Poster # H-1241
48th Annual ICAAC/IDSA 46th Annual
October 25-28, 2008
Washington, DC

Single Agent Therapy with Lopinavir/Ritonavir Suppresses HIV-1 Viral Replication in ARV Naïve Patients: IMANI II - 96 Week Final Results

Joseph C. Gathe, M.D., F.A.C.P., FI.D.S.A.
4900 Fannin Street
Houston, Texas 77004
Phone: (713) 526-9821
Fax: (713) 526-0614
drgathe@josephgathe.com

Gathe Jr. JC[1] Yeh RF[1,2], Mayberry C[1], Nemecek J[1], Miguel B[1], Lipman BA[3], Fath MJ[3], Norton
[1]Therapeutic Concepts, P.A., Houston, TX, [2]University of Houston, Houston, TX, [3]Abbott, Abbott Park, IL

Background

- Single agent therapy (SAT) with lopinavir/ritonavir (LPV/r) has demonstrated successful control of viral replication as part of a variety of treatment strategies.1,2,3,4,5,6,7,8 However, there are limited data in LPV/r SAT in ARV naïve patients.9,10 Recent data demonstrated durable virologic control in ARV naïve patients at 96 weeks with this strategy.11,12
- We present 96 week data of our IMANI II study of LPV/r SAT in ARV naïve subjects.

Methods

- IMANI II was a 48 week, phase II open label study examining, safety, virologic response and tolerability of LPV/r SAT in 39 ARV naïve patients. 48 week data showed 79% of subjects had VL<75 (ITT: M=F).[10]
- We now present the final 96 week analysis from this study.
- Eligible patients were all that completed the 48 week original study which was the entire group
- Primary endpoints:
  - Proportion of subjects with plasma HIV-1 RNA (BDNA) <75 at week 96 (ITT M=F) calculated from baseline
- Secondary endpoints
  - Virologic resistance in failing patients
  - CD4 count change
  - Change in lipid and triglyceride concentrations
- Adherence was assessed by returned pill counts
- All patients received LPV/r tablet formulation from weeks 48 to 96

Major Inclusion Criteria (day zero)

- VL ≥ 2000 copies /ml
- CD4+ < 400*
- ≥18 years of age
- PI –naïve or has < 7 days of prior ART with any licensed or investigational compound
- No active opportunistic infection

* CD4+≥ 400 allowed only with documented understanding of DHHS guidelines and desire for treat ment.

Major Exclusion Criteria (day zero)

- M184V mutation, or protease mutations at 32, 46, 47, 48, 50, 54, 73, 82, 84, or 90
- HBV co-infection, HCV requiring treatment
- Hypersensitivity, pregnancy, contraindicated concomitant meds
- Significant concomitant illness

Baseline Characteristics

	n = 39
Gender - n (%)	
Male	**27 (69)**
Female	**12 (31)**
Race/Ethnicity - n (%)	
Caucasian	**20 (51)**
African American	**17 (44)**
Asian	**1 (3)**
Hispanic	**1 (3)**
Age years – mean (range)	**41 (18-66)**
Viral load at baseline – median (range)	**4.48 (3.62 - >5.70) log copies/ml**
> 100,000 copies/ml – n (%)	**10 (26)**
CD4+ at baseline – median (range)	**258 (12-1165) cells/mm³**
>51-≤ 200 cells/mm³ – n (%)	**10 (26)**
< 50 cells/mm³ - n (%)	**3 (8)**

Results

Figure 1: Subject disposition through week 48

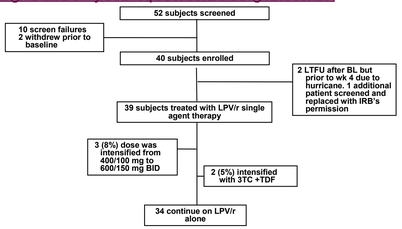


Figure 2: Subject Disposition 48 → 96 weeks

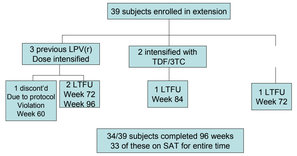
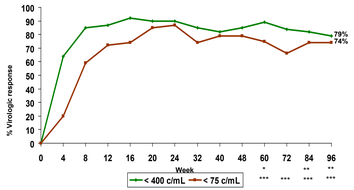
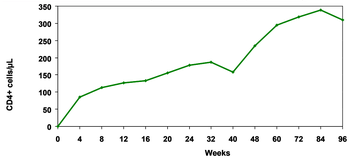


Figure 3: Viral suppression (ITT M=F)



* 1 subject week 60 lab lost, but week 72 and 84 VL <75
** 2 subjects week 84 lab lost, but VL < 75 at week 96
***Includes one subject intensified with TDF/3TC

Figure 4: Change in CD4+ from baseline through 96 weeks (median)



•10/11 subjects beginning with CD4 <200 had CD4 count >200 at week 96. Only subject (33) who was non-compliant had CD4<200

Figure 5: Point prevalence of virologic response

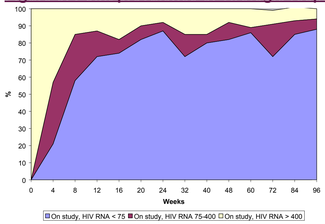


Table 6: Viremic subjects to week 48

Subject		Outcome Week 48-96
011	**Rebounded and resuppressed throughout study. Week 40 = VL 1210 c/mL, Week 44 VL = 793 c/mL and 139 c/mL at week 48. Dose intensified at week 48.**	Ongoing non-adherence LTFU week 96
013	**Dose intensified at week 40. Week 48 VL 139 c/mL. Patient withdrawn. Patient admitted he was not treatment naïve at study start. He was untruthful in order to gain access to free medication. He had been on several regimens previously, including taking his partner's Kaletra as single-agent "from time to time".**	Dropped at week 60 for protocol violation
030	**Poor compliance suspected. Adherence counseled. Rebounded throughout study. Intensified with tenofovir and emtricitabine at week 40. Suppressed to VL < 75 c/mL at week 44 and 48.**	LTFU week 84
033	**Poor compliance. Adherence counseled. Failure at week 16. Intensified with tenofovir and emtricitabine . Suppressed below 400 copies/mL by Week 44 (VL 120 = c/mL), Week 48 VL = 19950 c/mL.**	Non-compliant VL 24,778 at week 96
043	**Poor compliance. Reached one-log VL decrease by week 4. Reached < 400 c/mL by week 16. Rebounded at week 20. Adherence counseled. LPV/r dose intensified at week 28. Did not resuppress.**	LTFU week 60
049	**Periodic non-compliance suspected–Rebounded at week 32, resuppressed at week 44. VL 743 c/mL at week 48. Resuppressed again after week 48 with adherence counseling.**	VL<75 at week 96

Table 7: Viremic subjects weeks 60-96

Weeks	60	72	84	96
Subject ID				
1	<75	92	<75	<75
2	<75	181	125	<75
16	<75	6697*	NA	<75
22	<75	<75	276*	217
24	<75	<75	629	794
29	17,659*	79	<75	<75
32	116	<75	<75	101

•*Documented or suspected non-adherence

Table 8: Subjects who qualified for resistance testing to week 48

Subject	Baseline Protease Mutations	Baseline RT Mutations	On-therapy Protease Mutations	On-therapy RT Mutations	Phenotype in those with PI mutation on therapy – Fold Change (sensitivity)	
011	**L63P**	**98S**	**L63P**	**None**	**Phenotype not done due to no recognized change in genotypic resistance**	
013	**M36I, L63P, A71V, I93L, E35D**	**211K, 333E**	**L63P, A71V**	**None**	**Phenotype not performed as subject was untruthful regarding prior treatment at baseline. Subject was not ARV naïve and received PI medication prior to study.**	
030	**M36I**	**135wt/T**	**M36I**	**None**	**Phenotype not done due to no recognized change in genotypic resistance**	
033	**L63P**	**V179D**	**L63P**	**V179D**	**Phenotype not done due to no recognized change in genotypic resistance**	
043	**L10I, L63P**	**None**	**L10I, L63P, I13V**	**None**	**Lopinavir – 0.89 (sensitive) Ritonavir – 1.59 (sensitive) Atazanavir – 0.96 (sensitive) Darunavir – 1.25 (sensitive)**	**Fosamprenavir – 1.35 (sensitive) Nelfinavir – 1.58 (sensitive) Saquinavir – 1.30 (sensitive) Tipranavir – 1.1 (sensitive)**
049	**L10V, K20I, M36I**	**None**	**L10V, K20I, M36I, I13V, H69K, L89M, G16E.**	**None**	**Lopinavir – 0.52 (sensitive) Ritonavir – 0.53 (sensitive) Atazanavir – 0.58 (sensitive) Darunavir – 0.48 (sensitive)**	**Fosamprenavir – 0.34 (sensitive) Nelfinavir – 0.42 (sensitive) Saquinavir – 0.62 (sensitive) Tipranavir - 0.64 (sensitive)**

Table 9: Subjects who qualified for resistance testing weeks 48 to 96

Subject	Week	VL	Genotype
11	60	14,067	No mutations
24	96	794	RT I15V M36I PI – no mutations
33	96	24,778	No mutations

Table 10: Cholesterol and triglycerides through 96 weeks

N=33	Baseline	Week 24	Week 48	Week 96
Total cholesterol (mg/dL)				
Median	**163**	**209**	**213**	**204**
Range	**115-270**	**123-349**	**86-327**	**116-340**
HDL-c (mg/dL)				
Median	**39**	**51**	**51**	**46**
Range	**24-71**	**28-107**	**24-89**	**20-132**
Non-HDL-c (mg/dL)				
Median	**123**	**162**	**157**	**160**
Range	**66-235**	**67-299**	**62-276**	**73-304**
Triglyceride level				
Median	**119**	**189**	**214**	**275**
Range	**49-918**	**35 – 948**	**54-741**	**40-533**

Figure 11: Framingham Risk N=33

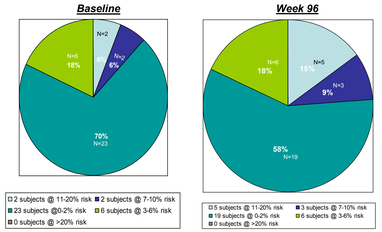


Table 12: All grade adverse events potentially related to study drug to week 48

	n (%)
Diarrhea†	**17 (44)**
Nausea	**4 (10)**
Abdominal upset	**3 (8)**
Fatigue	**2 (5)**
Increased abdominal girth	**2 (5)**
Vomiting	**2 (5)**
Diabetes (worsening)	**2 (5)**
Paresthesia	**1 (3)**
Headache	**1 (3)**
Increased appetite	**1 (3)**
Weight gain	**1 (3)**
Excessive thirst	**1 (3)**

*** Two drug-unrelated SAEs were reported. Subject 038 developed a low grade leiomyosarcoma of the neck and subject 009 was hospitalized with a bilateral buttock abscess with MRSA, and severe clostridium difficile colitis. However, the virologic responses were not compromised**

† 18/30 (33%) reported diarrhea onset while receiving soft-gel capsules. 7/39 (18%) reported new onset diarrhea while receiving tablets. No subjects withdrew due to adverse events.

Table 13: All grade adverse events potentially related to study drug week 48-96

	N (%)
Increased abdominal girth	1 (1)
Weight gain	1 (1)
Worsening of Diabetes Mellitus Begin insulin at week 60	1 (1)
Diarrhea	1 (1)
Diabetes Mellitus – new onset Begin oral hypoglycemic agent @ week 96	1 (1)

Conclusions

- In this study, the strategy of LPV/r SAT in ARV naïve patients, demonstrated durable virologic response through week 96 with 74% achieving <75c/ml and 79% <400c/ml; ITT: M=F
- Immunologic improvement continued over the entire study with a CD4 median increase of 310 cells
- When rebound occurred it appeared to be associated with documented or suspected non-adherence.
- In the first 48 weeks, 4 out of 6 rebounding patients re-suppressed upon adherence counseling and/or intensification. Low level viremia was seen in 5/39 (13%) following viral suppression without clinical or resistance sequele except in 1 subject who selected the I54V, but upon further investigation was not ARV naïve at baseline
- In the second 48 weeks, only 3 subjects required resistance testing. In each case, only wild type virus was seen. Low level viremia was noted in 8 subjects and 6 of the 8 responded to adherence counseling. No clinical or resistance sequele were noted and no intensification was necessary.
- LPV/r tablets were generally well tolerated with no significant adverse events seen from weeks 48 to 96.
- Framingham risk scores did not change significantly from baseline with one subject began lipid lowering agents during the entire study period
- Subjects who lost virologic response or had intermittent viremia did not develop protease inhibitor resistance.
- These 96 week results, as well as CNS and female genital tract virologic control response data from IMANI II presented previously13,14, support the ongoing research into LPV/r as single agent therapy.

Discussion

- The results from IMANI II provide complimentary data to the MONARK study which also showed 96 week virologic suppression and immunologic improvement with LPV/r SAT in ARV or PI naive pts. The results from these SAT trials are not dissimilar to observed outcomes from 96 week triple BPI HAART trials.15,16,17
- SAT gives an opportunity to see the direct safety and tolerability of LPV/r tablets. AE's of any grade were rare and there were no significant changes in Framingham risk score over the 96 weeks.
- Intermittent viremia was seen in a minority of subjects and were most often due to non-adherence. Different from the MONARK trial, in IMANI II, we did not document the development of major PI resistance mutations. Of note, in MONARK, 5/63 subjects on LPV/r SAT developed protease associated resistance mutations but without phenotypic resistance to LPV/r or other PIs13. To minimize resistance, clinicians should be intolerant of significant periods of viremia independent of regimen choice. The resistance consequences of LPV/r SAT are comparable to published BPI HAART with preservation of phenotypic class sensitivity and without the in class and/or multiclass resistance of NNRTI HAART. 17,18,19,20,21
- The success of IMANI II suggests LPV/r SAT may be an option for clinicians/patients. Specifically a desire to; avoid NRTI toxicity, reduce the cost of HAART, or simply patient preference are situations where this strategy could be applied.

Future Directions

- IMANI III – fully enrolled – LPV/r SAT qd as a 48 week extension of IMANI II
- Single Genomic Sequencing
  - Will begin late 2008 to analyze whether baseline and/or developing minority variants play any role in predicting subjects with low level viremia.
- Economics –planning stage- cost/efficacy analysis of LPV/r SAT in the IMANI II subjects
- Still needed: Large multi-centered comparative trials to confirm findings these pilot results.

References

[1]Cameron W, et al. JID. 2008; 22:385-393.
[2]Nunes E.P., Oliveira M.S., Almeida M.M.T.B., Piloto J.H., Ribeiro J.E., Faulhaber J.C. Norton M., Schechter M., Zajdenverg R. 48-week efficacy and safety results of simplification to single agent lopinavir/ritonavir (LPV/r) regimen in patients suppressed below 80 copies/mL on HAART - the KalMo study. Program and abstracts of the XVI International AIDS Conference; August 13-18, 2006; Toronto, Canada. Abstract TUAB0103.
[3]Arribas J, Pulido F, Delgado, R, et al. Lopinavir/ritonavir as single-drug maintenance therapy in patients with HIV-1 viral suppression: forty eight week results of a randomized, controlled, open label, clinical trial (OK04 Study). Program and abstracts of the XVI International AIDS Conference; August 13-18, 2006; Toronto, Canada. Abstract THLB0203.
[4]Arribas JR, et al. 11th EACS; Madrid 2007; #PS3/1.
[5]Pulido F, et al. AIDS 2008; 22:F1-F9.
[6]Nunes EP, et al. ibid, #P7.5/04
[7]Singh KP, e al. ibid. #P7.5/04
[8]Perone G, Mieras J, et al. A pilot study of switch to lopinavir/ritonavir (LPV/r) monotherapy from non-nucleoside reverse transcriptase inhibitor–based therapy. HIV Clinical Trials 2006;7:237–45
[9]Gathe JC Jr, Washington MY, Mayberry C, et al. IMANI-1 TC3WP Single drug HAART-proof of concept study. Pilot study of the safety and efficacy of Kaletra (LPV/r) as single drug HAART in HIV + ARV-naïve patients: interim analysis of subjects completing final 48 week data. Abstract MoOrB1057. Program and abstracts of the XV International AIDS Conference; July 11-16, 2004; Bangkok, Thailand.
[10]Gathe JC Jr, Yeh RF, Mayberry C, et al. Single-agent therapy with lopinavir/ritonavir suppresses plasma HIV-1 viral replication in HIV-1 naive subjects: IMANI-2 48-week results. Program and abstracts of the 4th IAS Conference; July 22-25, 2007; Sydney, Australia. Abstract WEPEB034.
[11]Gathe, J et al. A 48 Week Pilot Study of the Safety and Efficacy of Lopinavir/Ritonavir (LPV/r) a Single Agent. Therapy In ARV Naïve Patients Post Study Follow-up. The 8th International Congress On Drug Therapy in HIV Infection Glasgow, UK, November 12-16, 2006; 950521
[12]Delfraissy JF, Flandre P, Delaugerre C, et al, Lopinavir/ritonavir monotherapy or plus zidovudine and lamivudine in antiretroviral-naive HIV-infected patients. AIDS. 2008;22:385-396.
[13]Ghosn, J et al. XVII IAC, Mexico, August 3-8, 2008; ABS TUPE 0113.
[14]Yeh RF, Letendre S, Novak I et al. Single-agent therapy with lopinavir/ritonavir controls HIV-1 viral replication in the central nervous system. 14th Conference on Retroviruses and Opportunistic Infections. February 25-28, 2007; Los Angeles, California.
[15]Yeh RF et al. Single Agent Therapy (SAT) with Lopinavir/ritonavir (LPV/r) Controls HIV-1 Viral Replication in the Female Genital Tract. 11th European AIDS Conference (EACS) - Madrid, Spain - October 24-27, 2007; #7.70/2.
[16]Smith KY, et al. 17th IAC, Mexico 2008; #LB8PE1138
[17]Malan, N et al. 4th IAS Sydney 2007; WEPEB024.
[18]Rödtler SA, et al. N Engl J Med 2008;358:2095-106.
[19]MacArthur, R et al. IAC 2006, ABS TU ABB0102
[20]Vorwyl, et al. 14th CROI 2007, Los Angeles; ABS 667.
[21]Phillips, A et al. 14th CROI 2007, Los Angeles; ABS 532.