SYMTUZA® (darunavir, cobicistat, emtricitabine, and tenofovir alafenamide)
Safety Information of SYMTUZA - Hyperglycemia and Diabetes Mellitus

SUMMARY

- In the AMBER study, hyperglycemia adverse events of interest (AEOIs) were reported in 4 (1.1%) patients from baseline-week 48 and 6 (1.7%) patients from baseline-week 96.[1]
- In the EMERALD study, hyperglycemia AEOIs were reported in 16 (2.1%) patients from baseline-week 48 and 23 (3.0%) patients from baseline-week 96.[2]
- In the DIAMOND study, 3 (2.8%) patients reported hyperglycemic adverse events (AEs): 2 patients reported grade 1 hyperglycemic AEs (hyperglycemia and impaired fasting glucose) and 1 patient reported grade 2 type 2 diabetes mellitus (T2DM).[3]

CLINICAL DATA

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 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 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.
- The subsequent data are from the study group that received SYMTUZA for the entire 96-week period (n=362).

Results – Initial SYMTUZA arm

- From baseline-week 96, no serious or grade 3 or 4 hyperglycemia AEOI were reported and none led to permanent discontinuation.[1] See Table: Incidence (%) of Hyperglycemia Events by Preferred Term and AE Attributes in the Initial SYMTUZA Group; Intent-to-treat (AMBER)

Incidence (%) of Hyperglycemia Events by Preferred Term and AE Attributes in the Initial SYMTUZA Group; Intent-to-treat (AMBER)[1]

Incidence, n (%)	Baseline-Week 48 (N=362)		Baseline-Week 96 (N=362)	
	Any AEOI	Related	Any AEOI	Related
Any hyperglycemia AEOI	4 (1.1%)	1 (0.3%)	6 (1.7%)	2 (0.6%)
Blood glucose increased	0	0	1 (0.3%)	1 (0.3%)
Diabetes mellitus	1 (0.3%)	0	1 (0.3%)	0
Hyperglycemia	3 (0.8%)	1 (0.3%)	3 (0.8%)	1 (0.3%)
T2DM	0	0	1 (0.3%)	0

Abbreviations: AE, adverse event; AEOI, adverse event of interest; T2DM, type 2 diabetes mellitus.

- A small median (interquartile range [IQR]) increase from baseline was observed in fasting glucose (0.20 [-0.10 to 0.50] mmol/L at both week 48 and week 96). This was not considered clinically relevant.[1]
- Fasting hyperglycemia was reported by 49 (13.7%) patients from baseline-week 48 and 78 (21.8%) patients from baseline-week 96. Fasting glycosuria was reported by 4 (1.1%) patients from baseline-week 48 and 6 (1.7%) patients from baseline-week 96.[1]
    - Fasting hyperglycemia was graded as follows: grade 1: 110 to 125 mg/dL (6.11 to <6.95 mmol/L); grade 2: >125 to 250 mg/dL (6.95 to <13.89 mmol/L); grade 3: >250 to 500 mg/dL (13.89 to <27.75 mmol/L); grade 4: >500 mg/dL (≥27.75 mmol/L).[5]
    - Glycosuria was graded as follows: grade 1: trace to 1+ or ≤250 mg; grade 2: 2+ or >250 to ≤500 mg; grade 3: >2+ or >500 mg; grade 4: not applicable.[5]
    - Most laboratory findings of fasting hyperglycemia or glycosuria were grade 1 or 2.[1]
    - Grade 3 fasting hyperglycemia and glycosuria were each observed in 1 (0.3%) patient from baseline-week 48 and 1 (0.3%) patient from baseline-week 96.[1]
    - No grade 4 fasting hyperglycemia or glycosuria was reported.[1]
- From baseline-week 96, 4 (1.1%) patients were on an antidiabetic treatment, of which 3 (0.8%) patients had newly started.[1]

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).[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 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.
- The subsequent data are from the study group that received SYMTUZA for the entire 96-week period (n=763).

Results – Initial SYMTUZA arm

- From baseline-week 96, no hyperglycemia events led to permanent discontinuation.[2] See Table: Incidence (%) of Hyperglycemia Events by Preferred Term and AE Attributes in the Initial SYMTUZA Group; Intent-to-treat (EMERALD)

Incidence (%) of Hyperglycemia Events by Preferred Term and AE Attributes in the Initial SYMTUZA Group; Intent-to-treat (EMERALD)[2]

Incidence, n (%)	Baseline-Week 48 (N=763)		Baseline-Week 96 (N=763)	
	Any AEOI	Related	Any AEOI	Related
Any hyperglycemia AEOI	16 (2.1%)	3 (0.4%)	23 (3.0%)	3 (0.4%)
Blood glucose increased	3 (0.4%)	1 (0.1%)	3 (0.4%)	1 (0.1%)
Diabetic ketoacidosis	1 (0.1%)	0	1 (0.1%)	0
Diabetes mellitus	6 (0.8%)	1 (0.1%)	8 (1.0%)	1 (0.1%)
Diabetes mellitus inadequate control	1 (0.1%)	0	1 (0.1%)	0
Glucose tolerance impaired	0	0	1 (0.1%)	0
Glycosuria	1 (0.1%)	0	1 (0.1%)	0
Hyperglycemia	3 (0.4%)	1 (0.1%)	4 (0.5%)	1 (0.1%)

Hyperglycemic hyperosmolar nonketotic syndrome	0	0	1 (0.1%)	0
T2DM	2 (0.3%)	0	5 (0.7%)	0
Abbreviations: AE, adverse event; AEOI, adverse event of interest; T2DM, type 2 diabetes mellitus.				

- A small median (IQR) increase from baseline was observed in fasting glucose (0.10 [-0.30 to 0.40] mmol/L at week 48 and 0.10 [-0.30 to 0.50] mmol/L at week 96). This was not considered clinically relevant.[2]
- Two patients were reported with a serious hyperglycemia AEOI.[2]
  - One patient had a grade 4 diabetic ketoacidosis (not related, during the first 48 weeks).
  - One patient was reported with a grade 4 T2DM and a grade 4 hyperglycemic hyperosmolar nonketotic syndrome (not related, during the extension phase).
- Fasting hyperglycemia was reported by 149 (19.6%) patients from baseline-week 48 and 173 (22.8%) patients from baseline-week 96. Fasting glycosuria was reported by 27 (3.6%) patients from baseline-week 48 and 34 (4.5%) patients from baseline-week 96.[2]
  - Fasting hyperglycemia was graded as follows: grade 1: 110 to 125 mg/dL (6.11 to <6.95 mmol/L); grade 2: >125 to 250 mg/dL (6.95 to <13.89 mmol/L); grade 3: >250 to 500 mg/dL (13.89 to <27.75 mmol/L); grade 4: >500 mg/dL (≥27.75 mmol/L).[7]
  - Glycosuria was graded as follows: grade 1: trace to 1+ or ≤250 mg; grade 2: 2+ or >250 to ≤500 mg; grade 3: >2+ or >500 mg; grade 4: not applicable.[7]
  - Most laboratory findings of fasting hyperglycemia or glycosuria were grade 1 or 2.[2]
  - Grade 3 hyperglycemia was observed in 8 (1.1%) patients from baseline-week 48 and 11 (1.4%) patients from baseline-week 96.[2]
  - Grade 3 fasting glycosuria was observed in 13 (1.7%) patients from baseline-week 48 and 16 (2.1%) patients from baseline-week 96.[2]
  - No grade 4 hyperglycemia or glycosuria was reported.[2]
- From baseline-week 96, 46 (6.0%) patients were on an antidiabetic treatment, of which 21 (2.8%) patients newly started.[2]

DIAMOND

The DIAMOND study is 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).[8]

Study Design/Methods

- Eligible patients were enrolled and started on an STR consisting of SYMTUZA (800 mg/150 mg/200 mg/10 mg) orally once daily 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 – SYMTUZA Study population

- Overall, 3 (2.8%) patients reported hyperglycemic AEs: 2 patients reported grade 1 hyperglycemic AEs (hyperglycemia and impaired fasting glucose) and 1 patient reported grade 2 T2DM.[3]
- The AEs of grade 1 hyperglycemia and grade 2 T2DM were assessed by the investigator as not related to the study treatment and the AEs of grade 1 impaired fasting glucose was assessed by the investigator as possibly related to study treatment.[3]
- Concomitant antidiabetic drugs were received by 2 (1.8%) patients during the treatment phase only.[3]

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 23 May 2023.

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