SYMTUZA® (darunavir, cobicistat, emtricitabine, and tenofovir alafenamide)
Use of SYMTUZA in Pediatric Patients

SUMMARY

- SYMTUZA is a complete regimen for the treatment of HIV-1 infected adults and adolescents aged 12 years and older with body weight at least 40 kg who are treatment-naïve or treatment-experienced with no darunavir (DRV) resistance-associated mutations (RAMs).[1]
  - In adolescent patients aged 12 years and older weighing at least 40 kg, the recommended dosage is one tablet taken once daily (QD) with food.[1]
  - No dose has been established for pediatric patients 3-11 years of age or weighing less than 40 kg.[1]
  - SYMTUZA should not be used in pediatric patients below 3 years of age due to toxicity observed in juvenile rats dosed with darunavir (from 20 mg/kg-1000 mg/kg) up to days 23-26 of age.[1]
- The pharmacokinetics (PK) of SYMTUZA in pediatric patients have not been investigated.
  - However, available PK data for the components of SYMTUZA indicate that there were no clinically relevant differences in exposure between adults and adolescents weighing at least 40 kg.
- The safety and efficacy of SYMTUZA in pediatric patients has not been investigated; however, the use of the components of SYMTUZA in adolescent patients aged 12-<18 years of age and weighing at least 40 kg is supported by 3 open-label clinical studies in HIV-1 infected pediatric patients.[1] Data from these studies showed that the overall safety profile in adolescents was similar to that observed in the adult population.
  - TMC114-C230 (DRV boosted with ritonavir [RTV]; n=12)
    - Please refer to the local DRV prescribing information for more information on this study.
  - GS-US-216-0128 (DRV boosted with cobicistat [COBI]; n=7)
    - Available data from this study are summarized below.[2]
    - Please contact Gilead Sciences for more information on this study.
  - GS-US-292-0106 (elvitegravir, cobicistat, emtricitabine [FTC], and tenofovir alafenamide [TAF]; n=50)
    - Please contact Gilead Sciences for more information on this study.
- A phase 1, single-dose study in adolescents found that 93% (25/27) of patients rated SYMTUZA as easy to swallow.[3]
- In a retrospective study evaluating the tolerability and efficacy of DRV/COBI in 15 children, DRV/COBI + 2 nucleoside reverse transcriptase inhibitors (NRTIs) maintained viral suppression in those suppressed at the time of switch; however, 8/15 patients discontinued therapy due primarily to tolerance or adherence issues.[4]

DATA WITH SYMTUZA

Crauwels et al (2018)[3] evaluated the acceptability and swallowability of 2 placebo formulations equal in size and matching the fixed-dose combination products SYMTUZA (size, 22 mm X 10 mm) and DRV/COBI (size, 23 mm X 11.5 mm).

Study Design/Methods

- Phase 1, open-label, randomized, single-dose, crossover study that enrolled 27 HIV-1 infected adolescents 12 to <18 years old who weighed ≥40 kg.
  - Patients were stratified based on age: 12 to <15 years and 15 to <18 years.
  - Patients were virologically suppressed and had been on stable antiretroviral therapy for ≥3 months.

    - Patients' ability and willingness to swallow a DRV 800 mg placebo tablet was assessed in the screening phase.
- On day 1, patients were randomly assigned to receive SYMTUZA placebo tablets (N=12) or DRV/COBI placebo tablets (N=15). At least 30 minutes later, they received the opposite regimen.
- A 7-point swallowability questionnaire and a 3-point acceptability questionnaire were completed by each patient following administration of the placebo tablets.
- The SYMTUZA data are presented below.

Results

- The median age was 14 years (range, 12 to 17), 52% of patients were male, the median body mass index was 21.1 kg/m^2, and 78% were currently taking a fixed-dose combination product.
- All patients swallowed the placebo tablets on their first attempt and reported no problems taking the tablets.
- The SYMTUZA placebo tablets were rated as easy to swallow by 93% (25/27) of patients.
- The acceptability of taking a SYMTUZA tablet every day over a long period was rated good by 52% (14/27) of patients and acceptable by 41% (11/27).

ADDITIONAL STUDIES WITH DRV + COBI

McFarland Study (GS-US-216-0128)

McFarland et al (2017)[2] conducted a study in HIV-1–infected adolescents in order to determine pharmacokinetics (PK), safety, and efficacy of switching from DRV/RTV or atazanavir (ATV)/RTV to DRV + COBI or ATV + COBI, both in combination with 2 NRTIs.

Study Design/Methods

- Open-label switch study.
- HIV-1-infected, virologically-suppressed adolescents 12 to <18 years of age that were receiving DRV/RTV + 2 NRTIs or ATV/RTV + 2 NRTIs, had VL <50 copies/mL for ≥3 months, CD4+ count ≥200 cells/µL, and estimated glomerular filtration rate (eGFR) ≥90 mL/min/1.73 m^2 were eligible for inclusion.
- Patients received COBI 150 mg QD (adult dose), along with 1 of the following protease inhibitors (weight-based, QD dose): DRV 800 mg for ≥40 kg or 675 mg for 30 to <40 kg; ATV 300 mg for ≥40 kg or 200 mg for 20 to <40 kg.
- Other than PK, all other results were pooled.

Results

Baseline Characteristics

- There were 22 patients enrolled, eight (36%) who received DRV + COBI and 14 (64%) who received ATV + COBI.
- The median age was 14 years (range, 12-17 years).
- Median (quartile [Q] 1, Q3) duration of study drug exposure was 48 weeks (40, 61).

PK

- In the 7 DRV + COBI patients with PK data, the mean area under the curve for the dosing interval (AUC_{tau}) (% coefficient of variation [CV]) of DRV was found to be 81,200 (30) ng·h/mL, compared to a historical value of 81,600 (32) ng·h/mL in adult patients who received DRV 800 mg + COBI 150 mg QD in study GS-US-216-0130.
- The mean (%CV) DRV trough (C_{tau}) was 1310 (99) ng/mL, compared to a historical value of 1310 (74) ng/mL in adult patients.

- Median DRV exposures were also observed to be similar to those seen in adults, with the exception of a slightly lower C_{tau} level.
    - The median DRV C_{tau} level (494 ng/mL) was 9-fold above the half maximal inhibitory concentration (IC_{50}; 55 ng/mL).

Safety

- Study drug-related adverse events (AEs) were reported in 4/22 (18%) patients and were either grade 1 or 2. These included nausea (n=2), hyperlipidemia (n=2), decreased appetite (n=1), dyspepsia (n=1), and vomiting (n=1).
- Grade 3-4 AEs were reported in 3/22 (14%) and serious AEs were reported in 5/22 (23%); none were considered related to study drug.
- None of the patients discontinued treatment due to AEs, nor were any deaths reported.
- A small decline in median eGFR (-6.7 mL/min/1.73 m^2) was noted and expected with COBI, which inhibits tubular secretion of creatinine.

Efficacy (Week 12)

- A total of 21/22 (95.5%) patients had VL<50 copies/mL (1 patient, who withdrew consent at week 8, had undetectable VL at withdrawal).
- Median (Q1, Q3) change in CD4+ cell count: -16 cells/μL (-254, 151).

Dalton Study

Dalton et al (2019)[4] evaluated the tolerability and efficacy of DRV/COBI in 15 children.

Study Design/Methods

- This was a retrospective study using data from 2 National Health Service Trusts in the United Kingdom.

Results

Patient Characteristics[4]

	DRV/COBI (N=15)
Age at initiation, median (range), years	16 (14-17)
Duration of treatment with DRV/COBI, median (range), months	15 (2-27)
Weight change, median (range), kg	+1.69 (-1.7 to +4.7)
Backbone NRTIs, n	
FTC/TDF	10
FTC/TAF	3
ABC/3TC	2
CD4+ count	
At initiation, median (range), cells/μL	673 (397-995)
Latest, median (range), cells/μL	719 (169-1180)
% Change ALT, unit/L	-5.2%
Number of patients with a rise above ULN, n	0
% Change creatinine, μmol/L	+14%
Number of patients with a rise above ULN, n	0
VL of<200 copies/mL	
At initiation, %	60
Range, copies/mL	<20-60,321
Latest, %	67
Range, copies/mL	<20-9822

Abbreviations: ABC/3TC, abacavir/lamivudine; ALT, alanine aminotransferase; COBI, cobicistat; DRV, darunavir; FTC/TAF, emtricitabine/tenofovir alafenamide; FTC/TDF, emtricitabine/tenofovir disoproxil fumarate; ULN, upper limit of normal; VL, viral load.

- In 6/15 (40%) of the patients starting DRV/COBI, the only change in their regimen was the switch from RTV to COBI.
- At the time of data collection, 8/15 patients (53%) had stopped DRV/COBI (nausea/taste: n=3, poor adherence: n=3, simplification: n=1, and pill size: n=1).
- Patients who were suppressed at study entry maintained viral suppression.
- In patients with virological failure, no new HIV-1 associated resistance mutations were observed.

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 25 October 2023.

REFERENCES

1. Data on File. Darunavir/Cobicistat/Emtricitabine/Tenofovir alafenamide. Company Core Data Sheet. Janssen Research & Development, LLC. EDMS-ERI-119231875; December 2021.

2. McFarland E, Heresi G, Batra J, et al. Pharmacokinetics, safety, and efficacy of atazanavir or darunavir with cobicistat in adolescents (12 to <18 years of age). Poster 425 presented at: The 2017 Conference on Retroviruses and Opportunistic Infections (CROI); February 13-16; Seattle, WA.

3. Crauwels H, Chetty P, Opsomer M, et al. Assessment of the acceptability and swallowability of darunavir-containing fixed-dose combination (FDC) tablets in adolescents living with HIV-1, using matched placebo tablets. Poster presented at: HIV Glasgow Drug Therapy Meeting; October 28-31, 2018; Glasgow, UK.

4. Dalton C, Reis-Melo A, McGarrity O, et al. An evaluation of the tolerability and efficacy of the off license use of Rezolsta and Evotaz in children. Poster presented at: 25th Annual Conference of the British HIV Association (BHIVA 2019); April 2-5, 2019; Bournemouth, UK.