CLINICAL PHARMACOLOGY REVIEW

NDA: 21-251 SE5 022 &	Submission Date(s): December 21, 2007
Brand Name	Kaletra
Generic Name	Lopinavir/ritonavir
Reviewer	Yuanchao (Derek) Zhang, Ph.D.
Team Leader	Kellie S. Reynolds, Pharm.D.
OCP Division	Division of Clinical Pharmacology 4
OND Division	DAVP
Sponsor	Abbott
Formulation; Strength(s)	Tablet (200 mg) and Oral suspension (80 mg/mL)
Indication	Treatment of HIV-1 infection

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I. Executive Summary

Recommendations

The applicant submitted this supplemental NDA to support the proposed labeling changes to expand the pediatric use of Kaletra from 6 months – 12 years of age to 14 days – 18 years of age. In addition, this submission addresses several post marketing commitments (PMCs):

- PACTG Study 1038 fulfills Commitment 2 from NDA 21-226/S-003 and Commitment 2 from NDA 21-251/S-004. This commitment states "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."

- PACTG Studies 1030 and P1038 fulfill Commitment 1 from NDA 21- 226/S-014 and NDA 21-251/S-010. This commitment states "Multiple-dose pharmacokinetics, safety, and activity study of ABT-378/ritonavir in combination with other antiretroviral agents in HIV-infected pediatric patients."

- PACTG Study P1030 fulfills Commitment 2 from NDA 21-226/S-014 and NDA 21-251/S-010. The commitment states "Multiple-dose pharmacokinetic and safety study of ABT-378/ritonavir in HIV-exposed neonates (born to HIV-infected mothers)."

Finally, it supports the Pediatric Exclusivity claim for Kaletra.

The Office of Clinical Pharmacology (OCP) reviewed the information submitted and concluded the information is adequate for the proposed labeling revisions, fulfillment of PMCs, and support the Pediatric Exclusivity claim.

Phase IV Commitments

None.

Summary of Clinical Pharmacology Findings

This submission includes two clinical study reports. P1030 and P1038 were conducted by the Pediatric AIDS Clinical Trials Group (PACTG) and supported by Abbott to explore the safety, efficacy, and pharmacokinetics of lopinavir/ritonavir in combination with NRTI therapy in an expanded pediatric age range.

1. Study P1030 (supports dosing in infants 14 days to 6 months of age)

This was a prospective, phase I/II, open-label study to evaluate lopinavir/ritonavir plus two nucleoside reverse transcriptase inhibitors (NRTIs) in HIV-1 infected infants stratified into two cohorts by age at enrollment (from ≥ 14 days to < 6 weeks of age (N=10); and from 6 weeks to 6 months of age (N=21)). The study was designed to evaluate dose requirements for lopinavir/ritonavir that are safe and provide systemic exposure in infants similar to those observed in adults and children > 6 months of age. The initial lopinavir/ritonavir dose of 300/75 mg/m^2 BID was selected and administered using the lopinavir/ritonavir 80/20 mg/mL oral solution. At approximately Week 2, an intensive lopinavir/ritonavir pharmacokinetic evaluation was performed in all subjects.

In infants < 6 weeks of age who received lopinavir/ritonavir doses of 300/75 mg/m^2, 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 lopinavir/ritonavir dose of 230/57.5 mg/m^2 without an NNRTI (the approved dose) in Study M98 940 (Table 1).

In infants between 6 weeks and < 6 months of age who received lopinavir/ritonavir doses of 300/75 mg/m^2, 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 lopinavir dose of 230/57.5 mg/m^2 without an NNRTI in Study M98 940 (Table 1).

The lopinavir 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 lopinavir dose of 230 mg/m^2 without an NNRTI (Table 1). 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).

Phase II data from adults support the 300/75 mg/m^2 dose in children < 6 months old. Despite the lower lopinavir drug exposure observed with the 300/75 mg/m^2 dose in infants < 6 weeks and infants between 6 weeks and < 6 months of age cohorts in Study P1030, substantial antiviral activity was demonstrated as reflected in the high proportion of subjects who achieved HIV-RNA < 400 copies/mL at Week 24. This could be due to the fact that younger children were more likely to have less HIV resistance. In a phase II study (M97-720) in HIV-infected, antiretroviral naïve, adult patients, 200/100 mg BID cohort achieved similar efficacy endpoint compared to that of 400/100 mg BID cohort. The mean lopinavir trough plasma concentration of 200/100 mg BID regimen was 2.72 (53%CV) μg/mL, 30 -50% lower than that of 400/100 mg BID regimen. The higher dose (400/100) was selected for further development because it was safe and it provided a great margin between lopinavir trough concentration and wild type EC50. Please refer to

the Clinical Pharmacology and Biopharmaceutics reviews of Kaletra capsule formulation (NDA 21-226). Lopinavir trough plasma concentration of 1.0 μg/mL is about 15-fold of wild-type EC50. Thus, the collective data supports use of this dose across the age range of 14 days to 6 months.

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 difficulties associated with dose administration in infants could contribute to the overall variability. Further increasing lopinavir/ritonavir dose could lead to higher than needed exposure in some individuals and lead to undesired toxicity.

In summary, lopinavir/ritonavir 300/75 mg/m^2 BID was safe and well tolerated in infants initiating treatment from 3.6 to 25.7 weeks of age. Lopinavir/ritonavir in combination with two NRTIs provided favorable virologic and immunologic response in infants 3 weeks to 6 months of age, with a tolerability profile similar to that seen in older pediatric and adult HIV-1 infected patients.

Thus a dose of lopinavir/ritonavir 300/75 mg/m^2 is recommended in children < 6 months old. The sponsor proposed the [redacted] dose. However the average dose these patients received in Study P1030 was about 15 mg/kg (actual doses convert to mg/kg). Considering the low C_{min} in these pediatric patients, a dose of approximately 16/4 mg/kg seems more reasonable.

Table 1. Comparison of PK Results across Studies: Lopinavir Pharmacokinetic Parameters (Mean ± SD) by Age, Lopinavir/ritonavir Dose (without Concomitant NNRTI Use)

Age Group		Cmax	Cmin	AUC12	CL/F
Study Number (Dose Regimen)	N	(μg/mL)	(μg/mL)	(μg•h/mL)	(L/h)
< 6 Weeks P1030 (Approx. 300/75 mg/m2 BID)	9	5.17 ± 1.84	1.40 ± 0.48	43.39 ± 14.80	1.80 ± 0.49
6 Weeks to < 6 Months P1030 (Approx. 300/75 mg/m2 BID)	18	9.39 ± 4.91	1.95 ± 1.80	74.50 ± 37.87	1.50 ± 0.92
6 Months to < 2 Years M98-940 (230/57.5 mg/m2 BID*) M98-940 (300/75 mg/m2 BID)	3 5	7.18 ± 4.06 10.57 ± 4.05	2.17 ± 1.60 3.49 ± 1.80	58.60 ± 38.41 86.08 ± 36.34	6.10 ± 5.24 4.14 ± 2.03
2 Years to < 6 Years M98-940 (230/57.5 mg/m2 BID) M98-940 (300/75 mg/m2 BID)	6 3	7.57 ± 2.40 12.46 ± 2.06	3.24 ± 2.12 8.34 ± 1.62	67.28 ± 27.93 131.17 ± 22.90	4.02 ± 1.85 2.33 ± 0.49
6 Years to < 12 Years M98-940 (230/57.5 mg/m2 BID) M98-940 (300/75 mg/m2 BID)	3 7	10.32 ± 2.66 13.78 ± 7.78	4.76 ± 2.52 7.92 ± 5.83	97.30 ± 24.29 131.79 ± 73.40	2.43 ± 0.57 3.49 ± 3.12
Adults (From US Package Insert Label)					
M99-056 (400/100 mg BID)	19	9.8 ± 3.7	5.5 ± 2.7	92.6 ± 36.7	5.98 ± 5.75

*The 230/57.5 mg/m^2 dose without an NNRTI is the approved dose for children 6 weeks to 12 years old.

2. Study P1038 (supports dosing in 12 to 18 year old patients)

This was a phase I/II, open-label study to assess the safety, tolerability, and pharmacokinetics of higher-than-recommended doses of lopinavir/ritonavir, with or without saquinavir, in HIV-1 infected children and adolescents (between 2 and 18 years of age) who had at least six months of prior protease inhibitor experience and were failing their current antiretroviral therapy. The hypothesis of this study was that higher doses may inhibit a larger proportion of the viral quasispecies and that, for maximal antiviral activity, the highest tolerated doses should be employed.

Subjects in Group 1 received lopinavir/ritonavir 400/100 mg/m^2 orally every 12 hours in combination with two NRTIs. Subjects in Group 2 received lopinavir/ritonavir 480/120 mg/m^2 orally every 12 hours in combination with one or two NRTIs and one non-nucleoside reverse transcriptase inhibitor (NNRTI). At approximately Week 2, an intensive lopinavir/ritonavir pharmacokinetic evaluation was performed in all subjects.

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

However, changes in HIV-1 RNA were less robust than anticipated. This likely reflects the high degree of phenotypic resistance to lopinavir at study entry, a factor that could not be overcome by the increased drug exposure achieved in this trial.

At these higher doses of lopinavir/ritonavir, 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 lopinavir/ritonavir 400/100 mg twice daily 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 in the absence of inducing agents such as efavirenz, and 300/75 mg/m^2 when administered with inducing agents.

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

Table 2. Comparison of PK Results across Studies: Lopinavir Pharmacokinetic Parameters (Mean ± SD) by Age, Lopinavir/ritonavir Dose, and Concomitant NNRTI Use

Age Group		Cmax	Cmin	AUC12	CL/F
Study Number (Dose Regimen)	N	(µg/mL)	(µg/mL)	(µg•h/mL)	(L/h)
12 Years to < 18 Years					
P1038 (400/100 mg/m2 BID)	13	16.73 ± 5.78	10.32 ± 5.21	158.12 ± 61.31	4.31 ± 2.31
P1038 (480/120 mg/m2 BID) + NNRTI	2	16.50 ± 0.99	12.09 ± 4.40	173.90 ± 16.55	4.27 ± 0.93
6 Years to < 12 Years					
M98-940 (230/57.5 mg/m2 BID)	3	10.32 ± 2.66	4.76 ± 2.52	97.30 ± 24.29	2.43 ± 0.57
M98-940 (300/75 mg/m2 BID)	7	13.78 ± 7.78	7.92 ± 5.83	131.79 ± 73.40	3.49 ± 3.12
M98-940 (230/57.5 mg/m2 BID) + NNRTI	7	6.72 ± 2.71	1.74 ± 2.14	51.79 ± 29.28	5.56 ± 2.64
M98-940 (300/75 mg/m2 BID) +NNRTI	6	10.51 ± 3.81	3.96 ± 4.41	88.28 ± 47.93	4.02 ± 1.40
Adults (From US Package Insert Label)					
M99-056 (400/100 mg BID)	19	9.8 ± 3.7	5.5 ± 2.7	92.6 ± 36.7	5.98 ± 5.75

3. Overall Dosing Conclusions

Lopinavir/ritonavir is an established antiretroviral therapy for pediatric HIV infection. Treatment guidelines recommend lopinavir/ritonavir as the preferred protease inhibitor for treatment-naïve pediatric patients. Two clinical studies reported in this supplement plus Study M98-940 (previously reviewed at the time of original NDA approval) have evaluated lopinavir/ritonavir treatment in infants, children, and adolescents from ≥ 14 days to ≤ 18 years of age treated for 24 to 48 weeks.

We also propose to include body surface area (BSA)-based dosing recommendations for pediatric patients as well as body weight-based dosing recommendations. Most studies were conducted

using BSA-based dosing. Pediatric dosing was converted to mg/kg when the original NDA was approved, to make dosing more convenient. To allow more flexibility, we asked the sponsor to propose wording for the label that includes BSA and mg/kg doses, with appropriate regimens for different age or weight groups in a tabular format.

Dosing recommendations:

14 Days to 6 Months:

In pediatric patients 14 days to 6 months of age, the recommended dosage of lopinavir/ritonavir using KALETRA oral solution is 16/4 mg/kg or 300/75 mg/m^2 twice daily. Prescribers should calculate the appropriate dose based on body weight or body surface area. Because no data exists for dosage when administered with efavirenz, nevirapine, (fos)amprenavir, or nelfinavir, it is recommended that KALETRA not be administered in combination with these drugs in patients < 6 months of age.

6 Months to 18 Years:

Without Concomitant Efavirenz, Nevirapine, (Fos)amprenavir or Nelfinavir

In children 6 months to 18 years of age, the recommended dosage of lopinavir/ritonavir using KALETRA oral solution without concomitant efavirenz, nevirapine, (fos)amprenavir or nelfinavir is 230/57.5 mg/m^2 given twice daily, not to exceed the recommended adult dose. If weight-based dosing is preferred, the recommended dosage of lopinavir/ritonavir for patients < 15 kg is 12/3 mg/kg given twice daily and the dosage for patients > 15 kg to 40 kg is 10/2.5 mg/kg given twice daily.

Concomitant Therapy: Efavirenz, Nevirapine, (Fos)amprenavir, or Nelfinavir

A dose increase of KALETRA to 300/75 mg/m^2 is needed when co-administered with efavirenz, nevirapine, (fos)amprenavir, or nelfinavir in children (both treatment-naïve and treatment-experienced) 6 months to 18 years of age, not to exceed the recommended adult dose. If weight-based dosing is preferred, the recommended dosage for patients <15 kg is 13/3.25 mg/kg given twice daily and the dosage for patients >15 kg to 45 kg is 11/2.75 mg/kg given twice daily.

II. Question Based Review

A. General Attributes of the Drug

i. What is the proposed therapeutic indication?

Lopinavir is currently approved for the treatment of HIV-1 infection in adults and in children of 6 months – 12 years of age in combination with other antirectroviral agents. This supplement is seeking the approval for use in pediatric patients from 14 days – 18 years of age.

ii. What is the proposed dosage and route of administration?

The data provided in this efficacy supplement support the Applicant's proposed dosing recommendations for treatment naïve and experienced pediatric patients from 14 days – 18 years of age.

The approved Kaletra tablet or solution is used for pediatric patients.

14 Days to 6 Months:

In pediatric patients 14 days to 6 months of age, the recommended dosage of lopinavir/ritonavir using KALETRA oral solution is 16/4 mg/kg or 300/75 mg/m^2 twice daily. Prescribers should calculate the appropriate dose based on body weight or body surface area. Because no data exists for dosage when administered with efavirenz, nevirapine, (fos)amprenavir, or nelfinavir, it is recommended that KALETRA not be administered in combination with these drugs in patients < 6 months of age.

6 Months to 18 Years:

Without Concomitant Efavirenz, Nevirapine, (Fos)amprenavir or Nelfinavir

In children 6 months to 18 years of age, the recommended dosage of lopinavir/ritonavir using KALETRA oral solution without concomitant efavirenz, nevirapine, (fos)amprenavir or nelfinavir is 230/57.5 mg/m^2 given twice daily, not to exceed the recommended adult dose. If weight-based dosing is preferred, the recommended dosage of lopinavir/ritonavir for patients < 15 kg is 12/3 mg/kg given twice daily and the dosage for patients > 15 kg to 40 kg is 10/2.5 mg/kg given twice daily.

Concomitant Therapy: Efavirenz, Nevirapine, (Fos)amprenavir, or Nelfinavir

A dose increase of KALETRA to 300/75 mg/m^2 is needed when co-administered with efavirenz, nevirapine, (fos)amprenavir, or nelfinavir in children (both treatment-naïve and treatment-experienced) 6 months to 18 years of age, not to exceed the recommended adult dose. If weight-based dosing is preferred, the recommended dosage for patients <15 kg is 13/3.25 mg/kg given twice daily and the dosage for patients >15 kg to 45 kg is 11/2.75 mg/kg given twice daily.

iii. What efficacy and safety information contribute to the assessment of clinical pharmacology and biopharmaceutics study data?

For pediatric dosing instructions for HIV drugs, safety and PK are required. The proposed dose in pediatric provides exposures similar to exposure observed in adult patients with no new safety concerns. Limited efficacy data are only used as supporting evidence.

Studies P1030 and P1038 provided relevant safety, PK and efficacy data.

B. General Clinical Pharmacology

i. What is the basis for selecting the response endpoints, i.e., clinical or surrogate endpoints, or biomarkers (also called pharmacodynamics, PD) and how are they measured in clinical pharmacology and clinical studies?

The surrogate efficacy endpoints for HIV-1 infection are

1. plasma HIV viral load
2. CD4 cell counts.

The viral load tends to be more predictive of the progression of HIV infection than CD4 cell counts. The primary efficacy endpoint for Studies P1030 and P1038 was the proportion of subjects with a treatment response (HIV RNA < 400 c/mL) through Week 24.

ii. Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

The plasma concentrations of lopinavir were determined by a validated LC/MS/MS method.

iii. What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy and safety?

Please refer to the Clinical Pharmacology and Biopharmaceutics reviews of Kaletra tablet formulation (NDA 21-906) and capsule formulation (NDA 21-226).

C. Intrinsic Factors

i. What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, & organ dysfunction) influence exposure &/or response and what is the impact of any differences in exposure on the PDs? What dosage regimen adjustments, if any, are recommended for each of these subgroups

Age effect

Data from Studies P1030 and P1038 showed that the apparent CL/F normalized by body weight 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. However, the mean CL/F (L/hr/kg) in 12-18 year age group was similar to that observed in previous studies of adults (average CL/F is 86 to 100 mL/h/kg) who received a standard dose of lopinavir/ritonavir 400/100 mg twice daily without an NNRTI. See Individual Study Report Review below.

Please refer to the Clinical Pharmacology and Biopharmaceutics reviews of Kaletra tablet formulation (NDA 21-906) and capsule formulation (NDA 21-226) for information other than age effect.

D. Extrinsic Factors

Please refer to the Clinical Pharmacology and Biopharmaceutics reviews of Kaletra tablet formulation (NDA 21-906) and capsule formulation (NDA 21-226).

Lopinavir is a CYP3A4 substrate. Lopinavir is essentially completely metabolized by CYP3A. Ritonavir inhibits the metabolism of lopinavir, thereby increasing the plasma levels of lopinavir.

E. General Biopharmaceutics

Please refer to the Clinical Pharmacology and Biopharmaceutics reviews of Kaletra tablet formulation (NDA 21-906) and capsule formulation (NDA 21-226).

F. Analytical Section

A validated HPLC-UV assay was used to determine the plasma concentrations of lopinavir and ritonavir at [redacted] The calibration curves ranged from 50 ng/mL to 20,000 ng/mL for ritonavir and 100 ng/mL to 40,000 ng/mL for lopinavir. The accuracy and precision were < 2.0% and <2.5% respectively.

The analytical method is acceptable.

III. Labeling Recommendations

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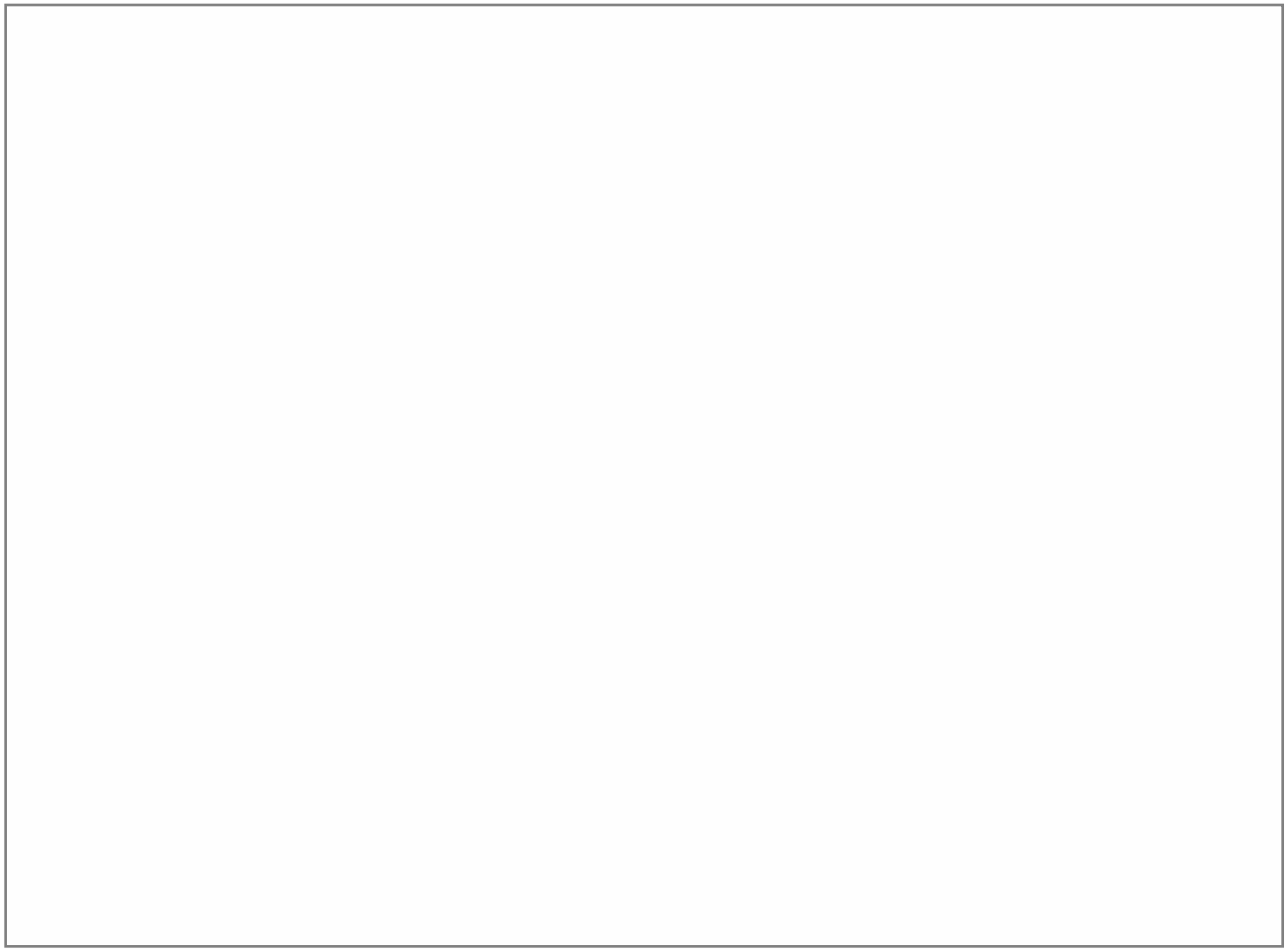

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IV. Individual Clinical Pharmacology Reports (2)

PACTG 1030

TITLE: A Phase I/II Study of Lopinavir/Ritonavir in HIV-1 Infected Infants < 6 Months of Age

BACKGROUND: Lopinavir/ritonavir has shown significant antiviral activity and tolerability in clinical trials in adults and children > 6 months of age. Dosing guidelines have not been established for infants < 6 months of age, most of them are in the early stages of primary infection. P1030 was intended to help identify an appropriate dose range of lopinavir/ritonavir and to evaluate response to therapy in infants < 6 months of age.

OBJECTIVES: The primary objectives were to evaluate LPV/RTV dose requirements for HIV-infected infants < 6 months of age that provide systemic exposure similar to that which has been shown to be safe and effective in older children and adults and to determine the short-term and long-term safety and tolerance of LPV/RTV initiated in HIV-infected infants < 6 months of age as part of a combination regimen including nucleoside analogs. The secondary objectives were to estimate pharmacokinetic parameters for lopinavir/ritonavir (LPV/RTV) in HIV-infected infants <6 months of age for comparison with existing data in older children and adults and to assess age-related changes in LPV/RTV pharmacokinetic parameters.

SUBJECTS AND STUDY DESIGN:

This was a prospective multicenter, Phase I/II open label study of lopinavir/ritonavir with concurrent NRTI therapy in very young infants conducted by the Pediatric AIDS Clinical Trials Group (PACTG) with clinical sites in United States, Brazil and Puerto Rico. The study assessed the safety, tolerability, and pharmacokinetics of lopinavir/ritonavir 300/75 mg/m^2 given orally twice daily as part of a combination regimen including 2 NRTIs. Treatment consisted of the liquid formulation of lopinavir/ritonavir. The lopinavir/ritonavir dosage was intended to provide systemic exposure similar to that which has been shown be safe and effective in older children and adults. There were two age cohorts in the study, the younger cohort of pediatric subjects (age ≥ 14 days to ≤ 6 weeks at study entry) and the older cohort of pediatric subjects (≥ 6 weeks to ≤ 6 months at study entry).

A total of 10 pediatric subjects were enrolled into the age ≥ 14 days to < 6 weeks cohort. The children were enrolled at eight clinical centers in the United States (n = 9 subjects) and 1 center in Brazil (n = 1 subject).

The actual age ranged from 3.6 to 6 weeks at the time of enrollment. Because of time of diagnosis, it was difficult to have infants enrolled at 2 weeks of age. The actual age at the time of PK analysis started at 5.6 weeks in the study because it took additional two more weeks for lopinavir/ritonavir to reach steady-state.

A total of 21 pediatric subjects were enrolled into the age ≥ 6 weeks to < 6 months cohort. The children were enrolled at 11 clinical centers in the United States (n = 15 subjects), two centers in Brazil (n = 5 subjects) and one in Puerto Rico (n = 1 subject).

Inclusion Criteria:

1. Age ≥ 14 days to < 6 months
2. Weight > 2.5 kg at the time of enrollment
3. A confirmed diagnosis of HIV-1 infection defined as 2 positive assays from two different samples
4. HIV-1 RNA > 10,000 copies/mL within 30 days of study entry
5. Agreement to take 2 NRTIs, chosen by the provider in addition to lopinavir/ritonavir

Exclusion Criteria:

1. Concurrent NNRTI use
2. Concurrent PI use
3. Prior treatment with lopinavir/ritonavir (prior treatment with other PIs was allowed). Prior or concurrent maternal treatment with lopinavir/ritonavir was acceptable
4. 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
5. Any ≥ Grade 3 laboratory toxicity at screening
6. Presence of a newly diagnosed acute opportunistic or serious bacterial infection requiring therapy at the time of enrollment
7. Chemotherapy for active malignancy
8. Any clinically significant diseases (other than HIV infection) or clinically significant findings during the screening medical history or physical examination that would have compromised the outcome of this study.

Subjects were treated with LPV 300mg/m^2/RTV 75mg/m^2 in combination with two nucleoside reverse transcriptase inhibitors (NRTIs), which were chosen by the provider based on prior maternal and infant therapy. Subjects were followed for 24 months after enrollment of the last evaluatable subject.

Subjects received oral solution lopinavir/ritonavir 300/75 mg/m^2 BID. Doses of lopinavir/ritonavir were taken with food or infant formula.

Intensive pharmacokinetics was performed at Week 2 in all patients. Dose increases were allowed based on PK results at week 2. No dose modifications were allowed prior to the successful assessment of LPV pharmacokinetics. Subjects with low trough LPV concentrations (<1 μg/mL) had their LPV/RTV dose increased by 50% and then had PK evaluation repeated (3 samples) at Week 6. Subjects with Week 2 LPV AUCs > 170 μg*hr/mL had their LPV/RTV dose reduced to 230/57.5 mg/m^2 BID. Subjects determined to be non-adherent were requested to have their intensive PK evaluation repeated after non-adherence had been addressed.

Subjects in the older cohort (≥ 6 weeks to < 6 months) were to remain on study treatment for twenty-four months (96 weeks) from enrollment of the last subject. Subjects in the younger cohort (≥ 14 days to < 6 weeks) were to remain on the study 48 weeks from enrollment of the last subject.

Table 1. Subject Demographic and Disease Characteristics at Baseline

Characteristic	Age ≥ 14 Days to < 6 Weeks Cohort	Age ≥ 6 Weeks to < 6 Months Cohort	Total
Total subjects	10 (100%)	21 (100%)	31 (100%)
Gender			
Male	7 (70%)	7 (33%)	14 (45%)
Female	3 (30%)	14 (67%)	17 (55%)
Race/Ethnicity			
White non-Hispanic	0 (0%)	2 (10%)	2 (6%)
Black non-Hispanic	7 (70%)	10 (48%)	17 (55%)
Hispanic	3 (30%)	9 (43%)	12 (39%)
Age (weeks), median (range)	5.7 (3.6 to 6.0)	14.7 (6.9 to 25.7)	NA
Height (cm), median (range)	52.0 (48.3 to 59.0)	58.0 (52.0 to 66.0)	NA
Height for Age Z-Score[a], median (range)	-1.5 (-2.9 to 0.9)	-0.7 (-4.7 to 1.2)	NA
Weight (kg), median (range)	4.0 (2.9 to 5.3)	5.2 (4.1 to 10.0)	NA
Weight for Age Z-Score[a], median (range)	-1.3 (-2.0 to 0.6)	-0.8 (-3.9 to 3.3)	NA
Log_{10} HIV-1 RNA (copies/Ml), median (range)	6.0 (4.7 to 7.2)	5.8 (3.7 to 6.9)	NA
CD4 Count (cells/mm^3), median (range)[b]	2426 (1204 to 2542)	2230 (304 to 5556)	NA
CD4%, median (range)	41 (16 to 59)	32 (11 to 54)	NA
CD8 Count (cells/mm^3), median (range)[b]	1089 (971 to 1328)	1203 (594 to 5719)	NA
CD8%, median (range)	21 (15 to 37)	24 (14 to 57)	NA
Helper/Suppressor ratio, median (range)	2 (0.8 to 3.93)	1.45 (0.33 to 3.86)	NA

a. Z-score indicates how many standard deviations an observation is above or below the mean.
b. Seven subjects ≥ 14 days to < 6 weeks of age and 15 subjects ≥ 6 weeks to < 6 months of age had absolute CD4 and CD8 counts measured at baseline.
NA = not available

FORMULATION: Lopinavir 80 mg/ritonavir 20 mg oral solution

PK SAMPLE COLLECTION: Blood samples for the determination of LPV/RTV concentrations in plasma were obtained at Week 2: pre-dose, 1, 2, 4, 8 and 12 hours post-dose. Repeat pharmacokinetic evaluations after dose modifications were performed at Week 6 and included collection of plasma samples at pre-dose, 4 and 12-hour post-dose.

BIOANALYTICAL ASSAYS: A validated HPLC-UV assay was used to determine the plasma concentrations of lopinavir and ritonavir at [redacted]. The calibration curves ranged from 50 ng/mL to 20,000 ng/mL for ritonavir and 100 ng/mL to 40,000 ng/mL for lopinavir. The accuracy and precision were < 2.0% and <2.5% respectively.

PHARMACOKINETIC DATA ANALYSIS:

Pharmacokinetic parameters were calculated using non-compartmental methods. Pharmacokinetic parameters, including $AUC_{0\text{-}12hr}$, C_{max}, C_{12hr}, and CL/F for each subject were calculated.

PHARMACOKINETIC RESULTS:

Table 2. Pharmacokinetic Subject Demographics at the Time of Pharmacokinetic Sampling

Subject Number	Weight (kg)	Height (cm)	BSA (m^2)	Lopinavir Dose (mg)	Lopinavir Dose (mg/m^2)	Age at Analysis (months)
Age ≥ 14 Days to < 6 Weeks Cohort (N = 9):						
Mean (SD)	4.81 (0.88)	55.74 (4.62)	0.27 (0.04)	71.89 (9.60)	267.19 (31.26)	1.93 (0.48)
Median	4.70	54.50	0.27	64.00	266.67	1.84
Range	3.60-6.10	49.50-65.50	0.21-0.33	64.00-87.00	206.45-304.76	1.38-3.12
Age ≥ 6 Weeks to < 6 Months Cohort (N = 18):						
Mean (SD)	6.03 (1.49)	59.89 (4.56)	0.32 (0.05)	87.56 (16.57)	274.17 (20.04)	4.21 (1.46)
Median	5.50	59.10	0.31	80.00	275.86	3.88
Range	4.40-10.50	53.00-66.00	0.25-0.44	64.00-128.00	235.29-305.88	2.10-6.38

SD = standard deviation
BSA = body surface area

Table 3. Lopinavir Noncompartmental Pharmacokinetic Results at Week 2

Pharmacokinetic Parameters	Units	Age: ≥ 14 days to < 6 weeks N = 9	Age: ≥ 6 weeks to < 6 months N = 18
Dose Administered^	mg/m^2	267.19 ± 31.26	274.17 ± 20.04
T_{max}	(h)	3.39 ± 1.01	2.87 ± 1.08
C_{max}	(µg/mL)	5.17 ± 1.84	9.39 ± 4.91
C_{min}	(µg/mL)	1.40 ± 0.48	1.95 ± 1.80
AUC_{12}	(µg•h/mL)	43.39 ± 14.80	74.50 ± 37.87
CL/F	(mL/h/kg)	394.45 ± 161.44	258.85 ± 159.11
	(L/h)	1.80 ± 0.49	1.50 ± 0.92

^ Dose administered at time of the pharmacokinetic sampling. All infants were started on a dose of 300 mg/m^2.

Figure 1. Median Lopinavir Concentrations over Time at Week 2 for the Younger Cohort (Age >= 14 Days to < 6 Weeks; Cohort 1) and the Older Cohort (Age >= 6 Weeks to < 6 Months; Cohort 2)

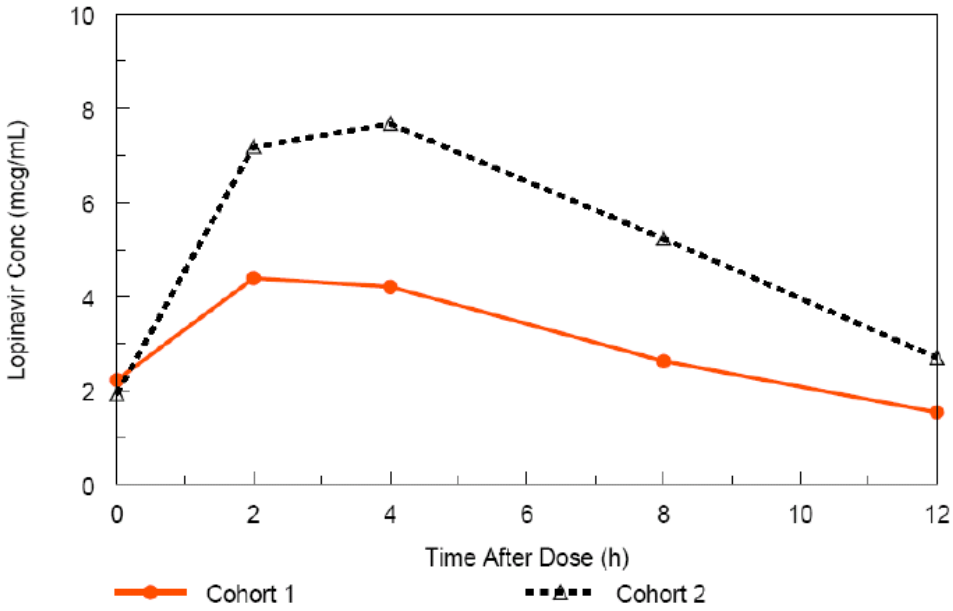
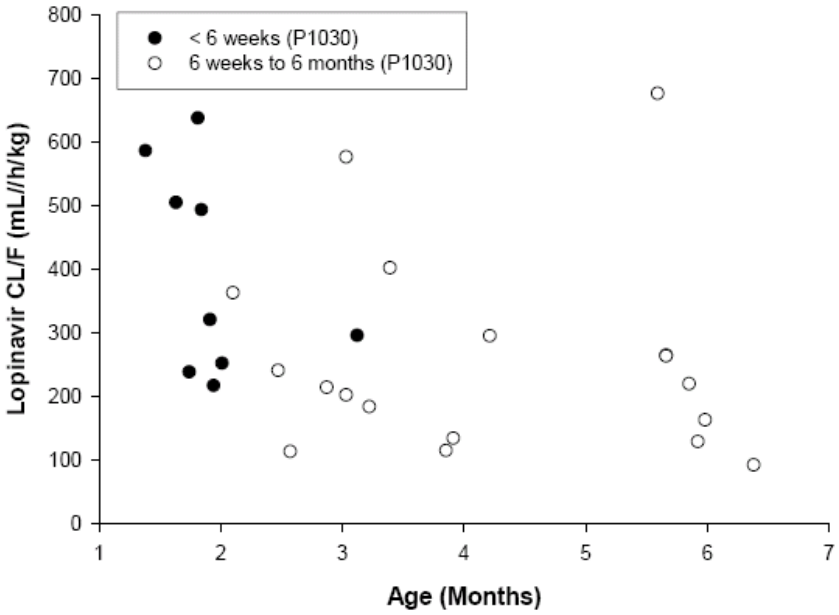


Figure 2. Lopinavir CL/F at Week 2 Intensive Pharmacokinetic Evaluation by Age



Note: One subject in <6 weeks of age group had PK evaluation repeated at Week 6 thus had age of 3 months at the time of PK analysis.

Table 4. Comparison of PK Results across Studies: Lopinavir Pharmacokinetic Parameters (Mean ± SD) by Age, Lopinavir/ritonavir Dose (without Concomitant NNRTI Use)

Age Group		Cmax	Cmin	AUC12	CL/F
Study Number (Dose Regimen)	N	(µg/mL)	(µg/mL)	(µg•h/mL)	(L/h)
< 6 Weeks P1030 (Approx. 300/75 mg/m2 BID)	9	5.17 ± 1.84	1.40 ± 0.48	43.39 ± 14.80	1.80 ± 0.49
6 Weeks to < 6 Months P1030 (Approx. 300/75 mg/m2 BID)	18	9.39 ± 4.91	1.95 ± 1.80	74.50 ± 37.87	1.50 ± 0.92
6 Months to < 2 Years M98-940 (230/57.5 mg/m2 BID)* M98-940 (300/75 mg/m2 BID)	3 5	7.18 ± 4.06 10.57 ± 4.05	2.17 ± 1.60 3.49 ± 1.80	58.60 ± 38.41 86.08 ± 36.34	6.10 ± 5.24 4.14 ± 2.03
2 Years to < 6 Years M98-940 (230/57.5 mg/m2 BID) M98-940 (300/75 mg/m2 BID)	6 3	7.57 ± 2.40 12.46 ± 2.06	3.24 ± 2.12 8.34 ± 1.62	67.28 ± 27.93 131.17 ± 22.90	4.02 ± 1.85 2.33 ± 0.49
6 Years to < 12 Years M98-940 (230/57.5 mg/m2 BID) M98-940 (300/75 mg/m2 BID)	3 7	10.32 ± 2.66 13.78 ± 7.78	4.76 ± 2.52 7.92 ± 5.83	97.30 ± 24.29 131.79 ± 73.40	2.43 ± 0.57 3.49 ± 3.12
Adults (From US Package Insert Label)					
M99-056 (400/100 mg BID)	19	9.8 ± 3.7	5.5 ± 2.7	92.6 ± 36.7	5.98 ± 5.75

*The 230/57.5 mg/m^2 dose without an NNRTI is the approved dose for children 6 weeks to 12 years old.

EFFICACY RESULTS:

Lopinavir/ritonavir provided favorable virologic outcomes in infants < 6 months of age in this study. In the younger cohort (age ≥ 14 days to < 6 weeks), 70% of subjects achieved reduction of viral load to < 400 copies/mL at Week 24, and in the older cohort (age ≥ 6 weeks to < 6 months) 48% of treated subjects achieved this level of HIV suppression at Week 24. Further, statistically significant median decreases from baseline in HIV-1 RNA levels were observed at all study visits in both the younger (age ≥ 14 days to < 6 weeks) and older (age ≥ 6 weeks to < 6 months) cohorts ($p \leq 0.016$). Lopinavir/ritonavir appears to have favorable immunologic response despite the facts that in the younger cohort (age ≥ 14 days to < 6 weeks), CD4 response was variable, likely reflecting the limited number of subjects with CD4 data available, and the natural evolution of CD4 counts in infants. In the older cohort (age ≥ 6 weeks to < 6 months) the CD4 counts and percentages were increased at Weeks 12 (CD4 percentage only) and 24, suggesting improvement in immunologic function through 24 weeks of study treatment in these subjects. See details in Medical Officer's review.

SAFETY RESULTS:

The adverse events seen in this pediatric study of very young infants were similar to those seen in previous pediatric and adult studies. There were no drug specific safety concerns regarding gastrointestinal, liver function, or metabolic effects that have not previously been noted in pediatric subjects receiving lopinavir/ritonavir. See details in Medical Officer's review.

DISCUSSION AND CONCLUSIONS:

In infants < 6 weeks of age who received lopinavir/ritonavir doses of 300/75 mg/m^2, 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 lopinavir/ritonavir dose of 230/57.5 mg/m^2 without an NNRTI (the approved dose) in Study M98 940 (Table 4).

In infants between 6 weeks and < 6 months of age who received lopinavir/ritonavir doses of 300/75 mg/m^2, 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 lopinavir dose of 230/57.5 mg/m^2 without an NNRTI in Study M98 940 (Table 4).

The lopinavir 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 lopinavir dose of 230 mg/m^2 without an NNRTI (Table 4). 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).

Phase II data from adults support the 300/75 mg/m^2 dose in children < 6 months old. Despite the lower lopinavir drug exposure observed with the 300/75 mg/m^2 dose in infants < 6 weeks and infants between 6 weeks and < 6 months of age cohorts in Study P1030, substantial antiviral activity was demonstrated as reflected in the high proportion of subjects who achieved HIV-RNA < 400 copies/mL at Week 24. This could be due to the fact that younger children were more likely to have less HIV resistance. In a phase II study (M97-720) in HIV-infected, antiretroviral naïve, adult patients, 200/100 mg BID cohort achieved similar efficacy endpoint compared to that of 400/100 mg BID cohort. The mean lopinavir trough plasma concentration of 200/100 mg BID regimen was 2.72 (53%CV) μg/mL, 30 -50% lower than that of 400/100 mg BID regimen. The higher dose (400/100) was selected for further development because it was safe and it provided a great margin between lopinavir trough concentration and wild type EC50. Please refer to the Clinical Pharmacology and Biopharmaceutics reviews of Kaletra capsule formulation (NDA 21-226). Lopinavir trough plasma concentration of 1.0 μg/mL is about 15-fold of wild-type EC50. Thus, the collective data supports use of this dose across the age range of 14 days to 6 months.

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 lopinavir/ritonavir dose could lead to higher than needed exposure in some individuals and lead to undesired toxicity.

In summary, lopinavir/ritonavir 300/75 mg/m^2 BID was safe and well tolerated in infants initiating treatment from 3.6 to 25.7 weeks of age. Lopinavir/ritonavir in combination with two NRTIs provided favorable virologic and immunologic response in infants 3 weeks to 6 months of age, with a tolerability profile similar to that seen in older pediatric and adult HIV-1 infected patients.

Thus a dose of lopinavir/ritonavir 300/75 mg/m^2 is recommended in children < 6 months old. The sponsor proposed the equivalent 1[redacted] dose. However the average dose these patients received in Study P1030 was about 15 mg/kg (actual doses convert to mg/kg). Considering the low C_{min} in these pediatric patients, a dose of approximately 16/4 mg/kg seems more reasonable.

PACTG 1038

TITLE: A Phase I/II Safety, Tolerability, and Pharmacokinetic Study of High Dose Lopinavir/ritonavir With or Without Saquinavir in HIV Infected Pediatric Subjects Previously Treated With Protease Inhibitors

BACKGROUND: Study P1038 was designed to offer therapeutic options for HIV positive children and adolescents who may have previously failed antiretroviral regimens, and to expand the experience and optimize therapy with protease inhibitors for HIV positive children and adolescents with late-stage HIV. The study used a higher-than-currently-recommended dose of lopinavir/ritonavir with a rationale that higher doses of drug may result in plasma drug concentrations that may suppress viral replication even in resistant clones with reduced susceptibility to those drugs. Higher doses of drug may suppress viral replication even in resistant clones with reduced susceptibility to those drugs. The limiting factor in intensive ARV regimens is often toxicity. Nevertheless, the risk of increased toxicity was warranted in this highly select patient population given their poor prognosis and limited therapeutic options. The maximally tolerated doses of most ARVs have not been established in children or adults. Further, pediatric doses have generally been extrapolated from, or based upon, adult dosing data.

OBJECTIVES: The primary objectives were to determine the safety and tolerability of high-dose lopinavir/ritonavir in Group 1 (400/100 mg/m^2 BID) and Group 2 (480/120 mg/m^2 BID) with concurrent non-nucleoside reverse transcriptase inhibitor (NNRTI) treatment, to evaluate the safety and tolerability of saquinavir (500 mg/m^2, 750 mg/m^2 or 1200 mg/m^2 BID) in combination with lopinavir/ritonavir in children and adolescents, and to estimate pharmacokinetic parameters for lopinavir in PI-experienced HIV-infected children and adolescents receiving combination ARV regimens.

SUBJECTS AND STUDY DESIGN:

This was a prospective multicenter, Phase I/II open-label study of high-dose lopinavir/ritonavir with or without concurrent non-nucleoside reverse transcriptase inhibitor therapy (NNRTI) (Group 1: 400/100 mg/m^2 twice daily + ≥ 2 NRTIs; Group 2: 480/120 mg/m^2 twice daily + ≥ 1 NRTI + 1 NNRTI). The study assessed the safety, tolerability, and pharmacokinetics of lopinavir/ritonavir with or without saquinavir in children and adolescents age ≥ 2 years to < 18 years of age who had failed prior therapy.

Treatment consisted of soft gelatin capsule and liquid formulations of lopinavir/ritonavir. The dosing regimen was intended to attain an inhibitory quotient sufficient for viral suppression (IQ ≥ 15) (IQ; ratio of lopinavir concentration 12 hours post dosing divided by the baseline HIV-1 isolate's fold change in phenotypic susceptibility × lopinavir IC50 of wild-type virus). Saquinavir was added to these regimens if the lopinavir IQ was < 15 and the subject could tolerate saquinavir. The protocol specified 48 subjects were to be treated for 48 weeks from the start of the initial lopinavir/ritonavir dose. Enrollment, however, was terminated after 26 subjects (7 to 17 years old) were enrolled due to slower-than-expected accrual.

The study regimen was divided into 3 steps as follows:

Step 1: Group 1: Lopinavir/ritonavir 400/100 mg/m^2 BID + No NNRTI

Step 1: Group 2: Lopinavir/ritonavir 480/120 mg/m^2 BID + Concurrent NNRTI

Step 2: Group 1a: Lopinavir/ritonavir 400/100 mg/m^2 BID + No NNRTI, add saquinavir 750 mg/m^2 BID

Step 2: Group 2a: Lopinavir/ritonavir 480/120 mg/m^2 BID + Concurrent NNRTI, add saquinavir 750 mg/m^2 BID

Step 3: Group 1b: For subjects in Group 1a, if the 12-hour post-dose plasma saquinavir concentration was < 500 ng/mL in the absence of saquinavir related toxicity, saquinavir was to be increased to 1200 mg/m^2 BID

Step 3: Group 2b: For subjects in Group 2a, if the 12-hour post-dose plasma saquinavir concentration was < 500 ng/mL in the absence of saquinavir related toxicity, saquinavir was to be increased to 1200 mg/m^2 BID

Subjects were PI experienced HIV-infected children and adolescents (≥ 2 years to < 18 years of age) who met all of the inclusion criteria and none of the exclusion criteria (See details in Medical Officer's Review).

15 out of 19 were between age of 12 to 17 at the time of PK analysis.

Table 1. Subject Demographic and Disease Characteristics at Baseline

Characteristic	Group 1 - No NNRTI	Group 2 - Concurrent NNRTI	Total
Total subjects	21 (100%)	5 (100%)	26 (100%)
Gender			
Male	10 (48%)	3 (60%)	13 (50%)
Female	11 (52%)	2 (40%)	13 (50%)
Race/Ethnicity			
White non-Hispanic	3 (14%)	0 (0%)	3 (12%)
Black non-Hispanic	11 (52%)	3 (60%)	14 (54%)
Hispanic	6 (29%)	1 (20%)	7 (27%)
American Indian, Alaskan Native	0 (0%)	1 (20%)	1 (4%)
More than 1 race	1 (5%)	0 (0%)	1 (4%)
Age (years), median (range)	15 (7-17)	15 (7-17)	15 (7-17)
Height (cm), median (range)	150.6 (116.0-170.8)	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-1 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 (12-1416)
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)	56.5 (17-66)
Fold Change, median (range)	152.00 (8.54-261.55)	76.50 (5.17-238.00)	142.50 (5.17-261.55)
Inhibitory Quotient, median (range)	1.280 (0.230-13.140)	1.735 (0.680-29.810)	1.280 (0.230-29.810)

FORMULATION: Lopinavir 80 mg/ritonavir 20 mg oral solution, 133.3 mg of lopinavir and 33.3 mg of ritonavir soft gelatin capsule

PK SAMPLE COLLECTION: Blood samples for the determination of LPV/RTV concentrations in plasma were obtained at Week 2: pre-dose, 1, 2, 4, 8 and 12 hours post-dose.

BIOANALYTICAL ASSAYS: A validated HPLC-UV assay was used to determine the plasma concentrations of lopinavir and ritonavir at [redacted] The calibration curves

ranged from 50 ng/mL to 20,000 ng/mL for ritonavir and 100 ng/mL to 40,000 ng/mL for lopinavir. The accuracy and precision were < 2.0% and <2.5% respectively.

PHARMACOKINETIC DATA ANALYSIS:

Pharmacokinetic parameters were calculated using non-compartmental methods. Pharmacokinetic parameters, including $AUC_{0\text{-}12hr}$, C_{max}, C_{12hr}, and CL/F for each subject were calculated.

PHARMACOKINETIC RESULTS:

Table 2. Pharmacokinetic Subject Demographics at the Time of Pharmacokinetic Sampling

Subject Number	Weight (kg)	Height (cm)	BSA (m^2)	Lopinavir Dose (mg)	Lopinavir Dose (mg/m^2)	Age at Analysis (months)
Group 1 - No NNRTI:						
111328	39.5	151.1	1.29	533	414	161
290115[b]	37.9	136.6	1.20	464	387	126
290133	66.8	160.1	1.72	667	387	212
290198	48.1	151.3	1.42	528	371	195
290204	61.7	172.4	1.72	667	388	190
290270	56.7	162.5	1.60	667	417	208
360048[a]	66.4	164.0	1.74	667	383	196
370233	44.7	154.7	1.39	533	385	206
370234	28.3	134.8	1.03	400	389	149
400337	64.4	150.8	1.64	667	406	183
470159[b]	22.7	117.7	0.86	336	390	92
500658	38.6	149.0	1.26	496	392	160
505949	45.5	144.0	1.35	533	395	200
650955	38.1	138.4	1.21	533	441	176
660061	51.5	149.4	1.46	533	365	171
690260[b]	37.9	145.0	1.24	464	375	129
Mean (SD)[c]	46.8 (13.5)	148.9 (13.2)	1.38 (0.26)	543 (102)	393 (19)	172 (34)
Median[c]	45.1	150.1	1.37	533	389	179.5
Range[c]	22.7 – 66.8	117.7 – 172.4	0.86 – 1.74	336 – 667	365 – 441	92 – 212

a. Week 8 results used as Week 2.
b. Subject was ≥ 2 and < 12 years of age at enrollment.
c. Additional Analysis performed by Abbott Laboratories.
SD = standard deviation
BSA = body surface area

Subject Number	Weight (kg)	Height (cm)	BSA (m^2)	Lopinavir Dose (mg)	Lopinavir Dose (mg/m^2)	Age at Analysis (months)
Group 2 - Concurrent NNRTI:						
400049	44.0	166.0	1.42	667	468	187
400125	61.5	157.0	1.64	800	488	195
401051[b]	25.7	125.0	0.94	448	474	95
Mean (SC)[c]	43.7 (17.9)	149.3 (21.6)	1.33 (0.36)	638 (178)	476.7 (10.3)	159 (55.6)
Median	44	157	1.42	667	474	187
Range	25.7 – 61.5	125.0 – 166.0	0.94 – 1.64	448 – 800	468 – 488	95 – 195
Overall:						
Mean (SD)	46.3 (13.7)	148.9 (14.0)	1.38 (0.26)	558 (116)	406 (36)	170 (37)
Median	44.7	150.8	1.39	533	390	183
Range	22.7 – 66.8	117.7 – 172.4	0.86 – 1.74	336 – 800	365 – 488	92 – 212

a. Week 8 results used as Week 2.

b. Subject was ≥ 2 and < 12 years of age at enrollment.

c. Additional Analysis performed by Abbott Laboratories.

SD = standard deviation

BSA = body surface area

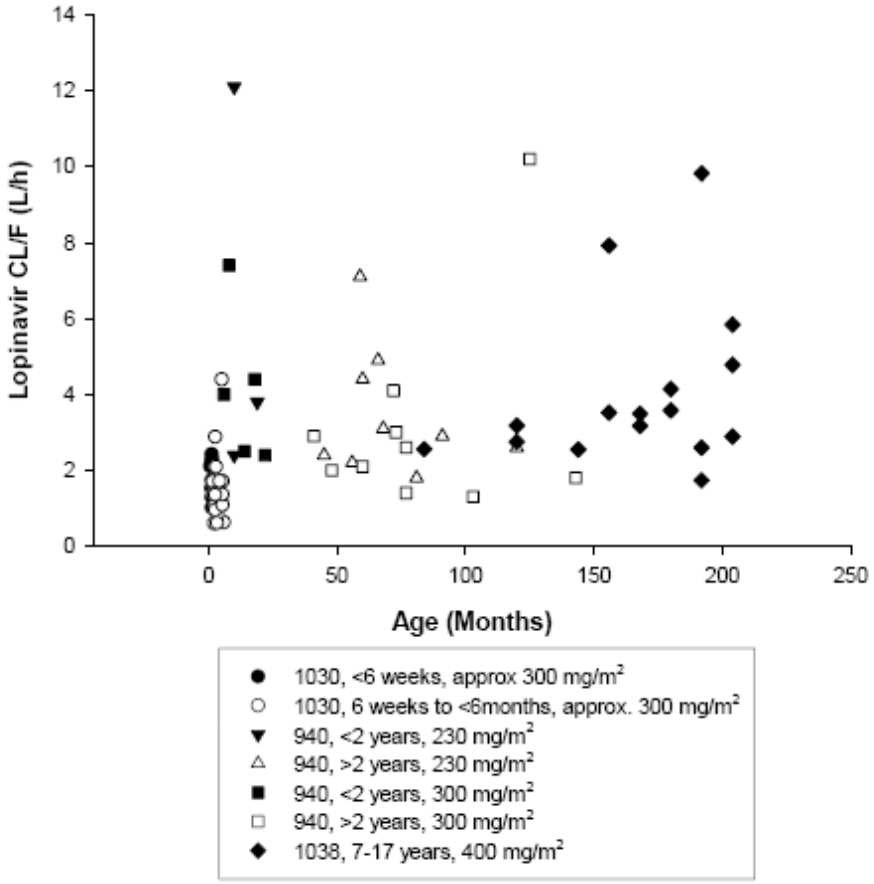
Table 3. Mean ± SD Lopinavir Noncompartmental Pharmacokinetic Parameters at Week 2 in Pediatric/Adolescent Subjects with HIV-1 Infection

		Group 1 (no NNRTI) LPV/r 400/100 mg/m2 BID	Group 2 (+NNRTI) LPV/r 480/120 mg/m2 BID
Parameter	(Units)	N = 16	N = 3
Doses	(mg/m2)	393 ± 19	477 ± 10
	(mg)	543 ± 102	638 ± 178
Tmax	(h)	2.54 ± 1.87	1.07 ± 1.85
Cmax	(µg/mL)	16.83 ± 5.27	13.76 ± 4.80
Cmin	(µg/mL)	9.92 ± 4.74	9.66 ± 5.23
AUC12	(µg•h/mL)	156.30 ± 55.4	137.20 ± 64.63
CL/F	(mL/h/kg)	87.88 ± 40.48	146.29 ± 112.91
	(L/hr)	4.03 ± 2.15	5.22 ± 1.77

Table 4. Comparison of PK Results across Studies: Lopinavir Pharmacokinetic Parameters (Mean ± SD) by Age, Lopinavir/ritonavir Dose, and Concomitant NNRTI Use

Age Group		Cmax	Cmin	AUC12	CL/F
Study Number (Dose Regimen)	N	(µg/mL)	(µg/mL)	(µg•h/mL)	(L/h)
12 Years to < 18 Years					
P1038 (400/100 mg/m2 BID)	13	16.73 ± 5.78	10.32 ± 5.21	158.12 ± 61.31	4.31 ± 2.31
P1038 (480/120 mg/m2 BID) + NNRTI	2	16.50 ± 0.99	12.09 ± 4.40	173.90 ± 16.55	4.27 ± 0.93
6 Years to < 12 Years					
M98-940 (230/57.5 mg/m2 BID)	3	10.32 ± 2.66	4.76 ± 2.52	97.30 ± 24.29	2.43 ± 0.57
M98-940 (300/75 mg/m2 BID)	7	13.78 ± 7.78	7.92 ± 5.83	131.79 ± 73.40	3.49 ± 3.12
M98-940 (230/57.5 mg/m2 BID) + NNRTI	7	6.72 ± 2.71	1.74 ± 2.14	51.79 ± 29.28	5.56 ± 2.64
M98-940 (300/75 mg/m2 BID) +NNRTI	6	10.51 ± 3.81	3.96 ± 4.41	88.28 ± 47.93	4.02 ± 1.40
Adults (From US Package Insert Label)					
M99-056 (400/100 mg BID)	19	9.8 ± 3.7	5.5 ± 2.7	92.6 ± 36.7	5.98 ± 5.75

Figure 1. Relationship Between Lopinavir CL/F and Age in Pediatric Subjects with HIV-1 Infection



EFFICACY RESULTS:

Changes in plasma HIV-1 RNA were less robust than anticipated. Of note, viral isolates from study subjects had a high degree of phenotypic resistance to lopinavir at baseline with only one subject able to achieve IQ > 15 despite the high doses of lopinavir/ritonavir employed in this study. Consistent with this, only three subjects from the overall study cohort achieved HIV-1 RNA < 400 copies/mL at Week 24. Nonetheless, significant increases in CD4 cell counts were seen in many subjects. See details in Medical Officer's review.

SAFETY RESULTS:

The adverse event profile and laboratory abnormalities, including those specifically identified in the WR (liver function test abnormalities, hyperglycemia, hyperlipidemia and abnormal body fat distribution) observed in these subjects receiving high-dose lopinavir/ritonavir were consistent with that previously observed with standard lopinavir/ritonavir doses in pediatric and adult subjects. See details in Medical Officer's review.

DISCUSSION AND CONCLUSIONS:

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

However, changes in HIV-1 RNA were less robust than anticipated. This likely reflects the high degree of phenotypic resistance to lopinavir at study entry, a factor that could not be overcome by the increased drug exposure achieved in this trial.

At these higher doses of lopinavir/ritonavir, 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 lopinavir/ritonavir 400/100 mg twice daily 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 in the absence of inducing agents such as efavirenz, and 300/75 mg/m^2 when administered with inducing agents.

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

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/s/

Derek Zhang
6/18/2008 03:29:52 PM
BIOPHARMACEUTICS

Kellie Reynolds
6/18/2008 04:29:20 PM
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