system; HADS, Hospital Anxiety and Depression scale; PSQI, Pittsburgh Sleep Quality Index.

- At week 4, significant improvement was observed in the proportion of patients reporting sleep disturbances, abnormal dreams, asthenia or fatigue, and impaired concentration in the DETOX questionnaire, see Table: Changes in the Proportion of Patients Reporting Any Neuropsychiatric Symptom in the DETOX Questionnaire at Week 4 and Week 8 After All Patients Switched to SYMTUZA

**Changes in the Proportion of Patients Reporting Any Neuropsychiatric Symptom in the DETOX Questionnaire at Week 4 and Week 8 After All Patients Switched to SYMTUZA**[6]

| Neuropsychiatric Items, n (%) | Baseline (n=69) | Week 4/8 (n=66) | Week 8/12 (n=66) |
|---|---|---|---|
| Sleep disturbances,[a,b] | 65 (94.2) | 32 (48.5)[c] | 26 (39.4)[c] |
| Abnormal dreams,[b] | 45 (65.2) | 14 (21.2)[c] | 13 (19.7)[c] |
| Dizziness,[b] | 23 (33.3) | 12 (18.2) | 6 (9.1)[c] |
| Headache,[b] | 30 (43.5) | 17 (25.8) | 15 (22.7)[c] |
| Impaired concentration,[b] | 37 (53.6) | 20 (30.3)[c] | 14 (21.2)[c] |
| Nervousness or irritability,[b] | 45 (65.2) | 32 (48.5) | 28 (42.4)[c] |
| Asthenia or fatigue,[b] | 52 (75.4) | 32 (49.2)[c] | 24 (36.4)[c] |
| Symptoms of anxiety,[b] | 43 (62.3) | 29 (43.9) | 22 (33.3)[a] |
| Symptoms of depression,[b] | 32 (46.4) | 21 (31.8) | 12 (18.2)[a] |
| Hallucinations | 4 (5.8) | 3 (4.6) | 1 (1.6) |
| Suicidality | 4 (5.8) | 3 (6.1) | 1 (3.0) |

**Abbreviation**: GEE, generalized estimated equation.
[a]Definition: Sleep abnormalities not fulfilling the diagnostic criteria for insomnia.
[b]Significant change over time associated with antiretroviral therapy switch (linear GEE model).
[c]Significant change from baseline to the setpoint (adjusted GEE model).

## LITERATURE SEARCH

A literature search of MEDLINE®, EMBASE®, BIOSIS Previews®, and DERWENT® (and/or other resources, including internal/external databases) was conducted on 22 August 2023.

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