CABOTEGRAVIR PHARMACOKINETIC TAIL IN PREGNANCY AND NEONATAL OUTCOMES

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Introduction

- Cabotegravir (CAB), an INSTI, is currently in development for HIV treatment as a long-acting (LA) injectable in combination with LA rilpivirine (RPV), an NNRTI, administered monthly or every 2 months. Phase 3 trials of CAB as a single agent for HIV pre-exposure prophylaxis (PrEP) are ongoing.
- Following discontinuation of CAB LA injections, detectable concentrations of CAB may persist in plasma for a year or longer.
- Nonclinical reproductive toxicology studies of CAB have not identified a birth defect risk at human supratherapeutic exposures.[1] An observation of fetal neural tube defects following dolutegravir (DTG) exposure in the first trimester remains under evaluation. CAB is structurally related to DTG.
- To date, this is the first evaluation of CAB pharmacokinetics (PK) and neonatal outcomes in women living with HIV (WLWH), who became pregnant in ViiV-sponsored clinical studies.

Methods

- In Phase 2/3 LA studies, CAB + RPV treatment was initiated with a short oral lead-in to assess individual tolerability followed by IM injections given monthly or every 2 months (Table 1).

Table 1. CAB + RPV Treatment and PK Sampling Scheme

Oral lead-in dosing (approximately 1 month)	Injectable maintenance dosing	
	Monthly	Every 2 months
CAB 30 mg + RPV 25 mg once daily	CAB LA 400 mg + RPV LA 600 mg	CAB LA 600 mg + RPV LA 900 mg

PK sampling scheme: pre-dose CAB at end of oral lead-in and prior to each injection. During long-term follow-up, CAB concentrations were obtained at 1 month and quarterly up to 52 weeks after last injection.

- Women of child-bearing potential (WOCBP) were required to use effective contraception on study and after the final injection during the 52-week long-term follow-up (LTFU) period. Urine pregnancy testing was assessed at baseline and prior to each injection. Women who became pregnant discontinued injections, began alternative HAART, and were requested to participate in LTFU.
- CAB PK was evaluated pre-pregnancy and following CAB LA discontinuation throughout pregnancy, at delivery, and post-partum in women participating in ViiV-sponsored studies who consented to PK sampling during pregnancy and had subsequent live births.

Results

- As of December 7, 2018, ≥594 WOCBP (HIV-infected or un-infected individuals <50 years of age) have been exposed to ≥1 dose of CAB (oral/LA) through Phase 3 in ViiV-sponsored and ViiV-supported clinical trials.
- Table 2 summarizes characteristics of women exposed to CAB at time of conception and subsequently confirmed to be pregnant in Phase 1 through 3 trials along with available obstetric history, pregnancy, and birth outcomes.
- 13 confirmed pregnancies following CAB exposure (9 on CAB LA; 4 on oral CAB) with known outcomes are listed in Table 2.
- 4/13 pregnancies resulted in live births (all exposed to CAB LA at pregnancy detection). CAB PK was summarized in 3/4 women.
  - 4th pregnancy occurred in an HIV-negative female exposed to CAB LA occurring during LTFU 8 months following the 5th and final CAB LA injection in the DAIDS-sponsored Phase 2b PrEP HPTN 077 study; PK was not summarized as case details pending.[2]
- 5/13 pregnancies were electively terminated, and 4/13 participants miscarried within the first 9 weeks of gestation.
  - No cases of birth defects have been reported.

Table 2. Summary of Confirmed Pregnancy Following CAB Exposure

Participant # (age range, years)	Past obstetric history	CAB exposure	Pregnancy outcome
1 (20-30)	None	CAB LA	Live birth (38 weeks) – no congenital anomaly reported
2 (30-40)	No pre-term and 2 full-term	CAB LA	Live birth (38 weeks) – no congenital anomaly reported
3 (20-30)	2 full-term normal births	CAB LA	Live birth (38 weeks) – no congenital anomaly reported
4 (20-30)[a]	1 prior spontaneous miscarriage	CAB LA	Live birth
5 (20-30)	1 normal live birth	CAB LA	Induced abortion at 10 weeks (non-medical reason)
6 (30-40)	2 full-term normal births	CAB LA	Induced abortion at 5 weeks (non-medical reason)
7 (30-40)	1 normal full-term birth, 3 pre-term (2 elective abortion, 1 stillbirth)	CAB LA	Induced abortion at 7 weeks (non-medical reason)
8 (30-40)	2 normal live births and 1 induced abortion	CAB LA	Induced abortion at 6 weeks GA (non-medical reason)
9 (20-30)[b]	2 full-term normal births, 1 stillbirth, 1 spontaneous abortion	CAB LA	Spontaneous abortion at 1 week GA
10 (30-40)	2 full-term pregnancies and 2 induced abortions	CAB oral	Medical abortion at 7 weeks GA
11 (40-50)	2 full-term pregnancies (normal births), 3 spontaneous abortions	CAB oral	Spontaneous abortion at 9 weeks GA
12 (20-30)	1 premature birth and 1 spontaneous abortion	CAB oral	Induced abortion at 7 weeks GA (medical reason)
13 (30-40)	2 previous pregnancies	CAB oral	Possible early miscarriage at 1-2 weeks GA

GA, gestational age. [a]Participant received oral CAB 30 mg × 5 weeks followed by 5 doses of CAB LA 600 mg IM every 2 months except for 1st 2 doses 4 weeks apart prior to pregnancy. [b]Participant received oral CAB 30 mg × 4 weeks followed by single CAB LA 600 mg IM dose prior to pregnancy.

- CAB PK was summarized for 3 WLWH with subsequent live birth outcomes (Table 3).
- All were receiving CAB LA + RPV LA monthly at time of conception for duration of 16 to 176 weeks pre-pregnancy (Table 3) and were virologically suppressed at time of pregnancy detection.
- Following pregnancy confirmation, all women discontinued CAB LA + RPV LA injections and started alternative HAART with HIV-1 RNA <50 copies/mL maintained throughout the LTFU period.

Table 3. Maternal CAB PK Profile Pre-Pregnancy and During PK Tail in Pregnancy and Post-Partum

Event	Maternal CAB concentration (μg/mL) Participant # (estimated gestational age in weeks)		
	Participant #1	Participant #2	Participant #3
Duration of CAB LA exposure prior to pregnancy (weeks)	16	176	32
Last available pre-pregnancy CAB trough concentration[a]	4.63	2.41	2.95
PK at pregnancy confirmation visit	4.83 (7 weeks)	2.10 (5 weeks)	5.04 (4 weeks)
LTFU PK 1	2.7 (15 weeks)	1.13 (14 weeks)	0.295 (13 weeks)
LTFU PK 2	1.13 (28 weeks)	0.439 (30 weeks)	Non-quantifiable (NQ) (28 weeks)
Predicted PK at delivery[b]	0.5 (39 weeks, healthy infant, birth weight 2800 g)	0.5 (37 weeks, healthy infant, birth weight 2666 g)	NQ (measured value) (38 weeks, healthy infant, birth weight unknown)
LTFU PK 3	0.82 (5 weeks post-partum)	0.578 (2 weeks post-partum)	NQ (6 weeks post-partum)
LTFU PK 4	0.054 (23 weeks post-partum)	0.353 (15 weeks post-partum)	NA

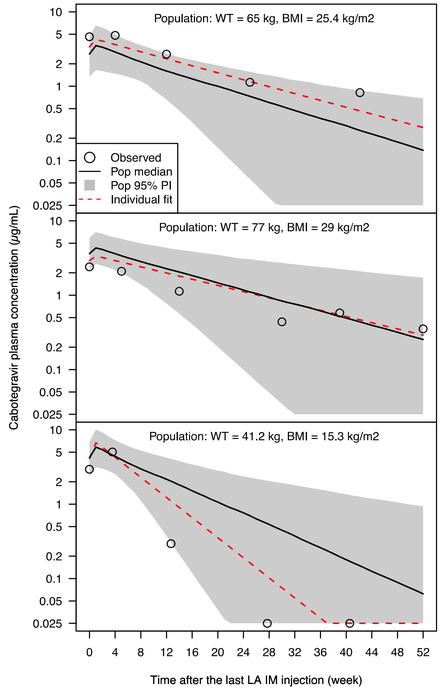
[a]Steady-state geometric mean (5th, 95th percentile) plasma CAB trough following 400 mg IM monthly dosing = 2.8 μg/mL (1.7, 4.6). [b]Prediction based on median half-life derived from population PK model.

- Pre-pregnancy CAB concentrations (range: 2.41-4.63 μg/mL) were within the expected range of 1.7 to 4.6 μg/mL at steady-state just prior to pregnancy identification and at time of pregnancy confirmation with HIV-1 RNA <50 copies/mL in all 3 women.
- After CAB LA discontinuation, residual CAB concentrations remained measurable throughout pregnancy in 2/3 women with predicted CAB concentrations equivalent to 3× protein-adjusted IC_{90} of 0.5 μg/mL (PA-IC_{90} = 0.166 μg/mL) at time of delivery.
- CAB concentrations remained measurable post-partum (range: 2-23 weeks) in 2/3 women. Low BMI (15.3 kg/m^2) may have contributed to faster decline of PK tail following discontinuation in the 3rd participant.
- Slow decline in CAB concentrations is consistent with absorption-rate limited PK following IM administration.

Discussion

- Following pregnancy confirmation and subsequent CAB LA withdrawal, systemic plasma CAB concentrations declined mono-exponentially as expected and similar to profiles in non-pregnant females. RPV concentrations in these participants were not assessed in this analysis.
- Unlike other drugs whose elimination can be affected by pregnancy, CAB's LA PK profile is primarily determined by its absorption rate, which appears to be unaffected by changes in metabolic enzymatic profile.
- In 3 women completing full-term pregnancies with CAB LA exposure, no drug-related adverse effects on maternal or neonatal health were reported.
- Additional CAB PK data from neonates and maternal breast milk will be informative.
- Data from pregnancies occurring in ongoing clinical studies will inform use of CAB in pregnancy.

Figure 1. Maternal CAB PK Tail Following CAB LA Discontinuation Throughout Pregnancy and Post-Partum



Conclusions

- Following pregnancy confirmation and discontinuation of CAB LA, CAB concentrations declined mono-exponentially during pregnancy with predicted CAB concentration 3× PA-IC_{90} at time of delivery in 2 of 3 WLWH with live birth outcomes.
- Rate of decline of CAB concentrations during the PK tail in pregnancy was within the expected range for non-pregnant women.
- Data from pregnancies occurring in ongoing clinical studies will inform use of CAB in pregnancy.

Acknowledgments: This study was funded by ViiV Healthcare. Editorial assistance and graphic design support for this poster were provided under the direction of the authors by MedThink SciCom and funded by ViiV Healthcare.

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