SYMTUZA® (darunavir, cobicistat, emtricitabine, and tenofovir alafenamide)
SYMTUZA - Safety Information - Cardiovascular Effect

SUMMARY

- In the AMBER study, coronary artery adverse events of interest (AEOIs) were reported in 4 (1.1%) SYMTUZA patients from baseline to week 96 and 1 control patient after switching to SYMTUZA (between weeks 48-96).[1]
- In the DIAMOND study, there were no coronary artery events reported in SYMTUZA patients from baseline to week 48.[2]
- In the EMERALD study, coronary artery AEOIs were reported in 15 (2%) of SYMTUZA patients from baseline to week 96 and 5 (1.4%) control patients after switching to SYMTUZA (between weeks 48-96).[3]

CLINICAL STUDIES

Treatment-Naïve Patients

AMBER

The AMBER study was a phase 3, randomized, active-controlled, double-blind study to evaluate efficacy and safety of SYMTUZA vs darunavir (DRV)/cobicistat (COBI) fixed dose combination co-administered with emtricitabine (FTC)/tenofovir disoproxil fumarate (TDF)/ in antiretroviral (ARV) treatment-naïve HIV-1-infected adults (N=725).[4]

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 (DRV 800 mg, COBI 150 mg, FTC 200 mg, and tenofovir alafenamide [TAF] 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 patients in the SYMTUZA group continuing on current therapy and patients in the control arm switching to SYMTUZA up to Week 96.

Results – Initial SYMTUZA arm

- No cardiac conduction AEOIs were reported from baseline to week 96.[1]
- Coronary artery AEOIs were reported in 4 (1.1%) SYMTUZA patients.
  - One (0.3%) patient was reported with nonserious angina pectoris (grade 1 and not related). This patient had a medical history of ongoing hypertension and did not use nicotine. Screening electrocardiogram was abnormal, but not clinically significant.
  - Three (0.8%) patients reported blood creatine phosphokinase (CPK) increased, none related to coronary artery disease.
- There were no serious or grade 3 or 4 coronary artery AEOIs, and none led to permanent discontinuation.

Results – Control arm after switching to SYMTUZA

- No cardiac conduction AEOIs were reported after switching to SYMTUZA (weeks 48-96).[1]
- One coronary artery AEOI was reported following switching to SYMTUZA (grade 4 blood CPK increased), not related to coronary artery disease.

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).[5]

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 cardiac conduction or coronary artery events reported from baseline to week 48.[2]

Treatment-Experienced Patients

EMERALD

The EMERALD study was a phase 3, randomized, active-controlled, open-label 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).[6]

Study Design/Methods

- Patients were stratified according to bPI (DRV/ritonavir [r] or DRV/COBI QD, atazanavir [ATV]/r or ATV/COBI QD, or lopinavir [LPV]/r BID) and then randomized 2:1 to switch to an STR consisting of SYMTUZA (DRV 800 mg, COBI 150 mg, FTC 200 mg, and TAF 10 mg) 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.

Results– Initial SYMTUZA arm

- A cardiac conduction AEOI was reported in 1 (0.1%) patient from baseline to week 96.[3]
  - This patient had serious grade 3 ventricular tachycardia (not related) which did not lead to study drug discontinuation.
- Coronary artery AEOIs were reported in 15 (2%) SYMTUZA patients (8 clinical events and 7 laboratory events) from baseline to week 96.
  - Five (0.7%) patients had serious AEOIs (angina pectoris [n=1], coronary artery disease [n=1], and MI [n=3]), of which:
    - All were grade 3 or 4.
    - One (MI) was considered study drug related.
    - Two led to discontinuation due to a fatal outcome (1 MI considered very likely related and 1 MI considered doubtfully related to study drug).
    - In all 5 patients, cardiovascular risk factors were present at baseline.
  - In the remaining 3 patients with clinical events, cardiovascular risk factors were present at baseline.
    - One patient was reported with atherosclerosis coronary artery that was considered related to the study drug.
  - For the 7 (0.9%) patients with laboratory events (all blood CPK increased), 2 were considered to be related to study drug, and none of the reports were related to coronary artery disease.

Results – Control arm after switching to SYMTUZA

- No cardiac conduction AEOIs were reported after switching to SYMTUZA (weeks 48-96).[3]
- Coronary artery AEOIs were reported in 5 (1.4%) patients after switching to SYMTUZA, none of which were related or led to permanent discontinuation of therapy.
    - One patient had an MI (grade 4) and nonserious coronary artery disease (grade 1).
    - One patient had angina pectoris (grade 3).
    - Three patients had blood CPK increased, none related to coronary artery disease.

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 30 October 2023. Studies specifically evaluating SYMTUZA were summarized.

REFERENCES

1. Data on File. 96 Week Clinical Study Report TMC114FD2HTX3001 (AMBER). Janssen Research & Development, LLC. EDMS-ERI-163159317; 2018.

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3. Data on File. 96 Week Clinical Study Report TMC114IFD3013 (EMERALD). Janssen Research & Development, LLC. EDMS-ERI-161190462; 2018.

4. Eron J, 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;32:1431-1442.

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

6. Orkin C, Molina J, 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:e23-e34.