IMPAACT 2007

PHASE I SAFETY AND PHARMACOKINETIC STUDY OF MARAVIROC IN HIV-1-EXPOSED INFANTS AT RISK OF ACQUIRING HIV-1 INFECTION

VERSION 1.0, 13 APRIL 2016

LOA #1, 12 AUGUST 2016

RATIONALE

- Neonates need ARV's for prophylaxis against HIV transmission and early treatment of HIV infection, but there are few ARV's with neonatal PK data and an appropriate formulation for neonates.

- Maraviroc is a CCR5 receptor antagonist currently approved for use in adults with the potential to play an important role in both prophylaxis and early treatment of infants at high risk of HIV-1 infection.

- Before maraviroc can be studied as part of a prophylaxis regimen to prevent perinatal HIV transmission, a Phase I study to investigate safety and PK of maraviroc in neonates is needed.

PRIMARY OBJECTIVES

1. To evaluate the safety and tolerability of maraviroc solution, during the first six weeks of life, when administered with ARV prophylaxis to HIV-1 exposed infants at risk of acquiring HIV-1 infection with and without exposure to maternal EFV.
2. To evaluate the pharmacokinetics of maraviroc solution, during the first six weeks of life, when administered with ARV prophylaxis to HIV-1 exposed infants at risk of acquiring HIV-1 infection with and without exposure to maternal EFV.
3. To determine an appropriate dose of maraviroc solution during the first six weeks of life.

STUDY POPULATION

- Full-term infants (breastfeeding and formula feeding) born to an HIV-1 infected mother will be enrolled up to 3 days old.
- Infants will be enrolled in pairs with their mothers – only infants receive study drug. Mother-infant pairs are enrolled after delivery.
- Recruitment should typically begin during pregnancy with the study specific consent form process typically conducted during the 2nd and 3rd trimester of pregnancy however, the process may be conducted after birth

STUDY DESIGN
COHORT 1

- Single doses of maraviroc given at two time points: within 3 days of birth and Week 1 (7-14 days of life).

- Stratified by infant in-utero exposure to maternal EFV
  - Stratum 1A: n = 6-18 infants without *in utero* exposure to maternal EFV (no EFV exposure during the 8 weeks immediately prior to delivery).
  - Stratum 1B: n = 6-18 infants with *in utero* exposure to maternal EFV (EFV exposure for a minimum of 2 weeks immediately prior to delivery).

- Up to 36 mother-infant pairs to achieve a target of 12 evaluable infants (6 in each stratum) receiving the dose of maraviroc that passes safety and PK guidelines for the relevant stratum and is recommended for Cohort 2.

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Cohort 1: Stratum 1A and 1B – open concurrently
The following will apply to each stratum, independently.

Initial (n=6) infants
Maraviroc Regimen: Single doses of maraviroc solution at two time points: within 3 days of birth and Week 1 (7-14 days of life).
Intensive PK Evaluation: Birth and Week 1
Safety Evaluation: through 7-days Post Last Dose**; Follow-Up: 16 weeks**

Guidelines for evaluating the dose (n=6): Safety and PK

Meets safety and PK guidelines

Dose is established for corresponding Cohort 2 stratum, which then can open with this dose.

Dose does not meet safety and/or PK guidelines

Core Protocol team will evaluate whether to:

- Adjust the current dose and enroll new infants (n=6), evaluate safety and PK on the adjusted dose (as above) OR
- Continue current dose OR
- Stop the study

STUDY DESIGN COHORT 2

- Daily dosing of maraviroc starting within 3 days of birth and continuing up to 42 days of life. The dose will be determined from Cohort I PK data from the corresponding stratum.

<u>Stratified by infant exposure to maternal EFV after birth</u>

  - Stratum 2A: n = 12-18 infants without any exposure to maternal EFV either in utero or if breastfeeding while breastfeeding.
  - Stratum 2B: n = 12-18 breastfeeding infants with exposure to maternal EFV both in utero and after birth while breastfeeding.

- Up to 36 mother-infant pairs to achieve a target of 24 evaluable infants (12 in each stratum) receiving the final recommended dose of maraviroc that passes safety and PK guidelines for each stratum.

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Cohort 2: Stratum 2A or 2B – will open once the dose is established in the corresponding stratum from Cohort 1.
The following will apply to each stratum, independently.

Initial (n=6) infants

Maraviroc Regimen: Maraviroc solution dose determined from Cohort 1 corresponding stratum. Daily dosing starting within 3 days of birth and continued through Week 6 (35-42 days of life)

Intensive PK Evaluation: Weeks 1 and 4

Safety Evaluation: through Week 6 (35-42 days)

Follow-Up: 16 weeks

Guidelines for evaluating the dose (n=6): Safety and PK

Meets safety and PK guidelines

Enroll additional n=6 infants to complete full accrual of n=12 at the dose being tested, THEN perform PK and safety evaluations on the full cohort of n=12.

If safety and PK guidelines are met, the dose is established for the stratum.

Dose does not meet safety and/or PK guidelines

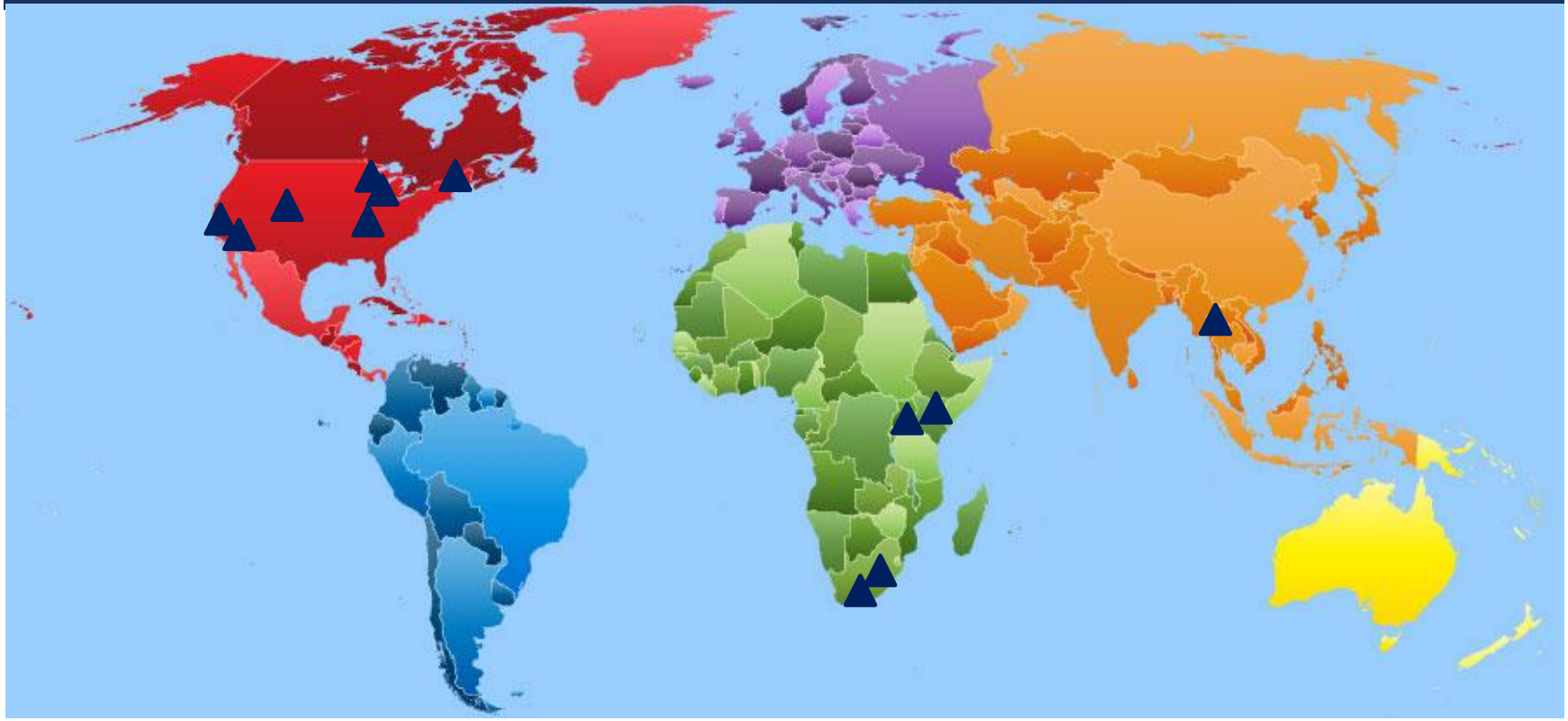
Core Protocol team will evaluate whether to:

- Adjust the current dose and enroll new infants (n=6), evaluate safety and PK on the adjusted dose (as above) OR
- Continue current dose OR
- Stop the study.

Dose does not meet safety and/or PK guidelines

STUDY STATUS

12 PARTICIPATING SITES ACROSS 5 COUNTRIES
OPEN TO ACCRUAL ON 1 MAY 2017



Kenya

South Africa (2)

Thailand

Uganda

United States (7)