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

SUMMARY

- Treatment with darunavir (DRV) boosted with cobicistat (COBI) during pregnancy results in low DRV exposure. Therefore, therapy with the single-tablet regimen (STR) SYMTUZA should not be initiated during pregnancy, and women who become pregnant during therapy with SYMTUZA should be switched to an alternative regimen. DRV/ritonavir (r) in combination with emtricitabine (FTC)/tenofovir alafenamide (TAF) may be considered as an alternative.[1]
- The Antiretroviral Pregnancy Registry (APR) is a pregnancy exposure registry that monitors pregnancy outcomes in individuals exposed to antiretroviral (ARV) agents during pregnancy, including SYMTUZA.[2]
    - For DRV, COBI, and TAF, sufficient numbers of first trimester exposures have been monitored to detect at least a two-fold increase in risk of overall birth defects. No such increases have been detected to date.
    - For FTC, sufficient numbers of first trimester exposures have been monitored to detect at least a 1.5-fold increase in risk of overall birth defects and a 2-fold increase in risk of birth defects in the more common classes, cardiovascular and genitourinary systems. No such increases have been detected to date.
- In a phase 3b study, DRV and COBI exposures in women receiving the fixed-dose combination DRV/COBI were substantially lower during pregnancy than postpartum (PP). No evidence of mother to child transmission was observed, and 5 of 6 women who completed the study were virologically suppressed.[3]
- DRV and COBI exposures were also significantly lower during pregnancy compared to PP in women in the IMPAACT P1026s study.[4]

RELATED DATA WITH DRV/COBI

Phase 3b, Open-label Study

A phase 3b study (NCT00855335) was conducted to investigate the pharmacokinetics (PK), efficacy, and safety of DRV/COBI during the 2nd and 3rd trimesters compared to PP in HIV-1 infected pregnant women.[3]

Study Design/Methods

- Phase 3b, open-label, multicenter study.
- Adult HIV-1 infected women between 18-26 weeks gestation receiving DRV/COBI at study entry were included.
- Patients received DRV/COBI 800/150 mg once daily plus a background ARV regimen.
- Adherence to study medication was assessed by patient-reported missed doses (in the 4 days preceding a study visit) and pill counts. In addition, DRV predose concentrations below the limit of quantification (BLQ) were considered an indication of suboptimal adherence.
- Blood samples for PK analysis were obtained over a 24-hour period at study visits during the 2nd and 3rd trimesters (24-28 and 34-38 weeks of gestation, respectively) and between 6-12 weeks PP (reference).
- Matching cord blood and maternal plasma samples were taken at the intrapartum visit, when feasible.
- Antiviral response (viral load [VL] <50 copies/mL) and immunological response were evaluated at each study visit.
- Maternal safety was evaluated based on adverse events (AEs), clinical laboratory tests, and vital sign measurements. Infant AEs were also assessed.

Results

Baseline Characteristics

- Seven women with a median (range) age of 27 (24-36) years were enrolled.
- Five out of seven (71%) were black or African American.
- The median (range) time since HIV-1 infection diagnosis was 0.9 (0.2-20) years.
- Median baseline CD4+ count was 671 (range, 230-892) cells/μL.
- Four (57%) women had a baseline VL <50 copies/mL; the remaining 3 women had a VL of 65, 79, and 1140 copies/mL.
- All 7 women had a clinical stage of HIV-1 infection at the time of screening that was classified as category A and used 2 nucleos(t)ide reverse transcriptase inhibitors in their background regimen at baseline.
- Five (71%) women had used ≤4 ARVs prior to their regimen at study enrollment.
- Genotyping and phenotyping were performed in 2 (29%) women at screening or baseline and both showed sensitivity to all ARVs tested.
    - One woman had 4 PI resistance-associated mutations (RAMs; M36I, D60E, I62V, and L63P). None were primary PI or DRV RAMs.
    - The other woman had 4 PI RAMs (L10I, I13V, L63P, and V77I), 1 primary PI RAM (M46L), 1 DRV RAM (V11I), and 1 nonnucleoside reverse transcriptase inhibitor RAM (V179L).
    - Enrollment of the second woman with the DRV RAM was a protocol violation; however, because she was sensitive to DRV and her VL at the 2nd trimester visit was <50 copies/mL, she remained in the study.
- The median (range) duration of DRV/COBI intake in the study was 22.7 (3-25.4) weeks, including 13.9 (3-18.6) weeks prebirth and 7.8 (6.9-11.4) weeks postbirth.
- Five of 7 (71%) women were fully adherent (ie, 0 patient-reported missed doses in the 4 preceding days) at at least 3 of the 4 study visits.
- Six patients completed the study; 1 discontinued during the 2nd trimester due to nonadherence but was included in the 2nd trimester PK evaluation.
- Six infants were born to the 6 women who completed the study (2 spontaneous deliveries and 4 caesarean sections).

Pharmacokinetics

- PK data were available for 7 patients during the 2nd trimester and 6 patients during the 3rd trimester and PP (see Table: Median (Range) PK Parameters and Within-Patient Comparisons for Total and Unbound DRV and COBI During Pregnancy and Postpartum).

Median (Range) PK Parameters and Within-Patient Comparisons for Total and Unbound DRV and COBI During Pregnancy and Postpartum[3]

	Second trimester (24-28 weeks of gestation) (n=7)	Third trimester (34-38 weeks of gestation) (n=6)	Postpartum (6-12 weeks postpartum) (n=6)	LSM ratio (95% CI)	
				Second trimester (n=7) versus postpartum (n=6)	Third trimester (n=6) versus postpartum (n=6)
Total DRV[a]					
C_{0h}, ng/mL	435 (BLQ-2300)	624 (247-1850)	2625 (BLQ-5820)	ND	ND
C_{min}, ng/mL[b]	134 (BLQ-369)	162 (50.9-304)	1381 (BLQ-3220)	0.08 (0.01-0.50)	0.11 (0.04-0.30)
C_{max}, ng/mL	4710 (1050-5760)	4855 (3530-6210)	7445 (5880-12,000)	0.51 (0.30-0.86)	0.63 (0.50-0.79)
t_{max}, h	4.00 (3.00-6.00)	3.50 (2.00-6.00)	4.00 (2.00-6.00)	ND	ND

AUC_{24h}, ng▪h/mL	52,009 (10,547-71,497)	50,214 (34,068-57,509)	91,644 (64,573-157,934)	0.44 (0.24-0.80)	0.50 (0.37-0.66)
Unbound DRV					
C_{0h}, ng/mL	56.5 (BLQ-361)	89.2 (56.7-439)	399 (BLQ-826)	ND	ND
C_{min}, ng/mL[c]	17.5 (BLQ-54.1)	31.2 (9.35-57.3)	229 (BLQ-420)	0.08 (0.02-0.42)	0.12 (0.05-0.27)
C_{max}, ng/mL	945 (168-1110)	1058 (777-1109)	1199 (866-2065)	0.59 (0.34-1.02)	0.77 (0.59-1.00)
t_{max}, h	4.05 (1.03-6.00)	4.00 (2.00-4.00)	3.50 (2.00-6.00)	ND	ND
AUC_{24h}, ng▪h/mL	9725 (1885-12,310)	8883 (6132-11,883)	15,429 (6958-23,792)	0.55 (0.28-1.06)	0.60 (0.44-0.83)
COBI					
C_{min}, ng/mL	BLQ (BLQ-10.0)	BLQ (BLQ-7.02)	29.1 (BLQ-134)	0.17 (0.05-0.61)	0.17 (0.04-0.74)
C_{max}, ng/mL[d]	523 (173-1190)	671 (365-1430)	971 (629-1460)	0.50 (0.28-0.91)	0.73 (0.52-1.02)
t_{max}, h	4.03 (2.00-6.00)	3.50 (2.00-4.00)	4.00 (2.00-4.00)	ND	ND
AUC_{24h}, ng▪h/mL	3654 (1088-8892)	4072 (1963-10379)	9424 (4801-11989)	0.37 (0.17-0.79)	0.51 (0.33-0.80)

Abbreviations: AUC_{24h}, area under the plasma concentration-time curve over 24 hours; BLQ, below the limit of quantification; C_{0h}, predose plasma concentration; CI, confidence interval; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; COBI, cobicistat; DRV, darunavir; LLOQ, lower limit of quantification; LSM, least squares mean; ND, not determined; PK, pharmacokinetic; SD, standard deviation; t_{max}, time to reach the maximum plasma concentration.

[a]The postpartum visit DRV AUC_{24h} and C_{0h} were similar to those observed in a historical phase 3b study of HIV-1-infected adults treated with a DRV/COBI-based regimen (mean±SD AUC_{24h}: 102,000±33,100 ng·h/mL; C_{0h}: 2150±1320 ng/mL.

[b]For within-subject comparisons, BLQ values were excluded for C_{min}; second trimester, n=6; third trimester, n=6; and postpartum, n=5. Statistical analyses were also performed including the BLQ values (included as 0.5 x LLOQ); the LSM ratio (90% CI) for the second trimester versus postpartum was 10.65 (0.48-236.11), and for the third trimester versus postpartum was 32.17 (2.57-402.89).

[c]For within-patient comparisons, BLQ values were excluded for C_{min}; second trimester, n=6; third trimester, n=6; and postpartum, n=5. Statistical analyses were also performed including the BLQ values (included as 0.5 x LLOQ); the LSM ratio (90% CI) for the second trimester versus postpartum was 11.66 (0.50-270.52), and for the third trimester versus postpartum was 37.39 (2.87-486.86).

[d]For within-patient comparisons, BLQ values were included as 0.5 x LLOQ.

- Total DRV exposure was lower during pregnancy than PP (area under the plasma concentration-time curve over 24 hours [AUC_{24h}], 50-56% lower; maximum plasma concentration [C_{max}], 37-49% lower; minimum plasma concentration [C_{min}], 89-92% lower).
- Unbound DRV concentrations were also lower during pregnancy than PP (AUC_{24h}, 40-45% lower; C_{max}, 23-41% lower; C_{min}, 88-92% lower).
- The median cord:maternal plasma ratio was 16.1% (range 12.3%-31.5%; n=5) for total DRV and 32.4% (29.1%-62.6%; n=4) for unbound DRV.
- COBI exposure was also lower during pregnancy than PP (AUC_{24h}, 49-63% lower; C_{max}, 27-50% lower; and C_{min}, 83% lower).
- The median cord:maternal plasma ratio of COBI on the day of delivery was evaluable for 2 women (10% and 7.7%, respectively). COBI concentrations were undetectable in maternal and cord blood for 2 women and in cord blood alone for another women (whose maternal plasma COBI concentration was 18 ng/mL). For 1 other woman, there were no PK samples taken on the day of delivery.

Efficacy Results

- At baseline, 3 of 6 (50%) women with available data showed virological suppression.

- Viral suppression was achieved or maintained in 6 of 7 (86%) women at the 2nd trimester visit, 5 of 6 (83%) women at the 3rd trimester visit, and 5 of 6 (83%) women at study completion (6-12 week PP visit).
- One woman was considered to have virological failure but completed the study.
  - Her VL at screening was between 50 and <400 copies/mL.
  - An initial decrease was observed at the 2nd trimester visit; however, her VL was ≥1000 copies/mL from the 3rd trimester visit until the 4-week follow-up visit.
  - She used DRV/COBI + lamivudine (3TC) + zidovudine (AZT) through delivery, and intravenous AZT was added on the day of delivery. From then on, she continued using DRV/COBI with a background therapy of FTC + tenofovir disoproxil fumarate (TDF).
  - She was considered nonadherent.
  - No emerging RAMs were observed, and susceptibility to ARVs was maintained.
- The median (range) CD4+ count increased from 671 (230-892) cells/μL at baseline to 815 (394-1343) cells/μL at the 6-12 week PP visit.
- No mother-to-child transmission was observed in the 6 infants born to the patients who completed the study.

Safety Results

- Five patients reported adverse events AEs.
  - None of the reported AEs were considered at least possibly related to the study drug.
  - The most common AE was vulvovaginal mycotic infection (n=2).
  - One patient experienced a serious AE, which was a grade 2 increase in blood pressure and was resolved after 3 days. About 3 weeks later the patient had another non-serious increase in blood pressure that resolved 8 days afterward. The investigator considered both episodes to be related to the pregnancy and not the therapy.
- There was no discontinuation of study drug due to AEs.
- Overall, 4 infants experienced at least 1 AE.
  - All AEs were grade 1 or 2.
  - The most common occurring AE was neonatal jaundice (n=2).
  - Serious AEs (omphalitis and transient tachypnea of the newborn) were reported for 2 infants.
  - For 2 infants, the reported AEs (omphalitis and neonatal jaundice) were considered by the investigator to be related to pregnancy.
  - There were no instances of neural tube defects.
  - Relatedness to study medication was not assessed for infant AEs.

IMPAACT P1026s Study

Momper et al (2021)[4] evaluated the PK of DRV when coformulated with COBI during the 2nd and 3rd trimesters compared to PP in HIV-1 infected pregnant women enrolled in the IMPAACT P1026s Study. The PK profile of DRV/COBI was also assessed in infants.

Study Design/Methods

- The IMPAACT P1026s study is a multicenter, international, open-label prospective study of antiretroviral PK in HIV-infected pregnant women.
- Data from patients receiving DRV/COBI 800/150 mg QD were reported.
- Intensive steady-state 24-hour PK profiles of DRV were performed during the 2nd trimester (2T; 20-26 weeks gestation), 3rd trimester (3T; 30-38 weeks gestation), and PP (6-12 weeks post-delivery).
- Four plasma samples were collected from infants after birth.

Results

Clinical Characteristics

- Twenty-nine women with median age of 27.4 years (range 17.2-43.2) were enrolled.
- Concomitant medications included the following:
  - 2T visit: FTC (n=10), TAF (n=8), 3TC (n=6), AZT (n=6), TDF (n=2), dolutegravir (n=1), lopinavir (n=1), ritonavir (n=1)
  - 3T visit: FTC (n=15), AZT (n=12), TAF (n=11), 3TC (n=9), TDF (n=4), dolutegravir (n=3), lopinavir (n=1), and ritonavir (n=1)
- The percentage of women virologically suppressed (HIV-1 RNA<50 copies/mL) was 68.8%, 84%, 86.2%, and 78.9% at 2T, 3T, delivery and PP, respectively.
- Twenty-six infants (93%) tested negative for HIV and 2 infants had no testing data available.

Pharmacokinetics

- PK data were available for 16 women at 2T, 26 women at 3T, and 19 women at PP.
- PP PK data were excluded in one woman as DRV and COBI plasma concentrations were below or near limit of quantitation of both the DRV and COBI assays.
- PK parameters are in Table: Maternal Darunavir and Cobicistat Pharmacokinetic Parameters.
- A total of 3/16, 4/26, and 14/20 women met the DRV AUC_{0-24} target (70.4 µg*h/mL) at 2T, 3T, and PP, respectively.
- A total of 6/16, 8/26, and 1/20 women had 24-hour DRV trough concentrations below the limit of quantitation of the assay (0.09 µg/mL) at 2T, 3T, and PP, respectively.
- Of the 20 maternal plasma samples at delivery, 6 maternal plasma samples were below the lower limit of quantitation of the assay for each DRV (0.09 µg/mL) and COBI (4.9 µg/mL). Of the 19 cord blood samples, 15 and 13 cord blood samples were below the lower limit of quantitation of the assay for DRV and COBI, respectively.
  - The median concentration (interquartile range [IQR]) of DRV and COBI in maternal plasma (n=20) at delivery was 0.61 µg/mL (0.045-1.78) and 27.1 ng/mL (2.45-112.3), respectively.
  - The highest concentration of DRV and COBI seen in cord blood was 0.30 µg/mL and 60.6 ng/mL, respectively.
  - The median (IQR) ratio of cord blood to maternal plasma was 0.07 (0.03-0.15) for DRV (n=13 sets of paired samples) and 0.08 (0.05-0.12) for COBI (n=14 sets of paired samples).
- Eighty-five washout samples were collected after birth from 26 infants. In 17 infants, all samples were below the quantitation limit for DRV, and in the remaining 9 infants, the median maximum observed plasma concentration was 0.43 µg/mL (IQR, 0.27-2.23).

Maternal Darunavir and Cobicistat Pharmacokinetic Parameters, median (IQR)[4]

Parameter	2T (n=16)	3T (n=26)	PP (n=19)	GMR (90% CI) 2T/PP (n=12)	GMR (90% CI) 3T/PP (n=18)
Darunavir					
AUC_{0-24} (µg*h/mL)	50.00 (27.03-58.90)	42.05 (26.83-50.50)	95.55 (67.20-118.95)	0.47[a] (0.33-0.68)	0.44[a] (0.36-0.54)
C_0 (µg/mL)	0.28 (0.045-0.60)	0.25 (0.045-1.13)	1.62 (0.045-3.44)	0.29[a] (0.07-1.16)	0.32[a] (0.10-1.05)
C_{max} (µg/mL)	4.59 (2.38-6.12)	3.67 (3.29-4.65)	7.04 (5.70-10.75)	0.56[a] (0.41-0.76)	0.54[a] (0.46-0.63)
T_{max} (h)	3 (2-4)	2 (2-4)	2 (2-4)	-	-
C_{24} (µg/mL)	0.33 (0.045-0.47)	0.27 (0.045-0.63)	1.43 (0.73-1.86)	0.15[a] (0.08-0.30)	0.21[a] (0.12-0.36)
C_{min} (µg/mL)	0.33 (0.045-0.47)	0.25 (0.045-0.45)	1.34 (0.56-1.86)	0.15[a] (0.08-0.30)	0.21[a] (0.11-0.38)
CL/F (l/h)	16.00 (13.64-29.74)	19.04 (15.84-29.82)	8.37 (6.73-11.91)	2.12[a] (1.47-3.05)	2.28[a] (1.87-2.77)
$T_{1/2}$ (h)	4.80	5.18	8.11	0.55[a]	0.62[a]

	(3.91-6.07)	(3.76-6.61)	(6.19-10.55)	(0.44-0.67)	(0.50-0.76)
Cobicistat					
AUC_{0-24} (µg*h/mL)	4.46 (3.21-5.69)	3.91 (3.15-6.24)	8.52 (6.28-11.39)	0.50[a] (0.36-0.69)	0.44[a] (0.35-0.55)
C_0 (ng/mL)	4.1 (2.5-10.8)	7.2 (2.5-26.3)	28.5 (2.5-171.0)	0.28 (0.07-1.10)	0.31[a] (0.09-1.07)
C_{max} (ng/mL)	713.5 (525.0-1050.5)	662.5 (497.0-969.0)	1190.0 (838.0-1300.0)	0.63[a] (0.51-0.78)	0.58[a] (0.48-0.70)
T_{max} (h)	2 (1-3)	2 (1-4)	2 (1-4)	-	-
C_{24} (ng/mL)	4.4 (2.45-8.9)	5.5 (2.45-8.8)	16.5 (7.2-50.1)	0.40[a] (0.23-0.69)	0.26[a] (0.16-0.43)
C_{min} (ng/mL)	3.3 (2.45-7.7)	5.5 (2.45-8.8)	12.0 (7.2-30.9)	0.32[a] (0.20-0.53)	0.29[a] (0.16-0.52)
CL/F (l/h)	33.67 (26.39-46.68)	38.38 (24.05-47.60)	17.61 (13.17-23.88)	2.01[a] (1.45-2.77)	2.27[a] (1.82-2.83)
$T_{1/2}$ (h)	2.87 (2.28-3.43)	2.81 (2.27-3.31)	3.43 (2.99-4.53)	0.86[a] (0.70-1.06)	0.75[a] (0.65-0.86)

Abbreviations: AUC, area under the concentration-time curve; CI, confidence interval; CL/F, apparent oral clearance; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; C_0, predose plasma concentration; C_{24}, last plasma concentration; GMR, geometric mean ratio; IQR, interquartile range; PP, postpartum; T_{max}, time of maximum plasma concentration; $T_{1/2}$, terminal elimination half-life; 2T, second trimester; 3T, third trimester.
[a]*P*<0.10 compared with PP

Safety Results

- Nine women reported grade 3 or higher AEs. All were unrelated to study drug except for preterm labor in two women which was possibly treatment related.
  - Grade 3-4 AEs reported included anemia (n=5), preterm delivery (n=2), severe pre-eclampsia (n=1), hypercalcemia (n=1), hyperglycemia (n=1), and hyperkalemia (n=1).[5]
- Grade 3 or higher AEs were reported in 6 infants and all but 1 were unrelated to study drug.
  - Grade 2 perimembranous ventricular septal defect was reported in one infant which was considered possibly treatment related.
- Birth abnormalities were reported in 6 infants including perimembranous ventricular septal defect and a patent foramen ovale, sacral dimple, congenital anemia from ABO incompatibility, bilateral undescended testes and inguinal hernias, ankyloglossia (tongue tie), and slate gray nevi (Mongolian blue spots).

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 29 March 2023.

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