IMPAACT P1090

A PHASE I/II, OPEN-LABEL TRIAL TO EVALUATE THE SAFETY, TOLERABILITY, PHARMACOKINETICS AND ANTIVIRAL ACTIVITY OF ETRAVIRINE (ETR) IN ANTIRETROVIRAL (ARV) TREATMENT-EXPERIENCED HIV-1 INFECTED INFANTS AND CHILDREN, AGED ≥2 MONTHS TO <6 YEARS

A Multicenter, Domestic & International Trial of
the International Maternal Pediatric Adolescent
AIDS Clinical Trials Group (IMPAACT)

Sponsored by:
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(NIAID)
and
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P1090 PROTOCOL TEAM ROSTER

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GLOSSARY

3TC	Lamivudine
ABC	Abacavir
AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
ALT	Alanine aminotransferase
ART	Antiretroviral therapy
ARV	Antiretroviral
AST	Aspartate aminotransferase
ATV	Atazanavir
AUC_{12h}	Area under the drug plasma concentration-time profile over 12 hours
BID	bis in die (twice daily)
C_{0h}	plasma concentration immediately prior to dosing
C_{12h}	plasma concentration at the end of the 12 hour dosing interval
C_{max}	Maximal observed plasma concentration during a dosing interval
C_{min}	Minimal observed plasma concentration during a dosing interval
CAP	College of American Pathologists
CART	Combination anti-retroviral therapy
cDNA	complementary DNA
CL/F	Apparent oral clearance
CLIA	Clinical Laboratory Improvement Amendments
CPK	Creatinine phosphokinase
CRPMC	Clinical Research Products Management Center
DAERS	DAIDS Adverse Experience Reporting System
DAIDS	Division of AIDS (United States)
DHHS	Department of Health & Human Services
DMC	Data Management Center
DNA	Deoxyribonucleic acid
DRV	Darunavir
DSMB	Data Safety and Monitoring Board
EAE	Expedited Adverse Event
EC	Ethics Committee
ECG	Electrocardiogram
EFV	Efavirenz
EIA	Enzyme immunoassay
EMA	European Medicines Agency
ETR	Etravirine
EU	European Union
FDA	Food and Drug Administration
FPV	Fosamprenavir
FTC	Emtricitabine
GI	Gastrointestinal
GM	Geometric mean
GMR	Geometric mean ratio
HIV	Human Immunodeficiency Virus

IB	Investigator's Brochure
IC_{50}	Half maximal inhibitory concentration
IMPAACT	International Maternal Pediatric Adolescent AIDS Clinical Trials Network
IgM	Immunoglobulin M
ICF	Informed consent form
IQ	Inhibitory quotient
INR	International normalized ratio
IRB	Institutional Review Board
ISRP	Independent Safety Review Panel
IUD	Intrauterine device
LAR	Legally authorized representative
LDH	Lactate dehydrogenase
LPV	Lopinavir
NIAID	National Institute of Allergy and Infectious Diseases
NICHD	National Institute of Child Health and Human Development
NIH	National Institutes of Health
NNRTI	Non-nucleoside reverse transcriptase inhibitors
NVP	Nevirapine
OBR	Optimized background regimen
OHRP	Office of Human Research Protections
PCR	Polymerase Chain Reaction
PI	Protease inhibitor
PID	Patient identifier
PK	Pharmacokinetic
PMTCT	Prevention of Mother to Child Transmission
PRO	Protocol Registration Office
QD	Quaque die (Once a day)
RAL	Raltegravir
RAM	Resistance associated mutations
RSC	Regulatory Support Center
RE	Regulatory entity
RNA	Ribonucleic acid
RTV	Ritonavir
SADR	Suspected adverse drug reaction
SAE	Serious adverse event
SDMC	Statistical and Data Management Center
sdNVP	Single dose nevirapine
SMC	Study Monitoring Committee
SUSAR	Suspected, unexpected serious adverse reaction
T_{max}	time at which C_{max} occurs
$T_{1/2}$	terminal elimination half-life
TB	Tuberculosis
TDF	Tenofovir disoproxil fumarate
TID	Ter in die (three times a day)
TPV	Tipranavir
ULN	Upper limit of normal

US	United States
WB	Western blot
Vd	Apparent volume of distribution
ZDV	Zidovudine

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SCHEMA
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A PHASE I/II, OPEN-LABEL TRIAL TO EVALUATE THE SAFETY, TOLERABILITY, PHARMACOKINETICS AND ANTIVIRAL ACTIVITY OF ETRAVIRINE (ETR) IN ANTIRETROVIRAL (ARV) TREATMENT-EXPERIENCED HIV-1 INFECTED INFANTS AND CHILDREN, AGED ≥2 MONTHS TO <6 YEARS

DESIGN: Phase I/II, multi-center, open-label, pharmacokinetic and safety study.

SAMPLE SIZE: It is expected that approximately 50 subjects will be accrued, to yield a minimum of 36 evaluable subjects (a minimum of 12 subjects in each cohort). Up to 18 subjects may be enrolled into Cohort I.
*See section 8.1 for definition of evaluable subjects

The total sample size will depend upon the number needed to complete the dose finding stage of the study, the number of subjects who discontinue the study and the number of subjects required for regulatory approval of etravirine in these populations.

POPULATION: HIV-infected treatment-experienced infants and children aged ≥ 2 months to < 6 years of age.

STRATIFICATION: This is a sequential study which started accrual with the oldest age cohort and will progress down to the youngest age cohort. Cohort III will open with the activation of Version 5.0.

Children will be stratified by age, as follows:

- Cohort I: ≥ 2 year to < 6 years who are treatment experienced*
- Cohort II: ≥ 1 year to < 2 years who are treatment experienced*
- Cohort III: ≥ 2 months to < 1 year who are treatment experienced*, †

*Treatment experienced children on a failing combination antiretroviral regimen (containing at least 3 ARVs) for at least 8 weeks OR Treatment experienced children on a treatment interruption of at least 4 weeks with a history of virologic failure while on a combination antiretroviral regimen (containing at least 3 ARVs)

† subjects below 6 months of age will only be enrolled upon availability of initial safety and PK data from subjects between 6 months and 1 year of age.

REGIMEN: Etravirine (ETR) will be administered as 25 mg scored tablets and/or 100 mg tablets swallowed as a whole or dispersed in an appropriate liquid vehicle (see Section 5.2). ETR will be started concurrently with an optimized background regimen (OBR), while OBR will be based on clinical status, treatment history, resistance data and availability of appropriate pediatric dosing and formulations. Refer to Section 3.1 and Table 6 for further information on regimen design per cohort.

STUDY DURATION: Minimum of 48 weeks

Long Term Safety Follow-up:
Subjects who successfully complete 48 weeks of ETR treatment will continue to receive ETR throughout the study, and be followed (see Appendix IE) for up to 5 years as part of long-term safety follow-up.

PRIMARY OBJECTIVES:

1. To evaluate the steady state pharmacokinetics of ETR in combination with an OBR in HIV-infected children aged ≥ 2 months to < 6 years.
2. To determine the safety and tolerability of ETR in combination with an OBR in children aged ≥ 2 months to < 6 years, through 48 weeks of therapy.
3. To determine the appropriate dose of ETR in combination with an OBR for children aged ≥ 2 months to < 6 years.

SECONDARY OBJECTIVES:

1. To assess the antiretroviral activity of ETR containing regimens through 48 weeks of therapy.
2. To determine the immunological changes (change in CD4 percent and absolute count; CD4/CD8 ratio and percent) through 48 weeks of ETR therapy in combination with an OBR.
3. To determine changes in viral drug resistance during 48 weeks of ETR therapy in combination with an OBR.
4. To assess the relationship between ETR pharmacokinetics and the antiviral activity and safety of ETR containing regimens.
5. To explore the relationship between subject-specific gene CYP profile, sex, age, weight, race, HIV regimen (e.g., boosted PI) and HIV response markers and pharmacokinetics of ETR.

1.0 **INTRODUCTION**

1.1 Background

Nevirapine (NVP) and efavirenz (EFV), the two most widely used NNRTI drugs, have a low genetic barrier for the development of drug resistance mutations, so that a single amino acid substitution in the viral reverse transcriptase (RT), such as K103N, leads to profound reduction in viral susceptibility to both drugs, conferring cross resistance with other agents in this class. Among HIV-infected Thai children failing a non-nucleoside reverse transcriptase inhibitor (NNRTI) based regimen, 97% had NNRTI-related resistance. The most common NNRTI related mutations were Y181C/I, in 58% of subjects, and 34% of subjects had the K103N mutation (1).

Short term use of these NNRTIs can select for NNRTI resistance mutations even after a single dose, as has been documented for NVP when used to prevent maternal to child transmission (PMTCT). A meta-analysis estimated NVP resistance in 52.5% of infants exposed only to single dose (sd) NVP and in 16.5% of infants receiving sdNVP with other postnatal antiretrovirals (2).

Early detection of NNRTI resistance mutations among infants at 6 to 8 weeks of life who had perinatal exposure to sdNVP has been reported at 46% for a Ugandan cohort (3) and 87% for a Malawian cohort (4). Similar confirmatory reports have emerged from South Africa (5) and India (6). In the P1060 IMPAACT treatment study, 12% of PMTCT-exposed infants who were 6 to 36 months of age at enrollment had baseline resistance to first generation NNRTIs (15/18 carried the Y181C mutation, and 3/18 the K103N) (7). The trial demonstrated superiority of a lopinavir/ritonavir-based first line treatment regimen in infants when compared with a NVP- based regimen in the setting of prior sdNVP-exposure and led to changes in the WHO pediatric treatment guidelines (8). The duration of persistence of these NNRTI mutations in individuals receiving MTCT prophylaxis regimens is not known and is the subject of ongoing studies.

With the widespread use of first generation NNRTIs (NVP and EFV) as components of combination antiretroviral therapy (cART), NVP as a component of neonatal PMTCT treatment regimens, and infant exposure to NVP during breastfeeding, the number of children harboring virus with one or two NNRTI-resistance mutations will continue to increase. Thus, there is an urgent need to develop alternative therapeutic options for newly diagnosed neonates and infants exposed to sdNVP containing regimens, as well as for infants and children failing their present cART regimens.

1.2 Etravirine Background

1.21 General

ETR (TMC125 from Janssen R&D) is a second generation NNRTI and has a diarylpyrimidine-based structure providing molecular flexibility relative to other NNRTIs, allowing ETR to maintain its binding affinity for HIV-1 reverse transcriptase despite binding site changes induced by the presence of common NNRTI resistance mutations. ETR exhibits potent in vitro anti-HIV activity against wild type and against HIV isolates with NNRTI resistance mutations such as K103N, Y181C and Y188L (9) (10).

1.22 Preclinical Studies

Preclinical studies noted EC_{50} values for wild-type laboratory and primary HIV-1 isolates of 0.9 to 5.5 nM (0.4 to 2.4 ng/mL) with little or no loss of activity against HIV-1 variants with the most common NNRTI-related mutations. During *in vitro* testing, ETR showed potent antiviral activity against a panel of > 6000 recombinant clinical isolates resistant to at least one of the first generation NNRTIs, with EC_{50} values below 10nM for 83% of isolates and below 100nM for 98% of isolates (9). In addition, ETR was noted to have an increased genetic barrier to the development of resistance compared to first generation NNRTIs. Non-clinical safety evaluations demonstrated that ETR was safe for use in clinical testing.

1.23 Pharmacokinetics

ETR absorption is increased 50% when taken with a meal (11); peak plasma concentrations occur 2 to 4 hours post dose. The absorption is not affected when the drug is taken with proton pump inhibitors or H_2 blockers (12). ETR is a weak inducer of CYP3A4 and a weak inhibitor of P-glycoprotein, CYP2C9 and CYP2C19. Therefore it is subject to drug-drug interactions that may result in lower serum concentrations of drugs metabolized by CYP3A4 such as HIV protease inhibitors, if not boosted with ritonavir, and higher concentrations of drugs metabolized by CYP2C9 and/or CYP2C19 and/or transported by P-glycoprotein (13-16).

1.3 Clinical Studies

1.31 Adult Studies

Trial TMC125-C228 established PK parameters for ETR administered as formulation F060, 200 mg BID in treatment experienced HIV-1 infected adults who were currently receiving a boosted PI (primarily LPV/rtv) (17). Formulation F060 is the commercial 100-mg tablet formulation.

In January of 2008 ETR was approved by the US Food and Drug Administration (FDA) for antiretroviral treatment-experienced adults at a dose of 200 mg BID, with similar European Union approval in August 2008. The approvals were based on the results of the DUET-1 and DUET-2 studies in treatment experienced HIV-1-infected adults (18). The DUET studies consist of two Phase III double- blind, placebo-controlled randomized trials of ETR, with an OBR that included darunavir/ritonavir (600/100 mg BID) plus other antiretrovirals in treatment experienced adults. In an intent to treat (ITT) pooled 24 week analysis (N = 1203), ETR was superior to placebo with respect to the following endpoints: viral load reduction to < 50 copies/mL (60% vs. 40%), viral load < 400 copies/mL (74% vs. 53%) and mean viral load reduction (2.4 vs. 1.7 $\log_{10}$ copies/mL). The 48-week efficacy results were consistent in the demonstration of a statistically significant superior efficacy for ETR versus placebo (19). The proportion of subjects with viral load < 50 copies/mL at week 96 was 57.4% in the ETR group and 36.3% in the placebo group (19). Genotypic analyses identified seventeen ETR resistance associated mutations (RAMs) predictive for decreased virologic response to ETR and a weighted genotypic score has been developed (20).

Population pharmacokinetic analysis of week 48 data from DUET-1 and DUET-2 revealed an ETR mean AUC_{12h} and C_{0h} of 5506ng•h/mL and 393 ng/mL respectively, at a dose of 200 mg BID (21). Neither AUC_{12h} nor C_{0h} were correlated with virologic suppression or adverse events (AEs). Other factors, including baseline viral load, CD4 cell count, number of active agents in the background regimen, fold change in EC_{50} to ETR and adherence were more important determinants of virologic success (18, 22). The adult dose is 200 mg BID. The formulation used for the clinical trials, and for commercial use, is a tablet containing 100 mg of ETR. The tablets may be dispersed in water or other liquid to facilitate administration (see Section 5.2) (23).

1.32 Pediatric Studies

Phase I trial (TMC125-C126)

A Phase I, open-label, dose-ranging trial (TMC125-C126) to evaluate the pharmacokinetics and short-term safety and tolerability of ETR at steady-state in HIV-1 infected children who were virologically suppressed has been completed. The objective of this trial was to obtain dose recommendations of ETR per body weight in treatment-experienced HIV-1 infected children ≥ 6 years old and weighing ≥ 20 kg (24).

ETR was administered as a 100 mg tablet and/or as a scored 25 mg tablet developed for pediatric use. The trial population was comprised of subjects taking a stable ARV regimen that included lopinavir/ritonavir (LPV/rtv) and a minimum of 2 NRTIs, with or without enfuvirtide. Trial TMC125-C126 was conducted in two sequential stages: in Stage I the dose of ETR was 4 mg/kg BID (dose derived from allometric scaling) and in Stage II the dose of ETR was 5.2 mg/kg BID (representing a 30% increase from 4 mg/kg BID). In each Stage, at least 20 virologically suppressed (VL < 50 copies/mL) children on a LPV/rtv-containing regimen received ETR for 7 days followed by an intensive 12-hour pharmacokinetic assessment of ETR on Day 8 (24).

Table 1. Summary of Adverse Events in TMC125-C126

Severity of AE	Number of subjects (%)	
	Stage I 4 mg/kg	Stage II 5.2 mg/kg
Grades 1 or 2	14 subjects (66.7%)[1]	9 subjects (42.9%)[4]
Grade 3	1 subject[2]	0
Grade 4	1 subject[3]	
SAEs	Grade 1 influenza during follow-up	

[1] Five subjects (23.8%) had an AE that was considered at least possibly related to ETR. One subject was reported with Grade 2 maculo-papular rash, which was considered very likely related to ETR.

[2] Grade 3 increased blood creatinine

[3] Grade 4 increased blood triglycerides

[4] Six subjects (28.6%) had an AE that was considered at least possibly related to ETR. One subject was reported with Grade 1 rash, which was considered probably likely related to ETR.

Safety analysis from Stage I showed that ETR at 4 mg/kg and 5.2 mg/kg BID was generally safe and well tolerated (Table 1). The majority of adverse events were Grade 1 (mild) or Grade 2 (moderate) in severity. No deaths were reported. No relevant difference was observed between the age groups.

Table 2 displays a comparison of the PK parameters for both stages of the pediatric dose-ranging studies with those from the adult study of ETR 200 mg BID with LPV/rtv (TMC125-C228) and the adult studies of ETR 200 mg BID with DRV/rtv (DUET).

Table 2: Pharmacokinetic Parameters of ETR at two Doses in HIV-1 Infected Subjects between the Ages of 6 and 17 years, Inclusive, at Day 8 (TMC125-C126), and in HIV-1 Infected Adult Subjects (TMC125-C228; Day 8 and DUET Trials population PK).

Pharmacokinetic parameters Mean (SD) tmax: median (range)	TMC125-C126 Stage I 4 mg/kg BID	TMC125-C126 Stage II 5.2 mg/kg BID	TMC125-C228 200 mg BID	DUET trials[a] 200 mg BID
N	19[c]	20	27	574
tmax (h)	4 (2-8)	4 (2-6)	4 (3-8)	-
Cmax (ng/mL)	495 ± 453	757 ± 680	451 ± 232	-
Cmin (ng/mL)	184 ± 151	294 ± 278	185 ± 128	393 ± 391[d]
AUC12h (ng·h/mL)	4050 ± 3602	6141 ± 5586	3713 ± 2069	5506 ± 4710
GMR[b]	1.02	1.58		

[a] Population PK at Week 48.
[b] Relative to TMC125-C228 (protocol-specified comparison).
[c] N=18 for AUC_{12h} [d] C_{0h} (ng/mL)

The exposure of ETR, expressed as C_{min} and AUC_{12h}, after administration of ETR 4 mg/kg BID to children and adolescents on a LPV/rtv containing regimen was comparable with the exposure of ETR administered as 200 mg BID in adults on a LPV/rtv containing regimen, although the 90% CIs were outside 80 to 125% for both C_{min} and AUC_{12h}. No age or weight difference was noticed within this dosing group. When ETR was administered as 5.2 mg/kg BID in children and adolescents, higher C_{min} and AUC_{12h}values were observed compared to administration of ETR as 200 mg BID in adults. Only the upper limit of the 90% CI was outside 80 to 125% for both C_{min} and AUC_{12h}. Furthermore, the exposure was higher for the younger children (6 to 12 years) in comparison to the adolescents (12 to 17 years), although the range in the exposure was large in both groups. The higher exposure in younger children was related to 1 outlier; no apparent cause could be established for this higher exposure. When compared to adults receiving DRV/rtv with ETR, the ETR exposures achieved in children and adolescents on LPV/rtv with 5.2 mg/kg BID ETR dose were comparable (pooled DUET results).

Based on the general concern for under dosing of ARVs in the pediatric population (25-28), the higher exposures of ETR achieved with ETR 5.2 mg/kg BID and the overall safety and tolerability during Stage II, the selected dose of ETR in children aged 6 to 17 is 5.2 mg/kg BID,which was also confirmed in a further trial (PIANO).

<u>Phase I/II trial (TMC125-C213, PIANO)</u>

Further long-term safety, tolerability, antiviral activity and pharmacokinetics of the selected dose was collected in trial TMC125-C213 (Pediatric Trial with Intelence as an Active NNRTI Option, PIANO). This was an open-label trial in 101 treatment-experienced HIV-1 infected children and adolescents 6 to 17 years of age, who were receiving ETR 5.2 mg/kg BID (up to a maximum of 200mg BID) in combination with an investigator-selected OBR comprising of select boosted PI

in combination with NRTIs over 48 weeks (29).

The 48 week safety and tolerability data with ETR in PIANO further confirm the favorable benefit/risk analysis in treatment-experienced pediatric patients. ETR was generally safe and well tolerated in the studied treatment-experienced HIV-1 infected pediatric population up to Week 48 with a safety profile comparable to that observed in the adult HIV 1 infected population and no new safety findings were identified. The Week 48 pharmacokinetic results re-confirm that pharmacokinetic exposure achieved in the pediatric population (6 – 17 years) with etravirine 5.2 mg/kg BID is comparable to that in the adult population. The Week 48 analysis also provides further confirmatory evidence of an effective viral suppression in treatment-experienced pediatric patients taking ETR.

A population pharmacokinetic model of ETR for the pediatric population was developed based on a previously developed population pharmacokinetic model of ETR used in adults, supplemented with rich and sparsely sampled pharmacokinetic data from pediatric subjects (6 to < 18 years). This model consisted of a sequential zero- and first-order absorption process with a lag-time and one-compartment disposition. A covariate effect of weight on volume of distribution (Vc/F) and clearance (CL/F) is included in the model.

Using the population pharmacokinetic model and sparse sampling data from study TMC125-C213, ETR pharmacokinetic parameters for all subjects were derived using Bayesian feedback. A total of 313 sparsely sampled ETR plasma concentration-time data were available from 78 subjects. ETR plasma concentrations were assumed to be at steady-state. Data for 4 subjects were excluded from analysis due to lack of dosing information (2 subjects) or ETR plasma concentrations below the lower limit of quantitation at all time-points (2 subjects). Therefore, pharmacokinetic parameters of ETR were available in 74 subjects. Table 3 summarizes the ETR AUC_{12h} and C_{0h} from the ISRP analysis**,** overall and by age cohort**,** with pediatric and adult historical controls for comparison (TMC125-C126 and pooled DUET, respectively).

In general, the pharmacokinetics of ETR when administered at 5.2 mg/kg BID (i.e., 100 mg BID for 16 to < 20 kg; 125 mg BID for 20 to < 25 kg; 150 mg BID for 25 to < 30 kg and 200 mg BID for ≥ 30 kg) were comparable in children (≥ 6 to < 12 years) and adults. In the adolescents (≥ 12 to ≤ 17 years), slightly lower ETR exposures were observed relative to adults. Of note, most of these adolescents (91%, 43 out of 47 adolescents) were on the adult dose of ETR (200 mg BID).

Table 3: Population Pharmacokinetics of ETR (AUC_{12h} and C_{0h}) by Age Cohort when ETR is Dosed at 5.2 mg/kg BID

	N	AUC_{12h} (ng•h/mL)	
		Mean (SD)	Median (Min - Max)
PIANO (TMC125-C213)[1]			
≥6 to <12 years	27	5260 (2845)	5090 (1722 - 13628)
≥12 to ≤17 years	47	4568 (4761)	3622 (113 - 29039)
All subjects	74	4820 (4157)	3990 (113 - 29039)
Pediatric dose finding (TMC125-C126)			
≥6 to <12 years	11	7713 (7160)	4559 (2967 – 27060)
≥12 to ≤17 years	9	4219 (1575)	4300 (1924 – 7142)
All subjects	20	6141 (5586)	4407 (1924 – 27060)
Adults (Pooled DUET)	575	5506 (4710)	4380 (458 – 59084)
	N	C_{0h} (ng/mL)	
		Mean (SD)	Median (Min - Max)
PIANO (TMC125-C213)[1]			
≥6 to <12 years	27	334 (222)	332 (38 - 996)
≥12 to ≤17 years	47	299 (378.2)	195 (2 - 2291)
All subjects	74	312 (328.7)	246 (2 - 2291)
Pediatric dose finding (TMC125-C126)			
≥6 to <12 years	11	453 (442)	273 (88 – 1620)
≥12 to ≤17 years	9	247 (155)	204 (115 – 627)
All subjects	20	360 (352)	241 (88 – 1620)
Adults (Pooled DUET)	575	393 (391)	298 (2 – 4852)

[1] ISRP analysis

The median baseline viral load was 3.9 $\log_{10}$ copies/mL, and the median baseline $CD4^+$ cell count was $385x10^6$ cells/L.

The virologic response rate was evaluated in pediatric subjects receiving ETR in combination with other ARVs. Virologic response was defined as achieving a confirmed undetectable viral load (<50 copies/mL).

The primary analysis was performed at Week 24, when all subjects had completed the 24-week assessment or discontinued earlier. The final analysis was performed when all subjects had completed the Week 48 assessment or discontinued earlier. An overview of the key efficacy findings at 48 weeks in the PIANO study is given in Table 4.

Table 4: Virologic Response to ETR at Week 48 in Treatment-experienced HIV-1 Infected Pediatric Subjects (PIANO Final Analysis)

Efficacy Outcome Measure	Children ≥6-<12 years N=41	Adolescents ≥12-<18 years N=60	All subjects N=101
<50 copies/mL (NC=F), n (%)	28 (68.3)	29 (48.3)	57 (56.4)
<50 copies/mL (TLOVR), n (%)	28 (68.3)	26 (43.3)	54 (53.5)
<400 copies/mL (TLOVR), n (%)	28 (68.3)	36 (60.0)	64 (63.4)
Decrease in VL vs BL of ≥1.0 $\log_{10}$, n (%)	27 (65.9)	34 (56.7)	61 (60.4)
Change in $\log_{10}$ VL, Mean (SE)	-1.67 (0.219)	-1.44 (0.163)	-1.53 (0.132)
$CD4^+$ Cell Count			
Change in $CD4^+$ cell count, Mean (SE)	+178 (39.7)	+141 (27.0)	+156 (22.7)

BL: Baseline; VL: Viral Load; NC=F: non-completer equals failure; TLOVR: time to loss of virologic response; SE: standard error, vs: versus, $CD4^+$: Cluster of differentiation 4 positive

At Week 24, 51.5% of all pediatric subjects had a confirmed undetectable viral load <50 copies/mL. The proportion of pediatric subjects with viral load <400 copies/mL was 65.3%. The mean change in viral load from Baseline to Week 24 was -1.51 $\log_{10}$ copies/mL, and the mean $CD4^+$ cell count increase from Baseline was $112x10^6$ cells/L.

At Week 48, 53.5% of all pediatric subjects had a confirmed undetectable viral load <50 copies/mL. The proportion of pediatric subjects with viral load <400 HIV-1 RNA copies/mL was 63.4%. The mean change in HIV-1 RNA from Baseline to Week 48 was -1.53 $\log_{10}$ copies/mL, and the mean $CD4^+$ cell count increase from Baseline was $156x10^6$ cells/L.By age group, virologic response at Week 48 was 68.3% in children and 48.3% in adolescents. Sensitivity analyses (including observed case, TLOVR and TLOVR non-VF censored analyses, and snapshot approach) showed that these results were robust and not driven by the imputation method.

Eighty-three percent of the children and 92% of adolescents experienced at least 1 adverse event (AE). By preferred term, the most commonly reported AEs (in at least 10.0% of all subjects) were upper respiratory tract infection (24.4% in children and 28.3% in adolescents), diarrhea (12.2% and 18.3%), cough (12.2% and 13.3%), vomiting (9.8% and 11.7%) and rash (individual preferred term; 4.9% and 15.0%).

Most AEs were grade 1 or 2 in severity. Grade 3 or 4 AEs occurred in 6 (14.6%) children and 8 (13.3%) adolescents. Each of the grade 3 or 4 AE preferred terms, except thrombocytopenia and hypertriglyceridemia (both in 2 subjects), were reported in only 1 subject. Only 2 subjects (both children) were reported with a grade 4 AE (both thrombocytopenia). Both grade 4 AEs were considered not related to ETR

No fatalities were reported. Five subjects, all adolescents, reported at least one SAE (abnormal lymphocyte morphology and oligoclonal immunoglobulins at electrophoresis; carbamazepine toxicity; ETR overdose; treatment noncompliance, drug resistance and weight decreased; ulcerative keratitis). The subject with the overdose was inadvertently treated with ETR 250 mg instead of 200 mg bid for 50 days without safety consequences. All SAEs, except the overdose (considered very likely related to ETR), were considered not related to ETR. A limited number of subjects in each age group had AEs leading to permanent discontinuation of treatment with ETR:

2 (4.9%) children and 6 (10.0%) adolescents. One adolescent permanently discontinued treatment because of an SAE (drug resistance).

Skin events were the most frequently reported events of interest. 'Rash cases', referring to a grouped term combining all rash-related AEs except events considered 'severe cutaneous reactions', were reported in 6 (14.6%) children and 17 (28.3%) adolescents. Consistent with other drug-related rashes, rashes with ETR occurred early during treatment, with a median time to first onset of 10 days; were self-limiting, with a median duration of 7 days; and were usually grade 1 or 2 in severity. One subject in each age group developed a grade 3 rash. Four subjects (1 child and 3 adolescents) discontinued treatment because of rash. No grade 4 rashes or rash related SAEs were reported. Other relevant skin events of interest included 1 case of erythema multiforme (grouped under severe cutaneous reactions) and 1 case each of hypersensitivity and urticaria papular (grouped under angioedema). The incidence of neuropsychiatric events of interest, pancreatic events, lipid-related events and neoplasms was low (≤ 2%). There were no hepatic, cardiac and bleeding events of interest reported in this study.

A slightly higher frequency of rash was observed in the PIANO study compared to the DUET studies in adults and therefore, a multivariate analysis was performed on the pooled data of the Week 48 data of the DUET studies and the Week 24 data of the PIANO study to investigate risk factors for developing rash when treated with ETR. The results of this analysis consistently showed that being female, but not age or participation in the PIANO study (a partial surrogate for age), is a risk factor for developing rash. No other risk factors could be firmly identified. This is also seen in the Week 48 PIANO data: Rash ≥ grade 2 was reported in 13/64 (20.3%) of females vs 2/37 (5.4%) of males; discontinuations due to rash were reported in 4/64 (6.3%) of females vs 0/37 (0%) of males. Most often, rash was mild to moderate, of macular/papular type, and occurred in the second week of therapy. Rash was mostly self-limiting and generally resolved within 1 week on continued therapy.

Mean changes over time in the clinical laboratory parameters were small in either age group and were generally not considered clinically relevant. There was an increase over time in total cholesterol, low-density lipoprotein (LDL) and triglycerides, as seen with many other ARV regimens. The majority of treatment-emergent laboratory abnormalities were grade 1 or 2 in severity. The most common treatment-emergent graded laboratory abnormalities were related to lipid related parameters, and mainly included increases in total cholesterol (50.0% in children and 38.8% in adolescents) and LDL calculated (31.6% and 25.0%). All abnormalities in total cholesterol and LDL were grade 1 or 2 in severity with the exception of 1 adolescent who had a grade 3 increase in LDL cholesterol.

There were no clinically significant changes over time in vital signs, nor findings suggestive of delayed sexual maturation. The mean age-adjusted z-scores for height, weight and body mass index remained stable over time.

Taken together, the administration of ETR at a weight-based dose revealed no new findings compared with the known ETR safety profile in HIV-1 infected adults.

In conclusion, the safety analysis shows that ETR is generally safe and well tolerated in treatment-experienced HIV-1 infected children and adolescents aged 6 to 17 years. There were no clinically relevant differences with the safety profile in adults. No new safety signals or consistent patterns in

the incidence of adverse events (AEs) were detected in the pediatric population studied. These safety results represent the clinical basis to start the clinical trial in children below the age of six years.

Data from the initial P1090 mini-cohort and rationale for revised ETR dose

At the start of the P1090 trial, the ETR starting dose for the first (mini)-cohort was 5.2 mg/kg BID, based on data from the TMC125-C213 trial in children aged 6 to 17 years. The first 6 children enrolled in P1090 received this dose, and the ETR exposure was assessed at an intensive PK visit performed between 1-2 weeks after initiating ETR. The aim was to achieve similar exposures compared to those in adults (geometric mean AUC_{12h} of the cohort between 3618-5879 ng.h/mL corresponding to 80% -130% of the geometric mean AUC_{12h} observed in adults).

The observed geometric mean ETR AUC_{12h} for the first six children was 2576 ng.h/mL. Two of the six children had an individual AUC_{12h} below 2350 ng.h/mL and had dose increases per protocol (see Section 9.34). Short-term safety and antiviral activity data did not reveal any concerns.

Based on the combined pharmacokinetic data, even though the mini-cohort had passed the applicable criteria at that time of no more than 2 subjects with AUC_{12h} <2350 ng.h/mL, and no safety or efficacy concerns, it was evident that with the 5.2 mg/kg dose, the probability of meeting the necessary criteria for the overall cohort (n=12, geometric mean AUC_{12h} 3618-5879 ng.h/mL) would be very low. Therefore, it was decided to modify the ETR dosing regimen for the cohort, prior to recruiting additional subjects.

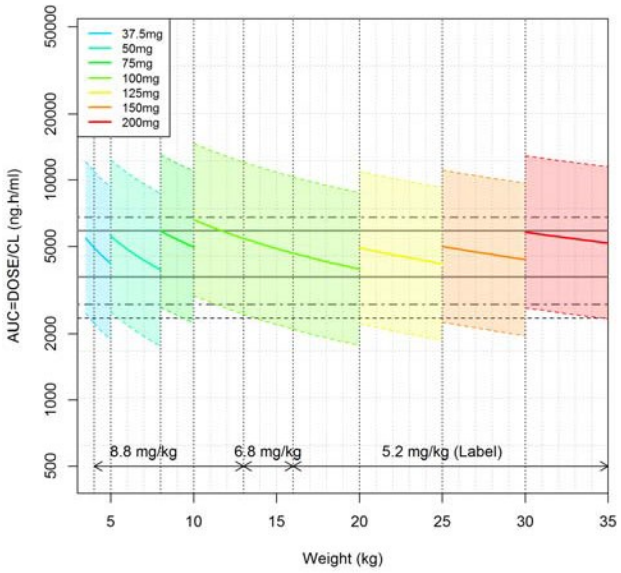
To determine the most appropriate dosing regimen, a modeling and simulation approach was applied. For this, a population pharmacokinetic model of ETR for the pediatric population was used which is structurally based on a previously developed ETR population pharmacokinetic model in adults, using all rich and sparsely sampled pharmacokinetic data from pediatric subjects (6 to 17 years from studies TMC125-C126 and TMC125-C213 [PIANO]; 2 to 6 years from the first mini-cohort in P1090 [all doses, all samples]). The model consists of a sequential zero- and first-order absorption process with a lag-time and one-compartment disposition, includes a covariate effect of body weight on volume of distribution (Vc/F) and clearance (CL/F), and an allometric exponent for CL/F and Vc/F of 0.75 and 1.00, respectively.

Standard graphical and numerical evaluation techniques (goodness-of-fit plots, including observed versus population and individual predicted ETR plasma concentrations, and conditional weighted residuals versus time since first dose and time since last dose), showed that the model fit the data with high precision and minimal bias. So far, no impact of age on the ETR CL/F has been observed. It was also shown specifically for the 6 subjects already enrolled in P1090 that their ETR pharmacokinetic parameters were well estimated with the model. Therefore, the final model was considered suitable for further simulations to evaluate potential dosing regimens for the pediatric population of interest for P1090.

The model was used to evaluate several potential weight-based dosing regimens, with the intent to achieve ETR exposures similar to those observed in adults. From these simulations, the weight-based ETR dosing regimens likely to result in similar ETR exposures as those observed in adults were selected for each weight band. This is presented in Figure 1, which shows the median simulated ETR AUC_{12h} (with 80% prediction interval) by weight, for different ETR mg/kg doses across different weight bands. This dosing regimen is also in line with the currently approved ETR

dosing regimen for children aged 6 years and above, as of 16 kg of body weight (reference: US Package Insert revised 08/2014).

Figure 1: Simulated ETR Exposures (AUC_{12h}) By Body Weight for Different ETR BID Doses, Aimed at Achieving a Geometric Mean ETR AUC_{12h} Similar to That in Adults.



The solid colored lines represent the median simulated AUC_{12h} and the shaded areas represent the 80% prediction interval. The two solid horizontal lines represent 80% and 130% of the geometric mean AUC_{12h} in adults; the two dashed horizontal lines represent 60% and 150% of the geometric mean AUC_{12h} in adults; the lower dotted line represents the 10th percentile of the adult AUC_{12h}.

Based on the above described approach, the revised ETR dosing regimen is presented in Appendix III.

To evaluate the probability of success for this regimen, 10000 virtual trials with 12 pediatric subjects each were simulated. The virtual pediatric subjects were randomly sampled from a database built based on WHO's age-gender-body weight distributions, assuming equal probabilities for gender and a uniform age distribution. With this, it was determined that for this dosing regimen (Appendix III), there is a very high probability to achieve a geometric mean exposure (AUC_{12h}) across the age cohort that is similar to that observed in adults (i.e., 80% probability for a geometric mean AUC_{12h} within 80-130% of adult geometric mean exposure; 96% probability for a geometric mean AUC_{12h} within 60-150%).

The inter-individual variability for apparent clearance in the population PK model is 62%. Given this rather high value, exposures in the study are expected to be as variable. Increasing the target band for the AUC_{12h} from 80-130% to 60-150% of the geometric mean AUC12h in adult would provide a more suitable criterion. Also, individual exposures are anticipated to fall in range of the exposures observed in adults, which have been shown to be safe and efficacious. Across previous trials of ETR in HIV-infected adults and children, there was no observation of a PK/PD relationship for adverse events of interest, nor was ETR exposure found to be a significant prognostic factor for virologic response.

Also in the currently enrolled pediatric subjects in the P1090 study, there have been no significant safety concerns. There was one case of virologic failure, which was first noted approximately 32 weeks after start of dosing (and confirmed at Week 40). The reason for the virologic failure is not clear, but it is unlikely to be related to ETR exposure and there was no evidence of ETR resistance. The observed ETR AUC_{12h} for this subject at the intensive PK visit (6165 ng.h/mL) was above the mean exposure in adults, and also based on the sparse sampling at later visits, there was no indication of low ETR exposures. All other subjects in the trial have had a good virologic response.

Data from the second P1090 mini-cohort and a) rationale for opening Cohort III and b) dose selection for Cohort III

As described in the section above, modelling of the initial mini-cohort led to a revision in the dosing for study participants and adoption of weight based dosing. Results from the second mini-cohort of Cohort I suggest that this approach is appropriate and that the weight-based population PK model used for dose selection can thus be assumed to be adequate. Estimation of the allometric exponents in the model revealed no significant improvement of the model compared to fixed theoretical values (3/4 for CL/F and 1 for V/F). This suggests that the standard theoretical model for pharmacokinetics in pediatric populations is applicable to ETR.
[http://www.ncbi.nlm.nih.gov/pubmed/18336053 / ;
http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2125.2010.03802.x/pdf]

Introduction of a maturation function did not show any significant improvement in the model based on the current data. As maturation is known to exist, these results suggest that the available data are insufficient to estimate the effect of age on the PK of ETR. Therefore, additional data in younger patients is needed (Cohorts II and III).

Given the uncertainties around maturation of CYP metabolism in subjects aged <1 year, some additional precautions are taken for Cohort III:

- 6 months to < 1 year: the dose (in mg/kg) is reduced by 25% compared to what the model suggests to adjust for possible ongoing maturation of enzymatic metabolism (30)
- 2 months to < 6 months: subjects in this age group will only be included once there are available data on subjects aged 6 months to 1 year

Safety of the weight-based dosing in the younger participants is anticipated to be acceptable based on the safety data collected so far among subjects in Cohorts I and II. The latter was opened 30 October 2015 and, based on input from participating sites in late 2015, the expectation is that there will be at least 2 and likely 6 participants already enrolled in Cohort II by the time of release of Version 5.0. There are adequate safeguards included in the protocol, which include:

- Intensive PK evaluation with individual dose adjustment if needed and continuous safety monitoring on an individual level,
- Close monitoring of PK data and continuous safety monitoring on a cohort level;
- Additional safety monitoring rules for first 6 patients entering cohorts II and III combined.

In conclusion, the added scientific value of the collected data -and the precautions taken to ensure safety and efficacy of the compound in this age group- justifies an early enrollment of Cohort III.

Other Available Data

In a Spanish cohort of five children (5 to 12 years old) and 18 adolescents (13 to 18 years old) of whom 22 had a history of NNRTI-based CART failure with proven genotypic NNRTI resistance mutations, salvage regimens including ETR at 5.2 mg/kg BID (for children) and 200 mg BID (for adolescents) and (in 21 of the patients) OBR with at least 2 active agents, 87% achieved HIV-1 RNA< 400 copies/mL and 78% achieved HIV-1 RNA< 50 copies/mL by 8 months. Mild (3 adolescents) or moderate (2 adolescents) rash was observed only in adolescents but not in children, and therapy was otherwise well tolerated (31).

Table 5. Adverse Events Summary (Adult Studies Phase IIb /III Pooled Analysis)

AEs during treatment period n (%)	Week 48 Placebo DUET N = 604	Week 48 ETR DUET N = 599	ETR Selected Dose N = 1043	All ETR N = 1223
Treatment duration (weeks), Median (range)	*51.0 (3 - 80)*	*52.3 (2 - 85)*	*51.7 (0 - 271)*	*52.3 (0 - 271)*
Subject years of exposure	556.8	583.4	1125.1	1476.2
Any AE	580 (96.0)	575 (96.0)	990 (94.9)	1164 (95.2)
Any Grade 1 or 2 AE	573 (94.9)	564 (94.2)	973 (93.3)	1143 (93.5)
Grade 1	512 (84.8)	511 (85.3)	877 (84.1)	1040 (85.0)
Grade 2	425 (70.4)	445 (74.3)	751 (72.0)	888 (72.6)
Any Grade 3 or 4 AE	211 (34.9)	199 (33.2)	347 (33.3)	434 (35.5)
Grade 3	190 (31.5)	177 (29.5)	311 (29.8)	387 (31.6)
Grade 4	64 (10.6)	59 (9.8)	106 (10.2)	135 (11.0)
Treatment-related AE[a]	285 (47.2)	320 (53.4)	557 (53.4)	671 (54.9)
Death	20 (3.3)	12 (2.0)	21 (2.0)	26 (2.1)
Any SAE	141 (23.3)	118 (19.7)	205 (19.7)	254 (20.8)
AE leading to temporary stop	57 (9.4)	64 (10.7)	131 (12.6)	161 (13.2)
AE leading to permanent stop	34 (5.6)	43 (7.2)	101 (9.7)	127 (10.4)
Most Common AEs[b]				
Diarrhea	142 (23.5)	108 (18.0)	202 (19.4)	266 (21.7)
Nausea	77 (12.7)	89 (14.9)	175 (16.8)	214 (17.5)
Headache	77 (12.7)	65 (10.9)	127 (12.2)	168 (13.7)
Injection site reaction	75 (12.4)	63 (10.5)	109 (10.5)	144 (11.8)
Fatigue	57 (9.4)	48 (8.0)	107 (10.3)	140 (11.4)
Nasopharyngitis	63 (10.4)	66 (11.0)	111 (10.6)	133 (10.9)
Upper respiratory tract infection	56 (9.3)	44 (7.3)	94 (9.0)	123 (10.1)
AEs of interest				
Any skin event of interest	110 (18.2)	159 (26.5)	288 (27.6)	353 (28.9)[c]
Rash (any type)	66 (10.9)	115 (19.2)	207 (19.8)	249 (20.4)
Any neuropsychiatric event of interest	205 (33.9)	181 (30.2)	338 (32.4)	427 (34.9)[d]
Nervous system events of interest	119 (19.7)	103 (17.2)	191 (18.3)	249 (20.4)
Psychiatric events	118 (19.5)	100 (16.7)	196 (18.8)	248 (20.3)
Any hepatic event	37 (6.1)	39 (6.5)	86 (8.2)	103 (8.4)

Any cardiac event	44 (7.3)	42 (7.0)	92 (8.8)	124 (10.1)
Coronary artery disorders	8 (1.3)	11 (1.8)	16 (1.5)	28 (2.3)
Any pancreatic event	27 (4.5)	24 (4.0)	38 (3.6)	51 (4.2)
Any bleeding event	39 (6.5)	33 (5.5)	59 (5.7)	76 (6.2)

N: number of subjects; n: number of subjects with observations

[a] defined as possibly, probably or very likely related to treatment in the opinion of the investigator

[b] > 10% of subjects in the All ETR group

[c] Of the total skin rashes, 1.5 % were Grade 3;there were no Grade 4 skin rashes

[d] Of neuropsychiatric events, 0.7% were Grade 3; 0.2% (1 patient had a Grade 4, and it was a suicide).

Additional Safety Data

Safety data derived from pooling of the results of 1,043 adult HIV-1-infected treatment-experienced subjects enrolled in the Phase III trial indicated that ETR is generally safe and well tolerated. The most common AEs reported during ETR treatment with the selected dose were rash (any type, 16.9%; Grade 2 to 4 rash 9%), diarrhea (any Grade 1: 9.4%; Grade 2 to 4: 5.2%), nausea (any Grade, 13.9%), and headache (Grade 1: 2.2%; Grade 2 to 4: 2.7%).

With the exception of rash, the incidence of AEs and laboratory abnormalities were generally comparable to placebo. Table 5 describes these results.

A recent double-blind placebo-controlled trial of ETR 400 mg QD versus EFV in HIV-infected adults, naïve to ART, compared neuropsychiatric side effects in the two arms. At week 12, 16.5% of ETR treated subjects reported at least one grade 1 to 4 treatment related neuropsychiatric AE, compared to 46.2% in the EFV treated subjects; for grade 2 to 4 AEs, the incidence was 5.1% in the ETR arm and 16.7% in the EFV arm (32).

Twenty-six subjects (2.1%) died during the study while on ETR; 25 of which were judged not, or unlikely, related to ETR therapy. One death, due to myocardial infarction with cardio respiratory failure, in a subject with risk factors for premature coronary artery disease, was considered possibly related to ETR therapy (18).

The rashes tended to be mild to moderate; they usually occurred in the second week of therapy, and resolved within 1 to 2 weeks on continued therapy. In the adult phase III trials, the cumulative incidence of Grade 3 and 4 rashes was 1.3% for subjects on ETR and 0.2% for those on placebo. A total of 2% of subjects discontinued study due to rash. There were no cases of Stevens Johnson Syndrome (SJS) or toxic epidermal necrolysis (TEN) reported due to ETR in any of the Phase IIb/III studies (18).

In August of 2009, the FDA issued a warning to physicians, related to the occurrence of severe, potentially life threatening, and fatal skin rashes (erythema multiforme, SJS and TEN) linked to ETR use during the post marketing period. Prescribing information has been updated to reflect this information. The rate of SJS and TEN was < 0.01% each. The hypersensitivity reactions manifested as rash along with constitutional findings. At times, evidence of impending organ failure existed. The current recommendation is to stop ETR at the onset of severe skin rash, with careful clinical monitoring (13).

As of February 12th, 2016, fourteen participants between the ages of 2 to 6 years have been

enrolled into P1090. To date, adverse events have been primarily unrelated to study product; none raised concerns regarding the safety of ETR in this population. Specifically, there has been no reported skin rashes related to study med, nor any safety events related to EKGs obtained on the day of pharmacokinetic testing.

1.4 Rationale

There is increasing use of NNRTI-based regimens as initial therapy for HIV-1 infected children, especially in areas where HIV-1 exposed newborns receive NVP as part of PMTCT regimens and/or daily NVP for prevention of breastfeeding transmission (33). Though NNRTI-based CART regimens are effective, first generation NNRTI agents have a low genetic barrier to the development of resistance.

As a result, there are an increasing number of treatment-experienced infected infants and children who have failed, or will fail, their initial regimen. The majority of these infants, at the time of virologic failure to a NNRTI based regimen, will have mutations associated with resistance to first generation NNRTIs (7). Similarly, a high percentage of infected infants exposed to NVP as a component of PMTCT regimens will harbor virus with NNRTI related resistance mutations.(3-7). Failure or intolerance of LPV/rtv based regimens, especially among infants and children with prior NNRTI exposure (as treatment or for PMTCT), leaves few or no alternative treatment options (7).

ETR, a second generation NNRTI, approved for adult use, has a higher genetic barrier to HIV drug resistance than EFV or NVP and retains activity against EFV and NVP drug resistant HIV-1 isolates harboring the K103N and Y181C mutations (9, 10). The drug dosing and tolerability have been established in adult registration studies. Skin rash was the main treatment-limiting significant adverse event. It was seen in up to 20% of subjects, with 1 to 2% of subjects showing Grade 3 or 4 severity (18). Phase I/II trials of ETR in children aged 6 to 17 years of age demonstrated acceptable safety and tolerability, and established suggested dosing for this age group (24). See Section 1.32.

We propose to investigate ETR, in combination with at least 2 active ARVs, one of which must be a boosted PI, for treatment experienced HIV-1 infected infants and children aged 2 months to < 6 years.

2.0 STUDY OBJECTIVES

2.1 Primary Objectives

2.11 To evaluate the steady state pharmacokinetics of ETR in combination with an OBR in HIV-infected children aged ≥ 2 months to < 6 years.

2.12 To determine the safety and tolerability of ETR in combination with an OBR in children aged ≥ 2 months to < 6 years, through 48 weeks of therapy.

2.13 To determine the appropriate dose of ETR in combination of an OBR for children aged ≥ 2 months to < 6 years.

2.2 Secondary Objectives

2.21 To assess the antiretroviral activity of ETR containing regimens through 48 weeks of therapy.

2.22 To determine the immunological changes (change in CD4 percent and absolute count; CD4/CD8 ratio and percent) through 48 weeks of ETR therapy in combination with an OBR.

2.23 To determine changes in viral drug resistance during 48 weeks of ETR therapy in combination with an OBR.

2.24 To assess the relationship between ETR pharmacokinetics and the antiviral activity and safety of ETR containing regimens.

2.25 To explore the relationship between subject-specific gene CYP profile, sex, age, weight, race, HIV regimen (e.g., boosted PI) and HIV response markers and pharmacokinetics of ETR.

3.0 STUDY DESIGN

This is a Phase I/II, multicenter, open label 48 week study of ETR in combination with at least 2 active agents (a boosted PI and at least one additional active drug), for treatment experienced HIV-1-infected infants and children ≥ 2 months to < 6 years separated by age into three cohorts.

The study will, in a sequential manner, accrue subjects for an initial dose finding intensive PK component for age related cohorts. It is expected that up to 50 subjects will be accrued, to yield data from at least 36 evaluable[1] subjects with a minimum of 12 subjects for each of the three cohorts, who were started on the final approved dose for that cohort**.** The total sample size will depend upon the number needed to complete the dose finding stage of the study, the number of subjects who discontinue the study and the number of subjects required for regulatory approval of ETR in these populations. Up to 18 subjects may be enrolled into Cohort I.

The P1090 core protocol team will be responsible for reviewing the PK and safety data and approving the dose selection for each full and mini-cohort. The P1090 core protocol team will consist of the protocol chair and co-chairs, clinical trials specialist, NIAID and NICHD Medical Officers, data manager, pharmacologists, pharmacist, statisticians and Janssen R&D representatives.

[1]NOTE: For the Week 24 (or Week 48) analysis, evaluable will be defined as having been treated exclusively on the dose determined to be optimal for a given age cohort and having either completed 24 (or 48) weeks of exposure to the study drug or having been classified as a safety failure, due to a study drug related adverse event occurring during the first 24 (or 48) weeks of treatment.

This study is designed to determine the appropriate ETR dose for HIV-1-infected infants and children and to evaluate the PK, safety and tolerability of ETR in this population. ETR will be administered as 25 mg scored tablets and/or 100 mg tablets swallowed as a whole or dispersed in an appropriate liquid vehicle (see Section 5.2).

3.1 Description of Cohorts

Subjects will be stratified by age and will undergo viral phenotype and genotype evaluations as described in Table 6 below.

3.2 Optimized Background Regimen

As described in Table 6, OBR for treatment experienced subjects must consist of at least two active agents, a boosted PI and at least one additional active drug, in addition to ETR.

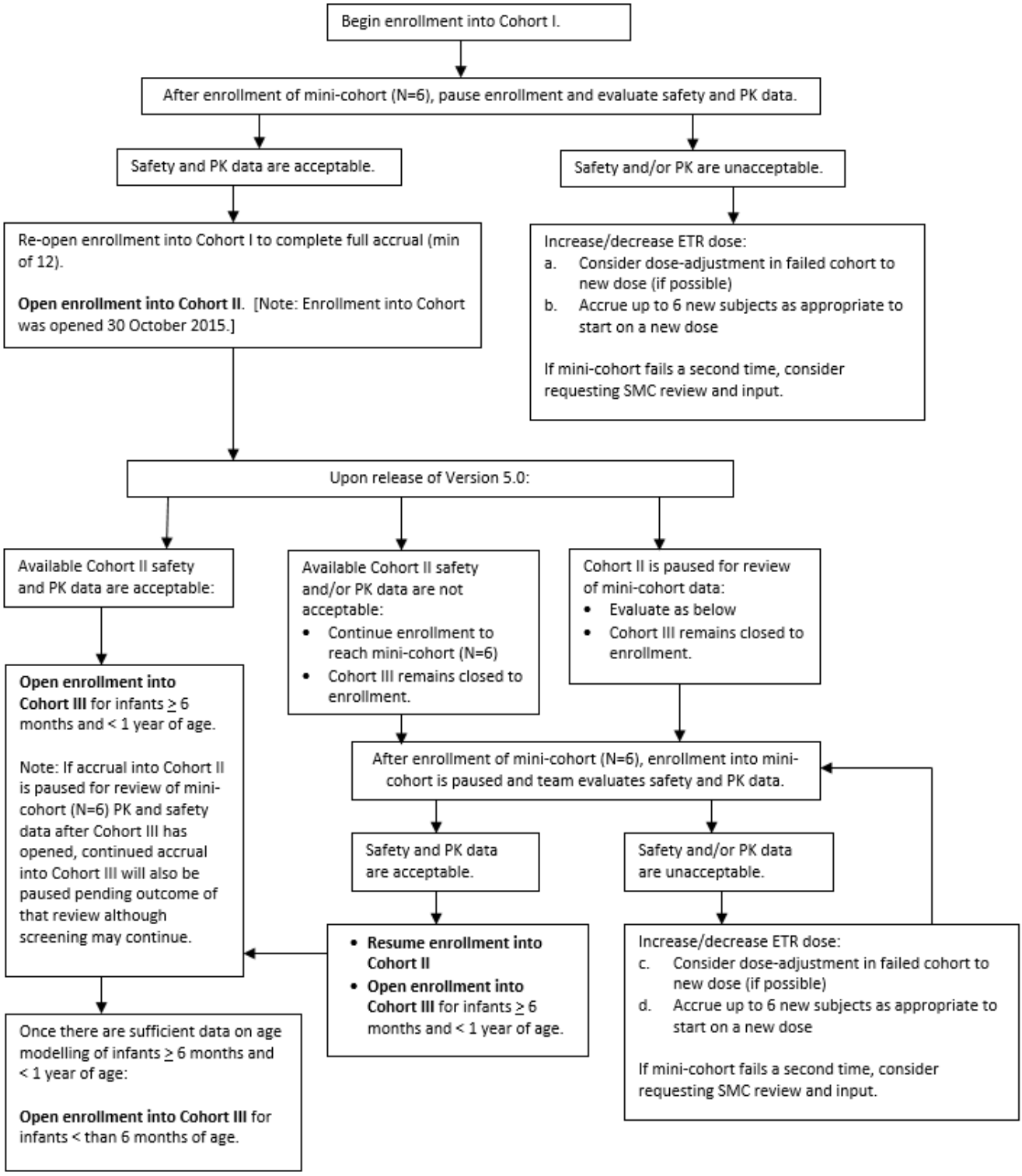
Prior to the enrollment visit (entry), the protocol team must be notified and approve the proposed OBR regimen. OBR should be based on clinical status, treatment history, resistance data as well as availability of dosing guidelines and appropriate pediatric formulations.

Table 6. Description of Cohorts

Cohort	Description of Subject	Drug Regimen	Phenotyping / Genotyping Information	Comments	Anticipated Accrual		
					Mini Cohort	To complete a full cohort	Total cohort size
I	≥ 2 year to < 6 years who are treatment experienced	ETR + OBR (1 active boosted PI+ at least 1 other active drug)	HIV genotype and phenotype assays should be performed in real time and results available prior to starting study drug	Subjects will be enrolled providing the phenotypic assay results indicate a ≤ 10 fold change in sensitivity to ETR	6	6	Up to 18
II	≥ 1 year to < 2 years who are treatment experienced	ETR + OBR (1 active boosted PI+ at least 1 other active drug)	HIV genotype and phenotype assays should be performed in real time and results available prior to starting study drug	Subjects will be enrolled providing the phenotypic assay results indicate a ≤ 10 fold change in sensitivity to ETR	6	6	12
III	≥ 2 months to < 1 year who are treatment experienced[1]	ETR + OBR (1 active boosted PI+ at least 1 other active drug)	HIV genotype and phenotype assays should be performed in real time and results available prior to starting study drug	Subjects will be enrolled providing the phenotypic assay results indicate a ≤ 10 fold change in sensitivity to ETR	6	6	12

1. Subjects below 6 months of age will only be enrolled upon availability of initial safety and PK data from subjects between 6 months and 1 year of age.

Figure 2: Algorithm for Cohort Management as of Version 5.0



The investigator-selected ARVs in the OBR will be used in doses that are specified in the individual package inserts. Brand name ARVs and generics with tentative approval from the US FDA may be prescribed. For a list of tentatively approved generics, please consult http://www.fda.gov/InternationalPrograms/FDABeyondOurBordersForeignOffices/AsiaandAfrica/ucm119231.htm

If the site intends to use study products not marketed in the United States, sites should consult the DAIDS SOP on "Use of Study Products Not Marketed in the United States" (Jun 24, 2011). It is the sites responsibility to ensure that they are in compliance with this policy. Please refer to http://www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/Documents/NonFDAapprovedProducts.pdf

Applicable procedures and treatment guidance based on package inserts of the selected ARVs should be respected. Proposed OBR regimens for individual subjects will need to be approved by the protocol team prior to the enrollment (entry) visit.

3.3 Mini-Cohorts

Under prior versions of the protocol, enrollment moved in a sequential manner, from the oldest cohort to the next youngest cohort (Cohort I→ Cohort II). Upon release of Version 5.0, the team will consider opening Cohort III while the first mini-cohort of Cohort II may still be enrolling based on available PK and safety data to ongoing participants. Subjects below 6 months of age will only be enrolled upon availability of initial safety and PK data from subjects of at least 6 months of age and less than 1 year of age (see Figure 2 and Section 3.5).

All cohorts will begin with enrollment into an initial mini-cohort of 6 subjects. Intensive PK on initial dose will be performed on Day 14 (± 4 days) (to allow ETR levels to reach steady-state) and the mini-cohort will be followed for 4 weeks to assess safety.

For all cohorts, plasma concentrations of ETR will be assayed in real time (within two weeks of sample receipt) by the protocol specified IMPAACT pharmacology laboratory. After the sixth subject is enrolled, enrollment into that cohort will pause so that the pharmacokinetics (PK) and safety data can be analyzed. The safety criteria are described in Section 8.52 and PK criteria are described in Section 9.0.

The P1090 core protocol team will review the PK and safety results of each mini-cohort, and if acceptable, enrollment will resume, at that dose, to complete enrollment of the remaining 6 slots.

Subjects who pass screening but cannot enroll because the mini-cohort is filled, will join a waiting list and will be given first priority to enroll when the remaining six slots are opened for that cohort. NOTE: Screening labs must be repeated if the subject is on the waiting list for ≥ 60 days.

In the rare event where the results of a single subject's intensive PK are extremely low, AND the site clinician/protocol team strongly suspect non-adherence, an additional subject may be enrolled into the mini-cohort to replace the non-adherent subject. The non-adherent subject may remain on study and on study drug (ETR), if the site investigator agrees it is in the best interest of the subject, but this subject will not be considered for dose-finding or safety final analysis.

If the PK or safety monitoring results of the mini-cohort suggest that a higher or lower dose is needed, the new dose will be agreed upon by the P1090 core protocol team (upwards for inadequate PK values; downwards for safety failure, or high PK values). Up to 6 new subjects will be enrolled as a new mini-cohort, for PK and safety evaluation of the new dose.

Those enrolled in a failed mini-cohort, who had acceptable PK parameters, antiviral activity and safety can remain on the same dose without dose adjustment and will be followed on study. Subjects from the failed mini-cohort may be dose adjusted to the new dose, if feasible and the site investigator and/or protocol team believe this is in the best interest of the patient. Such subjects will have truncated intensive PK evaluation (3 samples: pre-dose and samples 2h and 3-5h after dosing) 7-14 days after the dose change, for safety considerations, but will not be considered towards the cohort pass/fail criteria.

Two out of six of the children from the mini-cohort who passed the safety criteria in Version 3.0 would be on the same dose chosen for the new weight-banding dosing strategy in Version 4.0. Consequently, the team agreed that those two participants could be included in considering the Cohort I mini-cohort under V4.0; only four additional participants would be needed to complete enrollment into that mini-cohort. In future mini-cohorts, if dose adjustments need to be made but subjects in the prior failed cohorts were on the same dose that will be evaluated in the new cohort, the PK and safety data for these subjects will be carried forward and counted towards the number of evaluable subjects on the final dose.

Those who need an individual dose adjustment (see Section 9.34 for management of individual dose adjustments), will have a repeat 12 hour intensive PK performed between Day 7 to 14 following their dose adjustment. Subjects who require a dose adjustment but decline to undergo repeat intensive PK (see Section 9.34 for management of individual dose adjustments) will have ETR therapy discontinued and best available therapy by their clinician will be initiated.

If a subject discontinues therapy for a non-ETR related toxicity reason (e.g., drug intolerance to an OBR agent) the subject will be replaced. Subjects discontinued due to ETR toxicity will NOT be replaced; rather, they will continue to be counted as failures. However, the safety data from the subjects who replace them for PK purposes will also be used when applying the safety guidelines

3.4 Full Cohorts

Once PK and safety criteria have been met for a full cohort, subjects will continue their treatment in the specific cohort at the selected dose. The safety criteria are described in Section 8.52. In order to meet the PK criteria, the geometric mean AUC_{12h} in the cohort must be within 60 to 150% of the geometric mean AUC_{12h} in adults (i.e. between 2713 and 6783 ng•h/mL). The recommended dose must be approved by the P1090 core protocol team. If, however, the selected dose for a full cohort does not meet the PK and safety criteria, the dose may be adjusted for the subjects already in the cohort (as described above) and additionally new subjects will be enrolled, if needed, to have (at least) 12 subjects in total on the new starting dose. The evaluation of PK and safety will then be repeated. If the starting dose is still not acceptable, the dose selection process will be repeated.

Subjects from the failed cohort may be dose-adjusted to the new dose if the site investigator and protocol team believes this is in the best interest of the subject. These subjects will have a truncated intensive PK evaluation (sampling at pre-dose and 2hr and 3-5h after dose).
Those subjects that require an individual dose adjustment for high or low AUCs (see Section

9.34 for management of individual dose adjustments), will have a repeat intensive PK evaluation 7-14 days following their dose adjustment.

Those subjects from a failed cohort who are not dose-adjusted to the new dose, but had acceptable PK parameters and antiviral activity and safety can remain on the same dose and will be followed on study.

Subjects who require a dose adjustment but refuse to undergo repeat intensive PK (see Section 9.34 for management of individual dose adjustments) will have ETR therapy discontinued and will be replaced (but will be followed on study but off study drug).

If full cohort data are inconclusive, the protocol team may decide to enroll additional subjects at the starting dose, and/or the P1090 Study Monitoring Committee (SMC) may be asked to review the data and advise the team.

As enrollment into each cohort continues, the study team will review the data via conference call at least monthly, to ensure that the stated PK and safety targets are acceptable.

3.5 Cohort III

Upon release of Version 5.0, the P1090 core protocol team will review the available PK and safety results of Cohort II to determine whether Cohort III may be opened to enrollment of infants $\geq$ 6 months and < 1 year of age.

3.5.1 Available Cohort II PK and safety data are acceptable

If the available PK and safety data are acceptable, enrollment into Cohort III will commence starting with infants $\geq$ 6 months and < 1 year of age.

In the event that Cohort III is open to accrual at the time that Cohort II completes accrual of a mini-cohort (N=6), accrual into both cohorts will be paused as per Section 3.3.

3.5.2 Available Cohort II PK and safety data are not acceptable

If available safety and/or PK data from Cohort II are unacceptable at this time, Cohort III will remain closed to enrollment; Cohort II will continue to enroll to complete the mini-cohort of six subjects. At that point, the team will evaluate the mini-cohort as described in Section 3.3.

If the 4-week safety data from the six subjects in the Cohort II mini-cohort are deemed appropriate, and sufficient PK data are available to confirm the starting weight-based dose for the older infants in Cohort III as per Dosing Table 2, Cohort III will open to enrollment of infants $\geq$ 6 months and < 1 year of age.

If the 4-week safety data from the six subjects in the Cohort II mini-cohort are not deemed appropriate, and/or PK data confirm the starting weight-based dose for the older infants in Cohort III as per Dosing Table 2, Cohort III will remain closed to enrollment and a new mini-cohort will be enrolled into Cohort II as per Section 3.3.

3.5.3 Enrollment of Cohort II is paused at time of release of Version 5.0

If enrollment of Cohort II is paused for review of mini-cohort data at the time of release of Version 5.0, opening of Cohort III will be held until Cohort II is re-opened.

Once there are sufficient data of infants ≥ 6 months and < 1 year of age to assess the impact of age on the pharmacokinetics, enrollment of the youngest group of infants in Cohort III (≥ 2 months and < 6 months of age) will commence.

3.6 Long Term Safety Follow-Up

Long term safety follow-up is described in Section 5.5.

3.7 Early Discontinuation

Subjects who are withdrawn from study drug within the first 48 weeks of study will not enter long term follow-up but will be followed for safety for 4 weeks, as per Appendix ID. Additionally, any AEs will be followed until satisfactory clinical resolution (i.e. value returns back to subjects baseline value) or stabilization (to be agreed upon with the sponsor). All grade 3 and grade 4 laboratory abnormalities as well as any laboratory abnormalities resulting in an increase of 2 DAIDS Grades from baseline, will be followed until they return to baseline or within 1 Grade from baseline.

4.0 SELECTION AND ENROLLMENT OF SUBJECTS

4.1 Inclusion Criteria

4.11 Confirmed HIV-1 infection

NOTE: Results can be abstracted from the medical record to meet this criterion for HIV diagnosis.

Tests Performed at < 2 years of age

An infant will be considered to be infected with HIV if TWO separate peripheral blood specimens from different days are drawn and each specimen is positive by at least one of the following assays:

- HIV DNA PCR
- Plasma HIV RNA (quantitative or qualitative)
- HIV total nucleic acid tests

At least one of the above tests must be done in a VQA-certified laboratory that is approved to perform the assay for protocol testing. If the mother or infant is receiving antiretroviral drugs, then an HIV DNA assay may be more sensitive.

Tests Performed at ≥ 2 years of age

Documentation of HIV-1 infection is defined as positive results from two samples collected at different time points. All samples tested must be whole blood, serum or plasma. For studies

conducted under an IND, all test methods should be FDA-approved if available. If FDA- approved methods are not available, test methods should be verified according to GCLP and approved by the IMPAACT central laboratory.

- Sample #1 may be tested by non-study public or PEPFAR programs. However, both the result and the assay date must be recorded in subject's charts. Source documentation [patient's medical record/chart, Ministry of Health (MOH) registers, laboratory results, etc.] must be available if requested.
- Sample #2 must be performed in a CAP/CLIA-approved laboratory (for U.S. sites) or in a laboratory that operates according to GCLP guidelines and participates in appropriate external quality assurance program (for international sites).

Acceptable Tests

Sample #1 may be tested using any of the following:

- Two rapid antibody tests from different manufacturers or based on different principles and epitopes.
- One EIA OR Western Blot OR immunofluorescence OR chemiluminescence
- One HIV DNA PCR
- One quantitative HIV RNA PCR (above the limit of detection)
- One qualitative HIV RNA PCR
- One HIV culture (prior to August 2009)
- One total HIV nucleic acid test

If Sample #1 is positive, then collect and test Sample #2. Sample #2 may be tested using any of the following:

- Rapid antibody test. If this option is used in combination with two rapid tests for Sample
- #1, at least one of the three rapid tests must be FDA-approved and the third rapid test must be from a third manufacturer or based on a third principle or epitope.
- One EIA OR Western Blot OR immunofluorescence OR chemiluminescence
- One HIV DNA PCR
- One quantitative HIV RNA PCR (above the limit of detection)
- One qualitative HIV RNA PCR
- One HIV culture (prior to August 2009)
- One total HIV nucleic acid test

4.12 Age ≥ 2 months to < 6 years old at study entry. NOTE: For subjects who were born at ≤ 37 weeks gestational age, the subject must be at least 12 weeks of age, AND ≥ 46 weeks post-conceptual age at study entry.

4.13 HIV-1 RNA viral load > 1,000 copies/mL (within the previous 90 days prior to screening) AND an HIV-1 RNA viral load > 1,000 copies/mL at screening.

4.14 Treatment experienced children on a failing combination antiretroviral regimen (containing at least 3 ARVs) for at least 8 weeks OR Treatment experienced children on a treatment interruption of at least 4 weeks with a history of virologic failure while on a combination antiretroviral regimen

(containing at least 3 ARVs).

4.15 Ability to swallow ETR whole or dispersed in an appropriate liquid (see Section 5.2).

4.16 Parent or legal guardian able and willing to provide signed informed consent and to have the subject followed at the clinic site.

4.17 Availability of sufficient active ARV drugs to create an OBR consistent with protocol requirements (as outlined in Table 6).

4.2 Exclusion Criteria

4.21 Evidence of phenotypic resistance to ETR at screening. Phenotypic cutoffs of > 10 for loss of sensitivity for cohorts I, II, III.

4.22 Known history of HIV-2 infection in subject or subject's mother.

4.23 Diagnosis of a new CDC Stage C (per 1994 Revised Classification System for Human Immunodeficiency Virus Infection in Children Less than 13 Years of Age) criteria or opportunistic or bacterial infection diagnosed within 30 days prior to screening and not considered clinically stable.

4.24 Prior history of malignancy.

4.25 Any clinically significant diseases (other than HIV infection) or clinically significant findings during the screening medical history or physical examination that, in the investigator's opinion, would place the subject at an unacceptable risk of injury; render the subject unable to meet the requirements of the protocol; compromise the outcome of this study; or lead to the child being ineligible for participation.

4.26 Current ≥ Grade 3 of any of the following laboratory toxicities at screening: neutrophil count, hemoglobin, platelets, AST, ALT, lipase, serum creatinine.

4.27 Current or anticipated use of any disallowed medications (see Section 4.32).

4.28 Subject's family is unlikely to adhere to the study procedures, keep appointments, or is planning to relocate to a non-IMPAACT study site during the study.

4.29 History of non-adherence with ARV medications that in the investigator's opinion could affect the ability of the subject to comply with the protocol/procedures.

4.210 Subject is currently participating, or has participated within the previous 30 days prior to screening, in a study with a compound or device that is not commercially available.

4.211 Grade 3 or higher QTc or PR interval prolongation from the ECG at screening (see Appendix V).

NOTE: Subject may proceed to entry based on site investigator grading of ECG. If official central

ECG reading indicates Grade 3 or higher QTc or PR interval on the screening ECG that was not recognized by the site investigator, the Team will inform the site investigator, and the subject will be taken off study treatment.

4.3 Concomitant Medication Guidelines

4.31 Precautionary Medications

The following medications should be avoided, if possible, and alternative treatments sought. Please contact the protocol team at impaact.teamp1090@fstrf.org if treatment with any of these medications is necessary for clinical care.

- Clopidogrel
- Clarithromycin when used for the treatment of Mycobacterium avian complex (MAC) - other indications are acceptable
- ≥ 14 days of all inhaled/intranasal corticosteroids, except for fluticasone (see disallowed meds below), for subjects taking ritonavir-boosted PIs
- Rifabutin, when combined with a boosted protease inhibitor
- Any drugs not recommended in the package insert under concomitant medications.

4.32 Disallowed Medications

Anticonvulsants:

- Carbamazepine
- Oxcarbazapine
- Phenytoin
- Fosphenytoin
- Phenobarbital

Anti-infectives:

- Rifampin
- Rifapentine

Antiretrovirals:

- Darunavir use in subjects < 3 years old
- Fosamprenavir/ritonavir (etravirine increases fosamprenavir exposure posing a potential safety issue)
- Maraviroc
- Saquinavir/ritonavir
- Tipranavir/ritonavir (tipranavir/ritonavir significantly decreases etravirine)
- Ritonavir, used as sole PI therapy
- Unboosted PIs including nelfinavir (drug interaction unknown – etravirine may increase nelfinavir)
- Other NNRTIs

Corticosteroids:

- ≥ 14 days of continuous use of inhaled fluticasone (for subjects taking ritonavir-boosted PIs)
- ≥ 7 days of oral or IV steroids

Other:

- Products containing St. John's wort (*Hypericumperforatum*)
- Any drugs contraindicated in the package insert under concomitant medications

4.4 Enrollment Procedures

Prior to implementation of this protocol, and any subsequent full version amendments, each site must have the protocol and the protocol informed consent form(s) approved, as appropriate, by their local institutional review board (IRB)/ethics committee (EC) and any other applicable regulatory entity (RE). Upon receiving final approval, sites will submit all required protocol registration documents to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center (RSC). The DAIDS PRO will review the submitted protocol registration packet to ensure that all of the required documents have been received.

Site-specific informed consent forms (ICFs) WILL be reviewed and approved by the DAIDS PRO and sites will receive an Initial Registration Notification from the DAIDS PRO that indicates successful completion of the protocol registration process. A copy of the Initial Registration Notification should be retained in the site's regulatory files.

Upon receiving final IRB/EC and any other applicable RE approval(s) for an amendment, sites should implement the amendment immediately. Sites are required to submit an amendment registration packet to the DAIDS PRO at the RSC. The DAIDS PRO will review the submitted protocol registration packet to ensure that all the required documents have been received. Site- specific ICF(s) *WILL NOT* be reviewed and approved by the DAIDS PRO and sites will receive an Amendment Registration Notification when the DAIDS PRO receives a complete registration packet. A copy of the Amendment Registration Notification should be retained in the site's regulatory files.

For additional information on the protocol registration process and specific documents required for initial and amendment registrations, refer to the current version of the DAIDS Protocol Registration Manual.

Sites interested in screening or enrolling subjects in IMPAACT P1090 must send an email to the team at impaact.teamp1090@fstrf.org indicating the candidate's PID# (if no PID is assigned, the age of the subject is sufficient), cohort number and prior ART experience. If the participant has a milestone birthday that will change cohort assignment, it is the site's responsibility to notify the DMC data manager to request a cohort assignment change.

Sites should refer to subjects medical charts to ensure potential eligibility. Slots will be granted based on the date a slot was requested. Sites must receive authorization from the protocol team before proceeding with screening.

Enrollment slots will be granted only for a study candidate who:

- Receives permission to proceed with the screening visit

- Accepts the slot and completes the screening visit within two weeks of receipt of the slot (Sites MUST email the protocol team to accept the slot and to complete the Screening visit)
- Meets the study inclusion criteria

Sites should contact the protocol team at impaact.teamp1090@fstrf.org with any screening timeline deviations. A slot may be recalled if deviations from the timeline are not approved by the protocol team. Sites need to inform the protocol team of the proposed optimized background regimen (OBR) at least 24 hours prior to enrollment. Enrollment is contingent upon the protocol team and site agreeing on the OBR. Sites with study candidates who are granted a slot but fail to enroll will be required to complete an enrollment failure form which will collect general failure-to-enroll information.

4.5 Co-enrollment Procedures

Co-enrollment is permitted except for protocols that would violate the exclusion criteria. Co- enrollment in P1074 is strongly encouraged. With the exception of P1074, all co-enrollments in protocols require the prior approval of the P1090 protocol team and the co-enrollment protocol teams.

5.0 STUDY TREATMENT

Study treatment is defined as etravirine (ETR) 25 mg and 100 mg tablets. Both will be provided by the study. Darunavir 100 mg/mL suspension, darunavir 75 mg tablets, and darunavir 150 mg tablets, will be provided through the study if not reasonably available locally. (NOTE: Darunavir may only be used in children ≥ 3 years.). Other antiretrovirals (ARVs) will not be provided through the study.

The subjects will be accrued into the study for an initial dose finding intensive PK component for age related cohorts. It is anticipated that approximately 50 subjects will be accrued, to yield at least 36 evaluable subjects with a minimum of 12 subjects for each of the three cohorts, whose initial dose was the final optimal dose determined for their age cohort. The total sample size will depend upon the number of subjects needed to complete the dose finding stage of the study and the number of subjects who discontinue the study.

Subjects enrolled into the study will be stratified by age, as described in Section 3.1 and Table 6. In all cohorts, ETR will be started concurrently with an optimized ARV background regimen (OBR).

This study is designed to determine the appropriate ETR dose for HIV-1 infected infants and children and to evaluate the PK, safety and tolerability of ETR in this population.

5.1 Drug Regimens, Administration and Duration

All subjects enrolled into the study will be stratified by age into one of three cohorts.

Cohort I: ≥ 2 year to < 6 years who are treatment experienced

- ETR 25 mg and/or 100 mg tablet(s)
- Subjects will take the specified dose of ETR tablet(s) orally twice daily within 30 minutes following a meal per Dosing Table **1** in Appendix III

Cohort II: ≥ 1 year to < 2 years who are treatment experienced

- ETR 25 mg and/or 100 mg tablet(s)
- Subjects will take the specified starting dose of ETR tablet(s) orally twice daily within 30 minutes following a meal, per Dosing Table **1** in Appendix III

Cohort III: ≥ 2 months to < 1 year who are treatment experienced

- ETR 25 mg and/or 100 mg tablet(s)
- Subjects will take the specified starting dose of ETR tablet(s) orally twice daily within 30 minutes following a meal, per Dosing Table **2** in Appendix III

ETR will be administered as 25 mg scored tablets and/or 100 mg tablets swallowed as a whole or dispersed in an appropriate liquid vehicle following a meal. Refer to Section 3.1 and Table 6 for further information on regimen design per cohort.

Study Duration: Minimum of 48 weeks
Long Term Safety Follow-up: See Section 5.5

5.2 Dosing and Administration

ETR will be dosed orally according to the dosing table in Appendix III. The investigator will be notified by the P1090 Protocol Team in case there would be any change in the dosing table (see Appendix III).

ETR tablets should be swallowed whole with a sufficient amount of water or other liquid within 30 minutes following a meal. Subjects unable to swallow the tablets whole may disperse the tablets in a container with a minimum of 5 mL (1 teaspoon) of water. One minute should be allowed for the tablet(s) to be dispersed, stirring will aid in the dispersion. The dispersed tablet(s) in water may be further diluted with a beverage (see list below) not to exceed 30 mL (2 tablespoons) total volume. The recommendation for administration to infants is to disperse the tablet in approximately 10 mL of liquid (e.g. formula or milk). Once dispersed, subjects should drink the dispersion immediately.

The container should be rinsed with a minimum of 5 mL (1 teaspoon) of water or other beverage and the rinse completely swallowed to ensure the entire dose is consumed. This step may be repeated as needed. The dispersion should be consumed completely and immediately; it is not allowed to administer a portion.

Subjects must avoid the use of warm or hot (> 40°C) beverages and carbonated drinks when swallowing study drug. ETR can be dispersed in the following beverages without compromising drug stability:

- Water that is safe to drink (sterile water will be provided by the study staff**,** as appropriate)
- Mineral water that is safe to drink
- Orange juice
- Milk (whole milk, skim milk or chocolate milk)
- Various infant formula

5.21 Missed Doses

Any missed ETR study drug dose should be taken by the subject if it is within 6 hours of the scheduled missed dosing time.

5.22 Vomited Doses

If the subject vomits the ETR study drug dose within 15 minutes of taking the dose, then another full dose should be taken by the subject.

5.3 Drug Formulation

ETR 100 mg tablet and 25 mg scored tablet: store at 25°C (77°F); with excursions permitted to 15°to 30°C (59° to 86°F) [see USP controlled room temperature]. Store in the original bottle. Keep the bottle tightly closed in order to protect from moisture. Do not remove the desiccant pouches.

Darunavir (Prezista®) 100 mg/mL oral suspension: store at 25°C (77°F); with excursions permitted to 15° to 30°C (59°-86°F). Do not refrigerate or freeze. Avoid exposure to excessive heat. Store in the original container. Shake well before each use.

Darunavir (Prezista®) 75 mg and 150 mg tablets: Store at 25°C (77°F); with excursions permitted to 15° to 30°C (59°-86°F).

5.4 Drug Supply, Distribution and Pharmacy

ETR 100 mg tablet and 25mg scored tablet are provided by Janssen R&D and supplied through the study.

Darunavir 100 mg/mL suspension, and darunavir 75 mg and 150 mg tablets are provided by Janssen R&D and supplied through the study for OBR purposes if not reasonably available locally.

Study Product Acquisition

ETR 100 mg tablets and ETR 25 mg scored tablets will be available through the NIAID Clinical Research Products Management Center (CRPMC). Darunavir 100 mg/mL suspension, darunavir 75 mg tablets, and darunavir 150 mg tablets will be available through the NIAID Clinical Research Products Management Center (CRPMC) for OBR purposes if not reasonably available locally.

The IMPAACT pharmacist can obtain the study product by following the instructions in the manual "Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks" in the section Study Product Control.

The optimized background regimen to be used in this study (with the exception of darunavir, as noted) will not be provided by the study and must be obtained by non-study prescription (see Section 3.2).

5.41 Study Product Accountability

The IMPAACT site pharmacist is required to maintain complete records of all study products received from the CRPMC and dispensed. All unused study products must be returned to the CRPMC after the study is completed or terminated at U.S. sites.

Non-U.S. sites will receive instructions regarding the final disposition of any remaining study products. The procedures to follow for accountability can be found in the manual, “Pharmacy Guidelines and

Instructions for DAIDS Clinical Trials Networks" in the section entitled "Study Product Management Responsibilities."

5.5 Long Term Safety Follow-up

Provided that the overall data for this drug appear to be generally favorable, each subject who successfully completes 48 weeks of ETR treatment will continue to receive study drug through the study, and be followed on study for long-term safety follow-up (see Appendix IE) for up to 5 years or until any one or more of the following events occur within the 5 years:

- The age-appropriate formulations provided by the study are available locally from another source; OR
- The subject is no longer deriving benefit; OR
- The subject meets a protocol-defined reason for discontinuation; OR
- Pharmaceutical development of ETR for that age cohort is terminated

Subjects in countries where ETR, darunavir 100 mg/mL suspension, darunavir 75 mg tablets, and darunavir 150 mg tablets continue to be unavailable locally at the end of the planned 5 year long- term safety follow-up program will be provided the drug either through a P1090 protocol amendment or through other sources, such as another Janssen R&D-sponsored program, government programs, and aid and assistance programs. It is also expected that such programs will be in place in all countries where study sites are located within the planned 5 year duration of long-term safety follow-up phase.

Once subjects enter the Long Term Safety Follow-up phase, they will be seen in clinic every 12 weeks for safety visits and laboratory evaluations until one of the above criteria are fulfilled, as per Appendix IE. Sites should record any laboratory results, diagnoses etc. that are recorded as part of standard of care as well as perform the study mandated HIV-1 RNA assay (See Appendix IE).

6.0 SUBJECT MANAGEMENT

6.1 Toxicity Management

The DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, (DAIDS AE Grading Table), Version 1.0, December 2004, Clarification August 2009, must be used and is available on the RSC website at (http://rsc.tech-res.com/safetyandpharmacovigilance/).

Management of adverse experiences will be according to the best clinical practice and the judgment of the site investigator. Alternate explanations for clinical and laboratory abnormalities must be sought. Laboratory normal ranges will be the institutional values. However, if a site does not have an age-specific normal range/value for a particular laboratory, the site should use the latest edition of the Harriet Lane Handbook for normal ranges/values and document this for monitoring purposes. Abnormal clinical and laboratory findings should be followed until resolution to < Grade 2.

The toxicity management guidelines are for events for which a relationship to study drugs cannot be excluded. Clinical or laboratory adverse events (AEs) that are definitely unrelated to study drug(s) may not

result in study drug interruption. General guidelines for study drug suspected adverse drug reactions (SADRs) are provided below:

6.11 Reporting

- Grade 1: All study drug SADRs should be recorded on Case Report Forms (CRFs) at each visit.

- Grade 2: All study drug SADRs should be recorded on CRFs at each visit. Inform team monthly whether toxicity has resolved or not.

- Grade 3 or 4:
  - The protocol team must be notified of study drug SADRs within 24 hours at impaact.p1090cmc@fstrf.org
  - The investigator should attempt to confirm any unexpected laboratory test results as soon as possible but always within 72 hours to determine if the result was spurious.
  - Expedited Adverse Event (EAE) reporting must be done within 72 hours of the initial result. Reporting will occur whether the value is confirmed or if confirmatory results are not available within 72 hours.

6.12 General Management Guidelines

NOTES:
- All antiretroviral therapy including study drug should be started or stopped together whenever possible, except for when one antiretroviral agent can be substituted for another within the same class, when the etiology of the toxicity can be determined.
- If a subject is pending a safety event analyses or resolution, additional safety tests may be required by the team.

Grade 1

Continue study drug; routine monitoring.

Grade 2

Continue study drug; monitor closely with more frequent visits; as per site investigator, work-up to exclude other causes.

Grade 3

NOTE: Grade 3 triglycerides and cholesterol events will NOT require the subject to stop study drug or OBR.
- The protocol team should be notified of a Grade 3 event at impaact.p1090cmc@fstrf.org.
- Study drugs can be continued at the discretion of the site investigator/clinician while awaiting a repeat assessment/confirmation of an abnormal laboratory test as soon as possible (within 72 hours).
- If the repeat assessment confirms Grade 3 toxicity, AND if the investigator considers the event to be at least possibly related to study drug, ETR should be withheld and any abnormal laboratory values should be followed weekly (Except in Grade 3 cholesterol and triglycerides).

- OBR should be held at the discretion of the site investigator.
- If the toxicity resolves to ≤ Grade 2 within 21 days, ETR (and OBR if applicable) can be restarted.
- If the Grade 3 toxicity persists for > 21 days, or recurs at a ≥ Grade 3 after re-introduction of ETR; ETR must be permanently discontinued.

Grade 4: Non-Life-Threatening Toxicity

- Study drug (ETR) and concomitant antiretrovirals (OBR) should be discontinued immediately unless the clinician and P1090 core protocol team, believe that withholding OBR and/or ETR would be harmful to the subject and that continuing the drugs would pose little additional risk.
- Sites should attempt to confirm any unexpected laboratory results as soon as possible, but always within 72 hours of the event to determine if these results were spurious.
- The protocol team should be notified of a Grade 4 event at impaact.p1090cmc@fstrf.org.
- If the repeat assessment confirms Grade 4 toxicity, ETR should be permanently discontinued, HOWEVER, for Grade 4 adverse events that are determined to be unrelated to study drug, the investigator should contact the team to determine when study drug may be safely resumed.
- If the repeat assessment shows Grade 3 toxicity, continue to hold ETR and follow abnormal laboratory values weekly.
- If the toxicity resolves to ≤ Grade 2 within 21 days, all study drugs can be restarted.
- If ≥ Grade 3 toxicity recurs after re-introduction of ETR, the study drug (ETR) must be permanently discontinued.

Grade 4: Life-Threatening Toxicity

- Study drug (ETR) and concomitant antiretrovirals (OBR) should be discontinued immediately.
- Sites should attempt to confirm any unexpected laboratory results as soon as possible, but always within 72 hours of the event to determine if these results were spurious.
- The protocol team should be notified of a Grade 4 event at impaact.p1090cmc@fstrf.org.
- If the repeat assessment confirms Grade 4 toxicity, ETR should be permanently discontinued, HOWEVER, for Grade 4 adverse events that are determined to be unrelated to study drug, the investigator should contact the team to determine when study drug may be safely resumed.

6.13 Management of Cutaneous Adverse Events

Since cutaneous adverse events are of particular interest for this drug, the following guidelines on monitoring and management should be followed. The table in Appendix VII-A illustrates these grading and management guidelines. Additionally, please refer to Appendix IV which describes the visit schedule for management of cutaneous adverse events.

NOTE: These management guidelines are NOT applicable to rashes with clear alternative etiology, such as chicken pox, impetigo and cutaneous HSV.

Grade 1 cutaneous reaction/rash is defined as localized macular rash.

Grade 2 cutaneous reaction/rash is defined as diffuse macular, maculopapular or morbilliform rash or target lesions.

Subjects with Grade 1 or Grade 2 rash may continue ETR or temporarily interrupt therapy at the investigator's discretion. Close clinical follow up is recommended to monitor progression of rash. All subjects with Grade 2 rash must be seen by a dermatologist within 24 to 48 hours.

Grade 3 cutaneous reaction/rash is defined as:

- Diffuse macular, maculopapular or morbilliform rash with vesicles or limited number of bullae
- Cutaneous reaction/rash with superficial ulceration of mucous membrane limited to 1 mucosal site
- Cutaneous reaction/rash with at least 1 of the following:
  - Elevations of ALT/AST > 2 x baseline but at least 5 x upper limit of laboratory normal range (ULN)
  - Fever ≥ 38°C or 100.4ºF
  - Serum sickness-like reaction
  - Eosinophil count > 1000/mm³
- Subjects experiencing a Grade 3 rash or cutaneous event must have ETR discontinued permanently; but should remain on study for safety follow-up.
- OBR should be held at the discretion of the site investigator.
- Subjects must also be evaluated by a dermatologist within 24 to 48 hours.
- The protocol team should be notified of a Grade 3 event at impaact.p1090cmc@fstrf.org.

Grade 4 cutaneous reaction/rash is defined as:

- Extensive or generalized bullous lesions
- Stevens-Johnson syndrome (SJS)
- Ulceration of mucous membrane involving 2 or more distinct mucosal sites
- Toxic epidermal necrolysis (TEN)
- Subjects experiencing a Grade 4 rash or cutaneous event must have ETR discontinued permanently; but should remain on study for safety follow-up.
- OBR should be held at the discretion of the site investigator.
- Subjects must also be evaluated by a dermatologist within 24 to 48 hours.
- The protocol team should be notified of a Grade 4 event at impaact.p1090cmc@fstrf.org.

NOTE: Topical corticosteroids, topical anti-pruritic agents, and oral H1-antihistamines (such as cetirizine, diphenhydramine, hydroxyzine and levocetirizine but excluding astemizole and terfenadine) will be allowed at the investigator's discretion for all grades of rashes.

6.14 Management of Acute Systemic Allergic Reaction

The table in Appendix VII-B illustrates these grading and management guidelines. Grade 1

Localized urticaria with no medical intervention indicated. Subject may continue intake of ETR.

Grade 2

Localized urticaria with medical intervention needed, or mild angioedema with no medical intervention indicated. Subject may continue intake of ETR.

Grade 3

Generalized urticaria or angioedema with medical intervention indicated; or symptomatic mild bronchospasm.

- Subjects with Grade 3 acute systemic allergic reactions will be permanently discontinued from the investigational medication (ETR) and background regimen but will be followed on study on a modified schedule (Appendix ID) for safety outcomes.
- Subjects will be treated as clinically appropriate per the local physician.

Grade 4

Acute anaphylaxis; life-threatening bronchospasm; laryngeal edema.

- Subjects with Grade 4 acute systemic allergic reactions will be permanently discontinued from the investigational medication (ETR) AND background regimen (OBR) but will be followed on study on a modified schedule (Appendix ID) for safety outcomes.
- Subjects will be treated as clinically appropriate per the local physician.
- The protocol team should be notified of a Grade 4 event at impaact.p1090cmc@fstrf.org.

6.15 Management of Abnormal QTc or PR intervals noted onECG

NOTE: Please refer to Appendix V for grading of abnormal QTc or PR intervals by ECG. Any subject who is permanently discontinued from the investigational medication (ETR) because of toxicity will be followed on study on a modified schedule (Appendix IE) for safety outcomes. Subjects will be treated as clinically appropriate per the local physician.

Grade 1

Continue study drug; routine monitoring. Grade 2

Continue study drug; work-up to exclude other causes according to judgment of site investigator. Grade 3

- Study drugs may be continued at the discretion of the site investigator/clinician.
- Based on the local investigator reading of the ECG, sites should request a turnaround time of 24 hours for the ECG from the centralized reading service.
- If the central ECG reader confirms a Grade 3 ECG abnormality (QTc and/or PR interval), ETR must be permanently discontinued.
- For Grade 3ECG abnormalities that are determined to be unrelated to study drug, the investigator should contact the team to determine whether study drug may be safely resumed.

Grade 4: Non-Life-Threatening Toxicity

- Subjects experiencing a Grade 4toxicity must have ETR discontinued.
- OBR should be held at the discretion of the site investigator.
- Based on the local investigator reading of the ECG, sites should request a turnaround time of 24 hours for the ECG from the centralized reading service.

- The protocol team should be notified of a Grade 4 event at impaact.p1090cmc@fstrf.org.
- If the central ECG assessment confirms Grade 4 ECG abnormalities (QTc and/or PR interval), ETR must be permanently discontinued. OBR should be held at the discretion of the site investigator.
- For Grade 4ECG abnormalities that are determined to be unrelated to study drug, the investigator should contact the team to determine whether study drug may be safely resumed.
- If subjects are discontinued from ETR, they will still be followed on study on a modified schedule (Appendix ID) for safety outcomes. Subjects will be treated as clinically appropriate per the local physician.

Grade 4: Life-Threatening Toxicity

- Subjects experiencing a life-threatening Grade 4toxicity must have ETR discontinued
- OBR should be held at the discretion of the site investigator.
- Sites should request a turnaround time of 24 hours for the ECG from the centralized reading service.
- The protocol team should be notified of a Grade 4 event at impaact.p1090cmc@fstrf.org.
- For confirmed drug-related, life-threatening Grade 4 QTc or PR interval SAEs, study medication must be permanently discontinued.
- For life-threatening Grade 4 ECG abnormalities that are determined to be unrelated to study drug, the investigator should contact the team to determine whether study drug may be safely resumed.
- If subjects are discontinued from ETR, they will still be followed on study on a modified schedule (Appendix ID) for safety outcomes. Subjects will be treated as clinically appropriate per the local physician.

6.16 Management of Neurologic Adverse Events

NOTE: Please refer to Appendix VI for grading abnormal neurologic adverse events. Grade 1

Continue study drug; routine monitoring.

Grade 2

Continue study drug; work-up to exclude other causes according to judgment of site investigator. Grade 3

- Subjects experiencing a Grade 3toxicity must have ETR discontinued
- OBR may be discontinued at the discretion of the site investigator.
- The protocol team should be notified of a Grade 3 event at impaact.p1090cmc@fstrf.org.
- For Grade 3 adverse events that are determined to be unrelated to study drug, the investigator should contact the team to determine if/when the study drug may be safely resumed
- If the event is considered to be 'definitely related,' 'probably related' or 'possibly related'
- to study drug, AND is resolved to grade 2 or less, AND the site physician feels it is in the subjects best interest to re-try the drug, the investigator should contact the team to determine if/when the study drug may be safely resumed
- If subjects are permanently discontinued from ETR, they will still be followed on study on a modified schedule (Appendix IE) for safety outcomes. Subjects will be treated as clinically appropriate per the local physician.

Grade 4: Non-Life-Threatening Toxicity

- Subjects experiencing a Grade 4 adverse event must have ETR discontinued temporarily
- OBR should be held at the discretion of the site investigator.
- The protocol team should be notified of a Grade 4 event at impaact.p1090cmc@fstrf.org.
- For Grade 4 adverse events that are determined to be unrelated to study drug, the investigator should contact the team to determine when/if study drug may be safely resumed.
- If the event is considered to be definitely related, probably related or possibly related to study drug, ETR should be permanently discontinued.
- If subjects are discontinued from ETR, they will still be followed on study on a modified schedule (Appendix ID) for safety outcomes. Subjects will be treated as clinically appropriate per the local physician.

Grade 4: Life-Threatening Toxicity

- Subjects experiencing a Grade 4 toxicity must have ETR discontinued permanently; but should remain on study for safety follow-up.
- OBR should be held at the discretion of the site investigator.
- The protocol team should be notified of a Grade 4 event at impaact.p1090cmc@fstrf.org.
- If subjects are discontinued from ETR, they will still be followed on study on a modified schedule (Appendix ID) for safety outcomes. Subjects will be treated as clinically
- appropriate per the local physician.

6.2 Subject Management

The DMC will maintain a web page informing sites as to the availability of enrollment slots per cohort. The protocol team, including the co-chairs, medical officers, pharmacist, and pharmacologist, will respond to sites who contact the team with questions regarding toxicity management, dose modifications, or other issues within 1 business day. Team responses will include, at a minimum, the study team.

Sites will be given 7 days to respond to queries to allow the team to meet Janssen R&D data delivery requirements. Sites will be contacted by the protocol data manager or co-chairs regarding any query responses or data issues that are outstanding after 7 days. All dose modifications will be recommended by the protocol team. See Section 3.0 for detailed information on the review process and dose modifications for a mini-cohort or full cohort.

Information on permitted ARV changes can be found in Section 6.5.

6.3 Definition of Virologic Failure for Subject Management

NOTE: A confirmatory (repeat) HIV-1 RNA measurement MUST be performed within 1 to 4 weeks of the initial suspected failure or rebound.

Virologic FAILURE or lack of response in this study is defined as:

- A confirmed HIV-1 RNA at week 8 that is not at least 0.5 log lower than the HIV-1 RNA at entry (unless the viral load at week 8 or later is already ≤ 400 copies/mL)
  OR

- A confirmed HIV-1 RNA at or after week 12 that is not at least 1 log lower than the HIV RNA at entry (unless the viral load at week 12 or later is already ≤ 400 copies/mL

  OR

- A confirmed HIV-1 RNA ≥ 400 copies/mL at week 24
  Virologic REBOUND in this study is defined as:

  For subjects whose nadir was ≤ 400 copies/mL; a confirmed HIV-1 RNA >1000 copies/mL (on 2 consecutive measurements at least 1 week but no more than 4 weeks apart).

Subjects, who are confirmed as virologic failures (including virologic rebound) as defined above, should follow the schedule of evaluations for Virologic Failure as described in Appendix IA – IC. At the confirmed virologic failure visit, a specimen should be drawn that should be sent for resistance testing (genotyping and phenotyping), as described in Appendix IA – ID.

Subjects will then, at the discretion of the subject's clinician; with the approval of the protocol team and assuming the subject agrees to continue; be moved into one of the following three options:

- Off Study Drug – On Study: Be taken off study drug and followed as per Appendix ID, 'Follow up for Subjects who Discontinue Study Provided Etravirine;'

OR

- On Study Drug – re-optimize OBR: Have background therapy re-optimized, with the subject remaining on study drug;

OR

- On Study Drug: Continue with no changes made to the current regimen.

Any re-optimization of background therapy that includes experimental drugs must first be approved by the P1090 core team by emailing a request to impaact.p1090cmc@fstrf.org.

6.4 Viral Resistance Testing

For all subjects, blood samples for viral resistance assays will be collected at screening. In addition, to evaluate development of resistance to ETR and to other antiretroviral therapies, used in the treatment regimen, blood samples will be collected at any confirmed virologic failure (including virologic rebound) and at any early discontinuation visit (if not already obtained at virologic failure) to assess development of resistance to ETR and or OBT. (Refer to Appendix I for more information)

6.5 Permitted Changes to the ARV Optimized Background Therapy During the Study

Any changes in background ARV therapy after initial optimization must be approved by the P1090 core protocol team. Unless the change is specifically permitted, subjects who have one or more new agents added to the optimized background CART regimen will be considered virologic failures.
The following changes to optimized background therapy are permitted during the study. However, the P1090 core protocol team requests that they be notified of any of these changes BEFORE they occur (impaact.p1090cmc@fstrf.org).

- Subjects may discontinue a background ARV (if approved by the P1090 team) and remain on study and on study drug
- Formulation substitutions for NRTI class (substituting single agents for fixed dose combinations and vice versa of the same ARV, or switching from liquid to pill/capsule form) are allowed.
- Formulation substitutions for PI class (capsule to tablet or liquid, or vice versa) are permitted only after discussion with the P1090 core protocol team, including the pharmacologists. In certain cases, repeat PK evaluations may be requested
- Substitution within the NRTI or PI class, for reasons of toxicity or intolerance will be considered. If approved, the subject will remain on study drug, with the new PI, but considered as a virologic failure if the change occurs after the week 4 visit.

6.6 Concerns Regarding Non-Adherence

In the rare event where the results of a single subject's intensive PK are extremely low, AND the site clinician/protocol team strongly suspect non-adherence, an additional subject may be enrolled into the mini-cohort to replace the non-adherent subject. The non-adherent subject may remain on study and on study drug (ETR) but will not be considered for dose-finding or safety final analysis.

Medication adherence is critical to successful antiretroviral therapy. In addition to compromising the efficacy of the current regimen, suboptimal adherence has implications for limiting future effective regimens for subjects with resistant strains.

Evidence indicates that adherence problems occur frequently in children. Studies have reported that fewer than 50% of children and/or their caretakers reported full adherence to the regimens. Although a variety of factors have been associated with adherence, no clear predictors of either good or poor adherence have been consistently identified in children.

As a part of this trial, adherence to therapy should be stressed at each visit, along with continued exploration of strategies to maintain and/or improve adherence.

Multiple methods of determining adherence to ARV therapy will be used simultaneously (e.g., quantitative self-report, pill counts). Pill counts will take place at each visit and will be recorded on the drug accountability form. Adherence to the study drug, OBR, and assessment of the palatability of the study drug, will also be monitored in the form of questionnaires/CRF administered by the site staff.

6.7 Etravirine Dose Changes Due to Increases in Body Weight

Confirmed increases in subject's body weight will trigger an ETR dose increase as follows:

- If NO PK directed dose change was made following the day 14 (± 4 days) PK visit, i.e., the starting ETR dose from dosing tables provided an adequate AUC_{12h}, then as the subject's weight increases such that it crosses into a higher weight band, the dose will be changed to correspond with the new weight band, consistent with the Dosing Table provided in Appendix III.
- If an individualized PK directed dose change was made following the day 14 (± 4 days) PK visit, a dose increase is triggered when the subject's weight has increased by 25% from the weight at the most recent AUC_{12h} evaluation. Contact the protocol team at impaact.p1090cmc@fstrf.org for an individualized dosing recommendation based on the subject's pharmacokinetic parameters.

There will be no 12-hour pharmacokinetic studies for dose adjustments due to increase in body weight.

6.8 Criteria for Etravirine (Study Drug) Discontinuation

The following are criteria that will result in discontinuation of study treatment (ETR). Subjects who are withdrawn from study drug within the first 48 weeks of study will not enter long term follow-up, but will be followed for safety for 4 weeks, as per Appendix ID.

Additionally, any AEs will be followed until satisfactory clinical resolution (i.e. value returns back to subjects baseline value) or stabilization (to be agreed upon with the sponsor). All Grade 3 and Grade 4 laboratory abnormalities as well as any laboratory abnormalities resulting in an increase of 2 DAIDS grades from baseline will be followed until they return to baseline or within 1 grade from baseline.

- Grade 3 or higher events that are believed to be related, or possibly related, to study drug
- Treatment with disallowed medications
- Grade 3 or higher cutaneous reactions as outlined in section 6.13, that are not clearly related to a specific viral illness
- Grade 3 or higher acute systemic allergic reactions as outlined in section 6.14, that are related to study drug
- Other Grade 3 or higher toxicities that don't resolve to < Grade 3
- Grade 3 or higher ECG toxicities (QTc and/or PR interval) as outlined in Section 6.15, that are deemed related to study drug
- Grade 3 or higher neurologic adverse events as outlined in Section 6.16
- For subjects who have an AUC > 4380ng.h/mL, but who cannot be dose reduced
- Non-adherence to study medication or study medication administration instructions
- New data become available that indicate treatment should be discontinued
- Subject declines further study visits, including PK visits

6.9 Criteria for Study Discontinuation

Following are criteria for study discontinuation:

- The parent or legal guardian refuses to allow the subject further treatment and/or follow-up evaluations.
- The investigator determines that further participation would be detrimental to the subject's health or well-being.

- The subject fails to comply with the study requirements so as to cause harm to him/herself or seriously interfere with the validity of the study results.

7.0 EXPEDITED ADVERSE EVENT REPORTING

7.1 Adverse Event Reporting to DAIDS

Requirements, definitions and methods for expedited reporting of Adverse Events (AEs) are outlined in Version 2.0 of the DAIDS EAE Manual, which is available on the RSC website at: http://rsc.tech-res.com/safetyandpharmacovigilance/.

The DAERS internet-based reporting system must be used for expedited AE reporting to DAIDS. In the event of system outages or technical difficulties, expedited AEs may be submitted via the DAIDS EAE Form. For questions about DAERS, please contact CRMSSupport@niaid.nih.gov or from within the DAERS application itself.

Sites where DAERS has not been implemented will submit expedited AEs by documenting the information on the current DAIDS EAE Form. This form is available on the RSC website: http://rsc.tech-res.com/safetyandpharmacovigilance/. For questions about EAE reporting, please contact the RSC (DAIDSRSCSafetyOffice@tech-res.com).

7.2 Reporting Requirements for this Study

- The SAE Reporting Category, as defined in Version 2.0 of the DAIDS EAE Manual, will be used for this study.

The study agent for which expedited reporting is required is Etravirine

- In addition to the EAE Reporting Category identified above, other AEs that must be reported in an expedited manner are:
- Erythema multiforme
- Suspected transmission of an infectious agent by study product (as required by Vol. 9A, section 5.9 of the Rules Governing Medicinal Products in the European Union – Guidelines on Pharmacovigilance for Medicinal Products for Human Use. Such reporting is required irrespective of the presence of other seriousness criteria.)

7.3 Grading Severity of Events

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table, Version 1.0, December 2004, Clarification August 2009) is used and is available on the RSC website at http://rsc.tech-res.com/safetyandpharmacovigilance/.

To grade to the severity of any abnormal QTc or PR intervals, the DAIDS AE grading table for these events are described in Appendix V.

To grade the severity of any neurologic events, sites should use the grading table in Appendix VI.

7.4 Expedited AE Reporting Period

- The expedited AE reporting period for this study is as per the EAE manual.
- After the protocol-defined AE reporting period, unless otherwise noted, only SUSARs as defined in Version 2.0 of the EAE Manual will be reported to DAIDS if the study staff become aware of the events on a passive basis (from publicly available information).

NOTE: For reporting of all adverse experiences the Investigator will determine the causality and relationship to study drug. However, in regards to subject safety and PK evaluations which will support the selection of a dose for a given cohort, the protocol team will also have input as to the causality and drug relation of specific adverse experiences.

8.0 STATISTICAL CONSIDERATIONS

8.1 General Design Issues

This is a Phase I/II multicenter, open label study with primary objectives of assessing the safety/tolerability and pharmacokinetics of ETR in combination with optimized background regimen (OBR) administered to HIV-infected treatment-experienced children within the age range of ≥ 2 months to < 6 years.

Hypothesis: ETR will be safe, well tolerated, will have pharmacokinetics comparable to adults and will demonstrate antiviral activity when used with an optimized background therapy in HIV-1-infected, treatment experienced infants and children.

The sample will be stratified into the following age groups:

Cohort I ≥ 2 years to < 6 years of age who are treatment experienced*
Cohort II ≥ 1 year to < 2 years of age who are treatment experienced*
Cohort III: ≥ 2 months to < 1 year who are treatment experienced* †

*Treatment experienced children on a failing combination antiretroviral regimen (containing at least 3 ARVs) for at least 8 weeks OR Treatment experienced children on a treatment interruption of at least 4 weeks with a history of virologic failure while on a combination antiretroviral regimen (containing at least 3 ARVs)
†Subjects below 6 months of age will only be enrolled upon availability of initial safety and PK data from subjects between 6 months and 1 year of age.

A minimum of 12 subjects will be enrolled into each cohort of the study. Up to 18 subjects may be enrolled into Cohort 1. The total sample will include at least 36 evaluable subjects who have been treated exclusively at the doses judged to be optimal for their age cohorts.

NOTE: For the Week 24 (or Week 48) analysis, evaluable will be defined as having been treated exclusively on the dose determined to be optimal for a given age cohort and having either completed 24 (or 48) weeks of exposure to the study drug or having been classified as a safety failure, due to a study drug related adverse event occurring during the first 24 (or 48) weeks of treatment.

Accrual to the study will follow an algorithm in which younger children's (Cohort II and Cohort III) exposure to the study medication is contingent upon the older age cohort (Cohort I) having passed the safety criteria. In addition, sufficient pharmacokinetic data will be required to determine the starting dose for the younger cohort (see Section 3.3-3.4 for details).

Initial tests of safety and PK will examine data from the first 6 subjects (mini-cohort) of Cohort I to determine whether Cohort II and Cohort III will be allowed to open for its mini-cohort of 6 subjects. Subjects below 6 months of age will not be enrolled until there are initial safety and PK data from subjects between 6 months and 1 year of age. These tests will proceed as follows:

- The PK data for the first six subjects of the Cohort I will be evaluated on the basis of blood samples taken 14 days ±4 days after the start of therapy.

- Safety will be evaluated on the basis of all available data collected through the 28th day on the dose that is being evaluated (see Section 8.51 for the safety guidelines to be used in the dose-finding algorithm).

- For subjects failing to meet PK targets and requiring individual dose adjustments, safety will be evaluated on the basis of data gathered until the time of the visit at which the dose is adjusted. This will insure that, for subjects needing PK determined dose adjustment, adverse events attributed to the starting dose must have occurred while the subjects were still on that dose. However, this also means that for such subjects the safety of the starting dose may be assessed on the basis of less than 28 days of study drug exposure.

The overall safety and PK data of the first 6 subjects on a given cohort will be evaluated with respect to the guidelines specified in Section 8.512 and in Section 9.0 of the protocol. Once these subjects have passed both PK and safety criteria, 6 additional subjects will be accrued to complete each cohort (up to 12 additional subjects may be accrued to Cohort I). The full cohort must also pass the PK and safety criteria (see Section 8.513 and Section 9.0). If the mini or full cohort fails either the safety or the PK guidelines, then the starting dose will be adjusted in the appropriate direction, (upwards for inadequate PK values; downwards for safety failure), if this is feasible. Subjects in a cohort that failed PK or safety but were receiving the same dose as that recommended in the new dosing cohort will be included in PK and safety analysis of the new dose and additional new subjects will be enrolled as appropriate at the new dose in order to have a mini-cohort of 6 subjects treated with the new dose. An initial evaluation of safety and PK will be made on the basis of data from these subjects. The evaluation will proceed as described above. In the event that the mini- or full cohort fails the PK criteria before the cohort completes accrual, then safety will be evaluated on all available subjects to confirm that a dose increase is not contraindicated.

If the P1090 core protocol team judges a given subject's PK data to be unevaluable, the subject will be replaced for dose finding purposes. Note that the subject would be replaced for evaluating safety, as well as PK, criteria, since unevaluable PK data would reflect uncertainty about appropriate exposure to the study medication.
The study accrual is designed to yield at least 36 evaluable subjects for the Week 24 (and 48) safety analyses, which analyses will occur when the last subject of the last cohort has reached week 24 (or Week 48). For these safety analyses, "evaluable" will be defined as having been treated exclusively on the dose determined to be optimal for a given age cohort and having either completed 24 (or 48) weeks of exposure to the study drug or having been classified as a safety failure, due to a study drug related adverse event

occurring during the first 24 (or 48) weeks of treatment. Although the primary safety analyses will focus on the effects of exposure to the optimal dose level for 24 and 48 weeks, secondary analyses will include all safety data collected from first subject exposure to 24 (or 48) weeks and until the end of the study. This will include data representing the final dose for each cohort, as well as data gathered during the dose finding stage which may represent exposure to doses which have failed. This will also include data from subjects whose individual doses have been adjusted, with results broken down by the times at which different dose levels were taken.

8.2 Endpoints and Outcome Measures

8.21 Primary Endpoints:

Toxicity Endpoints:

- Termination from treatment due to a suspected adverse drug reaction (SADR)
- Adverse events of Grade 3 or higher severity
- Death

Pharmacokinetic Endpoint:

- Failure to meet PK targets (specified in Section 9.0)

8.22 Secondary Endpoints:

- Adverse events of Grade 3 or higher severity judged to be at least possibly attributable to the study medications
- Confirmed failure to suppress plasma HIV-1 RNA to ≤ 400 copies
- AND
- Failure to achieve at least a 2 log reduction (from baseline) in HIV-1 RNA at weeks 24 and/or 48 (confirmed in 1 to 4 weeks)
- Treatment discontinued due to toxicity or virologic failure
- Change in optimized background regimen due to virologic failure
- New onset OI or AIDS diagnosis
- Decline in absolute CD4 percent of > 5% any time after 12 weeks of therapy

8.23 Primary Response Variables:

- Pharmacokinetic parameters - AUC12h

8.24 Secondary Response Variables:

- Plasma HIV-1 RNA (copies/mL)
- CD4 counts and percent
- CD4/CD8 ratio and percent
- Genotypic and phenotypic measures of resistance at virologic failure and at early discontinuation

- Pharmacokinetic parameters - C_{12h} and C_{max}

8.25 Exploratory Response Variables:

- Patient-specific CYP gene profiles.

8.3 Randomization and Stratification

There will be no randomization. Subjects will be enrolled into one of the three cohorts described in the "General Design Issues" section above.

8.4 Sample Size and Accrual

8.41 Pharmacokinetics

Sample size for this study was estimated using a pharmacokinetic modeling and simulation approach. Details of this approach are provided in Supplemental Document I. Briefly, the objectives of this approach were to ensure that 1) the mean value of ETR apparent oral clearance (CL/F) has a standard error <20% on 80% of occasions and 2) that the 95% confidence interval for CL/F is 60 to 140% or 60 to 166.6% of the point estimate of the geometric mean on 80% of occasions in each of the above age groups. A third approach was developed and consisted of simulation-estimation platform incorporating data from previous trials. It was used to determine the number of pediatric subjects required across the age range of 2 months to <6 years to ensure the median estimate for CL/F for a typical subject within each age group has a reported standard deviation <20%. Based on a pharmacokinetic model adapted for pediatric maturation and incorporating prior data, a minimum of 12 subjects in each age group is deemed sufficient to provide pharmacokinetic data for pediatric subjects treated with ETR.

8.42 Safety

Total accrual will depend upon the number of subjects who must be accrued to yield a minimum of 36 evaluable subjects for purposes of the primary safety analyses. There is some uncertainty concerning the number needed to complete the dose finding procedures and the number who may be lost to follow-up for reasons other than treatment failure. Each successful age cohort will include at least 12 subjects. In total, it is anticipated that approximately 50 subjects may need to be enrolled in the protocol to yield 36 evaluable subjects for the weeks 24 and 48 safety analyses.

Table 7. Percent of Subjects Experiencing Grade 3+ Adverse Events (or Grade 3+ Adverse Events Attributed to the Study Medication) with Exact 95% Confidence Intervals

N	No. of Subjects (%) With Grade 3+ Adverse Events	95% C.I.
12	0 (0%)	0% -- 26%
24	0 (0%)	0% -- 14%
36	0 (0%)	0% -- 10%
12	1 (8%)	0.2% -- 38%
24	2 (8%)	1% -- 27%

36	4 (11%)	3% -- 26%
12	3 (25%)	5% -- 57%
24	6 (25%)	10% -- 47%
36	9 (25%)	12% -- 42%
12	4 (33%)	10% -- 65%
24	8 (33%)	16% -- 55%
36	11 (31%)	16% -- 48%

Table 7 presents exact 95% confidence intervals around various potential rates of Grade 3+ adverse events which might be observed in a total sample of 36 evaluable subjects, a sample of 12 subjects representing a minimal sample that might be accrued within any age stratum and potential sample size that might occur if a subgroup of N = 24 was analyzed. This table indicates that confidence intervals will be wide around the minimal sample size of 12 subjects within a given stratum, but would be reasonably precise around a sample size of 36 subjects.

8.5 Monitoring

The study will be monitored intensively by the core protocol team which will review safety and pharmacokinetic data at least twice a month during the dose-finding stage with the aim of determining the optimal dose for each cohort while protecting patient safety. In addition, the IMPAACT Network will appoint a study monitoring committee (SMC) to provide independent reviews when necessary to ensure subject safety. In accordance with IMPAACT and DAIDS procedures, this committee will be composed of two individuals from the Primary Scientific Committee, one PDMC member and a statistician, independent of both the P1090 protocol team and drug manufacturer (Janssen R&D). Members of said study monitoring committee will have:

1) No financial interest in the study;
2) No planned authorship in publication of study results; and
3) No involvement in the conduct of the study.

8.51 Safety Guidelines

8.511 Evaluation of the Starting Doses During the Dose-Finding Stage

The attribution of relationship of serious adverse events to study drug for the purposes of employing the start, stop and pause rules specified below will be by consensus among the site investigator, the protocol team and the DAIDS medical officers. If unanimous agreement between them cannot be established, the relevant data will be reviewed by the independent Study Monitoring Committee as described above, which will make the final judgment concerning the relationship between study drug and the adverse event. Within this committee the decision will be determined by the majority opinion of this study's independent Study Monitoring Committee clinicians.

Gradation of relationship will use the following terminology:

- Not related
- Probably not related
- Possibly related
- Probably related
- Definitely related

An event judged to be at least possibly related to the study treatment will be considered to be a Suspected Adverse Drug Reaction (SADR) for purposes of the dose finding algorithm which follows.

8.512 First Six Subjects Started at a Given Dose Level in Each Cohort

For each study cohort (Cohort I, Cohorts II & III combined), the frequency of adverse reactions to the starting dose of the study medication will be evaluated on the first 6 subjects. The data will extend to the week 4 visit for subjects not requiring dose adjustment or until the visit on which the dose is adjusted, as described above. Further accrual into this cohort will be contingent upon meeting the following safety guidelines:

If any of the first 6 subjects has a life threatening SADR or any Grade 4 event or death that is probably or definitely attributable to the study medication or 3 or more subjects have terminated study drug due to a Grade 3+ at least possibly treatment related SADR, stop accrual into this study cohort (Cohort I, Cohorts II & III combined) until a safety review by the P1090 core protocol team is conducted. If none of the first 6 subjects has experienced a life-threatening SADR or a Grade 4 event or death that is probably or definitely attributable to the study medication and at most 2 of these 6 subjects has terminated study drug due to a Grade 3+ at least possibly treatment related SADR, then this cohort has passed the initial safety guidelines. If these 6 subjects also meet the PK guidelines, accrue more subjects to this cohort and evaluate the safety and PK results of the overall cohort.

In cases where the mini-cohort has failed either the safety or pharmacokinetic guidelines, the P1090 core protocol team will conduct a thorough review before proceeding with accrual to the study. All of the relevant safety and pharmacokinetic data will be examined to determine whether it is safe to continue the attempt to find an optimal dose for this cohort. If the P1090 study team determines that it is safe to proceed, it will make specific changes in dosing and monitoring procedures which may be indicated. If there are any concerns regarding safety, the study's Study Monitoring Committee will then review all of the relevant safety and pharmacokinetic data, along with the recommendations of the core protocol team, and will determine whether and under what conditions further dose finding activities for this cohort may proceed.

The protocol will only proceed if this review has led to a recommendation that it is safe to do so. The safety review may lead to a recommendation that the dose be de-escalated. Before implementing such a recommendation, the P1090 core protocol team will review the PK data to determine whether a lower dose is likely to achieve adequate drug exposure.

Given the small sample sizes within each cohort, the information available for preliminary safety decisions will be imperfect. Two types of sampling errors are possible: 1) in a cohort where the true rate of toxicity is too high to warrant increased exposure to the current starting dose of the medication, the sample data may pass the safety guidelines; and 2) in a cohort where the true rate of toxicity is low enough that further

exposure to the current starting dose is warranted, the sample data may fail the guidelines.

The extent to which the safety guidelines protect against the errors described above can be assessed by examining various hypothetical rates of "true toxicity" which could occur, if the study medication were used extensively among the patient population at the dose level under question. The hypothetical situations presented in the immediately succeeding table range from conditions under which a given dose level would cause a high incidence of severe and life threatening SADRs to conditions under which severe SADRs would be relatively rare and would not be life threatening. For each of these hypothetical situations, we assume that a sample of 6 subjects is drawn from the patient population and that the safety guidelines, summarized above, are followed.

Table 8 shows that there is a 78% chance of failing the safety guidelines under conditions in which the true rate of life-threatening toxicity is 5% and the rate of non-life threatening SADR is 50%. Assuming that it would be undesirable to accrue additional subjects at a dose that had these true rates of adverse events, the 22% chance of NOT failing the safety guidelines would represent the probability of error. The table also shows that there is a 0.2 % chance of failing, when the true rate of non-life threatening SADR is only 5% and the true rate of life threatening SADR is zero. Assuming that the potential benefits associated with exposing additional subjects to this dose of the drug would outweigh the risks associated with this relatively low rate of toxicity, failing the safety guidelines under these conditions would be an error.

Table 8. Probability of Failing Dose Escalation Guidelines under Potential Rates of True Toxicity

True Toxicity Rates		Probability of Failing Safety Guidelines
Non-Life Threatening SADR that would result in treatment discontinuation, excluding Grade 4 events probably or definitely attributable to study medication	Life Threatening SADR or Grade 4 events probably or definitely attributable to study medication	
0.50	0.00	0.67
0.50	0.05	0.78
0.50	0.25	0.98
0.25	0.00	0.17
0.25	0.05	0.41
0.25	0.25	0.88
0.05	0.00	0.002
0.05	0.05	0.27
0.05	0.25	0.82
0.00	0.05	0.26
0.00	0.25	0.82

8.513 Total Group of Subjects (Minimum of Twelve) Started at a Given Dose Level of Each Cohort

The final safety guidelines applied to a given starting dose of the study medication within a cohort will make use of data from all subjects started at that dose. The data will extend to the week 4 visit for subjects in the cohort which do not require PK determined dose adjustments or until the visit on which the dose is adjusted, as described above. If none of these subjects has experienced a life-threatening SADR or a Grade 4 event or death that is probably or definitely attributable to the study medication and no more than 25% terminated study treatment due to Grade 3+ at least possibly treatment related SADR, then this starting dose will pass the safety guidelines for the cohort under investigation.

If any of these subjects has a life threatening SADR or any Grade 4 event or death that is probably or definitely attributable to the study medication or more than 25% terminated study treatment due to Grade 3+ at least possibly treatment related SADR, this starting dose will fail the safety guidelines for the cohort under investigation. If this occurs, the core protocol team will review all of the relevant safety and pharmacokinetic data in an attempt to determine whether it is safe to continue the attempt to find an optimal dose for the said cohort.

If the P1090 study team determines that it is safe to proceed, it will make specific changes in dosing and monitoring procedures which may be recommended. If there are any concerns resulting from an inconclusive safety/PK study team review, the study's independent Study Monitoring Committee will then review all of the relevant safety and pharmacokinetic data and will determine whether and under what conditions further dose finding activities for this cohort may proceed.

8.52 Study Safety Monitoring

Since Phase I and Phase II studies are not routinely reviewed by a Data and Safety Monitoring Board (DSMB), it is the responsibility of the Protocol Team to interpret safety data, and make decisions regarding SADRs that are needed to protect subjects from undue risk. In addition, the Study Monitoring Committee described above is appointed to provide impartial reviews in situations where patient safety is in question.

For safety monitoring, a drug related SAE is an SAE that is judged to be "definitely", "probably" or "possibly related" to study drug (ETR).

The safety and tolerability of the study agent will be monitored by means of adverse events reports and toxicity reports presenting laboratory and clinical events. It is required that the data required for the toxicity reports be entered into the database within 48 hours of the time at which the results of the laboratory tests or clinical examinations become available.

Reports compiled by the Data Management Center (DMC) will be reviewed and discussed by the Protocol Team on conference calls held at least twice a month during the dose-finding stage and every month thereafter and by the study's Study Monitoring Committee under conditions specified above. Data on accrual, pharmacokinetics and toxicity will be reviewed.

Adverse events will be monitored from screening onwards throughout the follow-up period. If the protocol team identifies any potentially treatment-related toxicities, which may compromise subject safety, the study will be paused and the Study Monitoring Committee will review all relevant data and will determine whether, and under what conditions, the study would be allowed to proceed.

8.521 Rules for Suspending Accrual to Assess Safety Following an Adverse Event

Accrual will be temporarily suspended if any subject has a life threatening Suspected Adverse Drug Reaction (SADR), or death**,** or any Grade 4 event that may not be judged to be life- threatening but is judged to be probably or definitely attributable to the study medication.

Following temporary suspension of accrual, the Study Monitoring Committee will be convened and will further review the safety data within 48 hours of notification of the event to determine if continuation of accrual is appropriate. If the Study Monitoring Committee agrees that the study drug is likely to be safe for additional subjects, they may allow accrual to resume. Regulatory agencies will be notified of the event and the team's decision after this review of the safety data has taken place.

8.522 Accrual Rate Evaluation

Accrual to this study will be monitored by the IMPAACT leadership in accordance with standard operating procedures. The team will monitor feasibility quarterly, first based on site registration and then on accrual. Initially, the team will monitor site registration monthly to ensure that an adequate number of sites have registered to complete the protocol. If relatively few of the eligible sites have registered after the protocol has been approved for 6 months, the team will re- assess the feasibility of the protocol and the reasons why sites have not registered, and may amend the protocol accordingly. Once one-third of eligible sites have registered, the team will assess accrual on a quarterly basis. If any cohort during the dose-finding stage has

not accrued half its subjects within 6 months of opening, the team will identify the reasons for lack of accrual and possibly amend the protocol accordingly.

A trial go/no-go decision point will be set approximately 2 years after opening of Cohort 2. At that time, an analysis across all age cohorts (irrespective of the number of enrolled subjects or length of follow-up within each age group and across the age groups) will be performed, for the purpose of complying with regulatory requirements for Janssen R&D. In addition, accrual rate and all of the relevant safety and pharmacokinetic data will be examined to determine whether it is safe and worth to continue the trial in an attempt to find an optimal dose for Cohorts II and III.

8.523 Long Term Follow-Up for Safety

Subjects who successfully complete 48 weeks of ETR treatment will be followed for clinical long term safety follow up every 12 weeks. Sites should refer to Section 5.5 and Appendix IE.

8.6 Analyses

8.61 Summary of Dose Finding Data

The analysis of dose finding data will consist of descriptive statistics summarizing the safety and PK data from the dose finding phase of the study. (See Section 9.0 for PK analysis). The safety data will be analyzed by cohort and will present the results of the safety evaluations applied to each starting dose regimen tested within each cohort, including information indicating which starting doses have passed or failed the safety guidelines. For each starting dose within each cohort, every adverse event of Grade 3 or higher will be listed, along with subject demographics, the dose prescribed to the patient at the time of the event and the protocol team's assessment of the probability that this event was due to the study treatment (not related, probably not related, possibly related, probably related or definitely related).

8.62 Analysis of Data Representing Exposure to the Doses Judged to be Optimal for Each Cohort

These analyses will be stratified by cohort. The findings will be presented in both in aggregate and broken down by cohort, with estimates bounded by 95% confidence limits. Given that the small sample sizes within cohorts will provide limited power for statistical tests of differences across age cohorts, interpretation of the results will depend upon whether differences across cohorts are great enough to be considered to be clinically significant. If no such differences are observed, then the clearest interpretation of the findings will come from the aggregated data, where analyses will have the greatest statistical precision. However, if results vary across cohorts to a clinically important extent, interpretation of results should take into account the issues represented by the stratification factor.

8.63 Primary Analyses - performed on data through the Week 24 and Week 48 visit

8.631 Safety

The primary safety analysis will include only subjects whose total exposure to ETR has been at the dose judged to be optimal for their cohorts. Subjects whose doses have been adjusted for inadequate PK will be excluded. Subjects who have been removed from treatment or have had their doses reduced due to toxicities while on the optimal dose will be included and treated as safety failures in the primary safety

analysis. Additional analyses will look at the combined data from subjects whose doses failed and those who have been treated solely at the optimal doses determined for their cohorts and without individual PK determined dose adjustments. Sensitivity analyses will be performed to determine whether the exclusion of subjects whose doses have been adjusted creates a selection bias which impacts upon any results.

Each subject's safety data will be summarized as: the worst grade of adverse event experienced during the first 24 weeks (and 48 weeks) of exposure to the optimal dose of the study treatment and the worst grade of adverse event judged to be at least possibly related to study treatment during this time period. Frequency distributions of these safety outcomes will be presented in the aggregate and broken down by age. Listings of all Grade 3+ events will be provided, broken down by type of toxicity (hepatic, hematologic etc.).

The proportions of subjects experiencing Grade 3+ adverse events will be presented in aggregate and broken down by age cohort, with these proportions bounded by exact 95% confidence intervals. Similar analyses will present the proportions of subjects exhibiting Grade 3+ events which have been judged to be at least possibly related to study medication, again bounded by exact 95% confidence intervals.

8.632 Key Secondary Analyses

8.6321 Viral Load

Virologic outcomes, based on HIV-1 RNA (copies/ml), will be assessed at weeks 8, 12, 24 and 48. The criteria for success are: at least a 0.5 log10reduction in HIV-1 RNA (copies/ml) at week 8, at least a 1 log10 reduction in HIV-1 RNA (copies/ml) at week 12 and either HIV-1RNA ≤400 copies/ml or at least a 2 log reduction in HIV-1 RNA at weeks 24 and 48.

For regulatory submissions, at each of these time points the primary definition of virologic outcome will be calculated according to a Missing, Switch or Discontinuation = Failure (MSDF) algorithm – as codified by the FDA's snapshot algorithm. Subjects may be classified as virologic failures if they have missing HIV-1 RNA data throughout the window surrounding the time point of interest. (This window and related details will be defined in the analysis plan.) In addition subjects will be classified as virologic failures at any of these time points if they meet any of the following conditions prior to that time point:

a) Discontinuation of study treatment due to reasons other than AE or death and viral load was > 400 copies/mL at last available visit.
b) Change in background therapy not allowed in the protocol.
c) Change in background ART substitutions permitted per protocol unless the decision to switch is documented as being before or at the first on-treatment visit where HIV-1 RNA is assessed (Week 4).

Subjects who only discontinued a background ARV or who had formula substitutions (substituting single agents for fixed dose combinations and vice versa of the same ARV) in their OBT are not considered as having OBT changes and will not be analyzed as virologic failures. Otherwise, virologic success will be defined as having HIV-1 RNA ≤400 copies/mL by the last available HIV-1 RNA assessment while the subject is on-treatment within the visit of interest window. The proportions of subjects meeting the criteria for virologic success at each of these time points will be bounded by exact 95% confidence intervals, and will be presented both in the aggregate and broken down by age cohort.

Table 9 presents exact 95% confidence intervals around various potential rates of virologic success which might be observed in a total sample of 36 subjects or in subsamples of various sizes (N = 12, 24).

Table 9. Percent of Subjects Meeting Criterion for Virologic Success with Exact 95% Confidence Intervals

N	No. of Subjects (%) with Undetectable RNA	95% C.I.
12	1 (8%)	0.2% -- 38%
24	2 (8%)	1% -- 27%
36	4 (11%)	3% -- 26%
12	3 (25%)	5% -- 57%
24	6 (25%)	10% -- 47%
36	9 (25%)	12% -- 42%
12	6 (50%)	21% -- 79%
24	12 (50%)	29% -- 71%
36	18 (50%)	33% -- 67%
12	9 (75%)	43% -- 95%
24	18 (75%)	53% -- 90%
36	27 (75%)	58% -- 88%
12	11 (92%)	62% -- 99.8%
24	22 (92%)	73% -- 99%
36	33 (92%)	78% -- 98%

8.6322 CD4 Response

Change from baseline to weeks 24 and 48 in CD4 count, CD4 percent and CD4/CD8 ratio and percent will be bounded by 95% confidence intervals and presented both in the aggregate and by age cohort. In addition, the proportions of subjects exhibiting an absolute drop of > 5% in CD4 percent from baseline to weeks 12, 24 and 48 will be presented, bounded by 95% confidence intervals. Subjects who meet any of the conditions (a) to (c) of Section 8.6321 or who have absolute drop of > 5% in their CD4% will be considered as treatment failures in these analyses.

8.6323 HIV Drug Resistance

Correlations between baseline HIV genotypic and phenotypic drug resistance and any subsequent virologic failure will be evaluated. Subjects will be assessed for HIV genotypic and phenotypic drug resistance to the OBT and ETR at screening, at the time of virologic failure (if this occurs) and at early discontinuation.

8.6324 Additional Interim Analyses for Regulatory Purposes

To comply with regulatory requirements, additional interim analyses of data from Cohort 1 will be performed when at least 12 evaluable subjects have reached Week 24 and Week 48. Also to address regulatory expectations, an additional analysis across all age cohorts will be performed through Week 48 on at least 18 subjects. These analyses will be performed by Janssen R&D and will focus primarily on safety data, presented as described in Section 8.631 and pharmacokinetic data, presented as described in Section 9.0. A secondary analysis of virologic success, as described in Section 8.6321 will also be presented. These analyses will be shared with the P1090 Team.

8.633 Exploratory Analyses

8.6331 CYP Gene Profiles

Descriptive analyses will examine the association between pharmacokinetic parameters of ETR and subject-specific CYP gene profiles.

9.0 CLINICAL PHARMACOLOGY PLAN

9.1 Pharmacology Objectives

The clinical pharmacology studies are designed to determine the steady-state pharmacokinetic (PK) profile and dosing schedule of orally administered etravirine (ETR) in HIV-1-infected children ≥ 2 months to < 6 years of age. ETR PK and dose requirements will be determined when given with other ARV agents. All subjects (in the mini cohort and then the full cohort for that age) will need to undergo an initial 12 hour intensive PK study on day 14 (± 4 days) of study drug administration.

9.2 Primary and Secondary Data

Primary: AUC_{12h}
Secondary: C_{max}, C_{12hr}, T_{max}, CL/F, $T_{1/2}$, Vd and PK parameters (C_{max} and C_{12hr}) by CYP2C9 and CYP2C19 genotype

9.3 Study Design, Modeling and Data Analysis

9.31 PK Criteria

For this study, the area under the plasma concentration-time curve over 12 hours (AUC_{12h}) of ETR, as determined following an observed dose under fed, steady-state conditions will be the PK parameter for determination of the acceptability of the ETR dose, and any individual subject dose adjustments. The target geometric mean ETR AUC_{12h} for this study is between 60% and 150% of the geometric mean AUC_{12h} observed in HIV-1-infected treatment-experienced adults from the DUET studies (i.e. between 2713 and 6783 ng•h/mL). For the individual subject management in this study, subjects with an individual AUC_{12h} below the 10^{th} percentile of adult exposure (i.e. <2350 ng•h/mL) will be dose-adjusted in order to meet an $AUC_{12h} \geq$ 2350 ng•h/mL.

No apparent pharmacodynamic relationship for ETR has been identified in adults, implying that the plasma concentrations achieved (in the DUET studies) were, largely, on the flat portion of the expected sigmoid exposure-response relationship. The threshold AUC_{12h} value of < 2350 ng•h/mL representing the 10^{th} percentile of AUC in adults was selected, with the objective of achieving a distribution for ETR AUC_{12h} values in children that approximates that in HIV- infected adults who received ETR 200 mg twice daily (in combination with darunavir/ritonavir). While the ETR AUC_{12h} will be the primary PK parameter for acceptability of dose determination, the P1090 core protocol team will also consider the C_{12h} of ETR in their evaluation.

9.32 Starting Dose

The starting dose for ETR in cohort I (≥ 2 years to < 6 years of age) was 5.2 mg/kg twice daily. This dose was based on the results of the analysis of trial TMC125-C213 (see Section 1.32). Based on the safety profile of ETR, the concern for under-dosing in children (25) (26) (27) (28) and the usual need for slightly higher C_{max} in children to achieve comparable trough concentrations (due to a faster apparent oral clearance) the initial starting dose of 5.2 mg/kg twice daily reflected an appropriate balance of these considerations based on available data at that time.

An evaluation of the PK data from the first 6 children enrolled in Cohort I of P1090 indicated that the geometric mean etravirine exposure (at the 5.2mg/kg BID dose for the whole cohort) was lower than expected, and the chance of meeting the required geometric mean etravirine AUC_{12h} (comparable to adults) for the full cohort was very low (see also section 1.32).

All available etravirine PK data in pediatric subjects, including the P1090 subjects, were used in a modeling and simulation approach to better inform the choice of a revised starting dose for ETR for Cohort I and the starting dose for other cohorts in this study. It was also decided that, instead of a mg/kg dose across all ages, it would be more appropriate to develop dosing based on weight bands. The starting doses for Cohorts II and III are also informed and chosen by the results of Cohort I, as detailed in Section 8.1. For example, after evaluation of the first 6 subjects of Cohort I and criteria were met, Cohort I re-opened to accrual of additional subjects to complete the full cohort. Opening of Cohort II to accrue the first mini-cohorts of 6 subjects was done based on the assessment by the protocol team that sufficient data (PK and safety) were available to appropriately inform the choice of starting dose regimen for this cohort. The same applies for opening of Cohort III. Within Cohort III, subjects below 6 months of age will only be enrolled upon availability of initial safety and PK data from subjects between 6 months and 1 year of age. Appendix III gives the tables for the revised starting dose for Cohort I, starting doses for Cohort II and III and guidelines about re-evaluating the dose regimen if warranted based on the PK data.

9.33 Intensive PK Evaluations

All subjects will undergo an intensive PK study. This PK evaluation will be conducted on day 14 (± 4 days). Subjects should have taken their ETR doses as directed by the study physician, for 7 days prior to the intensive PK visit, without any missed doses. Sites are encouraged to call the subjects family, the day before the intensive PK visit, so that the site staff can confirm that the subject has not missed any doses in the previous 7 days.

If the subject has missed a dose, the intensive PK visit should be rescheduled to occur 7- 14 days after the last missed dose. The site is again encouraged to call the subjects family the day before the rescheduled intensive PK Visit so the staff can confirm the subject has not missed any doses in the previous 7 days. If the subject has missed a dose, the PK visit will be cancelled, and the subject will be withdrawn from the study.

The intensive PK visit should be scheduled so that a witnessed dose of ETR is taken within a range of 11 to 13 hours after their previous dose. Once the subject has arrived at the clinic, he/she should be offered a meal appropriate for age. The team suggests that a heparin lock be used for the intensive PK visit if at all possible. The PK dose of medication should be administered within 30 minutes following the start of the meal. If the subject vomits within 15 minutes of taking their medication, the dose should be re-

administered. Re-dosing is not allowed if the subject vomits more than 15 minutes after study medication intake. In the event that the subject vomits more than 15 minutes after study medication intake on the day of pharmacokinetic evaluation, that assessment must be rescheduled. Subjects may resume food intake 2 hours after their dose of ETR at the intensive PK visit.

The intensive PK evaluation will consist of obtaining a pre-dose plasma concentration, and following an observed dose, post dose plasma concentrations at 1, 2, 4, 6, 9 and 12 hours. To allow for some flexibility, the 9-hour sample can be collected within a window of 8 to 10 hours post-dose and the 12-hour sample within a window of 11 to 13 hours post-dose. If necessary, the sample 1 hour post-dose and/or 9 hours post-dose can be deleted to reduce the amount of total blood drawn from 7 samples over 12 hours to 5 or 6 samples, over 12 hours. ETR plasma concentrations will be determined in "real time" in a CLIA-certified IMPAACT pharmacology laboratory. The goal is for ETR plasma concentration information to be available for individual and cohort dose evaluation within 2 weeks, or at study week 4.

If the protocol team believes the intensive PK was conducted incorrectly or the results inaccurate, subjects may be asked to repeat an intensive PK visit on the same dose.

For the intensive PK evaluations of ETR, the primary PK parameter will be AUC_{12h}. Other secondary parameters that will be calculated include CL/F, Vd,$T_{1/2}$, C_{max}, C_{12h} and T_{max}. Plasma concentration-time data will be graphically inspected, and standard non-compartmental techniques will be used to assess PK parameters. C_{max} and C_{12h} will be taken as the maximum and 12 hour observed concentration, respectively, and T_{max} is the time at which C_{max} occurs. The AUC_{12h} will be determined using the linear-linear trapezoidal rule. CL/F will be calculated as dose/AUC_{12h}. The terminal elimination half-life is also a secondary parameter and will be determined using regression analysis on a minimum of 3 points (not including C_{max}) in the terminal elimination phase when possible.

9.34 Individual Subject Dose Evaluation and Adjustments

Doses of ETR will be adjusted in an individual subject to attain an AUC_{12h} of < 2350 ng•h/mL.

- If the subject's current dose is well tolerated (no toxicity ≧ Grade 3) but AUC_{12h} is < 2350 ng•h/mL, then a new dose will be determined by prorating the current dose to attain an AUC_{12h} of approximately 2864 ng•h/mL (the 20th percentile of exposure in adults). The maximum dose increase for the initial PK-guided dose adjustment would be capped at the adult dose of 200 mg twice daily. If a second PK evaluation again reveals an AUC_{12h}< 2350ng•.h/mL, then the dose may be increased above the 200 mg twice daily initial BID cap, again, targeting an AUC_{12h} of approximately 2864 ng•h/mL.
- If the subject's AUC_{12h} is >4380 ng•h/mL(the median AUC_{12h} value in adults receiving ETR 200 mg twice daily) but current dose is not well tolerated (no toxicity ≥ Grade 3) then the dose will be prorated, if possible given available dosage forms to achieve an AUC_{12h} of 4380 ng•h/mL. If no dose reduction is possible, then the subject will be discontinued from study treatment.
- If a subject has not achieved an AUC_{12h} of < 2350 ng•h/mL, but is experiencing a Grade 3 or greater toxicity that is deemed probably or definitely related to study drug, that subject will be discontinued from study treatment.

Although ETR displays non-proportional PK, dose adjustments will be prorated on a linear scale using multiples of 12.5 mg (the smallest incremental dose change possible given the available formulations).

Initial PK-guided dose increases will be capped at the adult dose of 200 mg twice daily. However, if after a second PK evaluation the subject's AUC_{12h} has not achieved the minimum target (2350 ng•h/mL), doses may exceed 200 mg twice daily. The core protocol team will communicate all individual dose adjustments to the participating site.

All subjects with an individual dose adjustment (not related to weight gain) will have repeat intensive 12 hour PK evaluations performed between Day 7 to 14 after initiation of the new dose.

Subjects who require a dose adjustment but refuse to undergo repeat intensive PK (see Section 9.34 for management of individual dose adjustments) will have ETR therapy discontinued and will be replaced.

9.35 Cohort Dose Evaluation and Adjustment

Enrollment will be temporarily halted after PK data are obtained for 6 subjects within a given mini cohort. PK parameters and 28-day safety data will be reviewed for these subjects. If safety data are acceptable, and the geometric mean AUC_{12h} of the first six is judged acceptable, then an additional 6 subjects will be enrolled to equal N = 12 in each full cohort. Failure with respect to the safety and/or PK guidelines will result in a dose adjustment within this cohort, with the starting dose adjusted in the appropriate direction.

NOTE: Please refer to Sections 6.6 and 6.8 if non-adherence is suspected.

Subjects who require a dose adjustment but refuse to undergo repeat intensive PK (see Section 9.34 for management of individual dose adjustments) will have ETR therapy discontinued and will be replaced (will remain on study but off study drug).

PK parameters for ETR will be summarized and descriptive statistics calculated. As stated, the AUC_{12h} for ETR is the primary PK parameter.

9.351 The dose of ETR will be judged acceptable if:

- The ETR dose is tolerated
  AND
- The geometric mean ETR AUC_{12h} is between 60% and 150% of the geometric mean AUC_{12h} in HIV-1-infected treatment-experienced adults from the DUET studies (i.e. between 2713 and 6783 ng•h/mL)

If a revised starting dose of ETR is needed, modeling and simulation will be used (incorporating all available PK data at that time) to propose a revised weight-based dosing table for ETR for which the calculated chance of success for a given age cohort (i.e., geometric mean AUC_{12h} between 60 and 150% of adults) will be at least 80% (see also Appendix III).

In making any revision to the starting dose, the team will estimate the C_{12h} expected with the revised dose. The goal of dose finding is to identify a dose that approximates ETR exposure in adults who receive an ETR dose of 200 mg twice daily (when given with darunavir/ritonavir). The median AUC_{12h} in adults is 4380 ng•h/mL and 75th percentile is 6339 ng•h/mL. The median C_{12h} in adults is 298 ng/ml and the 75% percentile is 467 ng/ml. The team will compare the expected C_{12h} with that achieved in adults, and may use this comparison to refine the revised starting dose to approximate both the AUC_{12h} and C_{12h} exposure.

Any change in the starting dose will be communicated by the protocol team to all participating sites via written notification.

As detailed in Section 3.0 of the protocol, subjects may be dose-adjusted to the new dose and additional new subjects will be treated at the new dose, and safety and PK will be evaluated as described.

If more than 2 of the 6 children in a cohort has an AUC_{12h} greater than the 75th percentile of adult values (6339 ng•h/mL) and the cohort has passed the safety criteria, the team will review the starting dose and the expected distribution of ETR C_{12h} and AUC_{12h}. This review is to assess the goal of objective of achieving a distribution for ETR C_{12h} and AUC_{12h} values in children that approximates that in HIV-1-infected treatment experienced adults. The team may decide to revise the starting dose; however, there is no requirement for the team to adjust the starting ETR dose.

If the starting dose for a cohort of older subjects is revised, the protocol team may preemptively change the starting dose for subsequent younger cohort that has not yet opened to enrollment. Any change in the starting dose will be communicated by the protocol team to all participating sites, with instructions to use the appropriate table of starting doses. It is not unreasonable to suspect that the three cohorts planned for enrollment may each have different dosage requirements. This protocol will determine appropriate doses for each of these strata.

9.36 Population PK Evaluations

Blood samples for estimation of population PK characteristics of ETR will be collected at study weeks 4, 8, 12, 24 and 48, and at the determination of virologic failure, as outlined in the schedule of evaluations (Appendix I). At Weeks 4 and 24, one sample should be timed to fall within a window of 1 to 4 hours following a dose of ETR; at week 8, one sample should be timed to fall within a window of 4 to 8 hours following a dose of ETR; and at weeks 12 and 48, one sample should be timed to fall within a window of 8 to 12 hours following a dose of ETR. ETR plasma concentrations will be determined in a CLIA-certified IMPAACT Pharmacology Laboratory (refer to LPC).

9.4 Population Pharmacokinetic Study Design, Modeling and Data Analysis

For this analysis, the primary interest will be the PK characteristics of ETR and these will be evaluated using NONMEM version VII (GloboMax, Hanover, MD). NONMEM uses mixed effects (random and fixed) regression to estimate population means and variances of PK parameters and to identify intrinsic and extrinsic factors, such as body weight, sex or concomitant drug that may influence these parameters. Base models will be developed using first-order conditional estimation with or without interaction. A stepwise procedure will be used to determine whether a one- or two-compartment model best fits the plasma data under the principle of parsimony. A log-normal error distribution will be assumed for the description of both interpatient and intrapatient (residual) PK parameter variability. If necessary, poorly identified structural parameters, such as the absorption rate constant, may be fixed. The following covariates will be collected at baseline or during follow-up visits: sex, age, weight, race, HIV regimen (e.g., boosted PI) and HIV response markers. The influence of each covariate on the PK characteristics of ETR will be tested sequentially. At each step, the goodness of fit plots will also be evaluated. At the end of the analysis, all

covariates that show an influence on the parameters will be evaluated again by comparison of the full model (with all factors included) with a model from which each of the factors is deleted sequentially. For forward addition and backward elimination a decrease in objective function value by 3.84 ($p \leq 0.05$) and 6.64 ($p \leq 0.01$), respectively, would advocate sufficiently influential covariates. P1090 data may be supplemented with other pediatric PK data from previous etravirine studies (TMC125-C213, TMC125-C126) to support structural model and/or parameter precision if needed.

NONMEM uses extended least squares to calculate the objective function and the difference in the value of the objective function between models is approximately chi squared distributed. A difference in objective function of greater than 6.6 is considered significant (6.6 corresponds to a chi square for $p = 0.01$ with 1 degree of freedom) when one parameter is added or the covariate (e.g., body weight) is replaced. This is analogous to the commonly used F test to select among regression models. The primary outcome of this analysis is to identify the model that best describes the plasma PK of ETR and to investigate whether any of the covariates influences the PK of ETR. The final model will include all significant covariates (if any) and the parameter estimates for all parameters together with the estimates of residual and inter-individual variability. A secondary objective of this combined analysis will be to develop a linked population PKPD model in NONMEM to evaluate potential relationships between these plasma concentrations/PK characteristics and therapeutic outcomes (i.e. response to HIV therapy after 48 weeks of ETR and adverse events).

9.5 Anticipated Outcomes

The anticipated outcomes of the pharmacology evaluations are:

(1) A description of the pharmacokinetics of ETR, when given in combination with other antiretroviral agents including a ritonavir-boosted HIV PI, in children ≥ 2 months to < 6 years of age and;

(2) Identification of a dose of ETR, when given in combination with other antiretroviral agents including a ritonavir-boosted PI, which achieves etravirine exposures in a distribution comparable to a 200 mg twice daily dose in adults (when given with darunavir/ritonavir) and with a comparable geometric mean AUC_{12h}.

(3) An investigation of the pharmacodynamics of ETR, given in combination with an OBR, after 48 weeks of therapy.

10.0 HUMAN SUBJECTS

10.1 Institutional Review Board and Informed Consent

This protocol, the informed consent document (Appendix VIII), and any subsequent modifications must be reviewed and approved by the IRB or EC responsible for oversight of the study. Written informed consent must be obtained from the subject (or parents or legal guardians of subjects who cannot consent for themselves, such as those below the legal age). The subject's assent must also be obtained if he or she is able to understand the nature, significance, and risks of the study. The informed consent will describe the

purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the subject (or parent or legal guardian).

Each site which receives US DHHS funding and follows the United States Code of Federal Regulations Title 45-Public Welfare, Part 46-Protection of Human Subjects (also known as the Common Rule) should have on record at the site a plan that detects and addresses any change in guardianship occurring in pediatric subjects and determines when a study subject must have a consent process which involves a legally authorized representative (LAR) other than a family member with guardianship. The plan will include how the site determines when a LAR is initially or no longer needed and how frequently the LAR re-signs the consent. The plan should follow all IRB/EC, local, state, national and/or host country guidelines. Confirmation of such a plan at a site should be submitted with protocol registration materials.

The team has made a risk/benefit analysis for the P1090 protocol of "greater than minimal risk with prospect of direct benefit." The team anticipates that the study will lead to confirmation that this drug is safe for use in infants and young children and to determination of the appropriate dose in infants and young children. The approach of sequential cohorts and mini-cohorts serves to reduce the risk to participants.

10.2 Subject Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified only by a coded number to maintain subject confidentiality. All records will be kept in a secured area. All computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the FDA, the Office for Human Research Protections (OHRP), the NIH, the local IRB or Ethics Committee, Janssen R&D, host country regulatory agencies and by the study staff, and study monitors.

10.3 Study Discontinuation

The study may be discontinued at any time by the NIH, the FDA, the IRB or EC, Janssen R&D, OHRP or other governmental agencies as part of their duties to ensure that research subjects are protected.

11.0 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by IMPAACT policies. Any presentation, abstract, or manuscript will be made available for review by the pharmaceutical sponsors prior to submission.

12.0 BIOHAZARD CONTAINMENT

Transmission of HIV and other blood borne pathogens can occur through contact with contaminated needles, blood, and blood products. Respiratory viruses are transmitted by droplet aerosolization and fomites. Appropriate blood and secretion precautions will be employed by all personnel in the collection of samples and the shipping and handling of all specimens for this study, as currently recommended by the CDC.

All infectious specimens will be transported in compliance with Federal Regulations and the International Air Transport Association Dangerous Goods Regulations-Packing Instruction 602. Refer to individual carrier guidelines (e.g., Federal Express or Airborne) for specific instructions and to the ACTN Guidelines for Shipment and Receipt of Category B Biological Substance Shipment and ACTN Instruction for Overnight Shipments documents at
http://www.hanc.info/labs/labresources/procedures/Pages/actnShippingDemo.aspx

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APPENDIX IA: SCHEDULE OF EVALUATIONS - Cohort I

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	Study Visits												
	Screen[1]	Entry (Day 0)	Day 14 Intensive PK Visit	Week 4	Week 8	Week 12	Week 16	Week 24	Week 32	Week 40	Week 48	Early Study D/C	Virologic failure[21]
Visit Windows			±4 days	±1wk	±1wk	±1wk	±2wk	±2wk	±2wk	±2wk	±2wk		
CLINICAL EVALUATIONS													
Informed Consent	X												
History and Physical[2]	X	X	X	X	X	X	X	X	X	X	X	X	X
CDC Classification	X	X				X		X			X	X	X
Adherence / Pill Count Form			X[15]	X[15]	X	X	X	X	X	X	X	X[15]	X
Adherence phone call			X[16]										
Electrocardiogram (ECG)[3]	X		X[12, 17]										
STUDY DRUG													
Distribution of Study Drug[4]		X				X		X	X				
LABORATORY EVALUATIONS													
Hematology[5]	1mL	1mL	1mL	1mL	1mL	1mL	1mL	1mL	1mL	1mL	1mL	1mL	1mL
Chemistries[6]	2mL	2mL	2mL	2mL	2mL	2mL	2mL	2mL	2mL	2mL	2mL	2mL	2mL
Cholesterol/triglycerides[7]		2mL				2mL		2mL			2mL		
Coagulation assays[8]	2mL					2mL		2mL					
Urinalysis[9]	X	X						X			X	X	X
Virology Evaluations													
HIV-1 RNA PCR[10]	3mL	3mL[14]	3mL	3mL	3mL	3mL	3mL	3mL	3mL	3mL	3mL	3mL	3mL
CYP genotyping		X[14]											
HIV genotype & phenotype	4mL											4mL	4mL
Immunology Evaluations													
Lymphocyte subset[11]	2mL	2mL		2mL	2mL	2mL	2mL	2mL	2mL	2mL	2mL	2mL	2mL
Pellets / plasma for storage								2mL			2mL		
Pharmacology Evaluations													
Intensive Pharmacokinetics[12]			7mL										
Population PKs[13]				1mL[18]	1mL[19]	1mL[20]		1mL[18]			1mL[20]		1mL[22]
TOTAL BLOOD VOLUME	14mL	10mL	13mL	9mL	9mL	13mL	8mL	15mL	8mL	8mL	13mL	12mL	13mL

Footnotes

1. Informed consent must be obtained prior to performing Screening evaluations. The entry (Day 0) evaluations should be completed within 60 days following screening.
2. A complete history and physical should be done at screening. At subsequent visits, an interim history and physical should be performed. This should include history (including occurrence of adverse events since last study visit and any HIV-1 associated conditions) and physical exam (including height [without shoes], weight [with minimal clothing], vital signs [temperature, pulse, respirations, blood pressure and head circumference for those <3 years old]).
3. The electrocardiogram should be read locally by the investigator and also sent in duplicate to the ECG central reading service. Turnaround time for the central reading service is 72 hours. For normal values of PR see Appendix V; any value above the 98th percentile is considered abnormal. If there is evidence of significant abnormality on the ECG (including ≥Grade 3 PR or QTc interval, the site investigator should request a 24 hour turnaround on central reading of the ECG. A local cardiologist can also be consulted if the investigator wishes. For normal and abnormal values of PR and QTc intervals for this protocol, see Appendix V. Additional details regarding the ECG can be found in the MOPs. Note that a repeat EKG is required at the time of an intensive PK visit, including any PK-directed dose adjustments.
4. Study drug may be dispensed at other clinic study visits.
5. Hematology tests should include complete blood count (CBC), differential and platelets.
6. Electrolytes (sodium, potassium, and HCO_3), glucose, creatinine, lipase, phosphorus, and LFTs. LFTs should include total bilirubin, indirect bilirubin, direct bilirubin, alkaline phosphatase, AST, ALT, and albumin. If indirect bilirubin is not reported by the site laboratory, it should be calculated at the site and documented.
   The following (listed in order of preference) should be used to determine the upper limit of normal (ULN) values for indirect bilirubin.
   a. "ULN" values reported by the laboratory report for the test, or
   b. "ULN" values routinely used/established by the site, or
   c. "ULN" values as per the Harriet Lane Handbook
   Sites must be consistent with the way toxicities are evaluated for all subjects in the study; sites should use the same source throughout the study. Remember to have documentation of calculated indirect bilirubin and source of "ULN", when not reported by your laboratory.
7. If a subjects laboratory results show elevated cholesterol/triglycerides AND if the subject is ≥1 year old, the subject should be asked to return to clinic for fasting cholesterol/triglycerides. Children ≥1 year to ≤2 years of age, should be fasting for 4 hours. Children >2 years of age, should be fasting overnight.
8. Coagulation assays should include PT, PTT and INR. Required only from study sites with access to laboratories with existing coagulation testing capabilities for the tests as determined by IMPAACT.
9. A urine dipstick should be performed at each of the visits indicated. A complete microscopic urine assessment is required only if a urine dipstick is abnormal.
10. Virology assays should be performed at an IMPAACT/VQA approved laboratory. The Abbott platform MUST be used for the HIV-1 RNA assay.
11. Lymphocyte subsets include CD4 and CD8 assays.
12. Subjects should have taken ETR for at least 7 consecutive days prior to the intensive PK, without missing a dose. Intensive PK should be scheduled so that a witnessed dose of ETR is taken approximately 12 hours after the previous dose. PK dosing within a range of 11 to 13 hours after the previous dose is acceptable. The team suggests that an indwelling catheter such as a saline or heparin lock be used for the intensive PK. Once the subject has arrived at the clinic, he/she should be offered a breakfast appropriate for age. Within 30 minutes following breakfast, the PK medications should be administered followed by the PK sampling at the specified time points. If the subject vomits within 15 minutes of taking study drug, the dose should be repeated. Subjects may resume food intake 2 hours after their dose of ETR at the intensive PK visit. One (1) mL of blood will be collected at the following time points: pre-dose, 1, 2, 4, 6, 9 and 12 hours post dosing. To allow for some flexibility, the 9-hour sample can be collected with a window

of 8 to10 hours post-dose and the 12 hour sample with a window of 11 to 13 hours. If necessary, the 1-hour post-dose sample and/or the 9-hours post-dose sample can be deleted to reduce the amount of total blood drawn from 7 samples over 12 hours to 5 or 6 samples, over 12 hours.

If a subject requires individual dose adjustment for low or high AUCs, they will be asked to return to clinic to have an intensive PK evaluation between Day 7-14 on the new dose.

If a mini or full cohort fails, the failing subjects may have their ETR dose adjusted. In those cases, subjects will be asked to return to clinic to have a truncated intensive PK between Day 7-14 on the new dose with samples collected at the following time points: pre-dose, 2, and between 3-5 hours post dosing.

Note that a repeat EKG is required at the time of a PK visit required for any of the reasons described above.

13. 1.0mL of blood will be collected for each of the population pharmacokinetic samples. NOTE: An absolute minimum of 0.5 mL is necessary for population PK sample.
14. Wherever possible, the CYP genotyping and viral load PCR can be run from the same blood sample. The blood draw should be collected and spun down to isolate pellets for PBMCs (for CYP genotyping) and the plasma can be used for the viral load. Otherwise, a separate blood tube should be drawn.
15. Sites should also perform the palatability assessment at these visits.
16. Subjects must have taken their ETR doses as directed by the study physician, for 7 days prior to the intensive PK visit, without any missed doses. Sites are strongly encouraged to call the subject, the day before the intensive PK visit, so that the site staff can confirm that the subject has not missed any doses in the previous 7 days. If the subject has missed a dose, the PK visit must be re-scheduled within the Day 14 (± 4 days) window.
17. The ECG at the intensive PK visit should be collected following the 4 hour blood draw. This time point is generally when the drug level is at its highest.
18. At weeks 4 and 24, one sample should be timed to fall within a window of 1 to 4 hours following a dose of etravirine.
19. At week 8, one sample should be timed to fall within a window of 4 to 8 hours following a dose of etravirine.
20. At weeks 12 and 48, one sample should be timed to fall within a window of 8 to 12 hours following a dose of etravirine. (See Section 9.36 for additional information).
21. If a subject is experiencing virologic failure (as defined in section 6.3), a visit to confirm failure must be conducted between 1 to 4 weeks of the initial suspected failure or rebound.
22. At virologic failure, one sample may be collected at any time following a dose of etravirine.

For insufficient blood draws, priorities are as follows:
Hematology (1mL); Chemistry (2mL); Pharmacology (intensive [7mL] or population [1mL]);Virology (HIV-1 RNA PCR – 3mL); Resistance testing (HIV genotype and phenotype – 4mL); Lymphocyte subsets (2mL); CYP genotyping (2mL); Cholesterol / triglycerides (2mL); Coagulation assays (2mL); Plasma/cell pellet for storage (2mL)

APPENDIX IB: SCHEDULE OF EVALUATIONS – Cohort II

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	Study Visits												
	Screen[1]	Entry (Day 0)	Day 14 Intensive PK Visit	Week 4	Week 8	Week 12	Week 16	Week 24	Week 32	Week 40	Week 48	Early Study D/C	Virologic failure[21]
Visit Windows			±4 days	±1wk	±1wk	±1wk	±2wk	±2wk	±2wk	±2wk	±2wk		
CLINICAL EVALUATIONS													
Informed Consent	X												
History and Physical[2]	X	X	X	X	X	X	X	X	X	X	X	X	X
CDC Classification	X	X				X		X			X	X	X
Adherence / Pill Count Form			X[15]	X[15]	X	X	X	X	X	X	X	X[15]	X
Adherence Phone Call			X[16]										
Electrocardiogram[3]	X		X[12, 17]										
STUDY DRUG													
Distribution of Study Drug[4]		X				X		X	X				
LABORATORY EVALUATIONS													
Hematology[5]	1mL	1mL	1mL	1mL	1mL	1mL	1mL	1mL	1mL	1mL	1mL	1mL	1mL
Chemistries[6]	2mL	2mL	2mL	2mL	2mL	2mL	2mL	2mL	2mL	2mL	2mL	2mL	2mL
Cholesterol/triglycerides[7]		2mL				2mL		2mL			2mL		
Coagulation assays[8]	2mL					2mL		2mL					
Urinalysis[9]	X	X						X			X	X	X
Virology Evaluations													
HIV-1 RNA PCR[10]	3mL	3mL[14]	3mL	3mL	3mL	3mL	3mL	3mL	3mL	3mL	3mL	3mL	3mL
CYP genotyping		X[14]											
HIV genotype & phenotype	4mL											4mL	4mL
Immunology Evaluations													
Lymphocyte subset[11]	2mL	2mL		2mL	2mL	2mL	2mL	2mL	2mL	2mL	2mL	2mL	2mL
Pellets/plasma for storage								2mL			2mL		
Pharmacology Evaluations													
Intensive Pharmacokinetics[12]			7mL										
Population PKs[13]				1mL[18]	1mL[19]	1mL[20]		1mL[18]			1mL[20]		1mL[22]
TOTAL BLOOD VOLUME	14mL	10mL	13mL	9mL	9mL	13mL	8mL	15mL	8mL	8mL	13mL	12mL	13mL

Footnotes

1. Informed consent must be obtained prior to performing Screening evaluations. The entry (Day 0) evaluations should be completed within 60 days following screening.
2. A complete history and physical should be done at screening. At subsequent visits, an interim history and physical should be performed. This should include history (including occurrence of adverse events since last study visit and any HIV-1 associated conditions) and physical exam (including height [without shoes], weight [with minimal clothing], vital signs [temperature, pulse, respirations, blood pressure and head circumference]).
3. The electrocardiogram should be read locally by the investigator and also sent in duplicate to the ECG central reading service. Turnaround time for the central reading service is 72 hours. For normal values of PR see Appendix V; any value above the 98th percentile is considered abnormal. If there is evidence of significant abnormality on the ECG (including ≥Grade 3 PR or QTc interval, the site investigator should request a 24 hour turnaround on central reading of the ECG. A local cardiologist can also be consulted if the investigator wishes. For normal and abnormal values of PR and QTc intervals for this protocol, see Appendix V. Additional details regarding the ECG can be found in the MOPs. Note that a repeat EKG is required at the time of an intensive PK visit, including any PK-directed dose adjustments.
4. Study drug may be dispensed at other clinic study visits.
5. Hematology tests should include complete blood count (CBC), differential and platelets.
6. Electrolytes (sodium, potassium, and HCO_3), glucose, creatinine, lipase, phosphorus, and LFTs. LFTs should include total bilirubin, indirect bilirubin, direct bilirubin, alkaline phosphatase, AST, ALT, and albumin. If indirect bilirubin is not reported by the site laboratory, it should be calculated at the site and documented.
   The following (listed in order of preference) should be used to determine the upper limit of normal (ULN) values for indirect bilirubin.
   a. "ULN" values reported by the laboratory report for the test, or
   b. "ULN" values routinely used/established by the site, or
   c. "ULN" values as per the Harriet Lane Handbook
   Sites must be consistent with the way toxicities are evaluated for all subjects in the study; sites should use the same source throughout the study. Remember to have documentation of calculated indirect bilirubin and source of "ULN", when not reported by your laboratory.
7. If a subjects laboratory results show elevated cholesterol/triglycerides AND if the subject is ≥1 year old, the subject should be asked to return to clinic for fasting cholesterol/triglycerides. Children ≥1 year to ≤2 years of age, should be fasting for 4 hours. Children >2 years of age, should be fasting overnight.
8. Coagulation assays should include PT, PTT and INR. Required only from study sites with access to laboratories with existing coagulation testing capabilities for the tests as determined by IMPAACT.
9. A urine dipstick should be performed at each of the visits indicated. A complete microscopic urine assessment is required only if a urine dipstick is abnormal.
10. Virology assays should be performed at an IMPAACT/VQA approved laboratory. The Abbott platform MUST be used for the HIV-1 RNA.
11. Lymphocyte subsets should include CD4 and CD8.
12. Subjects should have taken ETR for at least 7 consecutive days prior to the intensive PK, without missing a dose. Intensive PK should be scheduled so that a witnessed dose of ETR is taken approximately 12 hours after the previous dose. PK dosing within a range of 11 to 13 hours after the previous dose is acceptable. The team suggests that an indwelling catheter such as a saline or heparin lock be used for the intensive PK. Once the subject has arrived at the clinic, he/she should be offered a breakfast appropriate for their age. Within 30 minutes following breakfast, the PK medications should be administered followed by the PK sampling at the specified time points. If the subject vomits within 15 minutes of taking study drug, the dose should be repeated. Subjects may resume food intake 2 hours after their dose of ETR at the intensive PK visit. One (1) mL of blood will be collected at the following time points: pre-dose, 1, 2, 4, 6, 9 and 12 hours post dosing. To allow for some flexibility, the 9-hour sample can be collected with a window

of 8-10 hours post-dose and the 12 hour sample with a window of 11 to 13 hours. If necessary, the 1-hour post-dose sample and/or the 9-hours post-dose sample can be deleted to reduce the amount of total blood drawn from 7 samples over 12 hours to 5 or 6 samples, over 12 hours.

If a subject requires individual dose adjustment for low or high AUCs, they will be asked to return to clinic to have an intensive PK evaluation between Day 7-14 on the new dose.

If a mini or full cohort fails, the failing subjects may have their ETR dose adjusted. In those cases, subjects will be asked to return to clinic to have a truncated intensive PK between Day 7-14 on the new dose with samples collected at the following time points: pre-dose, 2, and between 3-5 hours post dosing.

Note that a repeat EKG is required at the time of a PK visit required for any of the reasons described above.

13. 1.0mL of blood will be collected for each of the population pharmacokinetic samples. NOTE: An absolute minimum of 0.5 mL is necessary for population PK sample.
14. Wherever possible, the CYP genotyping and viral load PCR can be run from the same blood sample. The blood draw should be collected and spun down to isolate pellets for PBMCs (for CYP genotyping) and the plasma can be used for the viral load. Otherwise, a separate blood tube should be drawn.
15. Sites should also perform the palatability assessment at these visits.
16. Subjects must have taken their ETR doses as directed by the study physician, for 7 days prior to the intensive PK visit, without any missed doses. Sites are strongly encouraged to call the subject, the day before the intensive PK visit, so that the site staff can confirm that the subject has not missed any doses in the previous 7 days. If the subject has missed a dose, the PK visit must be re-scheduled within the Day 14 (± 4 days) window.
17. The ECG at the intensive PK visit should be collected following the 4 hour blood draw. This time point is generally when the drug level is at its highest.
18. At weeks 4 and 24, one sample should be timed to fall within a window of 1 to 4 hours following a dose of etravirine.
19. At week 8, one sample should be timed to fall within a window of 4 to 8 hours following a dose of etravirine.
20. At weeks 12 and 48, one sample should be timed to fall within a window of 8 to 12 hours following a dose of etravirine. (See Section 9.36 for additional information).
21. If a subject is experiencing virologic failure (as defined in section 6.3), a visit to confirm failure must be conducted between 1 to 4 weeks of the initial suspected failure or rebound.
22. At virologic failure, one sample may be collected at any time following a dose of etravirine.

For insufficient blood draws, priorities are as follows:
Hematology (1mL); Chemistry (2mL); Pharmacology (intensive [7mL] or population [1mL]);Virology (HIV-1 RNA PCR – 3mL); Resistance testing (HIV genotype and phenotype – 4mL); Lymphocyte subsets (2mL); CYP genotyping (2mL); Cholesterol / triglycerides (2mL); Coagulation assays (2mL); Plasma/cell pellet for storage (2mL)

APPENDIX IC: SCHEDULE OF EVALUATIONS – Cohort III

	Study Visits												
	Screen[1]	Entry (Day 0)	Day 14 Intensive PK Visit	Week 4	Week 8	Week 12	Week 16	Week 24	Week 32	Week 40	Week 48	Early Study D/C	Virologic failure[23]
Visit Windows			±4 days	±1wk	±1wk	±1wk	±2wk	±2wk	±2wk	±2wk	±2wk		
CLINICAL EVALUATIONS													
Informed Consent	X												
History and Physical[2]	X	X	X	X	X	X	X	X	X	X	X	X	X
CDC Classification	X	X				X		X			X	X	X
Adherence / Pill Count Form			X[17]	X[17]	X	X	X	X	X	X	X	X[17]	X
Adherence Phone Call			X[18]										
Electrocardiogram[3]	X		X[13, 19]										
STUDY DRUG													
Distribution of Study Drug[4]		X				X		X	X				
LABORATORY EVALUATIONS													
Hematology[5]	0.5mL	0.5mL	0.5mL	0.5mL	0.5mL	0.5mL	0.5mL	0.5mL	0.5mL	0.5mL	0.5mL	0.5mL	0.5mL
Chemistries[6]	1mL	3mL	1mL	1mL	1mL	3mL	1mL	3mL	1mL	1mL	3mL	1mL	1mL
Cholesterol/triglycerides[7]		X				X		X			X		
Coagulation assays[8]	2mL					2mL		2mL					
Urinalysis[9]	X	X						X			X	X	X
Virology Evaluations													
HIV-1 RNA PCR[10]	3mL	3mL[16]	3mL	3mL	3mL	3mL	3mL	3mL	3mL	3mL	3mL	3mL	3mL
CYP genotyping[11]		X[16]											
HIV genotype & phenotype	4mL[15]											4mL	4mL
Immunology Evaluations													
Lymphocyte subset[12]	1mL	1mL		1mL	1mL	1mL	1mL	1mL	1mL	1mL	1mL	1mL	1mL
Pellets/plasma for storage								2mL[11]			2mL[11]		
Pharmacology Evaluations													
Intensive Pharmacokinetics[13]			3.5mL										
Population PKs[14]				0.5mL[20]	0.5mL[21]	0.5mL[22]		0.5mL[20]			0.5mL[22]		0.5mL[24]
TOTAL BLOOD VOLUME	11.5mL	7.5mL	8.0mL	6.0mL	6.0mL	10.0mL	5.5mL	12.0mL	5.5mL	5.5mL	10.0mL	9.5mL	10.0mL

Footnotes

1. Informed consent must be obtained prior to performing Screening evaluations. The entry (Day 0) evaluations should be completed within 60 days following screening. For children of low weight, the screening laboratory evaluations may be split over 2 visits. Safety labs and lymphocyte subsets should be obtained at the first timepoint and HIV RNA and HIV genotyping and phenotyping a week later.
2. A complete history and physical should be done at screening. At subsequent visits, an interim history and physical should be performed. This should include history (including occurrence of adverse events since last study visit and any HIV-1 associated conditions) and physical exam (including height [without shoes], weight [with minimal clothing], vital signs [temperature, pulse, respirations, blood pressure and head circumference).
3. The electrocardiogram should be read locally by the investigator and also sent in duplicate to the ECG central reading service. Turnaround time for the central reading service is 72 hours. For normal values of PR see Appendix V; any value above the 98th percentile is considered abnormal. If there is evidence of significant abnormality on the ECG (including ≥Grade 3 PR or QTc interval, the site investigator should request a 24 hour turnaround on central reading of the ECG. A local cardiologist can also be consulted if the investigator wishes. For normal and abnormal values of PR and QTc intervals for this protocol, see Appendix V. Additional details regarding the ECG can be found in the MOPs. Note that a repeat EKG is required at the time of an intensive PK visit, including any PK-directed dose adjustments.
4. Study drug may be dispensed at other clinic study visits.
5. Hematology tests should include complete blood count (CBC), differential and platelets.
6. Electrolytes (sodium, potassium, and HCO_3), glucose, creatinine, lipase, phosphorus, and LFTs. LFTs should include total bilirubin, indirect bilirubin, direct bilirubin, alkaline phosphatase, AST, ALT, and albumin. If indirect bilirubin is not reported by the site laboratory, it should be calculated at the site and documented.
   The following (listed in order of preference) should be used to determine the upper limit of normal (ULN) values for indirect bilirubin.
   a. "ULN" values reported by the laboratory report for the test, or
   b. "ULN" values routinely used/established by the site, or
   c. "ULN" values as per the Harriet Lane Handbook

   Sites must be consistent with the way toxicities are evaluated for all subjects in the study; sites should use the same source throughout the study. Remember to have documentation of calculated indirect bilirubin and source of "ULN", when not reported by your laboratory.
7. Cholesterol/triglycerides should be tested from the sample drawn for chemistries. If a subjects lab results show elevated cholesterol/triglycerides AND if the subject is ≥1 year old, the subject should be asked to return to clinic for fasting cholesterol/triglycerides. Children ≥1 year to ≤2 years of age, should be fasting for 4 hours. Children >2 years of age, should be fasting overnight.
8. Coagulation assays should include PT, PTT and INR. Required only from study sites with access to laboratories with existing coagulation testing capabilities for the tests as determined by IMPAACT.
9. A urine dipstick should be performed at each of the visits indicated. A complete microscopic urine assessment is required only if a urine dipstick is abnormal.
10. Virology assays should be performed at an IMPAACT/VQA approved laboratory. The Abbott platform MUST be used for the HIV-1 RNA.
11. Collection of blood for genotyping and stored specimens may be omitted for the youngest infants if the necessary volume of blood is difficult to draw. Note that CYP genotyping and viral load PCR can be run from the same blood sample; see footnote 16.
12. Lymphocyte subsets should include CD4 and CD8 assays.
13. Subjects should have taken ETR for at least 7 consecutive days prior to the intensive PK, without missing a dose. Intensive PK should be scheduled so that a witnessed dose of ETR is taken approximately 12 hours after the previous dose. PK dosing within a range of 11 to 13 hours after the previous dose is acceptable. The team suggests that an indwelling catheter such as a saline or heparin lock be used for the intensive PK. Once the subject has arrivedat the clinic, he/she should be offered a breakfast appropriate for their age. Within 30 minutes following breakfast, the PK medications should be administered followed by the PK sampling at the specified time points. If the subject vomits within 15 minutes of taking study drug, the dose should be repeated. Subjects may resume food intake 2 hours after their dose of ETR at the intensive PK visit. One (1) mL of blood will be collected at the following time points: pre-dose, 1, 2, 4, 6, 9 and 12 hours post dosing. To allow for some flexibility, the 9-hour sample can be collected with a window

of 8 to 10 hours post-dose and the 12 hour sample with a window of 11 to 13 hours. If necessary, the 1-hour post-dose sample and/or the 9-hours post-dose sample can be deleted to reduce the amount of total blood drawn from 7 samples over 12 hours to 5 or 6 samples, over 12 hours.

If a subject requires individual dose adjustment for low or high AUCs, they will be asked to return to clinic to have an intensive PK evaluation between Day 7-14 on the new dose.

If a mini or full cohort fails, the failing subjects may have their ETR dose adjusted. In those cases, subjects will be asked to return to clinic to have a truncated intensive PK between Day 7-14 on the new dose with samples collected at the following time points: pre-dose, 2, and between 3-5 hours post dosing.

Note that a repeat EKG is required at the time of a PK visit required for any of the reasons described above.

14. 0.5mL of blood will be collected for each of the population pharmacokinetic samples. NOTE: An absolute minimum of 0.5 mL is necessary for population PK sample.
15. Cohort III subjects must wait until HIV-1 genotyping results are available BEFORE they can start ETR and OBR.
16. Wherever possible, the CYP genotyping and viral load PCR can be run from the same blood sample. The blood draw should be collected and spun down to isolate pellets for PBMCs (for CYP genotyping) and the plasma can be used for the viral load. Otherwise, a separate blood tube should be drawn.
17. Sites should also perform the palatability assessment at these visits.
18. Subjects must have taken their ETR doses as directed by the study physician, for 7 days prior to the intensive PK visit, without any missed doses. Sites are strongly encouraged to call the subject, the day before the intensive PK visit, so that the site staff can confirm that the subject has not missed any doses in the previous 7 days. If the subject has missed a dose, the PK visit must be re-scheduled within the Day 14 (± 4 days) window.
19. The ECG at the intensive PK visit should be collected following the 4 hour blood draw. This time point is generally when the drug level is at its highest.
20. At weeks 4 and 24, one sample should be timed to fall within a window of 1 to 4 hours following a dose of etravirine.
21. At week 8, one sample should be timed to fall within a window of 4 to 8 hours following a dose of etravirine.
22. At weeks 12 and 48, one sample should be timed to fall within a window of 8 to 12 hours following a dose of etravirine. (See Section 9.36 for additional information).
23. If a subject is experiencing virologic failure (as defined in section 6.3), a visit to confirm failure must be conducted between 1 to 4 weeks of the initial suspected failure or rebound.
24. At virologic failure, one sample may be collected at any time following a dose of etravirine.

For insufficient blood draws, priorities are as follows:
Hematology (0.5mL); Chemistry (1mL); Pharmacology (intensive [3.5mL] or population [0.5mL]);Virology (HIV-1 RNA PCR – 3mL); Resistance testing (HIV genotype and phenotype – 4mL); Lymphocyte subsets (1mL); CYP genotyping (2mL); Cholesterol / triglycerides (2mL); Coagulation assays (2mL); Plasma/cell pellet for storage (2mL)

APPENDIX ID: SCHEDULE OF EVALUATIONS FOR FOLLOW UP OF SUBJECTS WHO DISCONTINUE ETRAVIRINE (OFF STUDY DRUG – ON STUDY)

	Week 4 post ETR discontinuation (±2 weeks)
CLINICAL EVALUATIONS	
History and Physical[1]	X
CDC Classification	X
LABORATORY EVALUATIONS	
Hematology[2]	1mL
Chemistries[3]	3mL
Cholesterol / triglycerides[4]	1mL
Virology	
HIV-1 RNA PCR[5]	3mL
Immunology	
Lymphocyte subsets[6]	2mL
TOTAL BLOOD VOLUME (mL)	10mL

NOTE: Subjects who are withdrawn from study drug within the first 48 weeks of study will not enter long term follow-up, but will return to clinic 4 weeks after ETR discontinuation, as per Appendix ID. Subjects with AEs will be followed until satisfactory clinical resolution (i.e. value returns back to subjects baseline value) or stabilization (to be agreed upon with the sponsor). All grade 3 and grade 4 laboratory abnormalities as well as any laboratory abnormalities resulting in an increase of 2 DAIDS Grades from baseline, will be followed until return to baseline or within 1 Grade from baseline. If an AE resolves within 4 weeks of discontinuation of ETR, the subject should still return for the final 4 week study visit.

Footnotes

1. History (including occurrence of adverse events since last study visit and any HIV-1 associated conditions) and physical exam (including height [without shoes], weight [with minimal clothing], vital signs [temperature, pulse, respirations and blood pressure]).
2. Hematology tests should include complete blood count (CBC), differential and platelets.
3. Electrolytes (sodium, potassium, and HCO_3), glucose, creatinine, lipase, phosphorus, and LFTs. LFTs should include total bilirubin, indirect bilirubin, direct bilirubin, alkaline phosphatase, AST, ALT, and albumin. If indirect bilirubin is not reported by the site laboratory, it should be calculated at the site and documented.
   The following (listed in order of preference) should be used to determine the upper limit of normal (ULN) values for indirect bilirubin.
   a. "ULN" values reported by the laboratory report for the test, or
   b. "ULN" values routinely used/established by the site, or
   c. "ULN" values as per the Harriet Lane Handbook
   Sites must be consistent with the way toxicities are evaluated for all subjects in the study; sites should use the same source throughout the study. Remember to have documentation of calculated indirect bilirubin and source of "ULN", when not reported by your laboratory.
4. If a subjects laboratory results show elevated cholesterol/triglycerides AND if the subject is ≥1 year old, the subject should be asked to return to clinic for fasting cholesterol/triglycerides. Children ≥1 year to ≤2 years of age, should be fasting for 4 hours. Children >2 years of age, should be fasting overnight.
5. Virology assays should be performed at an IMPAACT/VQA approved laboratory. The Abbott platform MUST be used for the HIV-1 RNA.
6. Lymphocyte subsets should include CD4 and CD8.

For insufficient blood draws, priorities are as follows:
Hematology (1mL); Chemistry (2mL); Virology (HIV-1 RNA PCR – 3mL); Lymphocyte subsets (2mL); Cholesterol / triglycerides (2mL)

APPENDIX IE: SCHEDULE OF EVALUATIONS FOR LONG-TERM SAFETY FOLLOW-UP OF SUBJECTS RECEIVING STUDY-PROVIDED ETRAVIRINE

	Every 12 weeks (±2 weeks)	Every 24 weeks (±2 weeks)	Early Discontinuation	14 Days Post Therapy (±1 week)
CLINICAL EVALUATIONS				
History and Physical Exam[1]	X		X	X
Adherence follow-up	X			X
CDC Classification	X		X	X
STUDY DRUG				
Distribution of Study Drug	X			
LABORATORY EVALUATIONS				
Chemistries[2]	X[9]	2mL	2mL	3mL
Hematology[3]	X[9]	2mL	2mL	2mL
Cholesterol/triglycerides[4]	X[9]	2mL		
Urinalysis[5]		X	X	X
Urine pregnancy test (if applicable)[6]	X	X	X	X
Virology				
HIV-1 RNA PCR[7]	X[9]	3mL	3mL	3mL
HIV genotype & phenotype			4mL	
Immunology				
Lymphocyte subset[8]	X[9]	2mL	2mL	
TOTAL BLOOD VOLUME	None	11mL	13mL	8mL

NOTE: Visits during long term follow up are every 12 weeks with specific lab tests being collected every 24 weeks (for additional details, see footnote 9 below).

Footnotes

1. History (including occurrence of adverse events since last study visit and any HIV-1 associated conditions) and physical exam (including height [without shoes], weight [with minimal clothing], vital signs [temperature, pulse, respirations and blood pressure]).
2. Electrolytes (sodium, potassium, and HCO_3), glucose, creatinine, lipase, phosphorus, and LFTs. LFTs should include total bilirubin, indirect bilirubin, direct bilirubin, alkaline phosphatase, AST, ALT, and albumin. If indirect bilirubin is not reported by the site laboratory, it should be calculated at the site and documented.

The following (listed in order of preference) should be used to determine the upper limit of normal (ULN) values for indirect bilirubin.

a. "ULN" values reported by the laboratory report for the test, or
b. "ULN" values routinely used/established by the site, or
c. "ULN" values as per the Harriet Lane Handbook

Sites must be consistent with the way toxicities are evaluated for all subjects in the study; sites should use the same source throughout the study. Remember to have documentation of calculated indirect bilirubin and source of "ULN", when not reported by your laboratory.

3. Hematology tests should include complete blood count (CBC), differential and platelets.
4. If a subjects laboratory results show elevated cholesterol/triglycerides AND if the subject is ≥1 year old, the subject should be asked to return to clinic for fasting cholesterol/triglycerides. Children ≥1 year to ≤2 years of age, should be fasting for 4 hours. Children >2 years of age, should be fasting overnight.
5. A urine dipstick should be performed at each of the visits indicated. A complete microscopic urine assessment is required only if a urine dipstick is abnormal.
6. A urine pregnancy test should be performed at every visit on any female subject who is capable of becoming pregnant.
7. Virology assays should be performed at an IMPAACT/VQA approved laboratory. For protocol required plasma RNA testing, the Abbott platform MUST be used. During the long term follow up, any standard of care HIV-1 RNA results (i.e. those obtained at non-protocol required time points) available within ±4 weeks of the study visit should also be reported on the study CRF, even if done using non-Abbott assays.
8. Lymphocyte subsets should include CD4 and CD8.
9. If these tests are performed as part of standard of care for the subject within ±4 weeks of the visit, they should be recorded on the study CRFs. Otherwise; these tests should not be done for the study at this time point.

For insufficient blood draws, priorities are as follows:
Chemistry (2mL); Virology (HIV-1 RNA PCR – 3mL); Lymphocyte subsets (2mL); HIV genotype/phenotype (4mL); Cholesterol / triglycerides (2mL)

APPENDIX II: PLANNED LABORATORY TESTING ON COLLECTED SPECIMENS

Specimen	Assay	Investigator / Laboratory	Notes
EDTA blood	Hematology	Local IMPAACT laboratory	
EDTA blood	Lymphocyte subsets	Local IMPAACT laboratory	
Serum or LiHeparin (site /method dependent)	Chemistries/ cholesterol /triglycerides	Local IMPAACT laboratory	
EDTA plasma	HIV-1 RNA PCR (viral load)	Local IMPAACT laboratory	Laboratory must be using Abbott platform and be VQA certified
EDTA plasma	Resistance Testing (Genotyping) SCREENING Only	U.S. Sites: University of Washington Seattle WA	Specimens should be shipped in real time
		Africa Sites: Contract Laboratory Services, Johannesburg, SA	Specimens should be shipped in real time
		South America Sites: FioCruz, Brazil	Specimens should be shipped in real time
		Thailand Sites: PHPT Laboratory Chiang Mai, Thailand	Specimens should be shipped in real time
		India Sites: Testing will be performed in country at a DAIDS network laboratory	Specimens should be shipped in real time
EDTA plasma	Resistance Testing (Phenotyping) SCREENING Only	U.S. / Brazil Sites: Monogram Sciences	Specimens should be shipped in real time
		All Other Sites: BRI Repository	Specimens should be shipped in real time and will 'pass-through' BRI to Monogram
EDTA Plasma	Resistance Testing (Genotyping) VIROLOGIC FAILURE / EARLY STUDY D/C	U.S. Sites: University of Washington Seattle WA	Specimens should be batch shipped quarterly
		All Other Sites: BRI Repository	Specimens should be batch shipped quarterlyand will 'pass-through' BRI to Monogram
EDTA Plasma	Resistance Testing (Phenotyping) VIROLOGIC FAILURE / EARLY STUDY D/C	U.S. / Brazil Sites: Monogram Sciences	Specimens should be batch shipped quarterly
		All Other Sites: BRI Repository	Specimens should be batch shipped quarterly

APPENDIX III: ETRAVIRINE DRUG DOSING TABLE FOR ORAL TABLET

Note: If the protocol team determines that a revised starting dose of etravirine is needed, modeling and simulation will be used (incorporating all available PK data at that time) to propose a revised weight-based dosing table for ETR for which the calculated chance of success for a given age cohort (i.e., geometric mean AUC_{12h} between 60 and 150% of adults) will be at least 80%. For this, available doses of ETR (based on available formulations of 100 mg tablet and 25 mg scored tablet) between 12.5 mg orally twice daily (BID) and 200 mg orally twice daily, in increments of 12.5 mg, will be considered. The new dosing table and clear instructions on how to handle subjects will be provided to all participating sites by the protocol team via a written notification.

DOSING TABLE 1: 1 year – 6 years

Etravirine (ETR) dose per weight band				
Weight Band (kg)	Dose (mg/kg)	Dose (mg)	Number of Tablet(s) to Administer Orally per Dose	Frequency
<8	8.8	50 mg	2 x 25 mg tablets	Twice Daily
8-<10	8.8	75 mg	3 x 25 mg tablets	Twice Daily
10-<13	8.8	100 mg	1 x 100 mg tablet	Twice Daily
13-<16	6.8	100 mg	1 x 100 mg tablet	Twice Daily
16-<20	5.2	100 mg	1 x 100 mg tablet	Twice Daily
20-<25	5.2	125 mg	1 x 100 mg tablet PLUS 1 x 25 mg tablet OR 5 x 25 mg tablets	Twice Daily
25-<30	5.2	150 mg	1 x 100 mg tablet PLUS 2 x 25 mg tablets OR 6 x 25 mg tablets	Twice Daily
>=30	5.2	200 mg	2 x 100 mg tablets OR 8 x 25 mg tablets	Twice Daily

DOSING TABLE 2: 2 months to < 1 year

Etravirine (ETR) dose per weight band			
Weight Band (kg)	Dose (mg)	Number of Tablet(s) to Administer Orally per Dose	Frequency
<6	25 mg	1 x 25 mg tablet	Twice Daily
6-<8	37.5 mg	1 and a half scored 25 mg tablets	Twice Daily
8-<10	50 mg	2 x 25 mg tablets	Twice Daily
≥10	75 mg	3 x 25 mg tablets	Twice Daily
Note: as of the age of 1 year, doses should be adjusted according to the specific ETR dosing table for 1 year to 6 years (Dosing Table 1).			

APPENDIX IV: VISIT SCHEDULE FOR RASH MANAGEMENT IN PEDIATRIC SUBJECTS

This visit schedule summarizes the visits and assessments to be performed in case of rash. NOTE: At the investigator's discretion, whenever follow-up visits, laboratory tests or digital photos are NOT required by this schedule, these evaluations may be performed at the investigators discretion, if clinically indicated. All results should be documented in the study CRFs.

	Grade 1 Rash	Grade 2 Rash	Grade 3/4 Rash
Day 0[1]	• Study medication MAY be CONTINUED • Unscheduled visit for initial rash evaluation REQUIRED. • Referral to dermatologist ONLY IF rash diagnosis uncertain (within 24-48hr).	• Study medication MAY be CONTINUED. • Unscheduled visit for initial rash evaluation REQUIRED. • Referral to dermatologist REQUIRED (within 24-48hr). • Blood sample for safety evaluations by local laboratory ONLY IF requested by investigator or dermatologist. • Biopsy ONLY IF required by dermatologist.	• Study medication MUST be permanently DISCONTINUED. Re-challenge is NOT ALLOWED. • Unscheduled visit for initial rash evaluation REQUIRED. • Referral to dermatologist REQUIRED (within 24-48hr). • Blood sample for safety evaluations by local laboratory. • Biopsy REQUIRED within 24 hours after onset of rash • Digital pictures REQUIRED.
Day 1	• Follow-up visit REQUIRED	• Follow-up visit REQUIRED	• Follow-up visit REQUIRED. • Digital pictures REQUIRED.
Day 2	No follow-up visit required	• Follow-up visit REQUIRED	• Follow-up visit REQUIRED.
Day 3	No follow-up visit required	No follow-up visit required	• Follow-up visit REQUIRED.
Day 4	No follow-up visit required	No follow-up visit required	• Follow-up visit REQUIRED.
Day 5	No Rash follow-up visit required[2]	No Rash follow-up visit required[2]	• Follow-up visit REQUIRED.
Day 6	No Rash follow-up visit required	No Rash follow-up visit required	No Rash follow-up visit required
Day 7	• Follow-up visit REQUIRED.	• Follow-up visit REQUIRED.	No Rash follow-up visit required
Further Visits	If rash is unresolved after second follow-up visit, subject should be referred to a dermatologist for further evaluation.	If rash is unresolved after second follow-up visit, subject should be referred to a dermatologist for further evaluation.	Weekly follow-up visits REQUIRED (with digital pictures) until resolution of Grade 3-4 rash to Grade $\leq$ 2 rash (further follow-up visits according to Grade 1 or Grade 2 rash instructions).
Upon Rash Resolution/ Stabilization[3]	Complete final rash assessment pages in the CRFs	Complete final rash assessment in the CRFs	Complete final rash assessment pages in the CRFs

Footnotes:

1 Note that Day 0 of the rash is the first day of investigator assessment and not the first day of rash as reported by the subject.

2 In case rash progresses from a Grade 1 or a Grade 2 to a higher Grade, start follow-up schedule for Grade 2, 3 or 4 rash as appropriate.

APPENDIX V: GRADING FOR PR AND QTc INTERVALS

A. TABLE TO DETERMINE 98TH PERCENTILE FOR PR RESULTS IN LEAD II

This table should be used when evaluating ECGs for subjects <8 years of age. This table is to be followed in conjunction with exclusion criterion 4.211, toxicity management section 6.15, and Appendix IA-ID. If you have any questions regarding the implementation of this table, please contact the core protocol team at impaact.p1090cmc@fstrf.org.

Subject's Age	Normal PR-Interval (milliseconds)
≥3 to <6 months	≤ 150
≥6 to <12 months	≤ 160
≥1 to <3 years	≤ 150
≥3 to <5 years	≤ 160
≥5 to <8 years	≤ 160

Source: The Electrocardiogram in Infants and Children: A Systematic Approach. Arthur Garson, Jr. Lea and Febiger Publishers. Philadelphia, 1983. (Original table, labeled A-3 in the book, was modified by the IMPAACT P1090 Protocol Team to suit the specific needs of the protocol)

B. DETERMININGADVERSE EVENTGRADING OFPROLONGED QTcINTERVALS

Please refer to the DAIDS toxicity tables for adverse event grading of prolonged QTc intervals. The DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, (DAIDS AE Grading Table), Version 1.0, December 2004, Clarification August 2009, must be used and is available on the RSC website at (http://rsc.tech-res.com/safetyandpharmacovigilance/).

C. DETERMINING ADVERSE EVENT GRADING OF PROLONGED PR RESULTS

Please refer to the DAIDS toxicity tables for adverse event grading of prolonged PR intervals. The DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, (DAIDS AE Grading Table), Version 1.0, December 2004, Clarification August 2009, must be used and is available on the RSC website at (http://rsc.tech-res.com/safetyandpharmacovigilance/).

APPENDIX VI: SUPPLEMENTAL TOXICITY TABLE FOR GRADING SEVERITY OF NEUROLOGIC ADVERSE EVENTS

For the purposes of P1090, the following parameter and grading criteria are to be used in conjunction with the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, dated December 2004, Clarification August 2009, in grading neurologic adverse events. This parameter supersedes Row 1 (alteration in personality-behavior or in mood) and Row 2 (altered mental status) of the neurologic section of the DAIDS Toxicity Table.

	Grade 1	Grade 2	Grade 3	Grade 4
Sleepiness, lethargy, irritability	Transiently lethargic, irritable or fussy (above usual norm), but otherwise normal routine.	More sleeping or crying than usual, not on normal routine without alternate explanation.	≥7 days of a change in personality without alternate explanation and confirmed by objective observation by study staff OR Somnolent, needs to be stimulated to take feedings.	Somnolent, unable to be stimulated to take feedings. OR Inconsolable irritability or crying with unusually high pitch or screaming for > 3 hours

APPENDIX VII-A: SUPPLEMENTAL TOXICITY TABLE FOR GRADING SEVERITY AND MANAGEMENT OF ADULT AND PEDIATRIC CUTANEOUS ADVERSE EXPERIENCES

Since cutaneous adverse events are of particular interest for this drug, the following guidelines on monitoring and management should be followed. Please refer to Appendix IV which describes the visit schedule for management of cutaneous adverse events.

NOTE: These management guidelines are NOT applicable to rashes with clear alternative etiology, such as chicken pox, impetigo and cutaneous HSV. Cetirizine, levocetirizine, topical corticosteroids and anti-pruritic agents will be allowed at the investigator's discretion for all grades of rashes.

CUTANEOUS ADVERSE EVENTS			
	Grade	Description	Subject Management
Cutaneous rash / reaction	GRADE 1	Localized macular rash	• Subjects with Grade 1 or Grade 2 rash may continue etravirine or temporarily interrupt therapy at the investigator's discretion. • Close clinical follow up is recommended to monitor progression of rash.
	GRADE 2	Diffuse macular, maculopapular or morbilliform rash or target lesions	• Subjects with Grade 1 or Grade 2 rash may continue etravirine or temporarily interrupt therapy at the investigator's discretion. • Close clinical follow up is recommended to monitor progression of rash. • All subjects with Grade 2 rash must be seen by a dermatologist within 24 to 48 hours.
	GRADE 3	• Diffuse macular, maculopapular or morbilliform rash with vesicles or limited number of bullae • Cutaneous reaction /rash with superficial ulceration of mucous membrane limited to 1 mucosal site • Cutaneous reaction/rash with at least 1 of the following: o Elevations of ALT/AST > 2x baseline but at least 5x upper limit of laboratory normal range (ULN) o Fever ≥38°C or 100.4°F o Serum sickness-like reaction o Eosinophil count >1000/mm^3	• Subjects experiencing a Grade 3 rash or cutaneous event must have etravirine discontinued permanently; but should remain on study for safety follow-up • OBR should be held at the discretion of the site investigator • Subjects must also be evaluated by a dermatologist within 24 to 48 hours • The protocol team should be notified of a Grade 3 event at impaact.p1090cmc@fstrf.org

	GRADE 4	• Extensive or generalized bullous lesions • Stevens-Johnson syndrome (SJS) • Ulceration of mucous membrane involving 2 or more distinct mucosal sites • Toxic epidermal necrolysis (TEN)	• Subjects experiencing a Grade 4 rash or cutaneous event must have etravirine discontinued permanently; but should remain on study for safety follow-up • OBR should be held at the discretion of the site investigator • Subjects must also be evaluated by a dermatologist within 24 to 48 hours • The protocol team should be notified of a Grade 4 event at impaact.p1090cmc@fstrf.org

APPENDIX VII-B: SUPPLEMENTAL TOXICITY TABLE FOR GRADING SEVERITY AND MANAGEMENT OF ADULT AND PEDIATRIC ACUTE SYSTEMIC ALLERGIC ADVERSE EXPERIENCES

ACUTE SYSTEMIC ALLERGIC ADVERSE EXPERIENCES			
	Grade	Description	Subject Management
Urticaria	GRADE 1	Localized urticaria with no medical intervention indicated	Subject may continue intake of etravirine
	GRADE 2	• Localized urticaria with medical intervention indicated • Mild angiodema with no medical intervention indicated	Subject may continue intake of etravirine
	GRADE 3	• Generalized urticaria or angioedema with medical intervention indicated • Symptomatic mild bronchospasm	• Subjects with Grade 3 acute systemic allergic reactions will be permanently discontinued from the investigational medication (ETR) and background regimen but will be followed on study on a modified schedule (Appendix IE) for safety outcomes • Subjects will be treated as clinically appropriate per the local physician
	GRADE 4	• Acute anaphylaxis • Life-threatening bronchospasm • Laryngeal edema	• Subjects with grade 4 acute systemic allergic reactions will be permanently discontinued form the investigational medication (ETR) AND background regimen (OBR) but will be followed on study on a modified schedule (Appendix IE) for safety outcomes • Subjects will be treated as clinically appropriate per the local physician • The protocol team should be notified of a Grade 4 event at impaact.p1090cmc@fstrf.org

APPENDIX VIII: SAMPLE INFORMED CONSENT

DIVISION OF AIDS
INTERNATIONAL MATERNAL PEDIATRIC ADOLESCENT AIDS CLINICAL TRIALS GROUP (IMPAACT)

A Phase I/II, Open-Label Trial to Evaluate the Safety, Tolerability, Pharmacokinetics and Antiviral Activity of Etravirine (ETR) in Antiretroviral (ARV) Treatment-Experienced HIV-1 Infected Infants and Children, Aged ≥ 2 Months to < 6 Years

P1090, Version 5.0, dated March 10, 2016

SHORT TITLE FOR THE STUDY: Safety and Pharmacokinetics of Etravirine in HIV-1 Infected Infants and Children

INTRODUCTION

Your child is being asked to take part in this research study because he/she is infected with HIV. This study is sponsored by the National Institutes of Health (NIH). The doctor in charge of this study at this site is: (insert name of Principal Investigator). Before you decide if you want your child to be a part of this study, we want you to know about the study.

This is a consent form. It gives you information about this study. The study staff will talk with you about this information. You are free to ask questions about this study at any time. If you agree to allow your child to take part in this study, you will be asked to sign this consent form. You will get a copy to keep.

WHY IS THIS STUDY BEING DONE?

This study is being done to look at a new antiretroviral HIV medication called etravirine. This drug is a type of medicine called a non-nucleoside reverse transcriptase inhibitor (NNRTI). This drug has not been tested in younger children before but has been tested in animals, older children (6 to <18 years of age)and adults and is currently approved by the FDA for use in treatment-experienced HIV-1 infected adults and children>6 years of age. The study will help find the best amount or dose of etravirine for infants and younger children, when it is taken with other antiretroviral medications. This study will also find out the safety of using this medication in infants and children and if there are any side effects from the medication. This medication is produced by Janssen Research & Development, a pharmaceutical company.

WHAT DOES MY CHILD HAVE TO DO IF HE/SHE IS IN THIS STUDY?

If you decide to allow your child to enroll in this study, you will be asked to bring your child to the clinic approximately 11 times over 48 weeks. Your child will be asked to take the study drug (etravirine) 2 times a day, following a meal, in addition to his/her regular anti-HIV medicines. Your child's regular anti-HIV medications will NOT be provided by the study, however, Darunavir will be provided by the study if not reasonably available locally. Etravirine will be provided for your child by the study, at no cost to you or your insurance. It is available in tablet form that can be swallowed whole or can be dispersed in a liquid. The formulation your child receives will depend on your child's age and whether your child can swallow pills.

(Sites should delete the following sentence if appropriate):
The clinic will provide you with sterile water so that your child can take the medication safely.

This study will help doctors to find the right dose of study drug for your child; the study will then keep them on that dose to look for any side effects your child might experience.

If your child misses a dose of etravirine, a dose of etravirine should be taken if it is within 6 hours of the missed dose time. If your child vomits within 15 minutes of taking a dose of etravirine, a second dose of etravirine should be taken.

As part of this study your child will be assigned to a group (cohort), based on his/her age. There are 3 cohorts in this study, each with a minimum of 12 participants.

Screening:
If you are interested in allowing your child to enroll in this study, we will see if your child is eligible for the study:

- We will ask about your child's medical history including questions about your child's health and what symptoms, medications, and illnesses your child has had.

- We will do a special test called an electrocardiogram (ECG). Your child will have special electrical wires placed on their chest and a machine will read your child's heart rhythm. This is a painless test.

- We will do a physical exam including height, weight and vital signs (temperature, blood pressure, pulse and respiratory rate).

- We will also ask your child to provide a urine sample for a urine test.

- We will take a little less than 3 teaspoons (14mL) of blood if your child is older than 1 year of age and a little more than 2 teaspoons (10mL) of blood if your child is less than a year of age to check the following:
    - The amount of HIV in your child's blood;
    - How well your child's immune system and kidneys are working
    - Whether your child is resistant to certain HIV medications (if your child is resistant to the study drug, it will not work properly)

  You will be given the results of these tests as they become available.

On Study:
Your study doctor will tell you whether your child is eligible for this study. The study team will determine this based on the number of children in each age group that have already entered the study and your child's results from the laboratory tests, history and physical at screening.

If your child is eligible for this study, your child will come to the clinic approximately10 more times in about 48 weeks. Most of the visits will last about 1 to 2 hours. More visits will be needed if the amount of study drug (etravirine) in your child's blood is too low or too high and your child's dose needs to be adjusted. Your child will come to the clinic for the first study visit

within 60 days of the screening visit.

- At each visit, a medical history will be taken (including questions about your child's health and what symptoms, medications, and any illnesses your child has had) and your child will have a physical exam. You will also be asked some questions to see if your child has been taking his/her medicine as directed.
- We will draw between 5 to 15mL (1- 3 teaspoons) of blood at each visit, depending on the child's age and the specific study visit. You will be informed of results of routine blood tests when available. Some of the blood collected will be stored for later tests.
- We will also ask your child to provide a urine sample for a urine test.
- A staff member from the clinic will call you the day before the intensive PK visit to make sure your child did not miss any study medications.
- After your child has been taking the study medication for 14 days (± 4 days), your child will be asked to come to the clinic to have blood drawn 7 times over 12 hours during one visit (Intensive PK visit).

    - Before the intensive PK visit: Your child will be asked not to take their morning dose of etravirine but to bring it with them to the clinic. It is very important that your child take all their etravirine medications as directed by the clinic, for 7 days prior to the PK visit.

    - What will happen at the intensive PK visit:
        - This blood test is done to measure the amount of study drug in your child's blood.
        - Your child will be offered breakfast appropriate for his/her age prior to taking their morning dose of etravirine.
        - A small plastic catheter will be placed in your child's arm to draw blood samples up to seven times during the visit. A catheter is a needle that is placed in a vein for an extended period of time, so that blood can be collected several times, without having to stick your child with a needle each time. The needle will stay in place until all of the blood samples are drawn.
        - We will do a special test called an electrocardiogram (ECG). Your child will have special electrical wires placed on their chest and a machine will read your child's heart rhythm. This is a painless test.

    - After the intensive PK visit: Based on the results, a change in dose (either higher or lower) maybe required. If this test shows that the amount of study drug in your child's blood is not high enough or is too high, your child will be asked to take a higher or lower dose of etravirine and return to the clinic for an additional visit for a repeat intensive PK visit, so that blood can be collected again, up to 7 times over 12 hours. If you decide not to have this test repeated, your child will come off the study drug. An additional PK visit may also be required, if the results of the test are incomplete or hard to evaluate.

- Approximately four weeks after your child started the study medications, your child will be asked to come back to clinic for a population PK visit. Your child will have a little between 1 and 2 teaspoons of blood drawn (6 to 9mL) for tests depending on your

child's age, as well as a history and physical exam. Your child will also be asked to provide a urine sample.

- Your child will be asked to come back to clinic for a repeat population PK visit at week 8, week 12, week 24 and week 48 after starting study medications. Your child will have approximately 6-15mL (1 - 3 teaspoons) drawn at each visit for laboratory tests, as well as a history and physical exam. Your child will also be asked to provide a urine sample.

- The study team will be reviewing the PK results of all of the children who have been enrolled and may determine that your child should have a higher or lower dose of etravirine. If so, your child will be asked to return to the clinic for an additional PK visit, so that blood can be collected again, but only 3 times over no more than 5 hours.

- If during this research study, your child gets a rash, please contact the research doctor immediately (*please insert a daytime and after hours contact number here*) and make an appointment for your child to be seen the same day. The research doctor will help you decide if your child needs to stop taking etravirine. Your study doctor may want you to be seen by a dermatologist (a doctor that specializes in skin problems). This visit will be paid for by the study.

- In the case that your child has a severe rash, a skin doctor (dermatologist) may request that a small piece of skin is taken to see what type of rash it is. This is called a skin biopsy. There is a slight risk of infection or bleeding or scar formation with this procedure. The skin doctor may wish to take pictures of the rash so it can be documented. You may be asked to sign a separate consent form to allow the doctor to do the skin biopsy and/or take a photograph of the rash. This visit will be paid for by the study.

Long Term Follow-Up

After your child has been on study drug for approximately 48 weeks, he/she will enter the long term follow-up phase of the study which for up to 5 years. Your child will be asked to come back into the clinic every 12 weeks until the drug is available in your country by prescription. Most visits will last about 30 minutes.

- At each visit, a medical history will be taken and you/your child will have a physical exam. You will also be asked if you have missed taking any of your medications.
- 2 teaspoons of blood (10 mL) will be drawn every 24 weeks (at every other visit). You will be informed of results of routine blood tests as they become available.

Your child must continue to take his/her anti-HIV medications during the study as prescribed by your child's HIV care provider. If your child's HIV care provider changes your child's anti-HIV medications during the study, your child can still take the study drug. Your child will be asked questions about taking his/her anti-HIV medications and the schedule he/she takes them on and if you he/she has missed any medications.

Blood Samples

Some of your child's blood samples will be shipped to a central repository in the USA so that they can be sent to specialized laboratories for testing later in the study. You will not receive the results of these tests.

FOR NICHD Sites:
Some of your child's blood specimens collected as part of this study will be stored for testing at a later date as part of this study. There is a separate consent form to explain this and get your consent.

For NIAID Sites:
Storage of Blood Samples

Some of your child's blood will be stored (with usual protectors of identity) and used for future IMPAACT-approved, HIV-related research. About 1teaspoon (4 mL) of blood will be taken for this purpose.

Your child's samples will be stored at a special laboratory facility. Only approved researchers will have access to them. People who work at the facility will also have access to your child's samples to keep track of them. These people won't have information that directly identifies your child. Your child's samples will not be sold or directly used to produce commercial products. All proposed research studies using your child's samples will be reviewed by the National Institutes of Health (NIH). There is no time limit on how long your child's samples will be stored.

The researchers do not plan to contact you or your child's regular doctor with the results of studies done using your child's stored samples. This is because research studies are often done with experimental procedures. The results of such studies should not be used to make decisions about your child's medical care. If the researchers decide that the result of a certain study provides important information for your child's medical care, your child's study doctor will be notified. If you would like to be contacted with this sort of information, you must notify the study staff of any changes in your address or phone number.

You may decide that you do not want your child's samples stored for future research studies. Your child can still participate in this study even if you make this decision.

You may withdraw your consent for the storage and use of your child's samples at any time. If you withdraw your consent, these stored samples will be destroyed.

Please read the following statement carefully and then mark your initials in the appropriate space provided.

I agree to allow my child's blood samples to be stored for use in future IMPAACT-approved, HIV-related research studies.

_____ Yes _____ No _____ Date

OTHER INFORMATION
The information collected in this study may be used for other IMPAACT-approved HIV-related research.

HOW MANY CHILDREN WILL TAKE PART IN THIS STUDY?
Up to 50 babies and children will take part in this study.

HOW LONG WILL MY CHILD BE IN THIS STUDY?
Your child will be in this study for at least 48 weeks, depending on when your child joins, and how long it takes to find the right dose of study drug for children in your child's age group. As long as your child is doing well on the medicine, your child will then enter the long term safety follow-up phase of the study and will continue to come into clinic every 12 weeks, until the drug is available in your country by prescription.

WHY WOULD THE DOCTOR TAKE MY CHILD OFF THIS STUDY EARLY?
The study doctor may need to take your child off the study early without your permission if:

- The study is cancelled by the U.S. Food and Drug Administration (FDA), National Institutes of Health (NIH), the drug companies supporting this study, the Office for Human Research Protections (OHRP) or other governmental agencies, or the site's Institutional Review Board (IRB). An IRB is a committee that watches over the safety and rights of research subjects.
- A Study Monitoring Committee (SMC) recommends that the study be stopped early. An SMC is an outside group of experts that monitors the study.
- Your child is not able to attend the study visits as required by the study.
- Your child refuses to undergo repeat intensive PK for management of individual dose adjustments. Your child will have etravirine therapy discontinued and will be followed on study but off study drug.

The study doctor may also need to take your child off the study drug(s) without your permission if:

- Continuing the study drug(s) may be harmful to your child
- Your child needs a treatment that your child may not take while on the study
- Your child is not able to take the study drug(s) as required by the study

If your child needs to stop taking etravirine during the first 48 weeks of the study, he/she will be asked to come back to clinic four weeks after they stop taking etravirine for a final study visit. This visit will include a medical history, physical exam and 2 teaspoons (10mL) of blood will be drawn for blood tests to check the amount of HIV in your child's blood, to see how well your child's immune system is working, and for other routine tests. Your child will not enter the long term follow-up phase of the study.

IF MY CHILD HAS TO PERMANENTLY STOP TAKING STUDY-PROVIDED MEDICINE, OR ONCE HE/SHE LEAVES THE STUDY, HOW WOULD THE STUDY MEDICINE BE PROVIDED?

During the Study:
If your child must permanently stop taking study-provided medicine before your child's study

participation is over, the study staff will discuss other options that may be of benefit to your child.

After the Study:
After your child leaves the study, if he/she is gaining benefit from the study-provided drug (etravirine), this drug will continue to be provided until it is available to your child in your country.

EARLY STUDY DISCONTINUATION
In the event that you or your child decides to withdraw from the study prior to Week 48, we will ask that your child returns for a final visit. At this visit:

- A medical history will be taken (including questions about your child's health and what symptoms, medications, and any illnesses your child has had) and your child will have a physical exam. You will also be asked some questions to see if your child has been taking his/her medicine as directed.
- We will draw between 8 to 12mL (1½- 2½- teaspoons) of blood depending on the child's age.
- We will also ask your child to provide a urine sample for a urine test.

WHAT ARE THE RISKS OF THE STUDY?

The drug used in this study (etravirine) may have side effects, some of which are listed below. Please note that these lists do not include all the side effects seen with this type of drug. These lists include the more serious or common side effects with a known or possible relationship. If you have questions concerning additional study drug side effects please ask the medical staff at your site. It is important to report all side effects to your study doctor, even if not listed below. If any of the side effects gets serious, contact your study doctor immediately.

Use of Combination Antiretroviral Drugs

Immune Reconstitution Syndrome: In some people with advanced HIV infection, signs and symptoms of inflammation from other infections may occur soon after anti-HIV treatment is started.

The use of potent antiretroviral drug combinations may be associated with an abnormal placement of body fat and wasting. Some of the body changes include:

- Increase in fat around the waist and stomach area
- Increase in fat on the back of the neck
- Thinning of the face, legs, and arms
- Breast enlargement

Risks of Etravirine

The following side effects have been associated with the use of etravirine:

- Serious and life-threatening rash and allergic reactions (hypersensitivity). If you get a rash with any of the following symptoms contact your child's HIV care provider and the

study doctor or nurse right away:

- Fever
- Muscle or joint aches
- Hives or sores in your mouth, or your skin blisters and peels
- Trouble swallowing or breathing
- Swelling of the face, eyes, lips, tongue or throat
- Red or inflamed eyes, like "pink eye" (conjunctivitis)
- Yellowing of the skin or whites of the eyes, dark urine, or pain on the right side of the stomach.
- Your doctor might also find some abnormalities in a certain type of your white blood cells.

- Other serious side effects:
  - Muscle break down causing muscle aches, pain or weakness which can be serious
- Additional side effects include:
  - Skin rash, mostly mild to moderate was sometimes seen, usually during the first 2 weeks of taking etravirine and lasting for about a week. In clinical studies, rash occurred more frequently in females than in males.
  - Mild to moderate diarrhea (liquid stools), nausea (upset stomach or feeling the need to throw up), vomiting
  - Numbness, pain or tingling in the hands or feet
  - Headache, stuffy nose, tiredness
  - Some other less common, but serious reported side effects include a decrease in red blood cells or a decrease in the part of the blood that stops bleeding, decrease in kidney function, high blood pressure, increase in blood sugar, increase in cholesterol or fats in your blood and decreased appetite
  - Other less commonly occurring side effects of at least moderate intensity include gastro-esophageal reflux disease (GERD), flatulence, inflammation of the stomach, abdominal pain, anxiety, inability to sleep, and night sweats.

Immune Reconstitution Syndrome: In some people with advanced HIV infection, symptoms from other infections or certain diseases may occur soon after starting combination anti-HIV treatment. Other non-infectious diseases characterized by abnormal functioning of the immune system (so-called autoimmune disorders, like Graves' disease) have also been reported after the start of anti-HIV treatment, but sometimes with a delay of many months. Some of these symptoms may be life threatening. If you start having new symptoms, or notice that existing symptoms are getting worse after starting your antiretroviral therapy, tell your healthcare provider right away.

<u>Other Risks</u>

There is the risk of serious and/or life threatening side effects when non-study medications are taken with etravirine. For your child's safety, you must tell your child's HIV care provider and the study doctor or nurse about all medications your child takes before the start of this study and also before starting any new medications while your child is on the study. In addition, you must

tell the study doctor or nurse before enrolling your child in any other clinical trials while on this study.

The use of potent antiretroviral drug combinations may also be associated with abnormal processing of body and dietary fat including elevated triglycerides (fatty acid in the blood) and/or elevated cholesterol.

Other side effects besides those listed and side effects from taking these drugs together may occur. If any unusual symptoms or changes happen, you should call your child's doctor immediately. It is also important that while participating in the study, your child does not take any other prescription drugs or over-the-counter medications without first talking to your child's doctor or study nurse.

Blood Drawing and Heparin/Saline Lock Risks

Blood drawing may cause some discomfort, bleeding or bruising where the needle enters the body. A small blood clot may form at the site of venipuncture/heparin lock or there may be swelling in the area. There is a small risk of a minor infection at the blood draw/heparin lock site. Lightheadedness and fainting can also occur.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

If your child takes part in this study, the amount of HIV in your child's body may go down and your child's immune system may become stronger, but no guarantee can be made. Your child may receive no benefit from being in this study. Information learned from this study may help others who have HIV.

WHAT OTHER CHOICES DOES MY CHILD HAVE BESIDES THIS STUDY?

Instead of being in this study you have the choice of:

- Treatment with prescription drugs available to your child
- Treatment with other experimental drugs, if your child qualifies

Please talk to your doctor about these and other choices available to your child. Your doctor will explain the risks and benefits of these choices.

WHAT ABOUT CONFIDENTIALITY?

(US sites only)

To help us protect your child's privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. With this Certificate, the researchers cannot be forced to disclose information that may identify you, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below. The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA).

People who may review your child's records include the U.S. Food and Drug Administration, the site IRB (insert name of site IRB), the National Institutes of Health, the Office of Human Subjects Protection (OHRP), host country regulatory agencies, study staff, study monitors,

Janssen R&D and their designees.

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about you or your participation in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate of Confidentiality to withhold that information.

(For sites outside the U.S.)
Efforts will be made to keep your child's personal information confidential. We cannot guarantee absolute confidentiality. Your child's personal information may be disclosed if required by law. Any publication of this study will not use your child's name or identify your child personally. Your child's records may be reviewed by the Ministry of Public Health in your country, the FDA, the Office of Human Research Protections (OHRP), the NIH, (insert name of site) IRB, study staff, study monitors and the drug companies supporting this study.

WHAT ARE THE COSTS TO MY CHILD?
There are no costs to you/your child for study drug (etravirine), study visits or study procedures. However, taking part in this study may lead to added costs to you and your insurance company if medical complications arise or if your doctor decides extra tests are needed. You will be responsible for the cost of your child's anti-HIV medications that are not provided by the study. In some cases it is possible that your insurance company will not pay for these costs because you/your child are taking part in a research study.

WILL MY CHILD RECEIVE ANY PAYMENT?
You will receive [$XX] for each study visit you attend. If you attend all study visits, you may receive up to [$XX].

WHAT HAPPENS IF MY CHILD IS INJURED?
If you are/your child is injured as a result of being in this study, you/your child will be given immediate treatment for your/his/her injuries. The cost for this treatment will be charged to you or your insurance company. There is no program for compensation either through this institution or the National Institutes of Health (NIH). You will not be giving up any of your/your child's legal rights by signing this consent form.

WHAT ARE MY CHILD'S RIGHTS AS A RESEARCH SUBJECT?
Taking part in this study is completely voluntary. You may choose not to take part/not to allow your child to take part in this study or leave this study/take your child out of the study at anytime. Your decision will not have any impact on your participation in other studies conducted by the NIH and will not result in any penalty or loss of benefits to which you are otherwise entitled.

We will tell you about new information from this or other studies that may affect your health, welfare or willingness to stay in this study. If you want the results of the study, let the study staff know.

WHAT DO I DO IF I HAVE QUESTIONS OR PROBLEMS?

For questions about this study or a research-related injury, contact:

- Name of the investigator or other study staff
- Telephone number of above

For questions about your child's rights as a research subject, contact:

- Name or title of person on the Institutional Review Board (IRB) or other organization appropriate for the site
- Telephone number of above

SIGNATURE PAGE

If you have read this consent form (or had it explained to you), all your questions have been answered and you agree to allow your child to take part in this study, please sign your name below.

_____
Participant's Name (print)

_____ Participant's Mother (print)	_____ Mother's Signature and Date
_____ Father's Name (If father's consent is required)	_____ Father's Signature and Date (If father's consent is required)
_____ Participant's Legal Guardian (print) (As appropriate)	_____ Legal Guardian's Signature and Date
_____ Study Staff Conducting Consent Discussion (print)	_____ Study Staff Signature and Date
_____ Witness' Name (print) (As appropriate)	_____ Witness's Signature and Date

APPENDIX IX: FACT SHEET and TEMPLATE CONSENT FORM for SPECIMEN STORAGE AT REPOSITORIES FUNDED BY THE NATIONAL INSTITUE OF CHILD HEALTH AND HUMAN DEVELOPMENT (NICHD)

When your child joins this NICHD sponsored study, you will be asked to give permission for having some specimens that the doctor or nurse will take from your child's body saved in a repository. (A repository is a special laboratory with freezers where specimens like blood or tissue cells and body fluids that are taken from you during a study are kept. Your child's name will not be on these specimens, only a special study number. The people who run the repository laboratory will not know your child's name.)

Why have a repository?

Researchers can learn a lot from a study but as time goes by the tests that they used get better or brand new tests are developed, and more can be learned with these better or new tests. When study volunteers consent to put specimens in the repository and consent to the researchers doing new tests on the specimens at some time in the future after their time in the study is ended, researchers can learn new information by being able to use the specimens. Your child's rights and privacy will be protected in any of these new studies.

How will my child's privacy be protected?

The only record that your child participated in this NICHD sponsored study is at the clinic where it is kept separate from your child's health records and locked away.

Your child's specimens in the repository will not have your child's name on them. The specimens will have a special study code. It will be the same code that is on your child's information in the NICHD sponsored Study from your child's interviews and examinations. Again, none of this information will have your child's name on it.

How would a researcher get to use the specimens in the repository?

If a researcher wants to do a test on specimens from the NICHD sponsored repository in the future, he or she will write up the idea and it will have to be approved by a committee to make sure the research is worthwhile. If the idea is approved, then coded specimens and coded information will be given to the researcher. The researcher will not know the names, addresses, or phone numbers of the people who gave the specimens to the repository.

Why wouldn't I find out the results of the research using my child's specimens?

You will <u>not</u> receive the results of research done with your child's specimens. This is because research can take a long time and must use specimens from many people before results are known. Results from research using your child's specimens may not be ready for many years. Often when studies are first done, it is not always clear how to use the information from the study to change the health care that people receive. So none of these study results is likely to affect your child's care right now, but they may be helpful to people like your child in the future. Your child's specimens can last in the freezer for many years and there is no time limit to when

studies could be done in the future.

Would I ever be contacted in the future about research using my child's specimens?

All of the studies to be done in the future on your child's specimens in the repository will be for the particular reasons that you agreed to. Every study that is planned to use specimens from your child and others from this NICHD Study has to be reviewed to make sure that what is planned is the same kind of study that you agreed to. If it is, then the research will go ahead since you would have agreed that these particular tests could be done without anyone contacting you to get your permission in the future.

If the study to be done is not like the kind of tests you agreed could be done, then the committee will decide if you need to be contacted to give permission for the new study.

I gave my permission to testing my child's specimens in the repository, but what if I change my mind?

People always have the right to stop participating in research. So if you decide that you do not want researchers to be able to use the specimens from your child in the repository, you can contact the clinic staff. They will tell the repository that the specimens with the study code number linked to your child's name in the clinic should not be studied. These specimens can be removed from the repository and destroyed if you tell us to do that.

What type of research will be done with my child's specimens?

Many different kinds of studies use specimens. Some researchers may develop new tests to find diseases. Others may develop new ways to treat or even cure diseases. In the future, some of the research may help to develop new products, such as tests and drugs. If this would happen and these tests or drugs make money, there are no plans to share that money with the people who gave the specimens.

As part of this study (insert title), your child is being asked to have some (insert specimen source- blood, urine, tissue, genital fluid, saliva, etc.) taken. These specimens will go into the NICHD repository for research to be done at some time in the future so that more information can come from your child's time in this NICHD sponsored Study.

You do not have to agree to store your child's specimens for future tests for your child to take part in this study. Your child will not lose any benefits to which your child is entitled if you decide against storing your child's specimens.

You will also be asked to agree that these particular tests can be done without anyone contacting you to get your permission sometime in the future. No one doing these tests would know that these specimens came from your child and no one would contact you or your doctor or nurse with the results from these tests that might happen in the future.

What are the general HIV-related studies that can be done with the repository specimens?

Researchers would like to store your child's specimens to understand how HIV causes disease and complications, and how best to treat or prevent HIV infection and its complications. They need specimens from people who have HIV and from those who do not. Sometimes, too, the specimens can be used to learn something about new problems that people with HIV have like liver disease, diabetes, and heart disease. These general studies would not include any genetic testing (looking at your child's DNA).

Benefits: There are no direct benefits to your child. Your child will be helping researchers learn more about how to help people with HIV or at risk of HIV infection.

Risks: The specimens would be collected as part of your child's study visits. (Insert text about collection procedures.) Once in the repository, there are few risks. Your child's name will not be available to the repository or to the scientists who may be doing any future test.

I give permission for the use of my child's stored specimens for the purposes stated in the preceding section (general HIV-related tests).

_____	_____	_____
Parent or Legal Guardian Signature	Witness Signature	Date

I give my assent to the use of my stored specimens for the purposes stated in the preceding section (general HIV-related tests).

_____	_____	_____
Participant Signature	Witness Signature	Date

What are the special HIV-related studies that can be done with the repository specimens?

Researchers in this study would also like to store your child's specimens to understand how HIV causes disease and complications, and how best to treat or prevent HIV infection and its complications through looking at how each person's genetic makeup (your child's DNA) either protects them or puts them at greater risk. It may be that researchers use some of your child's blood to make a "cell line". That means the blood cells can keep dividing and give an endless supply of your child's DNA for tests to be done in the future. This kind of information will be particularly important as scientists work toward a vaccine that could protect people from AIDS. They need specimens from people who have HIV and from those who do not.

Benefits: There are no direct benefits to your child. Your child will be helping researchers learn more about how to help people with HIV or at risk of HIV infection.

Risks: The specimens would be collected as part of your child's study visits. (Insert text about

collection procedures.) Once in the repository, there are few risks. Your child's name will not be available to the repository or to the scientists who may be doing any future test. Since there are no plans to give participants the results of the tests performed on their stored specimens, you will not receive any information on your child's genetic makeup.

I give permission for the use of my child's stored specimens for the purposes stated in the preceding section (special HIV-related tests).

_____	_____	_____
Parent or Legal Guardian Signature	Witness Signature	Date

I give my assent to the use of my stored specimens for the purposes stated in the preceding section (special HIV-related tests).

_____	_____	_____
Participant Signature	Witness Signature	Date

What if I have more questions?

If you have any questions about the repository, about storage, or the use of your child's samples, contact (Study personnel) at (phone).

If you have questions about giving consent or your child's rights as a research volunteer, contact the (Name of Institution) Institutional Review Board at (phone).

I refuse to have any specimen collected from my child stored in the repository.

_____	_____	_____
Parent or Legal Guardian Signature	Witness Signature	Date