PREZCOBIX® (darunavir/cobicistat)
Use of PREZCOBIX in Pregnancy

SUMMARY

- Treatment with darunavir (DRV) boosted with cobicistat (COBI) during pregnancy results in low DRV exposure. Therefore, therapy with PREZCOBIX should not be initiated during pregnancy, and women who become pregnant during therapy with PREZCOBIX should be switched to an alternative regimen. DRV boosted with ritonavir 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 PREZCOBIX.[2]
    - For DRV and COBI, 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.
- In a phase 3b study, DRV and COBI exposures 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 receiving PREZCOBIX in the IMPAACT P1026s study.[4]

CLINICAL DATA

Phase 3b, Open-label Study

A phase 3b study (NCT00855335) was conducted to investigate the pharmacokinetics (PK), efficacy, and safety of PREZCOBIX 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 PREZCOBIX at study entry were included.
- Patients received PREZCOBIX 800/150 mg QD 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 (HIV-1 RNA <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 viral load <50 copies/mL; the remaining 3 women had a viral load 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 protease inhibitor (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 viral load at the 2nd trimester visit was <50 copies/mL, she remained in the study.
- The median (range) duration of PREZCOBIX 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 PREZCOBIX-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 viral load at screening was between 50 and <400 copies/mL.
  - An initial decrease was observed at the 2nd trimester visit; however, her viral load was ≥1000 copies/mL from the 3rd trimester visit until the 4-week follow-up visit.
  - She used PREZCOBIX + lamivudine (3TC) + zidovudine (AZT) through delivery, and intravenous AZT was added on the day of delivery. From then on, she continued using PREZCOBIX with a background therapy of emtricitabine (FTC) + tenofovir disoproxil fumarate (TDF).
  - She was considered nonadherent.
  - No emerging RAMs were observed.
  - 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 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 PREZCOBIX 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), tenofovir alafenamide (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 (3.91-6.07)	5.18 (3.76-6.61)	8.11 (6.19-10.55)	0.55[a] (0.44-0.67)	0.62[a] (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 Drug File (and/or other resources, including internal/external databases) pertaining to this topic was conducted on 31 May 2023.

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