TRIAL SUMMARY

PENPACT 1

(PENTA 9/PACTG 390)

A PHASE II/III RANDOMIZED, OPEN-LABEL STUDY OF COMBINATION ANTIRETROVIRAL REGIMENS AND TREATMENT-SWITCHING STRATEGIES IN **HIV-1-INFECTED** ANTIRETROVIRAL NAIVE CHILDREN >30 DAYS AND <18 YEARS OF AGE

PRIMARY OBJECTIVES

- To compare the combination of 2 NRTIs plus a protease inhibitor (PI) versus 2 NRTIs plus a non-nucleoside reverse transcriptase inhibitor (NNRTI) as initial therapy, followed by second-line therapy if **virologic** failure occurs, in terms of their effects on a long-term virologic endpoint.

- To compare two different viral load criteria for switching from first-line to second-line therapy.

SECONDARY OBJECTIVES

- To evaluate and compare the safety and tolerability of each drug combination (including first- and second-line therapies).

- To compare the long-term clinical and immunologic outcomes (by the initial randomization).

- To compare the proportions of children who have undergone one regimen switch or reached study end-point (by the initial randomization).

- To compare time from randomization to virologic failure (RNA $\geq$400 copies/mL at or after Week 24) of the first-line therapy analyzed by initial randomization to either protease inhibitor (PI) or NNRTI containing regimens.

- To compare time from randomization to virologic failure of the second line therapy (RNA $\geq$30,000 copies/mL) analyzed by the initial randomization.

- To compare the proportion of children with plasma HIV-1 RNA <400 copies/mL at 4 years (by the initial randomization).

- To describe resistance patterns at four years (by the initial randomization).

VIROLOGIC ENDPOINT DEFINITION

The virologic endpoint is change in HIV-1 RNA viral load between baseline and four years post randomization. It is likely that by four years post-randomization, nearly all children will have switched from first to second-line therapy.

STUDY DESIGN

This is an international multicenter Phase II/III, randomized, open label, and factorial (2x2) trial.

SAMPLE SIZE

256 children, approximately 50% from PACTG sites and 50% from PENTA sites.

POPULATION

HIV-1 infected **children who are** antiretroviral naïve or who have received less than 56 days of antiretroviral drugs used on consecutive days after birth to prevent mother-to-infant **HIV** transmission. **Prior exposure to NVP, including for prevention of mother-to-child transmission, is exclusionary.**

RANDOMIZATION AND STRATIFICATION

Children will be randomized to **one of** four groups **and** stratified by age (<3 years versus ≥3 years), origin (PACTG site or PENTA site), and exposure versus no exposure to antiretroviral therapy perinatally.

FIRST-LINE THERAPY

All study medications will be given by prescription (the child, child's parent**(s)**/legally **authorized** representative **(LAR)**, the child's health insurance, and/or, in Europe, the healthcare provider, are responsible for purchasing the study medications).

Children are randomized to one of four groups that are defined by the initial therapy to be given to a child as well as the virologic criterion for switching from first-line therapy (defined below) to second-line therapy:

- Group 1(A): **Initial therapy is** 2 NRTIs + PI
  (switch to second-line **therapy** when HIV-1 RNA is ≥1,000 copies/mL)
- Group 1(B): **Initial therapy is** 2 NRTIs + PI
  (switch to second-line **therapy** when HIV-1 RNA is ≥ 30,000 copies/mL)
- Group 2(A): **Initial therapy is** 2 NRTIs + NNRTI
  (switch to second-line **therapy** when HIV-1 RNA is ≥1,000 copies/mL)
- Group 2(B): **Initial therapy is** 2 NRTIs + NNRTI
  (switch to second-line **therapy** when HIV-1 RNA is ≥30,000 copies/mL)

First-line therapy includes the initial therapy to which a child is randomized as well as any antiretroviral therapies to which the child changes due to non-virologic reasons (e.g. toxicity, intolerability, request of child or child's parent**(s)**/**LAR**, etc.) prior to reaching the HIV-1 RNA switch criterion (≥1,000 copies/mL or ≥30,000 copies/mL, depending on the initial randomization). **Whenever possible, changes within first-line therapy should involve substitutions of one or more drugs in the initial therapy by drugs from the same class or classes.**

It is important to emphasize that the protocol will allow low doses of ritonavir as a boosting agent, creating drug combinations that will be counted as a single PI.

SECOND-LINE THERAPY

Second-line therapy will be initiated when the HIV-1 RNA switch criterion (≥1,000 copies/mL or ≥30,000 copies/mL, depending on the initial randomization) is reached. The following suggested drug regimens will be strongly encouraged as a second-line therapy for all

children failing **first-line therapy** (when HIV-1 RNA is ≥1,000 copies/mL or when HIV-1 RNA is ≥30,000 copies/mL, depending on the initial randomization)**, particularly those children who have remained on their initial (randomized) therapy**:

- For PI-containing Groups **1(A) and 1(B)**: two new NRTIs and an NNRTI
- For NNRTI-containing Groups **2(A) and 2(B)**: two new NRTIs and a PI

However, these regimens do not constitute the only options. Current clinical care guidelines will prevail over protocol **guidelines**, **(e.g.** a fourth drug as part of second-line therapy**)**.

The protocol will allow low doses of ritonavir as a boosting agent, creating drug combinations that will be counted as a single PI.

PENPACT 1 FOLLOW-UP PERIOD

All children will **be followed** until the last child enrolled has reached 204 weeks on **study** treatment from his/her original randomization. This last patient could be from a PACTG or PENTA site.

After Week 204 of treatment until the study ends, children will continue on study follow-up with regular study visits every 12 weeks as described in Appendix 1. This follow-up period will be used to address long-term time-to-event secondary objectives of the study.

PENPACT 1 COMPARISON FOR ALL CHILDREN IN THE STUDY

- PI versus NNRTI as part of the initial therapy

Switching to second-line therapy at an HIV-1 RNA level of ≥1,000 copies/mL versus switching at HIV-1 RNA level of ≥30,000 copies/mL