Poster PE7.9/3

Seven Year Follow-up of a Lopinavir/ritonavir (LPV/r)-Based Regimen in Antiretroviral (ARV)-Naïve Subjects

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Background

Lopinavir (LPV) is an HIV protease inhibitor (PI) that is co-formulated with ritonavir, which functions as an inhibitor of cytochrome P450 3A. Even at low ritonavir doses, there is a substantial increase in LPV exposure. At a dosage of 400 mg of LPV/100 mg ritonavir twice daily (3 co-formulated capsules BID), ritonavir concentrations are below those required for antiviral activity.[1] By contrast, the mean LPV C_{trough}/IC_{50} ratio (Inhibitory Quotient or IQ) for wild-type HIV type 1 (HIV-1) is ≥70 when lopinavir/ritonavir is dosed at 400/100 mg twice a day, potentially serving as a barrier to the emergence of drug resistance and providing activity against drug resistant virus.

Lopinavir/ritonavir (LPV/r, marketed as Kaletra™) has been studied in both antiretroviral-naïve and experienced HIV-1-infected subjects. The M97-720 study was a phase II trial of LPV/r in combination with stavudine (d4T) and lamivudine (3TC) in antiretroviral-naïve HIV-1-infected subjects. This study began in 1997 and was closed in 2005. This was the first trial of LPV/r in HIV-1-infected subjects and hence provides the longest duration of follow-up for subjects treated with LPV/r. This poster presents data on antiviral activity, immunologic parameters, and safety through 7 years (360 weeks).

Methods

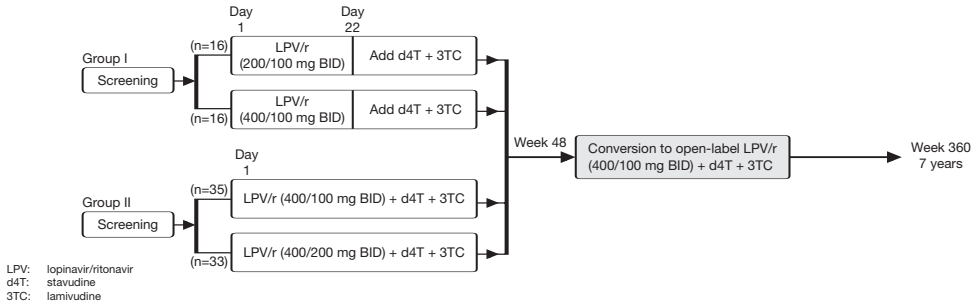
Entry Criteria

- Antiretroviral-naïve subjects with confirmed HIV-1 infection.
- Plasma HIV-1 RNA ≥5,000 copies/mL with no CD4 cell count restriction.
- Exclusion criteria included ALT or AST >2.5x Upper Limit Normal (ULN) and creatinine >1.5x ULN.

Study Design and Analysis

- One hundred antiretroviral-naïve HIV-1-infected subjects were randomized to receive one of three dosage levels of LPV/r (200/100 mg BID, 400/100 mg BID or 400/200 mg BID), together with d4T (40 mg BID) and 3TC (150 mg BID) given either after 3 weeks of monotherapy (Group I) or from study entry (Group II) (Figure 1).
- Enrollment into Group II began following an evaluation of preliminary efficacy and safety of LPV/r in Group I.
- After 48 weeks, all subjects converted to open-label LPV/r 400/100 mg BID dosing.
- Subjects were evaluated every 2–4 weeks for the first 24 weeks and every 12 weeks thereafter.
- At Year 6, 37 subjects treated with LPV/r + stavudine + lamivudine substituted stavudine with tenofovir disoproxil fumarate (tenofovir DF).

Figure 1. M97-720 Study Design



Efficacy

- Proportion of subjects with HIV-1 RNA either <400 copies/mL or <50 copies/mL was measured using an on-treatment method (missing values and values obtained during treatment interruptions excluded) and an intent-to-treat, noncompleter=failure method (ITT NC=F, missing values considered failure unless the immediately preceding and following values were either <400 copies/mL or <50 copies/mL).
- Immunologic response was assessed by the mean change in CD4 cell count from baseline to each study visit.

Virologic Evaluation

- Samples from any subject with HIV-1 RNA >500 copies/mL any time at or after Week 24 were submitted for genotypic and phenotypic drug resistance analyses. Genotype (GeneSeq™) and phenotype (PhenoSense™) analyses were performed by ViroLogic, Inc.

- Genotypic resistance to LPV was defined as the development of any primary or active site mutation in protease (amino acids 8, 30, 32, 46, 47, 48, 50, 54, 82, 84, and 90) confirmed by phenotypic analysis (≥2.5 fold increase in IC_{50} to LPV relative to wild type HIV-1).
- Resistance to lamivudine (3TC) was defined as the presence of an M184V and/or M184I mutation in reverse transcriptase.
- Resistance to stavudine (d4T) was defined as any thymidine analog mutation in reverse transcriptase (amino acids 41, 67, 70, 210, 215, 219).

Safety

- Cumulative incidence through Week 360 for adverse events and grade 3/4 laboratory values was summarized, as was the prevalence at Week 360, or the final visit.
- Laboratory measurements were obtained without regard to fasting, through year 6, after which all measurements were obtained in fasted state.
- Events of fat distribution changes/lipodystrophy were based on subject reports and investigator assessment of symptoms.

Results

Baseline Characteristics

1. Ninety-six male and 4 female subjects: 65% White, 29% Black, 6% Hispanic.
2. Mean age: 35 years (range 21–69).
3. Among all 100 subjects enrolled, the median baseline HIV-1 RNA and CD4 cell count were 4.8 $\log_{10}$ copies/mL and 326 cells/mm^3, respectively.

Efficacy

Viral Load Suppression Below the LOQ

- Based on the ITT NC=F analysis through Week 360, 61% of subjects had HIV-1 RNA <400 copies/mL (on-treatment analysis: 98%) (Figure 2) and 59% of subjects had HIV-1 RNA <50 copies/mL (on-treatment analysis: 95%) (Figure 3).

Figure 2. Study 720: HIV-1 RNA <400 copies/mL Through Week 360

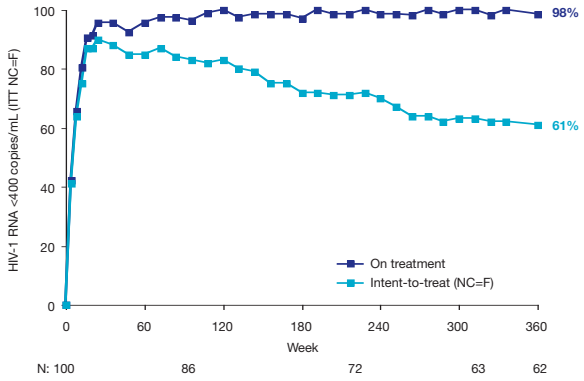
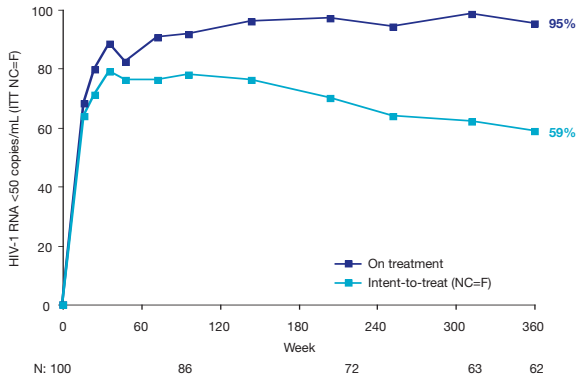


Figure 3. Study 720: HIV-1 RNA <50 copies/mL Through Week 360



Analysis of Genotypic and Phenotypic Drug Resistance

- A total of 33 samples from 29 subjects were submitted for resistance testing (Figure 4).
- 18 subjects met criteria for loss of virologic response, and 11 patients had at least 1 “blip” (single HIV-1 RNA value >500 copies/mL bracketed by HIV-1 RNA values <400 copies/mL) after Week 24.
- Genotypic drug resistance testing failed for 10 subjects whose median HIV-1 RNA was 575 copies/mL.
- In 19 subjects with available results, no lopinavir or stavudine resistance was observed, and 4 subjects demonstrated lamivudine resistance. Correspondingly, no evidence of phenotypic resistance to any PI was observed (Figure 5).
- 6 subjects demonstrated a substitution at a new position in protease during viral rebound (1 each at amino acids 15, 36, 43, 57, 63, 70). However, as demonstrated previously,[2] none of these substitutions are primary protease inhibitor mutations, no impact on protease inhibitor phenotypic resistance was observed, and all 3 of these subjects who completed the study demonstrated HIV-1 RNA <50 copies/mL at the final visit.

Figure 4. Study 720: Virologic Disposition

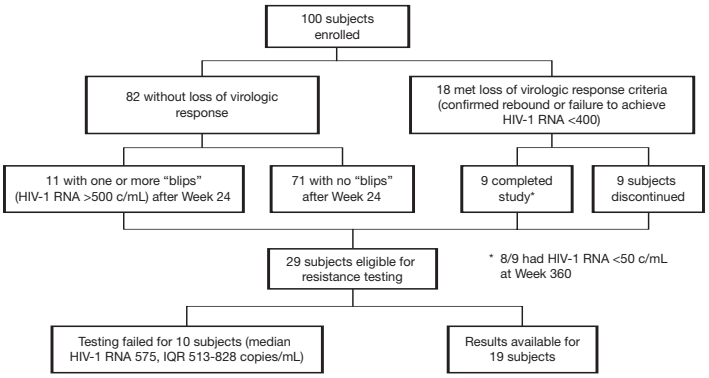
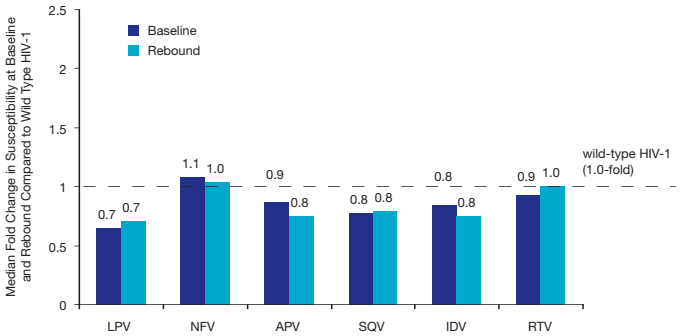


Figure 5. Study 720: No Change in Susceptibility to any Protease Inhibitor Between Baseline and Rebound



CD4 Cell Count Response

- Among subjects with values at both baseline and Week 360 (N=60), the mean CD4 cell count increased from 275 cells/mm^3 at baseline to 776 cells/mm^3 at Week 360, an increase of 501 cells/mm^3 (Figure 6).
- CD4 cell count response appeared to be consistent regardless of baseline CD4 cell count (Table 1). Among subjects with baseline CD4 cell count <50 cells/mm^3, mean CD4 cell count increased from 23 cells/mm^3 at baseline to 556 cells/mm^3 at Week 360, an increase of 533 cells/mm^3.

Figure 6. Study 720: Mean Change in CD4 Cell Count

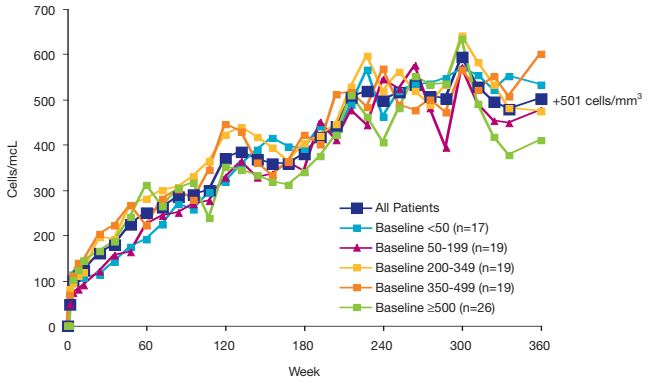


Table 1. CD4 Cell Count Increase at Week 360 by Baseline CD4 Cell Count

Baseline CD4 Cell Count in cells/mm^3 (Number of Subjects with Values at Baseline and Week 360)	Mean CD4 Cell Count Increase from Baseline to Week 360 (cells/mm^3)
<50 (n=15)	533
50-199 (n=12)	476
200-349 (n=11)	474
350-499 (n=11)	602
≥500 (n=11)	410

Safety

Table 2. Subject Disposition Through Week 360

Subjects Enrolled	100
Discontinuations prior to Week 360	38
Discontinuations probably or possibly related to study drugs	
AST/ALT increases	2
Diarrhea	1
Liver pain, enlargement, fatty deposits	1
Arthralgia	1
Elevated lipids	2
Fat distribution changes	5
Death[1]	1
Other reasons for discontinuation	
Adverse Event unrelated to study drugs (lymphoma-like reaction, hyperglycemia in diabetic patient, alcohol detoxification[2])	3
Lost to follow-up	9
Noncompliance	4
Personal/other reasons	9
Subjects completing study at Week 360	62

[1] Death of unknown cause occurred in a subject 10 days following thoracic spinal surgery with perioperative myocardial infarction.
[2] One subject was discontinued due to both noncompliance and alcohol detoxification.

Table 3. Most Common Adverse Events (occurring in ≥10% of subjects) Through Week 360

Moderate/Severe Drug-related AEs	Incidence Through Week 360 (n=100)	Prevalence at Week 360 (n=62)
Diarrhea	28%	0%
Nausea	16%	0%
Lipodystrophy	12%	11%
Abdominal pain	11%	0%

Table 4. Most Common Grade 3/4 Laboratory Abnormalities (occurring in ≥10% of subjects) Through Week 360

Grade 3/4 Lab Abnormalities	Incidence Through Week 360 (n=100)	Prevalence at Week 360 (n=62)
Cholesterol (>300 mg/dL)*	27%	2%
Triglycerides (>750 mg/dL)*	29%	3%
AST/ALT (>5X ULN)	11%	0%

* Taken without regard to fasting through year 6

Table 5. Distribution of Lipid Values at Week 360*

Category	Prevalence at Week 360 (n=62)	Prevalence at Week 360 or Last Available Value (n=100)
Total Cholesterol (mg/dL)		
Grade 1 <240	53 (85%)	79 (79%)
Grade 2 >240-300	8 (13%)	18 (18%)
Grade 3 >300-400	1 (2%)	3 (3%)
Grade 4 >400	0	0
Triglycerides (mg/dL)		
Grade 1 <400	56 (90%)	87 (87%)
Grade 2 >400-750	4 (6%)	10 (10%)
Grade 3 >750-1200	2 (3%)	3 (3%)
Grade 4 >1200	0	0

* Taken without regard to fasting through year 6
25 subjects with grade 2 or higher lipid values initiated lipid-lowering agents, and all but 2 subsequently demonstrated grade 0-1 lipid values.

- After Year 6, subjects were given the option to replace stavudine with tenofovir disoproxil fumarate. Subjects making this switch generally demonstrated improvements in lipids and other metabolic parameters.[3]
- The maximum effect of antihyperlipidemic agent use was assessed by comparing the final lipid values obtained prior to initiation of antihyperlipidemic agents to the minimum value obtained after the initiation of antihyperlipidemic agents and through the 7-year reporting period. The median decreases observed were 32% for total cholesterol and 59% for triglycerides. The pre-antihyperlipidemic agent value was also compared to the final value obtained through Week 360; the median decreases observed were 18% for total cholesterol and 42% for triglycerides.

Conclusions

- Through 7 years (360 weeks) of follow-up, antiretroviral-naïve subjects receiving LPV/r-based therapy exhibited sustained virologic responses, with 61% of subjects demonstrating HIV-1 RNA <400 copies/mL and 59% demonstrating HIV-1 RNA <50 copies/mL by intent-to-treat (NC=F) analysis. Corresponding on-treatment response rates were 98% and 95%, respectively.
- Mean CD4 cell count increased 501 cells/mm^3 over 360 weeks of follow-up with consistent CD4 cell count increases regardless of baseline CD4 cell count.
- Through 360 weeks of follow-up, no primary protease inhibitor resistance mutations have been observed in subjects with HIV-1 RNA >500 copies/mL any time at or after Week 24.
- LPV/r was safe and well tolerated on 7 years of therapy, as indicated by the low rate of study discontinuations due to LPV/r-related adverse events.
- This is the longest duration of follow-up for any study of an antiretroviral regimen, and clearly demonstrates the potency and durability of a LPV/r-based regimen in antiretroviral-naive HIV-1-infected patients.

Acknowledgments

M97-720 Study Subjects
Covance Central Laboratory Services
AIDS Research Consortium of Atlanta — *Dudley R*
Beth Israel Deaconess Medical Center–Harvard — *Fitch H*
Cornell Clinical Trials Unit — *Stroberg T*
Duke University Medical Center — *Harmon L*
Northwestern University — *Bruce J*
Pacific Oaks Research — *Simonson A*
Rush Presbyterian St. Luke's Medical Center — *Fritsche J*
Baylor College of Medicine — *Sepcie, B*
University of Colorado — *Putnam B, Basler C*
University of North Carolina at Chapel Hill — *Marcus C*
PPD Development — *Wheat R, Geigerman J*
Abbott Laboratories — *Sheehan K, Yang G*

References

1. Bertz R, Lam W, Brun S, et al. Multiple-dose pharmacokinetics (PK) of LPV/ritonavir (LPV/r) in HIV+ subjects. 39th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, USA, 1999 (abstract 0327).
2. Hicks C, da Silva B, King M, et al. Extensive Resistance Testing During 5 Years of Lopinavir/ritonavir Treatment in Antiretroviral-Naive HIV-Infected Patients: Results from Study 720. XV International AIDS Conference, Bangkok, Thailand, 2004 (WeOr-B1291).
3. da Silva B, Albrecht M, Benson C, et al. Improved metabolic profile with replacement of stavudine by tenofovir DF after 6 years of a LPV/r regimen. 7th International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV. Dublin, Ireland 2005 (abstract L957).