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 ≥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 ≥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.