CLINICAL REVIEW

Application Type	21-251
Submission Number	022
Submission Code	SE5
Letter Date	December 21, 2007
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Reviewer Name	Kirk M. Chan-Tack, MD
Draft Completion Date	March 28, 2008
Review Completion Date	June 18, 2008
Established Name	Lopinavir/ritonavir
(Proposed) Trade Name	Kaletra
Therapeutic Class	Antiretrovirals
Applicant	Abbott
Priority Designation	P
Formulation	Oral solution, capsules, tablets
Dosing Regimen	The recommended dosage of Kaletra in patients 14 days to 18 years should be calculated on body weight (kg) or body surface area (BSA) and should not exceed the recommended adult dose.
Indication	Treatment of HIV-1 infection
Intended Population	HIV-infected children with evidence of viral replication

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

From a clinical perspective, the current supplement should be approved. This supplemental application seeks to expand the pediatric patient population to include patients ≥ 14 days to 6 months and patients > 12 years to 18 years of age based on pharmacokinetic, safety, and antiviral activity data from PACTG Study 1030 (P1030) and PACTG Study 1038 (P1038).

In P1030, LPV/r, in combination with 2 nucleoside reverse transcriptase inhibitors, was efficacious in reducing HIV viral load and immunologic benefit by increasing CD4 cell counts over the 24-week study period in both treatment-naïve and treatment-experienced children ages ≥ 14 days to <6 months.

In P1038, LPV/r, in combination with saquinavir and other antiretroviral drugs, was overall safe and tolerable over the 48-week study period in treatment-experienced children ages **7** to <18 years of age. However, efficacy rates were low in this patient population with ongoing viremia (entry criteria, viral load > 5000 copies/mL) despite at least six months of continuous protease inhibitor (PI) therapy prior to study enrollment. The low response rates observed in P1038 were likely due to prior PI exposure and accumulation of multiple protease resistance mutations.

The applicant demonstrated an acceptable safety profile for LPV/r used in combination with other antiretroviral drugs. No new safety signals were definitively identified. While adverse events were common in the study population, relatively few were considered possibly drug related, few were severe in nature or required discontinuation of study drug, and many were clearly related to common childhood illnesses or conditions. Clinically significant laboratory abnormalities were also relatively uncommon and infrequently led to interruptions in the study regimen. The observed toxicities did not outweigh the clear benefit of LPV/r as an option for HIV-infected pediatric patients.

1.2 Risk Benefit Analysis

Review of the safety data provided in this supplement did not definitively identify any new or unexpected toxicities for LPV/r in pediatric patients. As expected, the most common adverse events (AE) reported among patients receiving LPV/r were gastrointestinal disorders, such as diarrhea, nausea, and vomiting. The majority of AEs reported in P1030 and P1038 are similar to those in other adult and pediatric studies with LPV/r. In P1038, transient cardiac conduction abnormalities were reported in six subjects (QT prolongation – 2 subjects, sinus bradycardia – 3 subjects, first degree AV block – 1 subject). All six subjects remained clinically asymptomatic.

Although cardiac conduction abnormalities could represent a potential new safety signal with higher exposures of LPV/r, it was difficult to definitively establish causality to LPV/r due to the presence of multiple confounders, such as electrolyte abnormalities, concomitant medications, and pre-existing cardiac abnormalities.

Laboratory abnormalities for liver function tests, lipids, and glucose were overall infrequent. Overall, the laboratory toxicity profile in P1030 and P1038 appears similar to other adult and pediatric studies with LPV/r.

The extrapolation of efficacy for antiretroviral drugs like LPV/r are based on the presumption that the course of HIV disease and the effects of the drug are sufficiently similar in adults and pediatric patients (21 CFR 201.57 (f)(9)(iv), Sec. 505B 21 USC 355c)[1]. DAVP agrees that HIV disease in pediatric patients is similar but not identical to adult HIV disease (Domachowske, JB; Pediatric Human Immunodeficiency Virus Infection; October 1996; Clin. Microbiol. Rev. 9(4) 448-468), although the route of transmission may be different. Vertical transmission from mother to child is the predominant means of infection for children less than 12 years of age in contrast to adolescent and adult patients in whom sexual contact or injection drug use are the primary modes of transmission. The pathophysiology of immune system destruction by HIV is similar in adult and pediatric patients. Consequently, infectious complications of pediatric HIV disease consist of both severe manifestations of common pediatric infections and also opportunistic infections like those seen in adults.

In pediatric and adult patients, treatment of HIV disease is monitored by the same two surrogate markers, CD4 count and HIV RNA load. Antiretroviral drugs including nucleoside reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs) have been shown to lower HIV RNA, improve CD4 count (or percentage) and improve general clinical outcome in all ages and treatment recommendations are very similar across all ages (see Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children. Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection. February 28, 2008 1-134. Available at http://aidsinfo.nih.gov/ContentFiles/PediatricGuidelines.pdf. for a review of studies and references).

For this supplement, approval is based on extrapolation of efficacy from adequate and well-controlled trials in HIV-infected adults, and supportive pharmacokinetic and safety data from Studies P1030 and P1038.

[1] TITLE IV—PEDIATRIC RESEARCH EQUITY ACT OF 2007 ‘‘(B) SIMILAR COURSE OF DISEASE OR SIMILAR EFFECT OF DRUG OR BIOLOGICAL PRODUCT — IN GENERAL —If the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients, the Secretary may conclude that pediatric effectiveness can be extrapolated from adequate and well-controlled studies in adults, usually supplemented with other information obtained in pediatric patients, such as pharmacokinetic studies. (ii) EXTRAPOLATION BETWEEN AGE GROUPS.—A study may not be needed in each pediatric age group if data from one age group can be extrapolated to another age group. (iii) INFORMATION ON EXTRAPOLATION.—A brief documentation of the scientific data supporting the conclusion under clauses (i) and (ii) shall be included in any pertinent reviews for the application under section 505 of this Act or section 351 of the Public Health Service Act (42 U.S.C. 262).

1.3 Recommendations for Risk Evaluation and Mitigation Strategies

The risk management program for LPV/r was discussed in the clinical review of the original NDA. No additional recommendations were provided with this supplement.

1.4 Recommendations on Post Marketing Activities/Phase 4 Commitments

No additional post-marketing commitments were requested with this supplement. The applicant has fulfilled the pediatric study requirements for investigation of LPV/r oral solution in all pediatric age groups as outlined in the post-marketing commitments.

PMC #2 as stated in the approval letter for SE-003, dated January 18, 2002:

> 2. Evaluate the use of Kaletra in a population of more extensively treated pediatric patients, with special attention to identifying whether the currently approved dosing recommendation are adequate for children who have failed treatment with multiple (>2) other PIs. The sponsor commits to support a pediatric study which will look at patients who have been previously treated. An example of the proposed study design is PACTG study P1038 which currently plans to enroll 32 patients between the ages of 2 to 18 years to achieve an IQ >15 in pediatric patients previously treated with PIs.

PMCs #1 and #2 as stated in the approval letter for SE-014, dated October 19, 2004:

> 1. Multiple-dose pharmacokinetics, safety and activity study of ABT-378/ritonavir in combination with other antiretroviral agents in HIV-infected pediatric patients
>
> 2. Multiple-dose pharmacokinetic and safety study of ABT-378/ritonavir in HIV-exposed neonates (born to HIV-infected mothers).

Study PACTG 1030 began enrollment in August 2002 and will continue follow-up until all subjects are followed for at least 48 weeks. Subjects in the younger cohort (≥ 14 days to < 6 weeks) will remain on the study for 48 weeks from enrollment of the last subject. Subjects in the older cohort (≥ 6 weeks to < 6 months) will remain on the study for 96 weeks from enrollment of the last subject.

Study PACTG 1038 began enrollment in December 2004 and prematurely terminated enrollment in May 2006 due to poor subject accrual.

2 Introduction and Regulatory Background

2.1 Product Information

Established Name: Lopinavir (LPV) co-formulated with ritonavir (RTV)

Trade Name: KALETRA

Chemical: $C_{37}H_{48}N_4O_5$

Class: Protease Inhibitor

Formulation: 1) Oral solution (LPV 80 mg/mL and RTV 20mg/mL)
2) Capsules (LPV 133.33 mg/RTV 33.3 mg)
3) Tablets (LPV 100 mg/RTV 25 mg, LPV 200 mg/RTV 50 mg)

Dosage: 1) In therapy-naïve adults, the recommended dosage of KALETRA is 400/100 mg BID or 800/200 mg QD.

KALETRA should not be administered as a once-daily regimen in combination with efavirenz, nevirapine, (fos)amprenavir, or nelfinavir. A dose increase of KALETRA tablets (to 600/150 mg BID) may be considered when used in combination with any of these agents. A dose increase of KALETRA solution (to 533/133mg BID) is recommended when used in combination with any of these agents.

2) In therapy-experienced adults, the recommended dosage of KALETRA is 400/100 mg BID. Once-daily KALETRA is not recommended in therapy-experienced adults.
3) The recommended dosage of KALETRA in pediatric patients 14 days to 18 years of age should be calculated based on body weight (kg) or body surface area (BSA) and should not exceed the recommended adult dose. Once-daily KALETRA is not recommended in pediatric patients 14 days to 18 years of age.

Indication: In combination with other antiretroviral agents for the treatment of HIV-1 infection.

2.2 Tables of Currently Available Treatments for Proposed Indications

As of May 2008, 26 drugs are approved for the treatment of HIV-1 infection (this list does not include fixed dose combinations or different formulations). These drugs fall into six classes based on mechanism of action in the HIV life cycle: nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), fusion/entry inhibitors, CCR5 co-receptor inhibitors, and integrase inhibitors (Table 1).

Table 1: Currently Approved Antiretrovirals

Drug Class	Generic Name	Trade Name
NRTI	Zidovudine†	Retrovir®
	Didanosine†	Videx®
	Stavudine†	Zerit®
	Lamivudine†	Epivir®
	Abacavir†	Ziagen®
	Tenofovir	Viread®
	Emtricitabine†	Emtriva®
	Zalcitabine*	Hivid®
NNRTI	Delavridine	Rescriptor®
	Nevirapine†	Viramune®
	Efavirenz†	Sustiva®
	Etravirine	Intelence®
PI	Indinavir	Crixivan®
	Ritonavir†	Norvir®
	Saquinavir, hard gel	Invirase®
	Saquinavir, soft gel*	Fortovase®
	Nelfinavir†	Viracept®
	Amprenavir*	Agenerase®
	Fosamprenavir†	Lexiva®
	Atazanavir†	Reyataz®
	Lopinavir/ritonavir† fixed dose combination	Kaletra®
	Tipranavir	Aptivus®
	Darunavir	Prezista®
Fusion Inhibitor	Enfuvirtide†	Fuzeon®
CCR5 Inhibitor	Maraviroc	Selzentry®
Integrase Inhibitor	Raltegravir	Isentress®

***Sale and distribution of zalcitabine (ddC, Hivid®) was discontinued on December 31, 2006. Sale and distribution of saquinavir soft gelatin capsules (SQV, Fortovase) was discontinued on February 15, 2006. Sale and distribution of amprenavir (AMP, Agenerase®) was discontinued on October 31, 2007 (Reference: Drug Discontinuation. Available at: http://www.fda.gov/CDER/Drug/shortages/default.htm#disc).**

†Current labels with approved pediatric dosing recommendations.

Pediatric dosing recommendations are currently available in the labels for six NRTIs (zidovudine, lamivudine, stavudine, didanosine, abacavir, emtricitabine), two NNRTIs (efavirenz, nevirapine), four PIs (lopinavir/ritonavir, nelfinavir, fosamprenavir, atazanavir), and enfuvirtide. For each of these antiretrovirals, the amount of data and ages of pediatric patients studied vary.

The use of highly active therapy (HAART) has decreased the morbidity and mortality of HIV disease. Of PI-based regimens, LPV/r is listed as a preferred option in the 2008 DHHS HIV-1 Pediatric Treatment Guidelines. These guidelines also state "the goal of antiretroviral therapy is to reduce plasma HIV RNA levels to below the limits of quantitation on ultrasensitive assays and to normalize immune status." Obstacles in achieving these goals include drug side effects, drug intolerance, and drug resistance. Antiretroviral therapy is often associated with significant drug toxicities such as hepatotoxicity, hyperlipidemia, hypertriglyceridemia, rash, fat redistribution, hyperglycemia, pancreatitis, and lactic acidosis. When selecting an antiretroviral (ARV) regimen, clinicians must carefully consider potential side effects, especially when the possibility for overlapping toxicities exists. Additional challenges in the pediatric population are presented by availability of relatively less data on some of these long-term toxicities compared with HIV-infected adults.

2.3 Availability of Proposed Active Ingredient in the United States

The active moiety is commercially available in the United States as both tablets and oral solution. The capsule and oral solution co-formulations of Kaletra were both studied under IND [redacted]. The adult Phase III treatment studies (using Kaletra capsules) submitted under NDA 21-226 and the pediatric study (using oral solution) submitted under NDA 21-251 were received in May 2000 and reviewed simultaneously. Both the capsule and oral solution formulations of Kaletra were granted accelerated approval on September 15, 2000 on the basis of 24-week data showing declines in HIV-1 RNA levels and improvements in CD4 cell counts over the 24-week study period.

A brief overview of supplements is outlined below:

- An efficacy supplement containing updated adult efficacy data for Kaletra was submitted to NDA 21-226 in March 2001.
- An efficacy supplement containing updated pediatric efficacy data for Kaletra was submitted to NDA 21-251 in July 2001.
- An efficacy supplement containing updated adult and pediatric efficacy data for Kaletra was submitted to NDA 21-226 and NDA 21-251 in January 2002. Traditional approval was granted in November 2002.
- A labeling revision to provide updates to the CLINICAL PHARMACOLOGY, INDICATIONS AND USAGE, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS: Drug Interactions, and DOSAGE AND ADMINISTRATION sections of the package insert and other minor labeling revisions throughout the package insert and patient package insert was submitted to NDA 21-226 and NDA 21-251 in June 2003.

- An efficacy supplement containing updated adult efficacy data for Kaletra was submitted to NDA 21-226 and NDA 21-251 in December 2003.
- A labeling revision to provide changes in labeling incorporating fluticasone and trazodone interaction information under the Drug Interactions subsection of the WARNINGS section and Table 9 under Drug Interactions subsection of the PRECAUTIONS section was submitted to NDA 21-226, NDA 21-251, and NDA 21-251 in October 2004.
- An efficacy supplement for the use of Kaletra 800/200mg once-daily administration for the treatment of HIV-infection in therapy-naïve adult patients was submitted to NDA 21-226 in June 2004.
- A new drug application (NDA 21-906) was submitted for Kaletra tablets (200mg/50mg) in April 2005.
- A supplemental new drug application to provide drug interaction information when Kaletra tablet formulation is co-administered with ranitidine or omeprazole was submitted to NDA 21-226, NDA 21-251, and NDA 21-906 in June 2006.
- A supplemental new drug application to provide revisions to the CLINICAL PHARMACOLOGY, Microbiology section, CLINICAL PHARMACOLOGY, Drug Interactions section, and the PRECAUTIONS section of the package insert was submitted to NDA 21-226, NDA 21-251, and NDA 21-906 in December 2006.
- A supplemental new drug application to provide for the use of a lower strength Kaletra tablet (100 mg LPV/25 mg RTV) to be used for twice daily dosing in pediatric patients weighing greater than 15 kg was submitted to NDA 21-226, NDA 21-251, and NDA 21-906 in May 2007.
- A labeling supplement to provide revisions to Table 4 under the CLINICAL PHARMACOLOGY, Drug-drug Interaction subsection and Table 11 under the PRECAUTIONS, Drug Interaction subsection to include rosuvastatin drug interaction information was submitted to NDA 21-226, NDA 21-251, and NDA 21-906 in July 2007.

2.4 Important Safety Issues With Consideration to Related Drugs

Class-related adverse events/laboratory abnormalities and potential for significant drug-drug interaction potential are common for the approved protease inhibitors (PIs). Ritonavir (RTV) is the hallmark PI for drug-drug interactions due to its potent inhibition of CYP3A4 metabolism. As with other PIs, the LPV/r label includes warnings and precautions for new onset diabetes, hyperglycemia, hepatotoxicity, rash, lipodystrophy, hypertriglyceridemia, hypercholesterolemia, hemolytic anemia, increased bleeding episodes in patients with hemophilia, and fat redistribution.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Investigation of the use of LPV/r oral solution in all pediatric age groups was requested in a formal Written Request dated March 31, 1999 and amended June 18, 2001, July 3, 2002, March 13, 2003, May 7, 2004, December 12, 2006, and May 3, 2007. As previously noted, pediatric

data for ages 6 months to 12 years are already included in the LPV/r label, following review of Study M98-940 with the original NDA 21-251 and supplement SE8-004. The current supplement provides adequate demonstration of the safety and efficacy of LPV/r in children ≥ 14 days to <6 months and 12 to 18 years of age. Based on the cumulative data from P1030, P1038, and Study M98-940, pediatric exclusivity was granted for LPV/r on March 17, 2008. Please refer to the Appendix (Table A1) for the template used for Pediatric Exclusivity Determination.

2.6 Other Relevant Background Information

In the original NDA 21-251 and supplement SE8-004, pharmacokinetic, safety, and efficacy data from Study M98-940 supported the indication for use of LPV/r in combination with other antiretroviral drugs for the treatment of HIV infection in pediatric patients over 6 months to 12 years of age.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Because of the relatively small number of patients enrolled in Study 1030 and the relative lack of subject drop-outs and missing data, no DSI audits were requested by the review team. Also, no DSI audits were requested for Study 1038 due to the relatively small number of patients and relative lack of missing data.

3.2 Compliance with Good Clinical Practices

Overall no issues with informed consent, specific study sites, or study conduct were identified. All studies were written to conform to accepted ethical standards and were reviewed by Institutional Review Boards overseeing each investigative site.

3.3 Financial Disclosures

Pursuant to 21 CFR 54.2(e), the financial certification statement provided by the applicant was reviewed. The applicant requested investigators and sub-investigators from all studies contained in the sNDA disclose proprietary interest or significant equity as defined in the regulations. The applicant included a list of all investigators and sub-investigators who responded to their request on form 3454. The applicant submitted updated financial disclosure information for review. One new financial interest was reported: holds a >$50,000 financial interest in Abbott stock options/equity because .

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

This sNDA contained no new chemistry and manufacturing data. Please refer to the original NDA review.

4.2 Clinical Microbiology

This sNDA contained no new resistance data. Please refer to the original NDA review.

4.3 Preclinical Pharmacology/Toxicology

This sNDA contained no new preclinical pharmacology/toxicology data. Please refer to the original NDA review.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Lopinavir, an inhibitor of the HIV-1 protease, prevents cleavage of the Gag-Pol polyprotein, resulting in the production of immature, non-infectious viral particles.

4.4.2 Pharmacodynamics

No new pharmacodynamics data were provided in this submission.

4.4.3 Pharmacokinetics

Please refer to Dr. Derek Zhang's Clinical Pharmacology review. A summary of the important pharmacokinetic issues raised in Dr. Zhang's review are presented below.

P1030
At approximately Week 2, an intensive LPV/r pharmacokinetic evaluation was performed in all subjects.

In infants < 6 weeks of age who received LPV/r doses of 300/75 mg/m^2 BID, the C_{max} was 28% lower, C_{min} was 35% lower, and AUC_{12} was 26% lower, respectively, compared to children 6 months to < 2 years of age who received a LPV/r dose of 230/57.5 mg/m^2 BID without an NNRTI (the approved dose) in Study M98 940.

In infants between 6 weeks and < 6 months of age who received LPV/r doses of 300/75 mg/m^2 BID, the C_{max} was 31% higher, C_{min} was similar, and AUC_{12} was 27% higher, respectively, compared to children 6 months to < 2 years of age who received a LPV/r dose of 230/57.5 mg/m^2 BID without an NNRTI in Study M98 940.

The LPV C_{min} values observed in Study P1030 were lower than those for children in older age groups in Study M98-940 (2 years to < 6 years and 6 years to <12 years) who received a LPV/r dose of 230 mg/m^2 BID without an NNRTI. The observations described above are consistent with the apparent CL/F normalized by body weight that appears to be higher in younger subjects. The mean CL/F normalized by body weight was 394, 259 and 88 mL/h/kg in < 6 weeks of age, between 6 weeks and < 6 months of age and 12 to 18 years of age, respectively (Data from Studies P1030 and P1038).

Despite the lower LPV drug exposure observed with the 300/75 mg/m^2 BID dose in infants < 6 weeks and infants between 6 weeks and < 6 months of age cohorts in Study P1030, antiviral activity was demonstrated by the proportion of subjects who achieved HIV-RNA < 400 copies/mL at Week 24. The efficacy data supports use of this dose across the age range of 14 days to 6 months. Please refer to Section 6.1.4 for additional discussion.

The degree of pharmacokinetic variability observed in infants < 6 weeks and infants between 6 weeks and < 6 months of age was consistent with that in other age groups. The instability of metabolic clearance and dose administration in infants could contribute to the overall variability. Further increasing LPV/r dose could lead to higher than needed exposure in some subjects and could lead to toxicity.

Based on favorable antiviral activity and immunologic response, a dose of LPV/r 300/75 mg/m^2 BID (approximately equivalent to 16/4 mg/kg) is recommended in children < 6 months old.

P1038
At approximately Week 2, an intensive LPV/r pharmacokinetic evaluation was performed in all subjects.

Average LPV C_{max} and AUC_{12} values in children (12 to 18 years of age) who received LPV/r dose of 400/100 mg/m^2 BID were approximately 60 -100% higher than those observed in Study M98-940 children 6 to < 12 years of age who received LPV/r 230/57.5 mg/m^2 BID in the absence of an NNRTI.

However, low virologic response rates were observed in P1038. This likely reflects the high degree of phenotypic resistance to LPV at study entry, a factor that could not be overcome by increased drug exposures achieved in this trial. Please refer to Section 6.1.4 for additional discussion.

At these higher doses of LPV/r, the mean CL/F (L/hr/kg) was similar to that observed in previous studies of adults (average CL/F is 6 to 7 L/hr, or 86 to 100 mL/h/kg based on a 70-kg adult) who received a standard dose of LPV/r 400/100 mg BID without an NNRTI.

The similar CL/F observed in children (12 to 18 years of age) as compared to adults supports dosing recommendations in this age group of 230/7.5 mg/m^2 BID in the absence of inducing agents such as efavirenz, and 300/75 mg/m^2 BID when administered with inducing agents.

Therefore, the currently approved LPV/r dose of 10/2.5 mg/kg BID without an NNRTI (approximately equivalent to 230/57.5 mg/m^2 BID studied in M98-940 in 6 – 12 year age group) is reasonable to recommend for pediatric patients 12 to 18 years of age with body weight between 15 to < 40 kg.

The recommended dosage of LPV/r in patients 6 months to 18 years of age should be calculated based on body weight (kg) or body surface area (BSA) and should not exceed the recommended adult dose.

Once-daily LPV/r has not been evaluated in pediatric patients.

5 Sources of Clinical Data

This review is primarily based on safety, efficacy, and pharmacokinetic data from PACTG 1030 and PACTG 1038. Data from the applicant's postmarketing database, as well as the FDA's Adverse Events Reporting System (AERS), were also reviewed for safety.

5.1 Tables of Clinical Studies

The following table outlines the study type, geographic location, numbers of patients, and status for the clinical studies submitted for this supplement.

Table 2: Pediatric Clinical Studies

Study	Study Type	Country	Design	Dose and Duration	Total No. of Subjects/ARV experience	Status
PACTG 1030 (P1030)	Phase I/II	United States, Brazil	open-label	LPV/r 300/75 mg/m^2 PO BID x 48 wks	31/ PI naïve or experienced	Ongoing
PACTG 1038 (P1038)	Phase I/II	United States	open-label	LPV/r 400/100 mg/m^2 PO BID or 480/120 mg/m^2 PO BID x 48 wks	26/ PI experienced	Closed

Source: December 21, 2007 submission.

5.2 Review Strategy

Efficacy data were reviewed for P1030 and P1038. Safety data for P1030 and P1038, as well as post-marketing safety data, were reviewed. This included case report tabulations and case report forms when applicable. The applicant's conclusions regarding safety and efficacy were confirmed by independent FDA analysis of the data. This MO reviewed study design, patient demographics, efficacy results, adverse events, and laboratory safety monitoring data.

During the review, there was significant interaction with the FDA clinical pharmacology team. Their assessments are summarized in this document, but complete details of their findings are available in the respective discipline reviews.

5.3 Discussion of Individual Studies

P1030
P1030 is a Phase I/II open-label, multi-center study to assess the safety, tolerability, pharmacokinetics and preliminary effectiveness of LPV/r (in combination with 2 NRTIs) in HIV-infected infants < 6 months of age (≥ 14 days to < 6 weeks cohort with 10 patients; ≥ 6 weeks to < 6 months cohort with 21 patients).

The LPV/r formulation used in this study was the oral solution (80 mg/20 mg per ml).

Key inclusion criteria were:

- HIV-1 infected children, age ≥ 14 days to < 6 months.
- Weight > 2.5 kg at the time of enrollment.
- HIV-1 RNA > 10,000 copies/mL within 30 days of study entry.
- Agreement to take 2 NRTIs, chosen by the provider in consultation with the Protocol Chair and/or Vice Chair, in addItion to LPV/r.

Key exclusion criteria were:

- Concurrent NNRTI use.
- Concurrent PI use.
- Prior treatment with LPV/r (prior treatment with other PIs was allowed).
- If < 6 weeks of age at time of enrollment: < 34 weeks gestation at delivery.
- If ≥ 6 weeks of age at time of enrollment: < 32 weeks gestation at delivery.
- Any ≥ Grade 3 laboratory toxicity at screening (EXCEPTION: ≥ Grade 2 hyperlipasemia was exclusionary).
- Presence of a newly diagnosed acute opportunistic or serious bacterial infection requiring therapy at the time of enrollment.
- Chemotherapy for active malignancy.
- 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 have compromised study outcome.

Study endpoints
Primary endpoint was proportion of patients with Grade 3/4 adverse events and clinical laboratory abnormalities at 24 weeks.

Secondary endpoints included

- Proportion of patients with HIV-RNA < 400 copies/mL at 24 weeks.
- Change from baseline in plasma HIV-1 RNA, CD4+ cell counts and percentages, and CD8+ cell counts and percentages.

- Duration of exposure to LPV/r.
- Number and proportion of subjects who prematurely discontinued LPV/r based study therapy.
- Change from baseline in laboratory parameters including serum ALT, AST, total cholesterol, triglycerides, and glucose.
- Change from baseline in height and weight (for age Z-scores).
- Estimation of lopinavir pharmacokinetic parameters at Week 2 including C_{max}, T_{max}, C_{min}, C_{12}, AUC_{12}, and CL/F.

P1038

P1038 is a Phase I/II, open-label, multi-center study to evaluate a treatment strategy of high-dose LPV/r in HIV-infected children and adolescents (ages 2-18 years) who have at least six months of prior PI experience and are failing their current antiretroviral therapy. The primary objectives were to evaluate the safety, tolerability, and pharmacokinetics of high-dose LPV/r (capsules or oral solution) in combination with saquinavir (SQV).

P1038 was designed to evaluate the feasibility of treating subjects with high-dose LPV/r who had failed PI-based antiretroviral regimens. P1038 was designed to offer therapeutic options to HIV-infected children and adolescents who had previously failed one or more antiretroviral (ARV) regimens, and to expand the clinical experience and attempt to optimize therapy with PIs for treatment-experienced HIV-infected children and adolescents. P1038 used high-dose LPV/r based on the rationale that resistance to many ARVs, such as PIs, is a relative phenomenon. Higher doses of LPV/r could have antiviral activity and suppress viral replication, even in quasispecies with reduced susceptibility to LPV/r or other PIs. Although the concern for toxicity as a potential limiting factor was considered during study design, the PACTG protocol team believed the risk of increased toxicity was justifiable in this treatment-experienced patient population due to their poor prognosis and limited therapeutic options.

The primary objectives of the study were to estimate pharmacokinetic parameters for LPV/r and SQV, and to examine the safety of LPV/r and SQV at the doses specified in the study protocol as described below.

Formulations of protease inhibitors used in this study were:

- LPV/r capsules (133.33mg/33.33 mg) or oral solution (80 mg/20 mg per ml).
- SQV hard gel capsules (200 mg) or tablets (500 mg).

Key inclusion criteria were:

- HIV-1 infected children, age $\geq$ 2 years to < 18 years.
- HIV-RNA >5,000 copies/mL.
- At least 6 months of prior continuous PI therapy.
- History of unchanged ARV therapy between the genotype or pre-screening phenotype resistance testing and the start of the P1038 study assigned regimen. Potential subjects should have remained on their pre-study failing ARV regimens until the genotype and

phenotype requirements were completed and they had begun to take their study assigned ARV regimen.

- Genotypic resistance testing within six months prior to the screening visit while on their failing regimen, that showed at least four of the protease mutations shown below:
    - The protease amino acid sequence contained a primary mutation at position 32, 47, 48, 50, 82, or 84; AND
    - At least three other mutations selected from positions 10, 20, 24, 30, 32, 33, 36, 46, 47, 48, 50, 53, 54, 71, 73, 77, 82, 84, or 90.

OR

- Phenotypic resistance testing with lopinavir fold change ≥ 5 compared to wild-type HIV within six months prior to the screening visit while on failing regimen.

Key exclusion criteria were:

- Serum glutamic pyruvic transaminase (SGPT, ALT) > 5x upper limit of normal (ULN) at screening.
- Hemoglobin < 8 g/dL at screening.
- Lipase ≥ Grade 2.
- Any toxicity ≥ Grade 3 at screening other than SGPT, hemoglobin, and lipase as noted above.
- Presence of an acute opportunistic or serious bacterial infection that required therapy at the time of enrollment.
- Chemotherapy for active malignancy.
- Phenotype resistance (ViroLogic PhenoSense® assay) of lopinavir at screening visit less than 5-fold change compared to wild-type HIV.
- 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 have compromised the outcome of this study.
- Pregnancy or breastfeeding.
- Documented history of cardiac conduction abnormalities, or significant cardiac dysfunction.
- History of syncope related to a cardiac conduction abnormality (i.e., history of > 3 episodes of unexplained syncope or any syncope secondary to cardiac abnormality).
- Family history of prolonged QTc-Interval Syndrome.
- Corrected QTc-Interval > 440 msec at screening.

Study design

Subjects were stratified by concurrent NNRTI treatment (Group 1 – no NNRTI; Group 2 – NNRTI). Subjects in Group 1 (n=21) received LPV/r 400/100 mg/m^2 PO BID in combination with 2 NRTIs. Subjects in Group 2 (n=5) received LPV/r 480/120 mg/m^2 PO BID in combination with 1 NNRTI and ≥ 1 NRTIs. The study schematic is outlined below:

STEP 1

Group 1 (No NNRTI): LPV/r 400/100 mg/m^2 PO Q12H + ≥ 2 NRTIs
Group 2 (+ NNRTI): LPV/r 480/120 mg/m^2 PO Q12H + ≥ 1 NRTIs + 1 NNRTI

After 2 weeks on LPV/r (Study Week 2), LPV levels are obtained for all subjects.

- Subjects with LPV Inhibitory Quotient (IQ)* < 15 and can tolerate saquinavir (SQV) hard gel caps can proceed to Step 2.
- All others remain on Step 1.

*The lopinavir inhibitory quotient (IQ; ratio of LPV concentration 12 hours post-dosing divided by the baseline HIV-1 isolate's fold change in phenotypic susceptibility x lopinavir IC_{50} of wild-type virus) was calculated using each subject's observed plasma LPV C_{12} measurement and the fold change in resistance for LPV (obtained from each subject's screening phenotype). Titrating LPV/r doses to achieve LPV IQ ≥ 15 was hypothesized as a potential therapeutic strategy to achieve antiviral activity in treatment-experienced pediatric patients.

STEP 2 (Study Week 4)
Group 1A (No NNRTI): add SQV 750 mg/m^2 PO Q12H
Group 2A (+ NNRTI): add SQV 750 mg/m^2 PO Q12H

SQV levels are obtained after 2 weeks of Step 2 treatment (Study Week 6).

- If SQV $C_{12\ hours}$ is ≥ 500 but ≤ 3000 ng/mL, subject will continue on Step 2.
- If SQV $C_{12\ hours}$ is >3,000 ng/mL and SQV AUC is greater than 100,000 ng*h/mL, then SQV will be decreased to 500 mg/m^2 PO Q12H.

STEP 3 (Study Week 8)
If SQV $C_{12\ hours}$ is < 500 ng/mL in the absence of SQV related toxicity, SQV will be increased to 1200 mg/m^2 PO Q12H. SQV levels are obtained after 2 weeks of Step 3 treatment (overall Study Week 10).

Primary endpoint was proportion of patients with Grade 3/4 adverse events and clinical laboratory abnormalities at 48 weeks.

Secondary endpoints included

- Proportion of patients with HIV-RNA < 400 copies/mL at 48 weeks.
- Proportion of PI-experienced patients achieving LPV IQ ≥ 15 while taking high dose LPV/r.

6 Review of Efficacy

Efficacy Summary

For efficacy analyses, FDA uses intent-to-treat (ITT) population. The analyses conducted were proportion of patients achieving HIV-RNA < 400 copies/mL at Week 24 (for P1030) and Week 48 (P1038) respectively. The applicant proposed labeling that included the proportion of patients

achieving HIV-RNA < 400 copies/mL at Week 24 in P1030. This analysis is included in other ARV labels for studies with 24 week results.

For the ITT analysis in P1030, an efficacy cohort of 31 patients was used. Of 10 infants between ≥14 days and <6 wks of age, 7 infants had HIV-RNA < 400 copies/mL at Week 24. Of 21 infants between 6 weeks and 6 months of age, 10 infants had HIV-RNA < 400 copies/mL at Week 24. Overall, the efficacy results seen in pediatric patients (≥14 days to < 6 months of age) were similar to the results in adults.

Of note, low virologic response rates were observed in P1038 (3 of 26 subjects had HIV-RNA < 400 copies/mL at Week 24 and Week 48, respectively). This could likely be due to prior PI exposure and accumulation of protease resistance mutations. Combination SQV and high dose LPV/r may not be efficacious for patients with genotypic or phenotypic resistance profiles similar to P1038 participants.

6.1 Indication

Lopinavir/ritonavir is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection. In the pediatric population, LPV/r is already approved for children over 6 months to 12 years of age. The Applicant is proposing to extend this indication to pediatric patients ≥ 14 days to 6 months and patients > 12 years to 18 years of age.

6.1.1 Methods

For efficacy analyses, FDA uses the intent-to-treat (ITT) population. The analyses conducted were the proportion of patients achieving HIV RNA < 400 copies/mL. Week 24 efficacy data for P1030 and Week 48 efficacy data for P1038 were reviewed in support of the proposed indication. This included review of the datasets, clinical study reports, and case report tabulations.

For P1030, the median change in HIV-RNA from baseline to Week 24 was determined. For P1038, the median change in HIV-RNA from baseline to Week 48 was determined. Also, measurements of CD4 cell counts were reviewed and median change from baseline was determined for subjects in P1030 and P1038 respectively. Patients who were withdrawn from study prior to Week 24 (P1030) or Week 48 (P1038) due to adverse events or HIV-related illness were considered virologic failures and were included in the calculations of median change in viral load and CD4 cell counts.

6.1.2 Demographics

P1030
The following table summarizes baseline demographic and disease characteristics for Subjects enrolled in P1030.

Table 3: Demographic and Baseline Disease Characteristics of Study Subjects (P1030)

Characteristic	Age ≥ 14 days to < 6 weeks (N = 10)	Age ≥ 6 weeks to < 6 months (N = 21)	Total (N = 31)
Gender			
Male	7 (70%)	7 (33%)	14 (45%)
Female	3 (30%)	14 (67%)	17 (55%)
Race/Ethnicity			
Black	7 (70%)	10 (48%)	17 (55%)
Hispanic	3 (30%)	9 (43%)	12 (39%)
Caucasian	0 (0%)	2 (10%)	2 (6%)
Age (weeks), median (range)	5.7 (3.6–6.0)	14.7 (6.9–25.7)	
Height (cm), median (range)	52.0 (48.3–59.0)	58.0 (52.0–66.0)	
Height for Age Z-score[a], median (range)	-1.5 (-2.9 to 0.9)	-0.7 (-4.7 to 1.2)	
Weight (kg), median (range)	4.0 (2.9–5.3)	5.2 (4.1–10.0)	
Weight for Age Z-score[a], median (range)	-1.3 (-2.0 to 0.6)	-0.8 (-3.9 to 3.3)	
Log_{10} HIV-RNA (copies/mL), median (range)	6.0 (4.7–7.2)	5.8 (3.7–6.9)	
CD4 count (cells/mm^3)[b], median (range)	2426 (1204–2542)	2230 (304–5556)	
CD4%, median (range)	41 (16–59)	32 (11–54)	
CD8 count (cells/mm^3)[b], median (range)	1089 (971–1328)	1203 (594–5719)	
CD8%, median (range)	21 (15–37)	24 (14–57)	
Treatment History			
Naïve	2 (20%)	3 (14%)	5 (16%)
Experienced (any ARV)	8 (80%)	18 (86%)	26 (84%)
Protease inhibitor	1 (10%)	2 (10%)	3 (10%)

[a]Z-score indicates number of standard deviations an observation is above or below the mean.

[b]Seven subjects in the younger cohort (≥ 14 days to < 6 weeks of age) and 15 subjects in the older cohort (≥ 6 weeks to < 6 months of age) had baseline CD4 and CD8 counts.

Treatment history

Of the 10 subjects ≥ 14 days to < 6 weeks of age, 8 subjects (80%) received ARV treatment prior to enrollment in P1030. Each of the 8 subjects received zidovudine (duration of treatment ranging from 17-41 days). In addition, one subject (370218) received nevirapine for 2 days, and one subject (8500077) received nelfinavir and lamivudine for 14 days.

Of the 21 subjects ≥ 6 weeks to < 6 months of age, 18 subjects (86%) received ARV treatment prior to enrollment in P1030. Each of the 18 subjects received zidovudine (duration of treatment ranging from 23 to 90 days). In addition, five subjects (400913, 450392, 450396, 509370 and 670448) received lamivudine (duration of treatment ranging from 8 to 90 days), 3 subjects (290267, 400913, 509907) received nevirapine (duration of treatment ranging from 2 to 7 days), and 2 subjects (450396, 670448) received nelfinavir for 30 and 90 days respectively.

Although additional details regarding the indications for ARV treatment in these 31 subjects were not provided in this submission, it is likely ARVs were used as prophylaxis while subjects underwent diagnostic evaluation of HIV status.

The concurrent ARVs used during P1030 reflected a variety of commonly used NRTI combinations: zidovudine and lamivudine (n = 16), stavudine and lamivudine (n = 12), zidovudine and didanosine (n = 1), and abacavir and stavudine (n = 2).

Table 4: Antiretroviral combinations used in P1030

Regimen	Frequency
3TC, ZDV	16
3TC, d4T	12
ABC, d4T	2
ddI, ZDV	1

ABC, abacavir; ddI, didanosine; d4T, stavudine; 3TC, lamivudine; ZDV, zidovudine

P1038

The following table summarizes baseline demographic and disease characteristics for Subjects enrolled in P1038.

Table 5: Demographic and Baseline Disease Characteristics of Study Subjects (P1038)

Characteristic	Group 1 – No NNRTI (N = 21)	Group 2 – NNRTI (N = 5)	Total (N = 26)
Gender			
Male	10 (48%)	3 (60%)	13 (50%)
Female	11 (52%)	2 (40%)	13 (50%)
Race/Ethnicity			
Black	11 (52%)	3 (60%)	14 (54%)
Hispanic	6 (29%)	1 (20%)	7 (27%)
Caucasian	3 (14%)	0 (0%)	3 (12%)
American Indian/Alaskan native	0 (0%)	1 (20%)	1 (4%)
More than one race	1 (5%)	0 (0%)	1 (4%)
Age (weeks), median (range)	15 (7–17)	15 (7–17)	15 (7–17)
≥ 2 years to < 12 years	4	1	5
≥ 12 years to < 19 years	17	4	21
Height (cm), median (range)	150.6 (116.0.3–170.8)	151.8 (124.7–200.0)	151.2 (116.0-200.0)
Weight (kg), median (range)	41.2 (23.1–67.9)	48.7 (25.0–69.8)	43.6 (23.1–69.8)
Body surface area (m^2), median (range)	1.4 (0.9–1.8)	1.5 (1.0–2.0)	1.4 (0.9–2.0)
Log_{10} HIV-RNA (copies/mL), median (range)	4.9 (3.5–6.0)	4.9 (4.3–5.3)	4.9 (3.5–6.0)
CD4 count (cells/mm^3), median (range)	205 (12–1416)	286 (31–508)	262 (31–508)
CD4%, median (range)	13 (1–24)	17 (4–20)	15 (1–24)
CD8 count (cells/mm^3), median (range)	1080 (121–4626)	723 (439–2118)	976 (121–4626)
CD8%, median (range)	57 (17–66)	47 (40–61)	57 (17–66)
Treatment History			
Prior NRTI	21 (100%)	5 (100%)	26 (100%)
Prior NNRTI	21 (100%)	3 (60%)	24 (92%)
Prior protease inhibitor (PI)	21 (100%)	5 (100%)	26 (100%)
Prior lopinavir/ritonavir	11 (52%)	1 (20%)	12 (46%)
Prior saquinavir	1 (5%)	1 (20%)	2 (8%)
Prior lopinavir/ritonavir and saquinavir	7 (33%)	1 (20%)	8 (31%)

Other protease inhibitor	2 (10%)	2 (40%)	4 (15%)
Baseline phenotypic resistance to LPV[a]			
Fold change in virus susceptibility to LPV relative to wild-type virus, median (range)	152.0 (8.5-261.6)	76.5 (5.2-238.0)	142.5 (5.2-261.6)

[a]Phenotypic resistance data were obtained for 16 subjects in Group 1, and 4 subjects in Group 2, respectively.
NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor

Treatment history

Analysis of treatment history was limited by unavailability of data regarding duration of exposure to antiretroviral agents. All 26 subjects enrolled in P1038 were both PI-experienced and NRTI-experienced prior to receiving the first dose of study medication. Also, 24 of 26 subjects (92%) were NNRTI-experienced prior to study enrollment. Only Subjects 400125 and 450084 were NNRTI-naïve; both subjects were assigned to Group 2 (concurrent NNRTI).

In Group 1 (n = 21), 11 subjects (52%) received previous treatment with LPV/r, 1 subject (5%) received previous treatment with SQV, and 7 subjects (33%) received previous treatment with both LPV/r and SQV. Two subjects (450367 and 470159) had not received previous treatment with LPV/r or SQV.

In Group 2 (n =5), 1 subject (20%) received previous treatment with LPV/r, 1 subject (20%) received previous treatment with SQV, and 1 subject (20%) received previous treatment with both LPV/r and SQV. Two subjects (400125 and 450084) had not received previous treatment with LPV/r or SQV.

A range of antiretroviral agents was given in combination with LPV/r beginning at Step 1 of the study. In Group 1, other antiretroviral agents included lamivudine (12 subjects), abacavir (15 subjects), stavudine (6 subjects), didanosine (13 subjects), zidovudine (7 subjects), emtricitabine, and/or enfuvirtide (5 subjects).

Table 6: Antiretroviral combinations used in P1038 – Group 1

Regimen	Frequency
3TC, ABC	1
3TC, ABC, d4T	1
3TC, ABC, ddI	1
3TC, ABC, ZDV	1
3TC, d4T	1
3TC, ddI, ZDV	1
3TC, ddI-EC, enfuvirtide	1
3TC, ABC, ZDV	2
3TC, ABC, ZDV, ddI-EC	2
3TC, ABC, ZDV, ddI-EC, enfuvirtide	1
ABC, d4T	1
ABC, d4T, ddI	1
ABC, ddI	1

ABC, ddI, enfuvirtide	1
ABC, ddI-EC	1
ABC, ddI-EC, FTC, enfuvirtide	1
ddI, enfuvirtide	1
d4T, ddI-EC	2

ABC, abacavir; ddI, didanosine; d4T, stavudine; FTC, emtricitabine; 3TC, lamivudine; ZDV, zidovudine

In Group 2, other antiretroviral agents included lamivudine (2 subjects), abacavir (2 subjects), zidovudine (2 subjects), didanosine (3 subjects), and efavirenz (5 subjects).

Table 7: Antiretroviral combinations used in P1038 – Group 2

Regimen	Frequency
3TC, ABC, EFV	1
3TC, ABC, ZDV, EFV	1
ddI-EC, ZDV, EFV	1
ddI-EC, EFV	2

ABC, abacavir; ddI, didanosine; d4T, stavudine; EFV, efavirenz; FTC, emtricitabine; 3TC, lamivudine; ZDV, zidovudine

6.1.3 Patient Disposition

P1030
The following table summarizes the disposition of all subjects in P1030. Most subjects (29 of 31, 94%) remained on study through Week 24.

Table 8: Disposition of Subjects in P1030

Disposition	Age ≥ 14 days to < 6 weeks	Age ≥ 6 weeks to < 6 months	Total
Total number enrolled	10	21	31
Completed through Week 24	10	19	29
Prematurely terminated	0	1[a]	1
Other reason for not completing study	0	1[b]	1
Number of subjects with evaluable PK data	9	18	27

[a]Subject 450392 was permanently off study treatment because of a clinical event (cytomegalovirus infection) at Week 7. Subject 450392 subsequently died at [redacted] due to respiratory acidosis, considered not related to study treatment.
[b]Subject 505934 discontinued study per guardian's request due to abnormal stools and vomiting.

Two subjects, both in the older cohort (age ≥ 6 weeks to < 6 months), were prematurely discontinued from P1030. Please refer to Section 7.3.3 for additional details.

P1038
Overall, 18 subjects prematurely discontinued from P1038 prior to Week 48 (virologic failure – 9, adverse events – 3, noncompliance – 4, protocol violation of using prohibited medications – 1, geographic displacement due to Hurricane Katrina – 1).

Three subjects discontinued from P1038 due to adverse events. Subject 290133 experienced recurrence of Grade 3 hypertriglyceridemia considered related to study treatment (LPV/r and SQV). Subject 450367 had allergic cutaneous reactions to LPV/r. Subject 660134 developed hypersensitivity to abacavir (not to LPV/r).

Table 9: Disposition of Subjects in P1038

Number of subjects	Group 1 (no NNRTI)	Group 2 (NNRTI)	Total
Total enrolled	21	5	26
Completed study			
Week 24	15	3	18
Week 48	5	3	8
Premature discontinuation prior to Week 48			
Virologic failure	9	0	9
Adverse events	3	0	3
Noncompliance	3	1	4
Protocol violation	1	0	1
Geographic displacement	1	0	1

Of 26 subjects, 18 subjects (69%) remained on study treatment by Week 24, and 8 subjects (31%) remained on study treatment by Week 48 (see Table). A total of 18 subjects (69%) went onto Step 2, while only 1 subject (4%) moved to Step 3.

Table 10: Distribution of subjects by treatment group and by week (P1038)

Week	Step 1 – Group 1	Step 1 – Group 2	Step 2 – Group 1A	Step 2 – Group 2A	Step 3 – Group 1B	Step 3 – Group 2B	Total
0	21	5	0	0	0	0	26
2	20	5	0	0	0	0	25
4	11	5	8	0	0	0	24
6	5	3	12	2	0	0	22
12	2	2	14	1	0	1	20
24	2	1	13	1	0	1	18
36	0	1	7	1	0	1	10
40	0	1	6	1	0	1	9
48	0	1	5	1	0	1	8

Step 1 – Group 1 - No NNRTI + Kaletra
Step 1 – Group 2 - On NNRTI + Kaletra
Step 2 – Group 1A - No NNRTI + Kaletra, Saquinavir added
Step 2 – Group 2A - On NNRTI + Kaletra, Saquinavir added
Step 3 – Group 1B - No NNRTI + Kaletra, Saquinavir increased
Step 3 – Group 2B - On NNRTI + Kaletra, Saquinavir increased

Reviewer Comment
In Group 1 (no NNRTI), combination SQV and LPV/r was associated with high rates of discontinuation due to virologic failure (9/21, 43%) and adverse events (3/21, 14%) in this

treatment-experienced patient population. In Group 2 (NNRTI), one subject discontinued study treatment due to noncompliance.

6.1.4 Analysis of Primary Endpoint(s)

P1030
24-week efficacy data from Study 1030 show LPV/r provides favorable virologic outcomes in infants from ≥ 14 days to < 6 months of age:

- In the ≥ 14 days to < 6 weeks cohort, 70% (7/10) of subjects achieved HIV-RNA < 400 copies/mL at Week 24.
- In the ≥ 6 weeks to < 6 months cohort, 48% (10/21) of subjects achieved HIV-RNA < 400 copies/mL at Week 24.
- In both age groups, HIV-RNA decreased by a median of at least 3 $\log_{10}$ copies/mL from baseline to Week 24.

Table 11: Summary of Week 24 efficacy results (P1030)

	Age ≥ 14 days to < 6 weeks (N = 10)	Age ≥ 6 weeks to < 6 months (N = 21)
HIV-RNA < 400 copies/mL	70% (7/10)	48% (10/21)
Median HIV-RNA change from baseline, log10 copies/mL	-3.61	-3.13

Reviewer Comment
Although the numbers for each subpopulation is small, the treatment response (HIV-RNA <400 copies/mL at Week 24) in pediatric patients ≥ 14 days to < 6 weeks was similar to treatment-naive adults. The treatment response (HIV-RNA <400 copies/mL at Week 24) in pediatric patients ≥ 6 weeks to < 6 months was similar to treatment-experienced adults.

P1038
P1038 was a treatment strategy based on the rationale that resistance to PIs could be overcome by high-dose LPV/r. Investigators hypothesized that high-dose LPV/r might inhibit a larger proportion of viral quasispecies and, for maximal antiviral activity, the highest tolerated doses should be used. This strategy targeted treatment-experienced subjects who had failed PI-based antiretroviral regimens.

However, a combination of treatment history and genotypic and/or phenotypic resistance likely contributed to low response rates observed. Of 26 subjects, 12 subjects (46%) received previous treatment with LPV/r, 2 subjects (8%) received previous treatment with SQV, and 8 subjects (31%) received previous treatment with both LPV/r and SQV. Four subjects (15%) had not received previous treatment with LPV/r or SQV. Additionally, most subjects had significant genotypic resistance to protease mutations and/or phenotypic resistance to LPV/r.

Overall, three subjects (12%) achieved HIV-RNA < 400 copies/mL at Week 24 and Week 48:

- One subject from Group 1 (290198)
- Two subjects from Group 2 (400125, 509229)

– Of note, all three subjects also had HIV-RNA < 400 copies/mL at Week 24.

No other subjects achieved HIV-RNA < 400 copies/mL at any other time-points during the study.

Only one subject (4%) achieved LPV IQ ≥ 15; this subject (290198, Group 2) received LPV/r 480/120 mg/m^2 BID and concomitant NNRTI. Of note, Subject 290198 achieved HIV-RNA < 400 copies/mL at Week 24 and Week 48, respectively.

As shown in the following table, some viral load decreases were observed at Week 24 (median HIV-RNA decrease: Group 1 [n=15] – 56 cells/mm^3, Group 2 [n=3] – 283 cells/mm^3) and Week 48 (median CD4 cell count increase: Group 1 [n=5] – 75 cells/mm^3, Group 2 [n=3] – 334 cells/mm^3) respectively.

Table 12: Summary of HIV-RNA changes from baseline to Week 24 and Week 48, respectively

	Group 1 – No NNRTI (N = 21)		Group 2 –NNRTI (N = 5)	
	Week 24	Week 48	Week 24	Week 48
Median HIV-RNA change from baseline, log10 copies/mL	-0.42 (n=15)	-0.41 (n=5)	-3.63 (n=3)	-3.82 (n=3)

Reviewer Comment
For subjects remaining on-treatment at Weeks 24 and 48 respectively, some antiviral activity was observed. The overall low virologic response rates (defined as HIV-RNA < 400 copies/mL at Week 24 and Week 48) observed in P1038 are likely due to prior treatment with PIs and accumulation of protease resistance mutations prior to study entry. Combination SQV and LPV/r may not be efficacious for patients with treatment history, genotypic and/or phenotypic resistance profiles similar to P1038 participants.

Although there are limited data evaluating the efficacy of combination SQV and LPV/r, the virologic response rates in P1038 are lower than other published reports (1 pediatric study and 2 adult studies). Of note, patients in 2 of these studies (pediatric – 1, adult – 1) were PI-naïve or had no history of PI failure or intolerance.

Review of the published literature (PubMed, Medline) only identified one pediatric study evaluating combination SQV and LPV/r [Pediatr Infect Dis J. 2005; 24:874-9]. The study objective was to assess pharmacokinetics and 24-week efficacy and safety of combination SQV and LPV/r in children. Twenty reverse transcription inhibitor-pretreated (PI-naïve) children at 2 centers in Thailand were treated with SQV and LPV/r in an open-label, single arm, 6-month prospective study. The dosage was 50 mg/kg twice daily (BID) for saquinavir and 230/57.5 mg/m BID for LPV/r. Ten children also received lamivudine. Samples were collected for a 12-hour pharmacokinetic profile in all children. Plasma concentrations of saquinavir, lopinavir and ritonavir were determined using a validated high performance liquid chromatography technique. At baseline, median age was 8.5 years (range 6.9-9.9 years), median HIV-RNA 4.9 log10

copies/mL (range 4.5-5.4 log10 copies/mL), median CD4 count 129 cells/μL (range 35-243 cells/μL), and median CD4% 6.5% (range 3.3-8.0%). Median area under the concentration curve at 0-12 hours and Cmin were 39.4 mg/L.h and 1.4 mg/L for SQV and 118 mg/L.hr and 5.9 mg/L for LPV. By ITT analysis, proportion of children with HIV-RNA < 400 copies/mL and < 50 copies/mL at Week 24 were 80% (16 of 20) and 60% (12 of 20), respectively. Median CD4% and CD4 increases were 6% and 216 cells/μL, respectively. Median changes in triglycerides and total cholesterol were 56 and 36.5 mg/dL, respectively (P = 0.01). Lopinavir Cmin <1 and SQV Cmin <0.28 mg/L correlated with HIV RNA >400 copies/mL, and LPV Cmax >15 mg/L correlated with rises in cholesterol (P < 0.05). The study authors concluded plasma drug concentrations of SQV, LPV, and RTV were at the higher limits of expected ranges for adult treatment at approved dosages (1000/100 mg bid for SQV/r, 400/100 mg bid for LPV/r).

In a small, open-label, randomized clinical trial, 60% (31 of 52) of adult subjects achieved HIV-RNA < 50 copies/mL at Week 48 by ITT analysis [HIV Med. 2007; 8:529-35]. Response rates were higher (40 of 52 subjects, 77%) with the secondary endpoint HIV-RNA < 400 copies/mL at Week 48. Laboratory abnormalities in the SQV/LPV/r group included elevated transaminases, hypercholesterolemia, and hypertriglyceridemia. Four patients (8%) had Grade 3/4 ALT elevations, 9 patients (17%) had cholesterol > 300 mg/dL, and 18 patients (34%) had triglycerides > 500 mg/dL. Key eligibility criteria included PI naïve or no history of PI failure or intolerance.

In an observational cohort study, 61% (78 of 128) of adult subjects achieved HIV-RNA < 400 copies/mL at Week 48 by ITT analysis [J Antimicrob Chemother. 2006; 58:1024-30]. Due to the observational design of this study, there is potential for selection bias due to lack of randomization. Twenty two subjects (17%) were PI-naïve. Median number of previous PIs was 2 (range 0-6). Mean number of PI mutations at study baseline was 2 (range 0-5). In univariate analysis, significant predictors of virological response included higher CD4 count (P<0.001), lower viral load (P=0.002), less PI-experience (P=0.006) at baseline, and fewer PI-resistance mutations (P=0.043) at baseline. In multivariate analysis, only higher CD4 count at baseline (P=0.009) and fewer number of antiretroviral drugs previously taken (P=0.003) were independent predictors for response. The authors suggest combination SQV and LPV/r may not be suitable for patients with low baseline CD4 cell counts, extensive antiretroviral therapy experience, or extensive PI-resistance mutations.

In conclusion, the low virologic response rates observed in P1038 are likely due to prior treatment with PIs and accumulation of protease resistance mutations. Combination SQV and LPV/r may not be efficacious for patients with genotypic or phenotypic resistance profiles similar to P1038 participants.

6.1.5 Analysis of Secondary Endpoints(s)

P1030
Assessing secondary endpoints such as changes in CD4, CD4%, CD8, and CD8% from baseline was complicated by absence of complete data for all time-points. In the younger cohort (≥ 14

days to < 6 weeks), four of 10 subjects had all of the required CD4 and CD8 evaluations through Week 24. Of the remaining six subjects, two missed one evaluation (at Week 24) and one had only baseline evaluations. Two other subjects had only CD4% and CD8% due to the lack of sufficient blood volume to obtain CD4 and CD8 counts at study visits. One subject also had only CD4% and CD8% for the same reason but did not have any results at Week 24. No imputation of missing values was performed. For subjects with available data, median CD4 cell counts increased by 629 cells/mm^3 (95% CI: -171, 1264) at Week 24, and median CD4% decreased by 1% (95% CI: -10, 18) at Week 24. Median changes in CD8 cell counts and CD8% were negative at Week 24 relative to baseline.

In the older cohort (≥ 6 weeks to < 6 months), eleven of 21 subjects had CD4 and CD8 evaluations at the required time-points prior to Week 24 or permanent treatment discontinuation, whichever occurred first. Nineteen subjects had CD4% and CD8% evaluations at the required time-points. Subject 505934 was prematurely discontinued and did not have any post-baseline CD4 and CD8 evaluations performed prior to being lost to follow-up at Week 4. A second subject (509370) missed Week 12 evaluation for CD4 and CD8 values. For subjects with available data, median CD4 cell counts increased by 739 cells/mm^3 (95% CI: -373, 2358) at Week 24. For subjects with available data, median CD4% increased by 4% (95% CI: -1, 9) at Week 24. Median changes in CD8 cell counts and CD8% were negative at Week 24 relative to baseline.

Table 13: Summary of CD4, CD4%, CD8, CD8% changes from baseline to Week 24 (As-Treated population)

	Age ≥ 14 days to < 6 weeks (N = 10)	Age ≥ 6 weeks to < 6 months (N = 21)
Median CD4 cell count change from baseline, cells/mm^3	+629 (n=4)	+739 (n=11)
Median CD4% change from baseline, cells/mm^3	-1.0 (n=6)	+4.0 (n=19)
Median CD8 cell count change from baseline, cells/mm^3	-35 (n=4)	-229 (n=11)
Median CD8% change from baseline, cells/mm^3	-7.0 (n=6)	-4.0 (n=19)

Reviewer Comment
As noted in the 2008 DHHS HIV-1 Pediatric Treatment Guidelines, clinicians interpreting CD4 count for children must consider age as a variable. CD4 count and CD4% values in healthy infants who are not infected with HIV are considerably higher than those observed in uninfected adults, and slowly decline to adult values by age 5 years. In children under age 5 years, the absolute CD4 count tends to vary more with age within an individual child than does CD4 percentage. Therefore, in HIV-infected children under age 5 years, CD4 percentage is preferred for monitoring immune status, whereas absolute CD4 count can be used in older children. In HIV-infected children, as in infected adults, the CD4 count and CD4% declines as HIV infection progresses, and patients with lower CD4 values have a poorer prognosis than patients with higher values

Among patients with evaluable data, CD4 count increases suggest improved immunologic function through 24 weeks of study treatment in P1030.

P1038
The following table summarizes CD4, CD4%, CD8, CD8% changes from baseline to Week 24 and Week 48, respectively.

Table 14: Summary of CD4, CD4%, CD8, CD8% changes from baseline to Week 24 and Week 48, respectively

	Group 1 – No NNRTI (N = 21)		Group 2 –NNRTI (N = 5)	
	Week 24	Week 48	Week 24	Week 48
Median CD4 cell count change from baseline, cells/mm^3	+56 (n=15)	+75 (n=5)	+283 (n=3)	+334 (n=3)
Median CD4% change from baseline, cells/mm^3	+2 (n=15)	+4 (n=5)	+6 (n=3)	+7 (n=3)
Median CD8 cell count change from baseline, cells/mm^3	-2 (n=15)	-113 (n=5)	+210 (n=3)	+72 (n=3)
Median CD8% change from baseline, cells/mm^3	-3 (n=15)	-4 (n=5)	-5 (n=3)	-9 (n=3)

Eighteen subjects (Group 1 – fifteen subjects, Group 2 – three subjects) remained on treatment at Week 24. In Group 1, median CD4 cell counts increased by 56 cells/mm^3 (95% CI: 7, 151) at Week 24, and median CD4% increased by 2% (95% CI: -1, 4) at Week 24. In Group 2, median CD4 cell counts increased by 283 cells/mm^3 (95% CI: -24, 367) at Week 24, and median CD4% increased by 6% (95% CI: 5, 9) at Week 24.

Eight subjects (Group 1 – five subjects, Group 2 – three subjects) remained on treatment at Week 48. In Group 1, median CD4 cell counts increased by 75 cells/mm^3 (95% CI: 11, 173) at Week 48, and median CD4% increased by 4% (95% CI: 1, 7) at Week 48. In Group 2, median CD4 cell counts increased by 334 cells/mm^3 (95% CI: 93, 342) at Week 48, and median CD4% increased by 7% (95% CI: 6, 9) at Week 48.

Lopinavir Inhibitory Quotient (LPV IQ)
Another secondary endpoint was proportion of PI-experienced patients achieving LPV IQ $\geq$ 15 while taking high dose LPV/r. Only one subject (4%) achieved LPV IQ $\geq$ 15; this subject (290198, Group 2) received LPV/r 480/120 mg/m^2 BID and concomitant NNRTI. Of note, Subject 290198 achieved HIV-RNA < 400 copies/mL at Week 24 and Week 48, respectively.

Reviewer Comment
Increases in CD4 counts and CD4% at Week 24 (18 subjects) and Week 48 (8 subjects) suggest some degree of immunologic benefit, even though most subjects (15 subjects at Week 24, and 5 subjects at Week 48) had ongoing viremia despite antiretroviral therapy. Addition of another active agent (NNRTI) in Group 2 improved immunologic responses compared to Group 1 (no NNRTI). However, the significance of these observations is limited by small patient numbers.

Also, based on P1038 study results, titrating LPV/r doses to achieve LPV IQ ≥ 15 does not appear to be an effective strategy with substantial antiviral activity in treatment-experienced pediatric patients.

6.1.6 Other Endpoints

Please refer to Section 6.1.4 and 6.1.5

6.1.7 Subpopulations

Efficacy analyses in P1030 were primarily conducted on two subpopulations stratified by age. Subjects ages ≥ 14 days to < 6 weeks comprised the younger cohort. Subjects ages ≥ 6 weeks to < 6 months comprised the older cohort. There were 10 subjects enrolled in the younger cohort and 21 subjects enrolled in the older cohort. The purpose of the age group stratification was to ensure at least 6 evaluable subjects were enrolled in the younger age group and to assist in assessing the dose requirements, safety, and antiviral activity of LPV/r in very young infants.

Efficacy analyses in P1038 were primarily conducted on two subpopulations stratified by presence or absence of concurrent NNRTI use.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

In summary, LPV/r 300/75 mg/m^2 BID was safe and well tolerated in pediatric patients ≥ 14 days to < 6 months. Lopinavir/ritonavir in combination with two NRTIs provided favorable virologic and immunologic response in pediatric patients ≥ 14 days to < 6 months, with a tolerability profile similar to that observed in older pediatric and adult HIV-1 infected patients. Based on Study P1030 results, a dose of LPV/r 300/75 mg/m^2 is recommended in children < 6 months old. The applicant initially proposed the [redacted]. However, the average dose received by subjects in P1030 was approximately 15 mg/kg. Considering the low C_{min} in these pediatric patients, FDA clinical pharmacology review team recommended a LPV/r dose of approximately 16/4 mg/kg and the applicant agreed with this recommendation.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Not applicable.

6.1.10 Additional Efficacy Issues/Analyses

Not applicable.

7 Review of Safety

Summary of Safety Results and Conclusions

The safety analysis in PACTG 1030 provides 24 week safety data for patients ages ≥ 14 days to 6 months who received LPV/r oral solution formulation. The safety analysis in PACTG 1038 provides 48 week safety data for patients ages 7 to 17 years who received LPV/r oral solution or LPV/r capsule formulation.

As discussed in Section 5.3, P1030 and P1038 had different study designs. These differences included patient population (especially age at enrollment), ARV treatment history, LPV/r dosing regimen, and concurrent ARVs used during the studies. These factors, combined with different length of follow-up data provided in this supplement (P1030 – 24 weeks, P1038 – 48 weeks) complicated attempts for pooling data between studies.

Overall the adverse event profile in pediatric patients was similar to adults. No new or unexpected toxicities were definitively identified as related to LPV/r.

One death (due to disseminated CMV infection) reported in P1030 was not considered treatment related by investigators. No deaths were reported in P1038. Five subjects (P1030 – 1 subject, P1038 – 4 subjects) discontinued due to toxicity. Discontinuations related to toxicity were due to gastrointestinal disorders (P1030 – 1 subject), hypertriglyceridemia (P1038 – 1 subject), allergic cutaneous reactions to LPV/r (P1038 – 1 subject), hypersensitivity to abacavir (P1038 – 1 subject), and disseminated CMV infection with sepsis (P1038 – 1 subject).

Serious adverse events (SAEs) were reported in 8 subjects in P1030 and 6 subjects in P1038, respectively. In P1030, SAEs included abnormal stools and vomiting (both occurring in the same subject). The other SAEs documented by investigators were laboratory abnormalities, such as decreased absolute neutrophil count, neutropenia, decreased hemoglobin, anemia, hyperkalemia, hyponatremia, increased ALT, and abnormal amylase. In P1038, SAEs included hypertriglyceridemia (1), hyperlipidemia (1), toxic epidermal necrolysis (1), rash (1), allergic rash (1), bradycardia (1), gastric discomfort (1), abnormal ECG (1), and hyponatremia (1). No SAE considered possibly or probably related to LPV/r occurred in more than one subject.

In both P1030 and P1038, the most common Grade 2–4 adverse events (≥5%, regardless of causality) reported in patients receiving LPV/r were gastrointestinal disorders, such as diarrhea, nausea, and vomiting. In P1038, other AEs of moderate to severe intensity occurring in 2 or more subjects were rash (N=3) and electrocardiogram QT prolonged (N=2). It is possible higher LPV/r exposures could have contributed to these ECG abnormalities. Both subjects with QT prolongation had additional predisposing conditions such as electrolyte abnormalities, concomitant medications, or pre-existing cardiac abnormalities. Due to the presence of these confounders, it is difficult to establish a causal relationship to LPV/r exposure.

In P1030, the most common laboratory abnormalities occurring in 2 or more subjects were neutrophil count decreased (N=3), anemia (N=2), high potassium (N=2), and low sodium (N=2).

In P1038, the most common laboratory abnormalities of moderate to severe intensity occurring in 2 or more subjects were blood triglycerides abnormal (N=3).

7.1 Methods

7.1.1 Clinical Studies Used to Evaluate Safety

The safety results from P1030 and P1038 were reviewed, which included review of the datasets, clinical study reports, the case report tabulations, and selected case report forms. For P1030, the applicant proposed to use the 24-week safety and efficacy results in the label to expand the pediatric population to include patients ages ≥ 14 days to 6 months. For P1038, the applicant proposed to use the 48-week safety results to expand the pediatric population to include patients ages >12 years to 18 years. Both P1030 and P1038 used DAIDS Table for Grading Severity of Pediatric Adverse Experiences (April 1994). However, both P1030 and P1038 also had a supplemental grading scale for cholesterol and triglycerides (refer to Section 7.4.2).

7.1.2 Adequacy of Data

The data from P1030 were overall adequate to evaluate safety, tolerability, pharmacokinetics, and efficacy of LPV/r for pediatric patients ages ≥ 14 days to 6 months. The data from P1038 were overall adequate to evaluate safety, tolerability, and pharmacokinetics of LPV/r for pediatric patients ages 7 years to 17 years.

7.1.3 Pooling Data Across Studies to Estimate and Compare Incidence

No data pooling for P1030 and P1038 were performed due to differences in study design, patient population (especially age at enrollment), antiretroviral treatment history, LPV/r dosing regimen, and concurrent antiretroviral drugs used during the studies.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

In P1030 and P1038, LPV/r exposure at appropriate doses and duration in the target population was overall adequate.

P1030
All subjects initiated LPV/r at 300/75 mg/m^2 twice daily. Protocol-directed dose increase to 450/112.5 mg/m^2 twice daily occurred in subjects whose adherence to therapy was assessed as

adequate and had LPV trough concentration (Ctrough) < 1 µg/mL from the pharmacokinetic study performed at Week 2. One subject (507737) in the age ≥14 days to < 6 weeks cohort had a protocol-directed dose increase to 450/112.5 mg/m^2 twice daily, but the dose was subsequently lowered because of a pharmacokinetic parameter that was above protocol threshold. One subject (509907) in the age ≥ 6 weeks to < 6 months cohort had a protocol directed dose increase to 450/112.5 mg/m^2 twice daily that was maintained for the duration of the study for that subject. All other subjects were maintained on LPV/r 300/75 mg/m^2 twice daily adjusted for changes in body surface area during the study.

The following table summarizes the extent of LPV/r exposure. Of 10 subjects ≥ 14 days to < 6 weeks, all 10 subjects (100%) received LPV/r for > 24 weeks, and 9 subjects (90%) received LPV/r for > 48 weeks. Of 21 subjects ≥6 weeks to < 6 months, 18 subjects (86%) received LPV/r for > 24 weeks and 17 subjects (81%) received LPV/r for > 48 weeks.

Table 15: LPV/r exposure by weeks of therapy (P1030)

LPV/r exposure (weeks)	Target LPV/r dose: 300/75 mg/m^2 BID	
	Age ≥ 14 days to < 6 weeks (n=10)	Age ≥ 6 weeks to < 6 months (n=21)
0-4	0	2
5-8	0	1
9-12	0	0
13-24	0	0
25-48	1	1
49-72	3	0
73-96	2	1
> 96	4	16
Total	10	21

P1038

Subjects in Group 1 (n=21) received LPV/r 400/100 mg/m^2 PO BID in combination with 2 NRTIs. Subjects in Group 2 (n=5) received LPV/r 480/120 mg/m^2 PO BID in combination with 1 NNRTI and ≥1 NRTIs. All 26 subjects also received saquinavir (SQV). The following table summarizes the extent of LPV/r exposure. Overall, 18 of 26 subjects (69%) – 15 subjects in Group 1 and 3 subjects in Group 2 – received LPV/r for > 24 weeks. However, only 8 subjects (31%) received LPV/r for > 48 weeks.

Table 16: LPV/r exposure by weeks of therapy (P1038)

LPV/r exposure (weeks)	Group 1 (no NNRTI) Target LPV/r dose: 400/100 mg/m^2 BID			Group 2 (+ NNRTI) Target LPV/r dose: 480/120 mg/m^2 BID		
	≥ 2 to < 12 yrs	≥ 12 to < 19 yrs	Total	≥ 2 to < 12 yrs	≥ 12 to < 19 yrs	Total
0-4	1	3	4	0	0	0
5-8	0	1	1	1	0	1
9-12	0	1	1	0	0	0
13-24	0	0	0	0	1	1

25-48	3	11	14	0	1	1
49-72	0	1	1	0	2	2
Total	4	17	21	1	4	5

7.2.2 Explorations for Dose Response

The size of the dosing cohorts in P1030 and P1038 was too small to make any conclusions about dose-response of adverse events.

7.2.3 Special Animal and/or In Vitro Testing

Not applicable.

7.2.4 Routine Clinical Testing

The extent and frequency of routine clinical testing was appropriate for both P1030 and P1038.

7.2.5 Metabolic, Clearance, and Interaction Workup

There has been adequate study of metabolism, clearance, and drug-drug interactions for LPV/r.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Adverse events observed with PIs include new onset diabetes, hyperglycemia, hepatotoxicity, rash, lipodystrophy, hypertriglyceridemia, hypercholesterolemia, hemolytic anemia, increased bleeding episodes in patients with hemophilia, and fat redistribution. There was adequate evaluation for potential adverse events in both P1030 and P1038.

7.3 Major Safety Results

7.3.1 Deaths

P1030
There were no deaths in P1030 considered possibly or probably related to LPV/r. There was one death (Subject 450392; age at enrollment, 6 months) due to respiratory acidosis secondary to disseminated cytomegalovirus (CMV) infection. Of note, this subject had congenital CMV as a pre-existing, baseline condition.

P1038
No deaths were reported in P1038 through Week 48.

7.3.2 Nonfatal Serious Adverse Events

Overall, no new safety signals were definitively identified as related to LPV/r.

P1030
Through Week 24 of Study P1030, a total of 12 SAEs occurred in 8 subjects that were considered probably or possibly related to study treatment by investigators. The majority of SAEs were laboratory abnormalities, such as decreased absolute neutrophil count, neutropenia, decreased hemoglobin, anemia, hyperkalemia, hyponatremia, increased ALT, and abnormal amylase. Many of these SAEs were also considered possibly related to concomitant antiretroviral medications, such as zidovudine (used by 16 subjects; 4 in the age ≥ 14 days to < 6 weeks cohort, 12 in the age ≥ 6 weeks to < 6 months cohort).

SAEs that were clinical symptoms included abnormal stools and vomiting – both occurring in the same subject (505934). The causality of these events were considered by investigators as "unable to judge."

Table 17: Treatment-Emergent Serious Adverse Events considered related or possibly related to treatment (P1030, total = 31 subjects) – Week 24

Total # of subjects with ≥ 1 SAE, n (%)	8 (25.8)
Abnormal stools	1 (3.2)
Vomiting	1 (3.2)
Anemia	2 (6.4)
Hemoglobin decreased	1 (3.2)
ALT increased	1 (3.2)
Amylase increased	1 (3.2)
Potassium increased	1 (3.2)
Neutropenia	1 (3.2)
Absolute neutrophil count decreased	1 (3.2)
Sodium decreased	1 (3.2)

Reviewer Comment
This reviewer believes it is possible the gastrointestinal adverse events experienced by Subject 505934 could have been related to LPV/r.

P1038
Through Week 48 of Study P1038, a total of nine SAEs considered possibly, probably, or definitely related to LPV/r were reported in 6 subjects. The SAEs included hypertriglyceridemia (1), hyperlipidemia (1), toxic epidermal necrolysis (1), rash (1), allergic rash (1), bradycardia (1), gastric discomfort (1), abnormal ECG (1), and hyponatremia (1). No SAE considered possibly or probably related to LPV/r occurred in more than one subject.

Some of these SAEs were also considered possibly related to concomitant antiretroviral medications (saquinavir – elevated cholesterol and triglycerides, abnormal ECG, hyponatremia; abacavir – cutaneous reactions).

Table 18: Treatment-Emergent Serious Adverse Events considered related or possibly related to LPV/r (P1038, total = 26 subjects)

Total # of subjects with ≥ 1 SAE, n (%)	9 (34.6)
Cholesterol increased	1 (3.8)
Triglycerides increased	1 (3.8)
Toxic epidermal necrolysis*	1 (3.8)
Rash*	1 (3.8)
Allergic rash*	1 (3.8)
Bradycardia	1 (3.8)
Gastric discomfort	1 (3.8)
Abnormal ECG	1 (3.8)
Sodium decreased	1 (3.8)

*All rash SAEs occurred in the same subject (450367).

The majority of SAEs reported in P1038 are similar to those in other adult and pediatric studies with LPV/r. Cardiac conduction abnormalities could represent a potential new safety signal with higher exposures of LPV/r. However, due to the presence of confounders (such as electrolyte abnormalities, concomitant medications, pre-existing cardiac abnormalities) it is difficult to establish a causal relationship to LPV/r exposure.

Cutaneous reactions
All rash SAEs occurred in the same subject (450367). Subject 450367 had Grade 2 toxic epidermal necrolysis at Week 2 considered possibly related to LPV/r and probably related to abacavir. Grade 3 rash at Week 2 was considered probably related to LPV/r. Grade 3 allergic rash at Week 6 was considered definitely related to LPV/r – this led to permanent discontinuation from all study drugs at Week 6. The narrative is provided below:

At enrollment Subject 450367 was a 10-year-old White non-Hispanic female. During the baseline visit, the investigator noted pre-existing esophageal reflux, HIV encephalopathy, and failure to thrive. Concomitant medications were metoclopramide and ranitidine via gastric tube. On Day 1, the subject was dosed with LPV/r liquid 352/88 mg BID, zidovudine liquid 150 mg BID, lamivudine liquid 100 mg BID, and abacavir liquid 200 mg BID. On Day 12, the subject was diagnosed with Grade 2 toxic epidermal necrolysis and Grade 3 rash. All medications were temporarily interrupted for 1 day except abacavir, which was permanently discontinued. Didanosine 90 mg BID was substituted for abacavir. On Day 30, Grade 3 allergic rash was diagnosed and all study medications were permanently discontinued. Grade 3 allergic rash was considered definitely related to LPV/r.

Hyperlipidemia
Grade 3 (sufficiently severe to require evaluation and treatment, including at least temporary suspension of study drug) elevations in fasting triglycerides and fasting cholesterol occurred in

the same subject (290133) at Weeks 3 and 12 respectively. Subject 290133 was permanently discontinued from study treatment (high dose LPV/r, 666/166 mg BID) at Week 13 due to hypertriglyceridemia. The narrative is provided below:

At enrollment, Subject 290133 was a 17-year-old Black non-Hispanic male. During the baseline visit, the investigator noted no current ongoing conditions. Baseline fasting lipids included triglycerides of 289 mg/dL and total cholesterol of 114 mg/dL. Concomitant medication at baseline was ferrous sulfate. On Day 1, the subject was dosed with lopinavir/ritonavir 666/166 mg BID, didanosine 400 mg daily, and stavudine 40 mg BID. Lipid results on Days 17 and 21 revealed triglycerides of 1237 and 3108 mg/dL and total cholesterol of 194 and 390 mg/dL, respectively. Study medications were interrupted per protocol. Repeat lipids on Day 29 revealed triglycerides of 502 mg/dL and total cholesterol of 183 mg/dL. Study medications were restarted. Saquinavir 1400 mg BID was added on Day 35. Repeat lipid results on Day 92 revealed triglycerides of 3951 mg/dL and total cholesterol of 555 mg/dL. This subject discontinued high-dose lopinavir on Day 92, but remained on lower-dose non-study lopinavir/ritonavir (standard dose of 400/100 mg BID) and was monitored through Week 48. Lipids on Day 309 were triglycerides of 1193 mg/dL and total cholesterol of 200 mg/dL.

Reviewer Comment
The lipid abnormalities observed in Subject 291033 are not surprising due to the high LPV/r dose, as well as concomitant SQV.

Cardiac Conduction Abnormalities
Two subjects reported cardiac conduction abnormalities as SAEs. Subject 500658 was clinically asymptomatic when sinus bradycardia was noted on ECG at Week 2. Study medications (LPV/r liquid 496/124 mg BID, didanosine 150 mg BID, stavudine liquid 30 mg BID, abacavir 300 mg BID) were continued without any modifications. The narrative is provided below:

Subject 500658 had Grade 3 bradycardia and abnormal rhythm at Week 2. The investigator was unable to judge the relationship of LPV/r to the event. At enrollment, Subject 500658 was a 13-year-old Black non-Hispanic female. During the baseline visit, the investigator noted a rectovaginal fistula. Concomitant medication was ranitidine via gastric tube. On Day 1, the subject was dosed with LPV/r liquid 496/124 mg BID, didanosine 150 mg BID, stavudine liquid 30 mg BID, and abacavir 300 mg BID. On Day 15, Grade 3 arrhythmia/sinus bradycardia was noted on ECG. Vital signs at that visit revealed heart rate 90 beats per minute and blood pressure 116/72 mm/Hg. Study medications were continued without change.

Subject 370233 was clinically asymptomatic when the abnormal ECG (QT prolongation) was noted on Week 12. The narrative is provided below (potential confounders in bold):

Subject 370233 had Grade 3 abnormal ECG at Week 12 considered possibly related to lopinavir/ritonavir and saquinavir. At enrollment, Subject 370233 was a 17-year-old Black, non-Hispanic male. During the baseline visit, the investigator noted pre-existing asthma, attention deficit disorder, HIV wasting, and a **'cardiac abnormality'** with no further explanation. Concomitant medications continued throughout the study and included nebulized albuterol, beclomethasone dipropionate, oral fluconazole, **azithromycin**, trimethoprim-sulfamethoxazole, ondansetron, ranitidine, prednisolone acetate eye drops, and cromolyn sodium eye drops. An additional concomitant medication, subcutaneous human growth hormone, was noted at baseline but was discontinued on Day 31. QTc interval at baseline was normal at 402 msec. On Day 1, the subject was dosed with lopinavir/ritonavir 533/133 mg BID, stavudine 30 mg BID, lamivudine 150 mg BID and abacavir 300 mg BID. Saquinavir 1000 mg BID was added on Day 29.

On Day 15, an ECG revealed a prolonged QTc interval of 502 msec. No new adverse events, diagnoses, signs or symptoms were reported and study medications were continued without modification. On Days 28 and 66, an ECG revealed normal QTc intervals of 441 and 416 msec, respectively. On Day 86, an ECG revealed a prolonged QTc of 522 msec. **Serum potassium was below normal at 2.7 mEq/L and serum magnesium was below normal at 1.4 mg/dL**. The investigator reported an acute coincidental event of oral candidiasis. All study medications were interrupted for 1 day. On Day 87, a repeat ECG demonstrated the QTc interval had returned to the normal range of 405 msec. Serum potassium had increased to the normal range at 3.9 mEq/L. Serum magnesium was not repeated. Study medication was resumed on Day 87. A follow up ECG on Day 197 showed a normal QTc interval of 431 msec.

Reviewer Comment
Bradyarrhythmias are described in the KALETRA label in the section for adverse reactions reported during postmarketing use of LPV/r. Because postmarketing data are reported voluntarily from a population of unknown size, it is not possible to reliably estimate their frequency or establish a causal relationship to LPV/r exposure. For the subject in P1038, this event was transient and occurred without any clinical symptoms.

QT prolongation is currently not listed in the KALETRA label. However, Subject 370233 had numerous concomitant medications, electrolyte abnormalities (hypokalemia and hypomagnesemia), as well as an unspecified baseline "cardiac abnormality" as potential confounders.

Hyponatremia
Subject 650955 did not report any signs or symptoms associated with hyponatremia. The narrative is provided below:

Subject 650955 had Grade 3 hyponatremia (124-129 mEq/L) at Week 6 considered possibly related to LPV/r and saquinavir. At enrollment Subject 650955 was a 14-year-old Black, non-Hispanic male. During the baseline visit, the investigator noted pre-existing cerebral palsy. On Day 1, the subject was dosed with LPV/r 533/133 mg BID, didanosine 250 mg daily, Trizivir 1 tablet BID, and enfuvirtide 65 mg BID. On Day 38, the subject was diagnosed with right upper lobe pneumonia and was treated with oral and intravenous antibiotics. Sodium was reported on Day 43 to be 129 mEq/L. Sodium on Day 58 was reported to be 138 mEq/L and thereafter remained in the normal range through Day 240. Between Days 43 and 53, lopinavir/ritonavir was temporarily interrupted. Pneumonia was reported resolved as of Day 65.

Reviewer Comment
Hyponatremia could have been possibly related to LPV/r, SQV, antibiotics, intravascular volume depletion, dehydration, or other causes.

7.3.3 Dropouts and/or Discontinuations

P1030
Most subjects (29 of 31, 94%) remained on study through Week 24 (Table 8). Two subjects, both in the older cohort (age ≥ 6 weeks to < 6 months), were prematurely discontinued from P1030.

Subject 450392 was discontinued from the study at Week 7 due to disseminated cytomegalovirus infection with severe respiratory involvement.

Subject 505934 (age at enrollment, 2 months) was discontinued from the study at Week 4 per guardian's request. The mother had previously discontinued study drug due to Grade 1 vomiting and soft stools at Week 2. The relationship of these adverse events to study treatment was not determined by the investigators.

Reviewer Comment
It is possible the gastrointestinal adverse events experienced by Subject 505934 could have been related to LPV/r.

P1038
As shown in Table 9, 18 subjects prematurely discontinued from P1038 prior to Week 48 (virologic failure – 9, adverse events – 3, noncompliance – 4, protocol violation of using prohibited medications – 1, geographic displacement due to Hurricane Katrina – 1).

Three subjects discontinued from P1038 due to adverse events. Subject 290133 experienced recurrence of Grade 3 hypertriglyceridemia considered related to study treatment (LPV/r and SQV). Subject 450367 had allergic cutaneous reactions to LPV/r. Subject 660134 developed hypersensitivity to abacavir (not to LPV/r).

An additional subject (690327) developed disseminated CMV infection with hepatomegaly, jaundice, cholangitis, pancreatitis, and sepsis at Week 3. These events resulted in discontinuation of all study medications. The subject was classified by investigators as discontinuation due to requirement for prohibited medications. However, Subject 690327 could also be classified as discontinuation due to adverse event. Using this conservative approach, four subjects discontinued from P1038 due to adverse events. However, these events were considered not related to study drugs.

Reviewer Comment
In Group 1 (no NNRTI), combination SQV and LPV/r was associated with high rates of discontinuation. Primary reasons for discontinuation in this treatment-experienced patient population were virologic failure (9/21, 43%) and adverse events (4/21, 19%). In Group 2 (NNRTI), one subject discontinued study treatment due to noncompliance.

7.3.4 Significant Adverse Events

HIV-related opportunistic infections and AIDS-defining illnesses
The occurrence of treatment-emergent HIV-related opportunistic infections was evaluated for P1030 and P1038.

P1030
Subject 509835 (age at enrollment, 5 months) had CMV with presumed pneumonia (diagnosed at Week 16). This subject did not report CMV as a documented baseline infection.

Oral candidiasis was reported in six subjects during the study period. No specific pattern of events was apparent.

Reviewer Comment
None of these events were considered related to study drug. Although Subject 509835 did not report CMV among baseline diagnoses, it is possible the patient might not have been evaluated for CMV. For Subject 509835, it was postulated whether CMV may have developed as a result of immune reconstitution inflammatory syndrome (IRIS). The following table shows the changes in CD4, CD4%, and HIV-RNA from baseline to Week 24.

Table 19: CD4, CD4% and HIV-RNA for Subject 509835

	CD4 (cells/mm^3)	CD4%	HIV-RNA* (copies/mL)
Baseline	1852	18	1,350,000
Week 12	1920	18	533
Week 24	2821	18	562

*HIV-RNA was 3480 (Week 2) → 1500 (Week 4) → 831 (Week 8) → 533 (Week 12) → 459 (Week 16) → 45,700 (Week 20) → 562 (Week 24).

Most published reports on IRIS are small, retrospective, and describe predominantly adults. Currently there is no validated, consensus definition for IRIS. A working definition derived from several adult literature sources[1-14] describes IRIS as a clinical or sub-clinical infection, or an immune response to antigens of ubiquitous or abundant exposure (such as CMV, cryptococcus). It is postulated that IRIS represents the recovery of CD4 function that is pathogen-specific or directed toward antigens of ubiquitous or abundant exposure. Other typical characteristics of IRIS cases include CD4 increases (usually >2-4 fold) and/or HIV-RNA decreases (usually >1-2 log_{10} copies/mL). Most cases of IRIS occur during the first 8-12 weeks of HAART. However, the time interval between the initiation of HAART and the evolution of IRIS ranges from <1 week to several months. In the adult literature, patients with CD4 <100 cells/mm^3 appear to be at greater risk for the development of IRIS. There is limited pediatric literature to definitively identify a CD4 range predictive of increased risk for the development of IRIS.

In Subject 509835, it seems less likely that IRIS contributed to development of CMV. The subject's young age probably suggests recent exposure or vertical transmission of CMV. IRIS is usually observed in patients who have had sub-clinical infection over some period of time. Although this subject experienced substantial decrease in HIV-RNA from treatment initiation to onset of the clinical adverse event, the CD4 profile (high baseline CD4, < 2 fold change from baseline to time of the event) do not appear consistent with published literature describing cases of IRIS.

P1038
Overall, the occurrence and distribution of HIV-related diseases reflected the treatment-experienced patient population in P1038.

Subject 690327 (age at enrollment, 15 years) developed disseminated CMV infection with hepatomegaly, jaundice, cholangitis, pancreatitis, and sepsis at Week 3. These events resulted in discontinuation of all study medications. There was no documentation of CMV status on baseline evaluation.

Other opportunistic infections reported during the study period were oral candidiasis (five subjects), orolabial/mucocutaneous herpes simplex virus infections (three subjects), herpes zoster (one subject), and pneumonia (three subjects).

Two subjects reported concurrent infections that were potentially bacterial in etiology. Subject 290115 reported concurrent otitis media, sinusitis, and right orbital cellulitis at Week 24. Subject 505949 reported concurrent sinusitis and pneumonia at Week 7.

Reviewer Comment
None of these events were considered related to study drug. Microbiologic data were not provided for cases of otitis media, sinusitis, or pneumonia.

Hepatic events
P1030
Although the study population was small, hepatic events were relatively infrequent overall. No subjects in the younger cohort (age ≥ 14 days to < 6 weeks) reported any hepatic adverse events or laboratory toxicities.

In the older cohort (age ≥ 6 weeks to < 6 months), four subjects reported Grade 2 hepatomegaly at baseline. For all four subjects, hepatomegaly remained at Grade 2 throughout the study period. Hepatomegaly is a common presenting physical finding among HIV-infected children. This event was not considered related to LPV/r.

One of these subjects (509655) reported transient Grade 2 total bilirubin (2-2.9 x ULN) elevation at Week 8; the bilirubin elevation resolved without any intervention. None of these hepatic events resulted in study drug interruption or discontinuation.

One additional subject (650988) in the older cohort reported clinically asymptomatic Grade 3 ALT (10-15 x ULN) and Grade 2 AST (5-9.9 x ULN) elevations at Week 24. Study treatment was withheld for 3 days until the ALT/AST levels declined to Grade 1. Study medication was resumed without recurrence of ALT elevation. Please refer to Section 7.4.2 for additional details.

P1038
There were no reports of Grade 3 or higher ALT/AST values during study. One subject (690327 – age at enrollment, 15 years) developed disseminated cytomegalovirus infection, hepatomegaly, jaundice, cholangitis, pancreatitis, and sepsis. The hepatic events (hepatomegaly, jaundice) were considered not related to study drug.

Reviewer Comment
Overall, there were no new safety signals regarding hepatotoxicity with LPV/r in P1030 or P1038.

Gastrointestinal disorders
P1030
All gastrointestinal AEs were Grade 1-2. There were no Grade 3-4 gastrointestinal AEs through 24 weeks.

P1038
Most gastrointestinal AEs were Grade 1-2. Grade 3 gastrointestinal AEs, regardless of causality, included anorexia (1 subject), gastric discomfort (1 subject), nausea (1 subject), nausea and vomiting (2 subjects). No subjects had Grade 3/4 vomiting considered related to study drug treatment. One subject (505949) had Grade 3 gastric discomfort and nausea considered related to study drug treatment; these symptoms occurred at Week 4 and resolved after protocol-directed LPV/r dose reduction.

Reviewer Comment
Overall, there were no new safety signals regarding gastrointestinal disorders with LPV/r in P1030 or P1038.

Pancreatitis
P1030
Through Week 24, there were no reports of pancreatitis.

P1038
Over 48 weeks, one subject (690327) reported pancreatitis; of note, this case was not associated with hypertriglyceridemia. Pancreatitis was considered not related to study drug, but was considered due to CMV sepsis.

Reviewer Comment
There were no new safety signals regarding pancreatitis with LPV/r in P1030 or P1038.

Metabolic abnormalities (fat redistribution, hyperglycemia, hyperlipidemia)
P1030
Through Week 24, there were no reports of fat redistribution. Additionally, no subjects were reported with Grade 2 or higher cholesterol or triglycerides during the study period.

Through Week 24, three subjects each had a single Grade 2 (160-249 mg/dL) elevation in non-fasting glucose. No subjects were diagnosed with diabetes mellitus.

P1038
Over 48 weeks, no subjects reported abnormal fat redistribution during study follow up. There were no reports of Grade 3 or higher glucose values. One subject (290133) had a Grade 3 fasting triglyceride and Grade 3 fasting cholesterol.

Reviewer Comment
Overall, there were no new safety signals regarding fat redistribution, hyperglycemia, or hyperlipidemia with LPV/r in P1030 or P1038.

Cutaneous events
P1030
Cutaneous events were infrequently reported; one subject (450283) reported Grade 2 maculopapular rash on his face, trunk, and arms at Week 8. This event was considered related to bactrim. Antiretroviral medications (zidovudine, lamivudine, LPV/r) and bactrim were continued. The rash worsened to Grade 3 intensity at Week 12 (including blisters and ulcers). Bactrim was discontinued and the cutaneous event was assessed as resolved at Week 16. All antiretroviral medications (zidovudine, lamivudine, LPV/r) were continued without any interruption.

P1038
Three subjects reported rash during the study. Two subjects (450084, 400337) had Grade 2 rash considered possibly related to LPV/r. Study treatment was continued for both subjects.

As discussed in the Section 7.3.2 under SAEs, Subject 450367 had Grade 2 rash at Week 2 considered possibly related to LPV/r. LPV/r was continued. The subject also developed Grade 3 allergic rash at Week 6 considered definitely related to LPV/r. This led to permanent discontinuation from all study drugs at Week 6.

Reviewer Comment
Overall, there were no new safety signals regarding cutaneous events with LPV/r in P1030 or P1038.

Cardiac conduction abnormalities
P1030
At Week 24, no cardiac conduction abnormalities were reported in P1030.

P1038
At Week 48, transient cardiac conduction abnormalities were reported in 6 subjects (QT prolongation – 2, sinus bradycardia – 3, first degree AV block – 1). All subjects remained clinically asymptomatic. Narratives are provided below (potential confounders in bold):

1) Subject 370233 (QTc Prolongation; please refer to Section 7.3.2 for narrative).

2) Subject 401051 (QTc Prolongation)
At enrollment, Subject 401051 was a 7-year-old Black, non-Hispanic male. During the baseline visit, the investigator noted pre-existing diagnoses of left ventricular hypertrophy (reported resolved 2 weeks later) and HIV encephalopathy. Concomitant medication continued throughout the study was oral clonidine. QTc interval at baseline was normal at 435 msec. On Day 1, the subject was dosed with lopinavir/ritonavir liquid 448/112 mg BID, zidovudine 200 mg BID, didanosine 250 mg QD and efavirenz 350 mg QD. Saquinavir 600 mg BID was added on Day 41 and saquinavir dose was increased to 1200 mg BID on Day 65. On Day 84, an ECG revealed a prolonged QTc interval of 478 msec. No new adverse events, diagnoses, signs or symptoms were reported. Serum electrolytes

were reported as within the normal range. All study medications were interrupted for 1 day. On Day 85, a repeat ECG demonstrated the QTc interval had returned to normal at 453 msec. Study medications were resumed on Day 85. A follow up ECG done on Days 91 and 167 showed normal QTc intervals of 454 and 456 msec, respectively.

3) Subject 111328 (Sinus Bradycardia)
At enrollment, Subject 111328 was a 13-year-old male described as "more than one race." During the baseline visit, the investigator noted no significant pre-existing conditions. Concomitant medications continued throughout the study were **oral azithromycin** and trimethoprim-sulfamethoxazole. Baseline heart rate by ECG was normal at 70 beats per minute. On Day 1, the subject was dosed with lopinavir/ritonavir 533/133 mg BID, didanosine 250 mg QD, and abacavir 300 mg BID. Saquinavir 1000 mg BID was added on Day 28. On Day 15, an ECG revealed sinus bradycardia with a heart rate of 51 beats per minute. The subject was described as 'sleeping' during the ECG. No new adverse events, diagnoses, signs or symptoms were reported. Serum electrolytes were reported within the normal range. Study medications were continued without modification. A repeat ECG done on Day 91 revealed a normal heart rate of 65 beats per minute.

4) Subject 370234 (Sinus Bradycardia)
At enrollment, Subject 370234 was a 12-year-old Black, non-Hispanic male. During the baseline visit, the investigator reported pre-existing conditions of HIV encephalopathy and spastic cerebral palsy. Concomitant medications continued throughout the study were oral baclofen and acyclovir and nebulized albuterol. Baseline heart rate by ECG was normal at 71 beats per minute. On Day 1, the subject was dosed with lopinavir/ritonavir 400/100 mg BID, stavudine 30 mg BID, and lamivudine 150 mg QD. Saquinavir 800 mg BID was added on Day 35. On Days 147 and 202, ECG revealed sinus bradycardia with heart rates of 59 and 56 beats per minute, respectively. The investigator noted "normal sinus rhythm" and "borderline biventricular hypertrophy" for the Day 147 tracing. In addition, the investigator reported a new diagnosis of iron deficiency anemia (hemoglobin 12.1 mg/dL) on Day 147. Study medications were continued without modification. The subject was discontinued from the study on Day 195 due to meeting a protocol-defined end point (viral load did not decrease more than 0.75 $\log_{10}$ copies from baseline and CD4 did not increase more than 5% from baseline). Repeat ECG was not reported.

5) Subject 500658 (Sinus Bradycardia; please refer to Section 7.3.2 for narrative).

6) Subject 400337 (First Degree AV block)
At enrollment, Subject 400337 was a 15-year-old White, non-Hispanic female. During the baseline visit, the investigator reported no ongoing pre-existing conditions. Concomitant medication at baseline was topical hydrocortisone discontinued on Day 51. A baseline ECG revealed a normal PR interval of 130 msec. On Day 1, the subject was dosed with lopinavir/ritonavir 666/166 mg BID and trizivir BID. Saquinavir 1200 mg BID was added on Day 36. On Day 92, an ECG revealed a prolonged PR interval of 230 msec. No new adverse events, diagnoses, signs or symptoms were reported. Serum electrolytes were reported within the normal range. Study medications were continued without modification. On Day 148, a repeat ECG demonstrated a normal PR interval of 188 msec.

Reviewer Comment
The majority of AEs reported in P1038 are similar to those in other adult and pediatric studies with LPV/r. Cardiac conduction abnormalities could represent a potential new safety signal with higher LPV/r exposures. However, due to the presence of confounders (such as electrolyte abnormalities, concomitant medications, pre-existing cardiac abnormalities) it is difficult to definitively establish a causal relationship to LPV/r exposure.

7.3.5 Submission Specific Primary Safety Concerns

As discussed above, submission specific primary safety concerns with LPV/r include gastrointestinal disorders, hepatotoxicity, pancreatitis, diabetes mellitus/hyperglycemia, fat

redistribution, and lipid abnormalities. Overall, no new safety signals were identified with regards to these toxicities.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Clinical toxicities previously reported with LPV/r include gastrointestinal disorders, hepatotoxicity, pancreatitis, diabetes mellitus/hyperglycemia, fat redistribution, and lipid abnormalities.

P1030
Through Week 24 of P1030, the most common adverse events (AE) reported among patients receiving LPV/r were gastrointestinal disorders, such as diarrhea, nausea, and vomiting. Overall, no new adverse events were identified in pediatric patients (age ≥ 14 days to < 6 months) receiving LPV/r.

Most of the adverse events in the following table were Grade 2.

Table 20: Treatment-Emergent Adverse Reactions of at Least Moderate Intensity (Grades 2-4) at Week 24 Regardless of Causality (P1030, total = 31 subjects)

Body System/Adverse Event	Number of patients with AE, n (%)
Digestive System	6 (19.3)
Diarrhea/loose stools	4 (12.9)
Nausea and/or vomiting	3 (9.7)
Abdominal distention	1 (3.2)
Appetite loss/decrease/anorexia	1 (3.2)
Respiratory System	4 (12.9)
Breath sounds abnormal	2 (6.4)
Difficulty breathing/SOB	2 (6.4)
Respiratory system dysfunction	1 (3.2)
Hematology and Lymphatic System	2 (6.4)
Lymphadenopathy	2 (6.4)
Skin and Appendages	3 (9.7)
Macules/papules/rash	2 (6.4)
Blister/ulcer	1 (3.2)
Erythema/redness/inflammation	1 (3.2)
Patch/plaque	1 (3.2)

Special Senses	5 (16.1)
Otitis media	5 (16.1)
Conjunctivitis	1 (3.2)
Neurological System	2 (6.4)
Seizure	1 (3.2)*
Weakness (generalized)	1 (3.2)
Body as a Whole	8 (25.8)
Ache/pain/discomfort	1 (3.2)
Cachexia/wasting/weight loss	1 (3.2)
Fever	6 (19.3)
Other	2 (6.4)
Cytomegalovirus infection	1 (3.2)
Sepsis	2 (6.4)
Pneumonia (presumed due to CMV)	1 (3.2)

*associated with drug withdrawal from heroin

Overall, the majority of AEs reported were considered unrelated to LPV/r and of mild intensity. The most commonly reported events regardless of causality were those related to infections (such as otitis media) or gastrointestinal events (such as vomiting, diarrhea). Many of these events are ones that would be frequently encountered in this age group, regardless of study participation.

P1038

Through Week 48 of P1038, the most common adverse events (AE) reported among patients receiving LPV/r were gastrointestinal disorders, such as diarrhea, nausea, and vomiting.

Most of the adverse events in the following table were Grade 2.

Table 22: Treatment-Emergent Adverse Reactions of at Least Moderate Intensity (Grades 2-4) Regardless of Causality (P1038, total = 26 subjects)

Body System/Adverse Event	Number of patients with AE, n (%)
Digestive System	6 (23.1)
Diarrhea/loose stools	2 (7.7)
Nausea and vomiting	3 (11.5)
Nausea	1 (3.8)
Gastric discomfort	1 (3.8)
Constipation	1 (3.8)
Appetite loss/decrease/anorexia	2 (7.7)

Hepatic System	1 (3.8)
Jaundice	1 (3.8)*
Hepatomegaly	1 (3.8)*
Respiratory System	4 (15.4)
Breath sounds abnormal	1 (3.8)
Congestion	1 (3.8)
Cough	2 (7.7)
Difficulty breathing/SOB	1 (3.8)
Respiratory system dysfunction	1 (3.8)
Hematology and Lymphatic System	2 (7.7)
Anemia	1 (3.8)
Bleeding/bruising/petechiae	1 (3.8)
Lymphadenopathy	1 (3.8)
Skin and Appendages	6 (23.1)
Macules/papules/rash	2 (7.7)
Allergic rash	1 (3.8)
Blister/ulcer/lesions	3 (11.5)
Itchy/pruritus	1 (3.8)
Patch/plaque	1 (3.8)
Special Senses	5 (19.2)
Otitis media	3 (11.5)
Conjunctivitis	1 (3.8)
Orbital cellulitis	1 (3.8)
Sinusitis	2 (7.7)
Cardiac System	5 (19.2)
Bradycardia	2 (7.7)
QT prolongation	2 (7.7)
1st degree AV block	1 (3.8)
Body as a Whole	6 (23.1)
Ache/pain/discomfort	5 (19.2)
Asthenia/fatigue/malaise	1 (3.8)
Cachexia/wasting/weight loss	1 (3.8)
Headache	1 (3.8)
Fever	2 (7.7)
Other	4 (15.4)
Cytomegalovirus infection	1 (3.8)*

Cholangitis	1 (3.8)*
Pancreatitis	1 (3.8)*
Sepsis	1 (3.8)*
Pneumonia	3 (11.5)

*Subject 690327 (age at enrollment, 15 years) developed disseminated cytomegalovirus infection, hepatomegaly, jaundice, cholangitis, pancreatitis, and sepsis.

Overall, the majority of AEs reported were considered unrelated to LPV/r. The most commonly reported AEs regardless of causality were those related to infections (such as otitis media) or gastrointestinal events (such as vomiting, diarrhea). Many of these AEs are ones that would be frequently encountered in this age group, regardless of study participation.

Nine subjects (34.6%) had AEs considered related or possibly related to study drug. These AEs were rash (3 subjects), sinus bradycardia (2 subjects), QT prolongation (2 subjects), elevated triglycerides (1 subject), and nausea (1 subject).

7.4.2 Laboratory Findings

P1030
Overall, no new laboratory abnormalities were identified in pediatric patients (age ≥ 14 days to < 6 months) receiving LPV/r.

In the younger cohort (age ≥ 14 days to < 6 weeks), 3 subjects had Grade 3 absolute neutrophil count (ANC) decreases (500-899 cells/mm^3) considered possibly related to study treatment. For Subject 370218, this laboratory abnormality resulted in a switch from zidovudine to stavudine. For Subjects 507737 and 690913, these laboratory abnormalities resulted in temporary discontinuation of stavudine and lamivudine until the toxicities resolved. There were no Grade 4 laboratory abnormalities observed in the younger cohort.

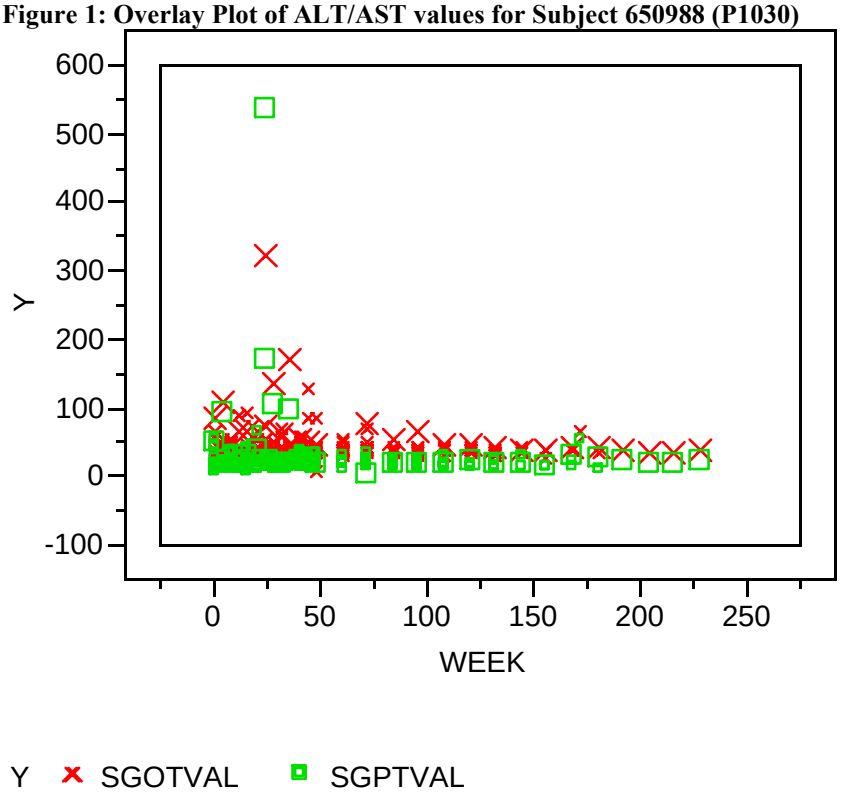
In the older cohort (age ≥ 6 weeks to < 6 months), Grade 3 laboratory abnormalities considered possibly related to study treatment included hyperkalemia (1 subject), hypernatremia (1 subject), hyponatremia (1 subject), and elevated ALT (1 subject). In these cases, study treatments were temporarily discontinued until the laboratory abnormalities resolved.

One subject had Grade 3 amylase – onset at Week 4 (57 U/L) and remained elevated (51 to 65 U/L) through Week 24. During the study period, the subject reported no new clinical adverse events, diagnoses, signs or symptoms. Also, lipase remained normal throughout the study period. Study medications were not interrupted in this subject.

There was one case of asymptomatic Grade 3 ALT in P1030 and the narrative is provided below. Subject 650988 (age at enrollment: 4 months; study site: [redacted] had Grade 3 ALT at Week 24 considered by the investigator as possibly related to LPV/r and/or lamivudine. At enrollment, this subject was a 131-day-old black non-Hispanic female. There was no travel history. The subject was not on any concomitant medications and none were added through

Week 24. Baseline ALT was 51 U/L (upper limit of normal at study site, 52 U/L) and AST was 81 U/L (upper limit of normal at study site, 60 U/L). On Day 1, the subject received LPV/r liquid 208/52 mg BID, zidovudine liquid 154 mg BID, and lamivudine liquid 44 mg BID. Study medication dose was weight-adjusted, as appropriate, during follow-up study visits. From Day 34 through Day 114, ALT ranged from 30 to 91 U/L and AST ranged from 60 to 103 U/L. On Day 143 (at Week 20 visit), ALT was 37 U/L and AST was 63 U/L. On Day 167 (at Week 24 visit), ALT was 537 U/L (Grade 3, 10-15 x ULN) and AST was 320 U/L (Grade 2, 5-9.9 x ULN). No new adverse events, diagnoses, clinical signs or symptoms were reported. On Day 167 all study drugs were interrupted. On Day 170, ALT was 170 U/L and AST was 71 U/L; study drugs were resumed. On Day 192, ALT was 103 U/L and AST was 133 U/L; study medications were continued. On Day 225, ALT was 19 U/L and AST was 56 U/L. Of note, Subject 650988 has follow-up data to Week 240 (ALT 23 U/L, AST 33 U/L). The following figure illustrates the temporal trends in ALT/AST values.

Figure 1: Overlay Plot of ALT/AST values for Subject 650988 (P1030)



Reviewer Comment
It is difficult to determine the potential contribution of LPV/r to these LFT elevations. These clinically asymptomatic laboratory abnormalities resolved without having to make any long interruptions in treatment or dose changes. Emails from site investigator and study nurse to the PACTG protocol chair mention the possibility that the baby's father (primary caregiver, since baby's mother had dementia) might have given double the LPV/r dose. However, these emails also state that the subject's father did not admit to any extra LPV/r doses.

Grade 3-4 laboratory abnormalities regardless of causality are shown in the following table. There were no Grade 4 laboratory abnormalities considered possibly related to study treatment.

Table 22: Treatment-Emergent, Grade 3-4 Laboratory Abnormalities regardless of causality (n=31) – Week 24

Laboratory abnormality	Number of subjects	Number of occurrences
Absolute neutrophil count (ANC) decrease		
Grade 3 (500-899 cells/mm^3)	3	6
Hemoglobin		
Grade 3 (<7.0 g/dL)	2	3
Platelets		
Grade 4 (<25,000 cells/mm^3)	1	1
High Potassium		
Grade 3 (6.5-7.0 mEq/L)	2	3
High Sodium		
Grade 3 (150-155 mEq/L)	1	2
Low Sodium		
Grade 3 (124-129 mEq/L)	2	2
Creatinine		
Grade 3 (1.2-1.5 mg/dL)	1	1
ALT		
Grade 3 (10-15 x ULN)	1	1
Amylase[a]		
Grade 3 (2-3 x ULN)	1	1
Low glucose		
Grade 4 (<30 mg/dL)	1	1

[a]Lipase remained normal throughout the study period. Subject was clinically asymptomatic throughout the study period.

Through Week 24, a small proportion of treatment-emergent laboratory abnormalities were considered related to study treatment.

Table 23: Treatment-Emergent, Grade 3-4 Laboratory Abnormalities considered related or possibly related to treatment (n=31) – Week 24

Laboratory abnormality	Number of subjects	Number of occurrences
Absolute neutrophil count (ANC) decrease		
Grade 3 (500-899 cells/mm^3)	3	4
High Potassium		
Grade 3 (6.5-7.0 mEq/L)	1	2
High Sodium		
Grade 3 (150-155 mEq/L)	1	2
Low Sodium		
Grade 3 (124-129 mEq/L)	1	1
ALT		
Grade 3 (10-15 x ULN)	1	1

Overall, these laboratory abnormalities resolved after temporary discontinuation of study treatments.

Other laboratory abnormalities of interest (class specific)
As a class effect, LPV/r and other protease inhibitors can cause abnormalities in liver function tests, lipids, and glucose (Tables 24, 25, 27, 29, 30).

Liver function test abnormalities
As discussed previously, one subject developed Grade 3 ALT through Week 24.

Table 24: ALT* (U/L) at baseline and Week 24

	Age ≥ 14 days to < 6 weeks (N = 10)	Age ≥ 6 weeks to < 6 months (N = 21)	Total (N = 31)
Week 0	N = 10	N = 21	N = 31
Median (range)	22 (8-84)	26 (10-207)	24 (8-207)
Mean (SD)	26 (21.8)	41 (43.2)	36 (37.9)
Week 24	N = 10	N = 19	N = 29
Median (range)	19 (13-43)	22 (14-537)	22 (13-537)
Mean (SD)	21 (8.9)	52 (117.7)	41 (95.7)

*Normal ALT range: 0-54 U/L (Reference: The Harriet Lane Handbook, 17th Edition, 2005)

No subjects reported Grade 3/4 AST through Week 24.

Table 25: AST* (U/L) at baseline and Week 24

	Age ≥ 14 days to < 6 weeks (N = 10)	Age ≥ 6 weeks to < 6 months (N = 21)	Total (N = 31)
Week 0	N = 10	N = 21	N = 31
Median (range)	31 (15-69)	45 (26-272)	40 (15-272)
Mean (SD)	36 (15.0)	58 (53.2)	51 (45.5)
Week 24	N = 8	N = 18	N = 26
Median (range)	33 (24-46)	39 (26-320)	36 (24-320)
Mean (SD)	34 (6.2)	56 (66.7)	49 (56.1)

*Normal AST range: 20-65 U/L (Reference: The Harriet Lane Handbook, 17th Edition, 2005)

Cholesterol abnormalities

According to study protocol, non-fasting total cholesterol values were obtained at defined study time-points. If non-fasting total cholesterol ≥ 500 mg/dL, then fasting total cholesterol was obtained and all subsequent total cholesterol levels were obtained in the fasting state for the subject and used for grading.

Through Week 24, no Grade 3/4 elevations in total cholesterol were reported in P1030. The following table summarizes the supplemental grading scale used for cholesterol and triglycerides in P1030.

Table 26: Supplemental grading scale for cholesterol and triglycerides*

	Cholesterol	Triglycerides
Grade 0	0-170 mg/dL	0-135 mg/dL
Grade 1	171-499 mg/dL	136-749 mg/dL
Grade 2	500-749 mg/dL	750-1199 mg/dL
Grade 3	≥750 mg/dL	≥1200 mg/dL

*P1030 and P1038

In P1030, total cholesterol was the only laboratory value with statistically significant median increases (82 mg/dL) from baseline to Week 24 (Table 27). The maximum cholesterol values reported were Grade 1 according to the protocol toxicity grading scale.

Table 27: Total cholesterol* (mg/dL) at baseline and Week 24

	Age ≥ 14 days to < 6 weeks (N = 10)	Age ≥ 6 weeks to < 6 months (N = 21)	Total (N = 31)
Week 0	N = 9	N = 20	N = 29
Median (range)	91 (51-143)	96 (73-268)	95 (51-268)
Mean (SD)	100 (27.6)	117 (47.7)	112 (42.8)
Week 24	N = 10	N = 18	N = 28
Median (range)	186 (89-230)	177 (84-263)	177 (84-263)
Mean (SD)	178 (46.7)	177 (53.1)	177 (50.0)

*Normal fasting total cholesterol range: <170 mg/dL (Reference: The Harriet Lane Handbook, 17th Edition, 2005)

Reviewer Comment
Several studies have demonstrated that the atherosderotic process begins in childhood and is affected by high blood cholesterol levels (National Cholesterol Education Program (NCEP): highlights of the report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents. Pediatrics 1992; 89:495-501). However, there are limited data concerning long-term safety and efficacy of drug therapy in childhood to reduce coronary heart disease (CHD) morbidity and mortality in adulthood. The NCEP panel recommends considering drug therapy in children aged 10 years and older if, after an adequate trial of diet therapy (6 months to 1 year):

1) LDL cholesterol remains ≥190 mg/dL; ***or***
2) LDL cholesterol remains ≥160 mg/dL ***and***
    a. There is a positive family history of premature (before 55 years of age) cardiovascular disease (CVD) *or*
    b. Two or more other CVD risk factors are present in the child or adolescent, (e.g., low HDL cholesterol (<35 mg/dL), cigarette smoking, high blood pressure, obesity, or diabetes) after vigorous attempts have been made to control these risk factors.

Table 28: NCEP classification of total and low-density lipoprotein (LDL) cholesterol levels in children and adolescents from families with hypercholesterolemia or premature CVD

Category	Total cholesterol (mg/dL)	LDL cholesterol (mg/dL)
Acceptable	170	110
Bordeline	170-199	110-129
High	≥200	≥130

Although no subjects initiated lipid lowering agents during the study period in P1030, these changes in cholesterol may have implications for long term therapy, especially among children and adolescents with high-risk lipid disorders, such as familial hypercholesterolemia, diabetes, or a family history of cardiovascular disease. Also, there is accumulating evidence that HIV-1 infection itself may be a risk factor for cardiovascular disease.

Triglyceride abnormalities
According to study protocol, non-fasting triglyceride values were obtained at defined study time-points. If non-fasting triglyceride ≥ 750 mg/dL, then fasting triglyceride was obtained and all subsequent triglyceride levels were obtained in the fasting state for the subject and used for grading.

Through Week 24, there were no Grade 3/4 elevations in triglycerides in P1030. The maximum triglyceride values reported were Grade 1 according to the protocol toxicity grading scale.

Table 29: Triglyceride* (mg/dL) at baseline and Week 24

	Age ≥ 14 days to < 6 weeks (N = 10)	Age ≥ 6 weeks to < 6 months (N = 21)	Total (N = 31)
Week 0	N = 8	N = 20	N = 28
Median (range)	88 (58-221)	169 (39-646)	138 (39-646)

Mean (SD)	116 (57.6)	206 (153.7)	180 (138.5)
Week 24	N = 10	N = 18	N = 28
Median (range)	157 (34-308)	166 (57-329)	163 (34-329)
Mean (SD)	159 (76.7)	170 (77.2)	166 (75.8)

*Normal fasting triglyceride range: males, 30-86 mg/dL; females, 32-99 mg/dL (Reference: The Harriet Lane Handbook, 17th Edition, 2005)

No subjects initiated triglyceride lowering agents during the study period in P1030.

Glucose abnormalities
According to study protocol, non-fasting, random blood glucose values and urine dipstick were obtained at defined study time-points. If either random blood glucose ≥ 250 mg/dL or urine dipstick was positive for glucose, then fasting blood glucose was obtained and all subsequent glucose levels were obtained in the fasting state for the subject and used for grading.

Through Week 24, no Grade 3/4 elevations in glucose were reported in P1030.

Table 30: Glucose* (mg/dL) at baseline and Week 24

	Age ≥ 14 days to < 6 weeks (N = 10)	Age ≥ 6 weeks to < 6 months (N = 21)	Total (N = 31)
Week 0	N = 10	N = 21	N = 31
Median (range)	83 (67-100)	79 (50-99)	80 (50-100)
Mean (SD)	83 (9.5)	78 (11.4)	80 (10.9)
Week 24	N = 10	N = 19	N = 29
Median (range)	77 (69-98)	82 (51-113)	78 (51-113)
Mean (SD)	79 (7.9)	80 (18.6)	80 (15.6)

*Normal glucose range, 6-105 mg/dL (Reference: The Harriet Lane Handbook, 17th Edition, 2005)

Reviewer Comment
Based on the safety data presented for PACTG 1030, LPV/r appears safe for the intended pediatric patient population (age ≥ 14 days to < 6 months).

P1038
Laboratory analyses were complicated by small sample size and study design. Overall, no new laboratory abnormalities were identified in pediatric patients (age ≥ 2 years to < 18 years) receiving LPV/r through Week 48. Most of the laboratory abnormalities in the following table were considered not related to study treatment.

Table 31: Week Treatment-Emergent, Grade 3-4 Laboratory Abnormalities regardless of causality (P1038) – Week 48

Laboratory abnormality	Number of subjects	Number of occurrences
Hemoglobin		
Grade 3 (<7.0 g/dL)	2	2

Platelets		
Grade 3 (25,000-49,999 cells/mm^3)	1	4
Uric acid		
Grade 3 (12.5-15 mg/dL)	1	1
Low Sodium		
Grade 3 (124-129 mEq/L)	1	1
Bilirubin[a]		
Grade 3 (3.0-7.5 x ULN)	1	2
Grade 4 (> 7.5 x ULN)	1	3
Total cholesterol		
Grade 3	1	1
Triglycerides		
Grade 3	1	3

[a]Subject had CMV sepsis at time of Grade 3 and Grade 4 bilirubin elevations.

Laboratory abnormalities of interest (class specific)
As a class effect, LPV/r and other protease inhibitors can cause abnormalities in liver function tests, lipids, and glucose.

Liver function test abnormalities
No Grade 2 or higher elevations in ALT/AST were reported throughout the study period.

Two subjects (500607, 660061) reported transient Grade 2 bilirubin (2-2.9 x ULN). Neither subject had bilirubin elevations considered related to study treatment.

One subject (690327) had Grade 2 jaundice, Grade 2 hepatomegaly, Grade 2 alkaline phosphatase elevation, and Grade 4 increases in total bilirubin and GGT at Week 4. This subject was diagnosed with cholangitis and CMV sepsis (please refer to SAE section). None of these abnormalities were considered related to study treatment. Subject 690327 was taken off study at Week 5 due to requirement for prohibited medications (for treatment of CMV).

Cholesterol abnormalities
Grade 2 (500-749 mg/dL) elevations in fasting total cholesterol were reported in one subject (290133 – 17 years old). This was considered probably related to study treatment (SQV and LPV/r). Maximum total cholesterol value was 555 mg/dL (Step 2 – Week 8). As previously discussed (in SAE and Premature Discontinuation sections), study treatment was discontinued at Week 13 due to these laboratory abnormalities.

Two subjects (290270 – 17 years old; 660061 – 14 years old) had Grade 1 (171-499 mg/dL) elevations in fasting total cholesterol. In both subjects, these laboratory abnormalities were considered probably or definitely related to study treatment (SQV and LPV/r). Maximum cholesterol values were 229 mg/dL (subject 290270, Step 2 – Week 16) and 254 mg/dL (subject 660061, Step 2 – Week 2) respectively. No changes in antiretroviral medications were made for either subject.

No subjects initiated lipid lowering agents during the study period in P1038.

Reviewer Comment
According to study protocol, non-fasting total cholesterol values were obtained at defined study time-points. If non-fasting total cholesterol ≥ 500 mg/dL, then fasting total cholesterol was obtained and all subsequent total cholesterol levels were obtained in the fasting state for the subject and used for grading.

Among treatment-experienced pediatric patients with limited antiretroviral options, risk/benefit assessment is challenging. In clinical practice, if patients with elevated total cholesterol are clinically asymptomatic, and have no other potential cardiac risk factors (such as diabetes), the immunologic and virologic benefits of antiretroviral therapy generally outweigh potential cardiovascular risks.

Triglyceride abnormalities
According to study protocol, non-fasting triglyceride values were obtained at defined study time-points. If non-fasting triglyceride ≥ 750 mg/dL on two consecutive samples, then fasting triglyceride was obtained and all subsequent triglyceride levels were obtained in the fasting state for the subject and used for grading.
Grade 3 (≥1200 mg/dL) elevations in fasting triglycerides were reported in one subject (290133). This was considered probably related to study treatment (SQV and LPV/r). Maximum triglyceride value was 3951 mg/dL (Step 2 – Week 8). As previously discussed (in SAE and Premature Discontinuation sections), study treatment was discontinued at Week 13 due to these laboratory abnormalities.

Three subjects (290270, 400337, and 660061) had Grade 2 (750-1199 mg/dL) elevations in fasting triglycerides. For all three subjects, these laboratory abnormalities were considered probably or definitely related to study treatment (SQV and LPV/r). Maximum triglyceride values were 945 mg/dL (Subject 290270, Step 2 – Week 16), 772 mg/dL (Subject 400337, Step 2 – Week 6), and 1170 mg/dL (Subject 660061, Step 2 – Week 2) respectively. No changes in antiretroviral medications were made for either subject.

No subjects were treated with triglyceride lowering agents during the study period in P1038.

Reviewer Comment
In clinical practice, if patients with elevated triglycerides are clinically asymptomatic, and have no comorbidities that can be exacerbated by hypertriglyceridemia (such as history of

pancreatitis), the immunologic and virologic benefits of antiretroviral therapy generally outweigh potential cardiovascular risks.

Glucose abnormalities
According to study protocol, non-fasting, random blood glucose values and urine dipstick were obtained at defined study time-points. If either random blood glucose ≥ 250 mg/dL or urine dipstick was positive for glucose, then fasting blood glucose was obtained and all subsequent glucose levels were obtained in the fasting state for the subject and used for grading.

No Grade 3/4 elevations in glucose were reported throughout the study period. Two subjects reported non-fasting Grade 2 elevations in glucose (160-249 mg/dL) during the study period.

Summary of Laboratory analyses – P1038
Laboratory analyses were complicated by study design issues and relatively small numbers of subjects with baseline and Week 48 values for ALT, AST, cholesterol, triglycerides, and glucose. Overall, the laboratory toxicity profile appears similar to other studies with LPV/r.

In P1038, cholesterol was the only laboratory value with statistically significant median increases from baseline (maximum median increase from baseline, 49 mg/dL at Week 40; n=9). Although these changes were not considered clinically relevant and the number of subjects evaluated was small, these findings may have implications for long term therapy.

Reviewer Comment
Based on the safety data presented for PI-experienced pediatric patients (age ≥ 7 to 17 years) in PACTG 1038, combination high-dose SQV and high-dose LPV/r appears to cause clinical and laboratory toxicities, and possibly ECG abnormalities as well. With the availability of other antiretroviral medications, clinical need for this dual-boosted PI regimen should be infrequent. Additionally, dual-boosted PI regimens are not recommended in the 2008 DHHS HIV-1 Pediatric Treatment Guidelines. Patients receiving combination SQV and LPV/r should be closely monitored for clinical adverse events, ECG abnormalities, and laboratory toxicities. Concurrent use of high-dose SQV and high-dose LPV/r should only be considered if the benefit clearly outweighs the risk.

The applicant's common pediatric Grade 2-4 adverse event rates were within 1-2% of the review team's rates, so the applicant's rates will be used in the updated product label. Based on the requirements outlined in the FDA Amendments Act of 2007 (FDAAA), clinical adverse events and laboratory abnormalities from both Study P1030 and Study P1038 will be included in the label. Consistent with safety data provided for Study M98-940 (pediatric patients 6 months to 12 years of age), clinical adverse events and laboratory abnormalities of moderate-to-severe intensity will be included for both Study P1030 and Study P1038 respectively.

7.4.3 Vital Signs

No significant vital sign changes of concern were noted in P1030.

As discussed in Section 7.3.2 and 7.3.4, two subjects in P1038 reported sinus bradycardia. Both subjects were clinically asymptomatic. No other potentially significant vital sign changes of concern were noted in P1038.

7.4.4 Electrocardiograms (ECGs)

No ECGs were obtained in P1030. Please refer to Section 7.3.2 and 7.3.4 for discussion of ECG findings observed in P1038.

7.4.5 Special Safety Studies

Not applicable.

7.4.6 Immunogenicity

Not applicable.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The evaluation of dose-response relationship was not possible because too few patient data were available in each dosing cohort.

7.5.2 Time Dependency for Adverse Events

Not applicable.

7.5.3 Drug-Demographic Interactions

Not applicable.

7.5.4 Drug-Disease Interactions

Not applicable.

7.5.5 Drug-Drug Interactions

Not applicable.

7.6 Additional Safety Explorations

7.6.1 Human Carcinogenicity

No new data was provided in this supplement.

7.6.2 Human Reproduction and Pregnancy Data

No new data was provided in this supplement.

7.6.3 Pediatrics and Effect on Growth

P1030
In the younger cohort (≥ 14 days to < 6 weeks), median changes from baseline were positive at all measurement times for both height and weight for age Z-scores.

In the older cohort (≥ 6 weeks to < 6 months), seventeen of 21 subjects had all of the required height and weight evaluations prior to Week 24 or permanent treatment discontinuation. The remaining 4 infants each missed one height and weight evaluation (at Week 2, Week 4, Week 12 and Week 24, respectively). From baseline to Week 24, median changes were positive at all measurement times for height for age Z-score. From baseline to Week 16, median changes in weight for age Z-score were positive. Subsequently, median changes in weight for age Z-score were negative at Week 20 and Week 24, respectively. However, these negative trends were neither clinically nor statistically significant.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

KALETRA oral solution contains 42.4% alcohol. Accidental ingestion of the product by a young child could result in significant alcohol-related toxicity and could approach the potential lethal dose of alcohol. The potential for toxicities due to overdose with LPV/r oral solution, including death, is already included in the label (Section 10, Overdosage). No new data regarding overdosage was provided in this supplement. No overdose or symptoms of alcohol toxicity were reported in P1030.

8 Postmarketing Experience

This supplement included a summary of postmarketing reports of pediatric patients (ages 0-18) receiving LPV/r during the period September 15, 2000 to May 23, 2007. The most frequent adverse events reported were gastrointestinal disorders. Overall, no new safety findings were identified.

Table 32: Number of subjects with selected AEs in applicant's postmarketing database (September 15, 2000 - May 23, 2007)

Age range	# of reports	Death	↑ LFTs	↑ Chol	↑ TGs	↑ glucose	Abnormal fat redistribution
0 to < 6 weeks	2	1	0	0	0	0	0
6 weeks to < 6 months	5	2	0	0	0	0	0
6 months to < 2 years	7	1	1	0	0	0	0
2 years to < 6 years	27	2	0	0	0	0	0
6 years to < 12 years	72	3	3	2	1	1	1
12 years to 18 years	66	7	5	0	1	0	0
Age not specified	16	0	0	0	0	0	1
Total	195	16	9	2	1	1	1

LFTs, liver function tests; Chol, cholesterol; TG, triglycerides.

Deaths
Reported causes of death included sudden infant death syndrome (1), gastroenteritis (1), failure to thrive (1), intraventricular hemorrhage (1 subject, AER# 0254260, developed IVH 199 days after starting LPV/r, zidovudine, lamivudine; no additional details were provided), myeloblastic leukemia (1), sepsis (1), hepatic failure (2), unknown (1), fever (1), encephalopathy (1), cryptococcal meningitis (1), AIDS (2), progressive multifocal leukoencephalopathy (1).

One subject, a 30-day-old female (AER# 036591), received an overdose of LPV/r oral solution. This 2.1 kg female infant received a single dose of 6.5 mL of LPV/r oral solution (~245 mg/kg). She developed hemodynamic instability, cardiogenic shock, and died 9 days after onset of the adverse event. Preferred terms reported were neonatal respiratory arrest, sinoatrial block, acute renal failure, blood potassium increased, incorrect dose administered, accidental overdose, haemoglobin decreased, hyperbilirubinemia, vomiting, malaise, bradycardia, oxygen saturation decreased, anion gap decreased, electroencephalogram abnormal.

Reviewer Comment
The potential for toxicities due to overdose with LPV/r oral solution, including death, is already included in the label. The above case (AER# 036591) is referenced in the LPV/r label (Section 10, Overdosage).

Hepatotoxicity
In the applicant's postmarketing database, most cases with transaminase elevations were clinically asymptomatic.There were two subjects (AER# 0267008, 0233970) with reported clinical hepatitis; however, no laboratory data was available for either subject. Also, two subjects

(AER# 0238960, 0368222) were reported with hepatic insufficiency/failure. Their narratives are presented below:

1) AER# 0238960: 10 year-old female (concomitant meds: LPV/r, amprenavir, nevirapine, ddI). This literature report described a drug interaction between voriconazole and lopinavir/ritonavir, amprenavir and nevirapine [**Clin Infect Dis. 2003; 37(6):828-30**]. For approximately 8 months, the patient was on LPV/r, amprenavir, nevirapine, and didanosine therapy. The patient developed esophageal candidiasis and was placed on voriconazole 400 mg daily. One day, after introducing voriconazole, there was an elevation in the patient's liver enzymes and, after 7 days, liver function deteriorated rapidly. The patient died 28 days after voriconazole was initiated from irreversible liver failure followed by hepatic coma. The author believed the patient died from non-infectious toxic liver failure caused by a drug interaction between one or both of the protease inhibitors and voriconazole. No autopsy was performed. There have been reports of hepatic adverse events in patients taking voriconazole, amprenavir or nevirapine.

2) AER# 0368222: 17 year-old male (concomitant meds: LPV/r, trizivir). Seven days prior to starting lopinavir/ritonavir therapy, the patient was hospitalized for a fever, hepatosplenomegaly, systemic candidiasis, and cachexia. The systemic candidiasis was treated with oral flucovin and diflucan. The worsening of pneumocystis Carinii pneumonia was treated with oral clotrimoxazole/trimetoprim, and worsening of sepsis with mycoplasma tuberculosis was treated with ciprinol (ciprofloxacin). The patient had been on Kaletra for 20 days. Three days after discontinuing Kaletra the patient died from cardio-respiratory insufficiency, acute liver insufficiency, and acute renal insufficiency. The reporter assessed the cause of death as not related to lopinavir/ritonavir therapy. An autopsy was not performed.

In addition to reviewing the postmarketing reports, the FDA's AERS database was searched for any cases of hepatic failure among pediatric patients (0-18 years) receiving LPV/r. One additional pediatric case of hepatic failure was identified (ISR# 5340185-6) and the narrative is presented below:

This six-month-o1d male subject was enrolled in an open-label collaborative study comparing three treatment strategies in infants with perinatally acquired HIV-1 infection diagnosed between 6 and 12 weeks of age. The subject received oral zidovudine from 27 November 2006, oral lamivudine from 27 November 2006 and oral ritonavir+lopinavir (Ka1etra) at 1.5 ml twice per day from 27 November 2006. Concomitant medications included Cotrimoxazole and pneumococcal vaccines (three vaccines received on 27 November 2006, 29 December 2006, and 16 Februar 2007). One week prior to the hepatic event, the subject had experienced a loss of appetite, fever and cough. On [redacted], approximately six months after the start of zidovudine, 1amivudine and kaletra, the subject developed grade 3 or severe pneumonia and grade 1 or mild gastroenteritis. The subject was hospitalised as a pediatric patient on [redacted] and diagnosed with suspected grade 4 liver failure. Clinically the subject had tachypnea, hepatosplenomegaly and irrstability. The subject was treated with cefotaxime. Relevant tests performed on 07 May 2007 included; white blood cell count 1.3 x 10^9/L, hemoglobin 9.9 g/dL (10.5 - 13.7), platelets 64 x 10^9/L (140 - 350), GGT 133 U/L, aspartate aminotransferase 1588 U/L (0 -79) and alanine aminotransferase 272 U/L (3 - 30). On 08 May 2007, the subject developed hypog1ycemia and passed blood in his stool. He was given a bolus of glucose and was placed on fluid restrction. Laboratory results on the same day revealed white blood cell count 1.32 x 10^9/L, hemoglobin 9.9 g/dL, platelet 64 x 10^9/L, total bilirubin 34 µmol/L, conjugated bilirubin 29 µmol/L, urea 7 mmol/L, c-reactive protein 79.9mg/L, GGT 133 U/L, alanine aminotransferase 272 U/L, alkaline phosphatase 231 U/L, and asparate aminotransferase l588 U/L. Renal function test was normal. Chest x-ray was performed and showed right upper lobe consolidation and hi1ar adenopathy. On 09 May 2007, the subject's condition further deteriorated. Laboratory results showed prothrombin time of 43.6 seconds, international normalized ratio (INR) of 3.02, Hepatitis A and Hepatitis B were negative, Cytomegalovirus IgM and IgG were negative, Coombs test was positive, white blood cells count of 0.38 x 10^9/L, hemoglobin 8.2 g/dL, platelet count 42 x 10^9/L, total bilirubin 54 µmol/L, conjugated bilirubin 2 µmol/L, GGT 157 U/L, alanine aminotransferase 1206 U/L, alkaline phosphatase 246 U/L, and aspartate aminotransferase 8769 U/L. The result of gastric washing for

tuberculosis is still pending. The subject was then treated with fresh frozen plasma, vitamin k, cimetidine, gentamicin sulphate and lactulose. After contact with the unit, treatment with zidovudine, 1amivudine and ka1etra was discontinued on 09 May 2007 due to suspected liver failure. The subject died on [redacted] The investigator confirmed that an autopsy was to be performed and results would be made available. The investigator reported the suspected liver failure, pneumonia and gastroenteritis as possibly related to treatment with zidovudine, 1amivudine and ka1etra. As preliminary conclusion, death occurred as a result of suspected liver failure.

Reviewer Comment
These three pediatric cases of hepatic insufficiency/failure and death have multiple confounders. Because these reactions are reported voluntarily from a population of unknown size, it is not possible to reliably estimate their frequency or establish a causal relationship to KALETRA exposure. Of note, there are no distinctive clinical features between the pediatric and adult reports of hepatic insufficiency/failure.

As shown below, this adverse event is already described in the label and the current wording remains overall appropriate:

> Warnings and Precautions
> Section 5.3 Hepatotoxicity
> There have been postmarketing reports of hepatic dysfunction, including some fatalities. These have generally occurred in patients with advanced HIV disease taking multiple concomitant medications in the setting of underlying chronic hepatitis or cirrhosis. A causal relationship with LPV/r has not been established.

Summary of Postmarketing Experience
No additional considerations for changes to the label are warranted based on review of the postmarketing data provided by the applicant and from the FDA AERS search.

9 Appendices

9.1 Literature Review/References

Literature reviewed for this sNDA is cited in relevant sections of this document. The exception is the references cited for immune reconstitution inflammatory syndrome (Section 7.4.1).

1. Cheng VC, Yuen KY, Chan WM, et al. Immunorestitution disease involving the innate and adaptive response. Clin Infect Dis 2000;30:882-892.

2. Shelburne SA, Hamill RJ, Rodriguez-Barradas MC, et al. Immune reconstitution inflammatory syndrome: emergence of a unique syndrome during highly active antiretroviral therapy. Medicine 2002;81:213-227.

3. Cooney EL. Clinical indicators of immune restoration following highly active antiretroviral therapy. Clin Infect Dis 2002;34:224-233.

4. French MA, Price P, Stone SF. Immune restoration disease after antiretroviral therapy. AIDS 2004;18:1615-1627.

5. Hirsch HH, Kaufmann G, Sendi P, Battegay M. Immune reconstitution in HIV-infected patients. Clin Infect Dis 2004;38:1159-1166.

6. Shelburne SA, Visnegarwala F, Darcourt J, Graviss EA, Giodano TP, Clinton White A Jr, et al. Incidence and risk factors for immune reconstitution inflammatory syndrome during highly active antiretroviral therapy. AIDS 2005; 19:399–406.

7. Lipman M, Breen R. Immune reconstitution inflammatory syndrome in HIV. Curr Opin Infect Dis 2006;19:20–25.

8. French MA, Lenzo N, John M, et al. Immune restoration disease after the treatment of immunodeficient HIV-infected patients with highly active antiretroviral therapy. HIV Med 2000; 1:10715.

9. Koval CE, Gigliotti F, Nevins D, Demeter LM. Immune reconstitution syndrome after successful treatment of *Pneumocystis carinii* pneumonia in a man with human immunodeficiency virus type 1 infection. Clin Infect Dis 2002;35:491-493.

10. Aberg JA, Chin-Hong PV, McCutchan A, et al. Localized osteomyelitis due to *Mycobacterium avium* complex in patients with human immunodeficiency virus receiving highly active antiretroviral therapy. Clin Infect Dis 2002;35:e8-e13.

11. Jenny-Avital ER, Abadi M. Immune reconstitution cryptococcosis after initiation of successful highly active antiretroviral therapy. Clin Infect Dis 2002;35:e128-e133.

12. Breton G, Duval X, Estellat C, et al. Determinants of immune reconstitution inflammatory syndrome in HIV type 1-infected patients with tuberculosis after initiation of antiretroviral therapy. Clin Infect Dis 2004;39:1709-1712.

13. Lawn DS, Bekker L-G, Miller RF. Immune reconstitution disease associated with mycobacterial infections in HIV-infected individuals receiving antiretrovirals. Lancet Infect Dis 2005; 5:361–373.

14. Leidner RS, Aboulafia DM. Recrudescent kaposi's sarcoma after initiation of HAART: a manifestation of immune reconstitution syndrome. AIDS Patient Care STDs 2005;19:635-644.

9.2 Labeling Recommendations

As discussed in this review, this supplement seeks to expand the pediatric patient population to include patients ages ≥ 14 days to 6 months and patients > 12 years to 18 years of age based on the results (PK, safety, and activity) from PACTG Study 1030 and PACTG Study 1038. Pediatric and safety related changes excerpted from proposed labeling are summarized below.

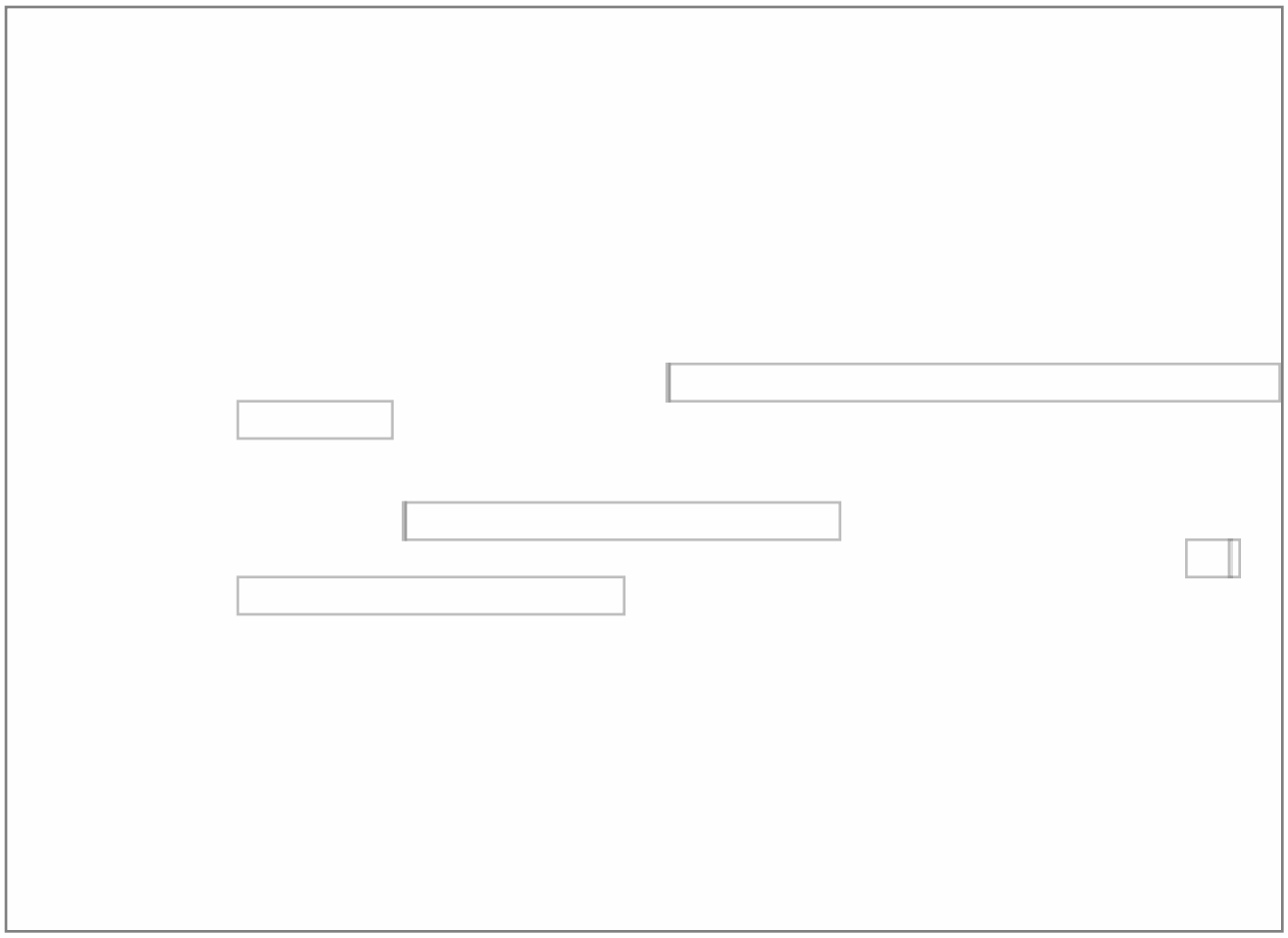
On January 4, 2002, the Best Pharmaceuticals for Children Act (BPCA) was enacted to provide a process for studying on-patent and off-patent drugs for use in pediatric populations, and to improve pediatric therapeutics through collaboration on scientific investigation, clinical study design, weight of evidence, and ethical and labeling issues. The reauthorization of BPCA, effective October 2007, requires all pediatric studies conducted in response to a Written Request or post-marketing commitment be described in the label. This includes study results that show lack of efficacy.

For P1038, this information is summarized in section 8.4 (Use in Specific Populations, Pediatric Use) of the label. Safety results for P1038 were added to section 6.2 (Adverse Reactions, Pediatric Patients – Clinical Trials Experience). Pharmacokinetic results were described in section 12.3 (Clinical Pharmacology – Pharmacokinetics).

Study P1030 provided the basis for approval of LPV/r in pediatric patients ages ≥ 14 days to 6 months. These results are included in section 2.2 (Dosage and Administration – Pediatric Patients), section 6.2 (Adverse Reactions, Pediatric Patients – Clinical Trials Experience), section 8.4 (Use in Specific Populations, Pediatric Use), section 12.3 (Clinical Pharmacology – Pharmacokinetics), and section 14.4 (Clinical Studies – Pediatric Studies)

The proposed package insert (PI or label) has been reviewed by all disciplines involved in the NDA review of LPV/r. The major recommendations for revisions to the clinical sections of the proposed label are listed below. These changes were discussed with and agreed upon by the applicant.

FDA Comment
We are reviewing your pediatric efficacy supplements for Kaletra and we are requesting the following revisions to the package insert:



Pages 65 through 69 redacted for the following reasons:
- -
Pages removed for the following reason:

The Applicant agreed to the proposed revisions outlined above.

9.3 Advisory Committee Meeting

Not applicable.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Kirk M Chan-Tack
6/18/2008 10:19:03 AM
MEDICAL OFFICER
NDA 21-251/SE5-022 and [redacted] (pediatric efficacy supplement): review

Kimberly Struble
6/18/2008 10:55:50 AM
MEDICAL OFFICER