Maraviroc Safety & Pharmacokinetics In HIV-Exposed Neonates

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BACKGROUND

- Lack of safety and pharmacokinetic (PK) data in neonates limits options for HIV-1 prophylaxis and treatment.
- Maraviroc (MVC), a CCR5 receptor antagonist approved for treatment of HIV-1 infection in adults, is attractive as a potential component of neonatal antiretroviral therapy (ART).
- MVC is available as an oral solution licensed for treatment of HIV-1 in children ≥2 years and ≥10kg.
- MVC is metabolized by CYP3A4 and in adults requires an increased dose when administered with efavirenz (EFC), a CYP3A4 inducer.

OBJECTIVES

- To evaluate the safety, tolerability, and PK of MVC during the first 6 weeks of life when administered with antiretroviral (ARV) prophylaxis to HIV-1 exposed infants with and without exposure to maternal EFV.
- To determine an appropriate dose of MVC solution during the first 6 weeks of life.

METHODS

- IMPAACT 2007 is a Phase I, multi-center, open label study designed to evaluate safety and PK of MVC in HIV-exposed neonates in addition to standard ARV prophylaxis.
- Two sequential dosing cohorts were enrolled.
- Cohort 1 infants received 8 mg/kg MVC oral solution as two single doses at entry and week 1, with intensive PK sampling after each dose.
  - Stratified by *in utero* exposure to maternal EFV:
    - **1A**: infants without *in utero* exposure to maternal EFV
    - **1B**: infants with *in utero* exposure to maternal EFV
- Cohort 2 infants received chronic dosing with 8 mg/kg MVC oral solution twice daily from entry through 6 weeks of life, with intensive PK sampling at weeks 1 and 4.
  - Dosing regimen based on PK data from Cohort 1
  - Stratified by exposure to maternal EFV during breastfeeding:
    - **2A**: infants without exposure to maternal EFV either *in utero* and/or during breastfeeding
    - **2B**: infants with exposure to maternal EFV both *in utero* and during breastfeeding
- PK samples were analyzed for MVC concentration by validated high-performance liquid chromatography.
- PK parameters were estimated using standard non-compartmental methods.
- MVC exposure target was C_{avg}≥ 75ng/mL, determined by adult treatment studies.
- Laboratory and clinical evaluations assessed infant safety at entry and weeks 1, 2, 6, and 16 in Cohort 1; weeks 1, 4, 6, 12, and 16 in Cohort 2.

MVC exposures met treatment PK targets in ~2/3 of infants receiving 8mg/kg BID, but with considerable variability. MVC appears safe and well-tolerated in the first 6 weeks of life.

METHODS (2)

- Primary (through 6 wks) and secondary (through 16 wks) safety endpoints:
  - Any life-threatening adverse event (AE), including death, assessed by the Core Protocol Team as at least possibly related to the study drug.
  - AEs of Grade 3+ judged by the Core Protocol Team to be probably or definitely related to the study drug, or that result in permanent discontinuation of study drug due to an AE, judged by the Core Protocol Team to be at least possibly related to study drug.

RESULTS: SAFETY

- Forty-seven MVC-naïve, HIV-exposed neonates and their mothers were enrolled: USA (20), Thailand (3), Kenya (2) and South Africa (22). (Table 1)
- No participants met safety endpoints at week 6 and through week 16 of follow-up as determined by the Core Protocol Team.
- No early study or early treatment discontinuations were noted due to MVC.
- No enrolled infant acquired HIV-1 infection during and through the end of follow-up.

Table 1. Infant Baseline Characteristics and Background ARVs (All Treated Infants)

	Cohort 1			Cohort 2		
	Cohort 1A N=8 (%)	Cohort 1B N=7 (%)	Total N=15 (%)	Cohort 2A N=16 (%)	Cohort 2B N=16 (%)	Total N=32 (%)
Sex						
F	5 (62.5)	4 (57.1)	9 (60)	7 (43.8)	7 (43.8)	14 (43.8)
Race						
Asian	0 (0)	0 (0)	0 (0)	3 (18.8)	0 (0)	3 (9.4)
Black or African American	5 (62.5)	7 (100)	12 (80)	10 (62.5)	16 (100)	26 (81.3)
White	3 (37.5)	0 (0)	3 (20)	3 (18.8)	0 (0)	3 (9.4)
Gestational age (weeks)						
Median	38.5	39.0	39.0	39.0	40.0	39.0
Q1,Q3	38.0,39.50	38.0,39.00	38.0,39.00	38.0,39.50	39.0,40.50	38.5,40.00
Birth Weight (kg)						
Median	3.2	3.4	3.3	3.0	3.0	3.0
Q1,Q3	2.8,3.50	2.9,3.64	2.9,3.54	2.9,3.19	2.8,3.16	2.8,3.18
Background ARVs NRTI Only						
3TC,ZDV	0 (0)	0 (0)	0 (0)	1 (6.3)	0 (0)	1 (3.1)
ZDV	7 (87.5)	0 (0)	7 (46.7)	11 (68.8)	0 (0)	11 (34.4)
NNRTI(+/- NRTI)						
3TC,NVP	0 (0)	0 (0)	0 (0)	3 (18.8)	0 (0)	3 (9.4)
NVP	0 (0)	7 (100)	7 (46.7)	0 (0)	12 (75.0)	12 (37.5)
NVP,ZDV	1 (12.5)	0 (0)	1 (6.7)	1 (6.3)	4 (25.0)	5 (15.6)

RESULTS: PK

Table 2: Cohort 2 PK Parameters by Study Strata[a]

		N	Dose (mg/kg)	AUC (ng*h/mL)	Cavg (ng/mL)	Cavg ≥ 75 ng/mL	Cmax (ng/mL)	Tmax (h)	t1/2 (h)
Week 1	**EFV-naïve (2A)**	13	8.5 [7.4-9.5]	1,827 [237-6,788]	152 [20-566]	**10 / 13 (77%)**	257 [52-1468]	1.5 [0.8-4.0]	3.6 [2.0-12.3]
	EFV-exposed (2B)	12	7.7 [6.8-8.3]	1,496 [205-6,610]	125 [17-551]	**8 / 12 (67%)**	309 [34-1274]	3.0 [1.0-6.2]	3.3 [2.2-5.6]
Week 4	**EFV-naïve (2A)**	13	7.5 [6.1-9.9]	1,123 [395-5,859]	94 [33-488]	**9 / 13 (69%)**	417 [125-793]	1.5 [1.0-4.0]	3.8 [2.0-16.1]
	EFV-exposed (2B)	12	7.4 [6.6-8.9]	1,217 [512-4,214]	101 [43-351]	**7 / 12 (58%)**	222 [77-739]	2.2 [0.0-11.4]	6.0 [2.3-144.0]

[a]Median [Min/Max] except for N, number of patients with C_{avg} ≥ 75 ng/mL, number/total (% achieving PK target); AUC=Area under the concentration time curve to infinity to 12 hours for Cohort 2 (steady-state); C_{avg} = average concentration (AUC divided by tau set to 12 hours); C_{max} = maximum observed concentration; T_{max} = time of C_{max}; $t_{1/2}$ = half-life.

Figure 1A: Plot of Median Plasma Maraviroc Concentration-Time (Linear) for Cohort 1 All Dose-Finding Evaluable Infants. Semi-Log data (inset).

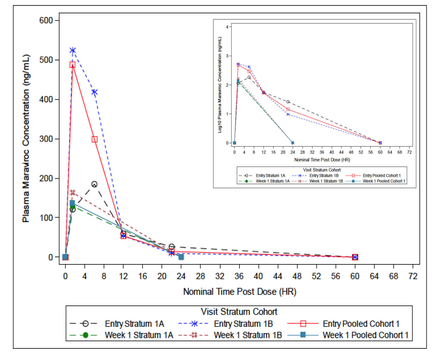
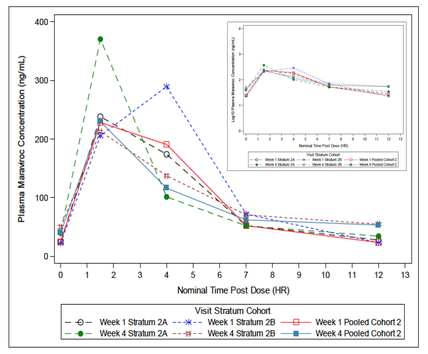


Figure 1B: Plot of Median Plasma Maraviroc Concentration-Time (Linear) for Cohort 2 All Dose-Finding Evaluable Infants. Semi-Log data (inset.)



Values below the Lower Limit of Quantification (<5.00ng/mL) are set to 0.

CONCLUSIONS

- MVC appears safe and well-tolerated in this cohort of neonates treated over the first 6 weeks of life and followed through 16 weeks of age.
- MVC exposures met treatment PK targets in ~2/3 of infants receiving 8mg/kg BID, but with considerable variability in exposure.
- Maternal EFV use appeared to have no effect on MVC exposure.
- MVC is a promising agent for prophylaxis and early treatment of HIV-1 exposed and infected neonates.

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