Tolerability and Therapy Preference of Lopinavir/ritonavir (Kaletra®) Soft-gel Capsules and Tablets as Single Agent in a Cohort of HIV Positive Adult Patients (IMANI-2)

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Background

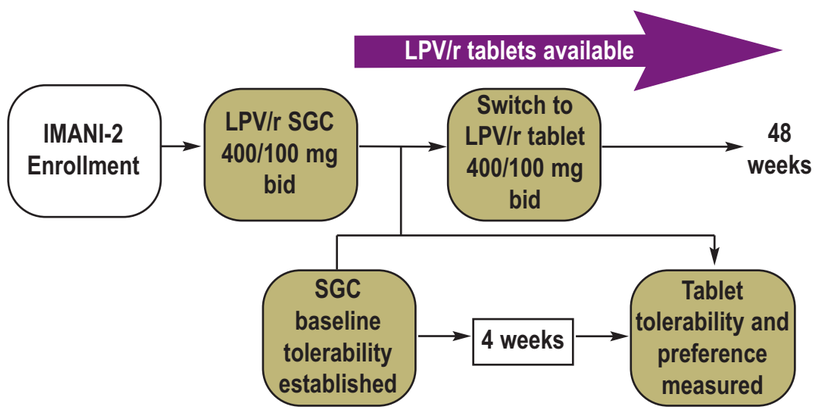
- Lopinavir (LPV) is an HIV protease inhibitor that is co-formulated with Ritonavir {r}. The ritonavir acts as a pharmacokinetic enhancer for LPV. The co-formulation is marketed as both Kaletra® and Aluvia® (LPV/r).
- The originally available versions of LPV/r were soft gelatin capsules (SGC) 133/33 mg and liquid solution formulation. Limitations of the SGC's include a requirement to be taken with a meal to improve pharmacokinetics.[1,2] Also patients reported diarrhea. Excipients in the SGC, including oleic acid, polyethylene glycol, and sorbitol, can be associated with diarrhea.[3] A new formulation of LPV/r received US FDA approval, October 2005. LPV/r tablets 200/50 mg employ a novel technique, Meltrex, for drug delivery that does not require the inclusion of many excipients required for the SGC's. Due to improved pharmacokinetics, the tablet formulation can be taken without food.
- Studies have been done on LPV/r as triple drug therapy, but there are no studies of single-agent LPV/r tablet tolerability that have been published to date.

LPV/r SGCs

LPV/r tablets

Methods

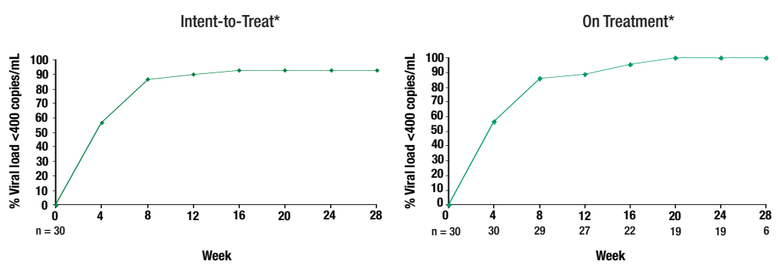
- IMANI-2 is a prospective, single center, single-arm, open-label, ongoing trial exploring LPV/r single agent therapy in 40 antiretroviral naïve, HIV-1 infected patients. Subject monitoring for the first 48 weeks is frequent, q 4 weeks. Primary objective of the trial is to determine the proportion of patients with HIV RNA <400 copies/mL at weeks 24 and 48.
- Thirty (30) of the IMANI-2 subjects had received at least 4 weeks of LPV/r SGC therapy at the time of enrollment for this sub-study. All 30 were enrolled in the sub-study examining quality of life, tolerability, and treatment preference prior to and following switch from LPV/r 400/100 mg bid soft-gel capsule formulation to LPV/r 400/100 mg bid tablet formulation.



Key Entry Criteria

- ≥18 years of age
- ARV naïve
- No current opportunistic infections or acute illness
- No concurrent HCV interferon therapy
- As a condition of the IRB, patients must have been responding to be retained on single agent therapy (responding defined as demonstrated one log-reduction in viral load by week 4 and virologic suppression <400 copies/mL for those beyond week 16). All 30 patients who had reached at least 4 weeks at the time of this sub-study were responding. In addition, the IRB required that week 24 viral response be no more than five percentage points lower than LPV/r pivotal trial results to continue the study (Figure 1).

Figure 1: Viral Load at Time of Tablet Switch



*ITT with last observation carried forward

Study Design and Analysis

Responding subjects were administered a series of questionnaires immediately prior to and 4 weeks following switch from soft-gel capsule to tablet formulation. These include:

- ***Medical Outcomes Study-HIV (MOS-HIV)*** – a validated instrument assessing quality of life consisting of 35 questions to assess physical, social, and emotional well-being during the previous 4 weeks. Scores are standardized to a reference population with higher values representing better quality of life. Two summary scores are computed, including physical health summary score (PHSS) and mental health summary score (MHSS).[4]
- ***Center for Epidemiologic Studies-Depression (CES-D)*** – a 20 item questionnaire assessing factors consistent with a depressive state during the previous week.[5] A score of 16 or higher indicates that the subject is experiencing symptoms of depression.
- ***Modified Global Condition Improvement (GCI)*** – measures overall tolerability and HIV treatment preference.

Prevalence of diarrhea was captured via adverse event reporting prior to and following tablet switch.

Statistics were conducted using two-tailed t-tests for paired comparisons with 0.05 level of significance.

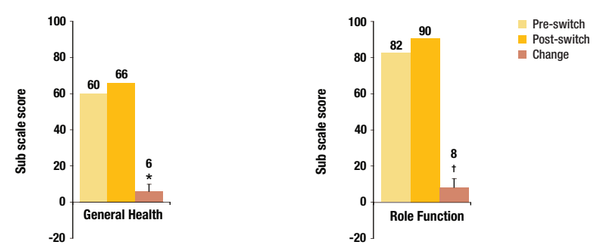
Results

Table 1: Summary of Characteristics at Time of Formulation Switch

	n = 30	
Gender – n (%)		
Male	22	(73.3)
Female	8	(26.7)
Race/Ethnicity – n (%)		
Caucasian	19	(63.3)
African American	9	(30.0)
Asian	1	(3.3)
Latin American	1	(3.3)
Age – mean (range)	41.5	(18-61)
Time (weeks) from IMANI-2 entry until tablet switch – mean (range)	24	(8-28)
Viral load at time of switch – mean copies/mL (range)	<75	(<75-293)
CD4+ at switch – cells/mm³ – mean (range)	454	(88-1303)

- MOS-HIV scores are summarized in Figure 2 and Table 2. Post-formulation switch, statistically significant increases in general health perception and role functioning were reported compared to baseline.
- General health perception includes degree of illness, perception of health compared to others, degree of agreement that health is "excellent", and whether or not one has been feeling badly lately.
- Role functioning includes whether or not one is able to work at a job or around the house, and the degree to which ability to do certain kinds of work has changed from baseline.

Figure 2: MOS-HIV General Health and Role Function Scores



*Statistically significant change from pre-switch (p = 0.047) – paired t-test
†Statistically significant change from pre-switch (p = 0.023) – paired t-test

Modest improvements were also reported in overall quality of life, social functioning, health transition (e.g., perceived health compared to 4 weeks ago), and pain scores. Little or no changes were observed in overall physical functioning, reported mental health, vitality, or cognitive functioning, health distress, or the physical and mental health summary scores. There was also no significant difference in CES-D score from pre- to post-switch (Table 2).

Table 2: MOS-HIV Subscales and CES-D

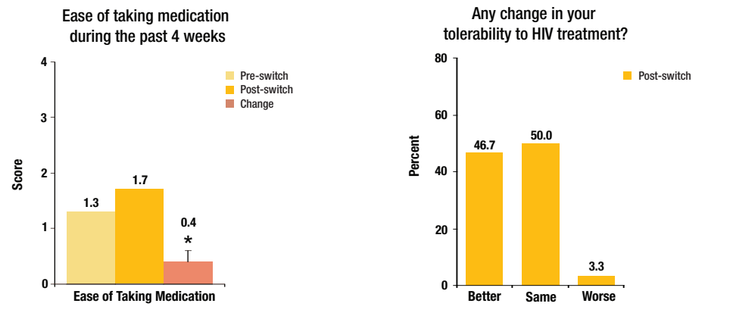
	Pre-switch	Post-switch	Change*
MOS-HIV			
Health Transition	61	68	+7
Pain	80	86	+6
Quality of Life	70	74	+4
Social Function	85	89	+4
Cognitive Function	83	86	+3
Vitality	64	66	+2
Physical Health Summary Score	53	55	+2
Mental Health Summary Score	51	52	+1
Mental Health	74	74	–
Physical Function	84	83	-1
Health Distress	79	76	-3
CES-D	13	12	-1

*p > 0.05

Results – continued

Self-reported ease of taking medication was significantly improved, and 46.7% reported improved medication tolerability post-switch (Figure 3).

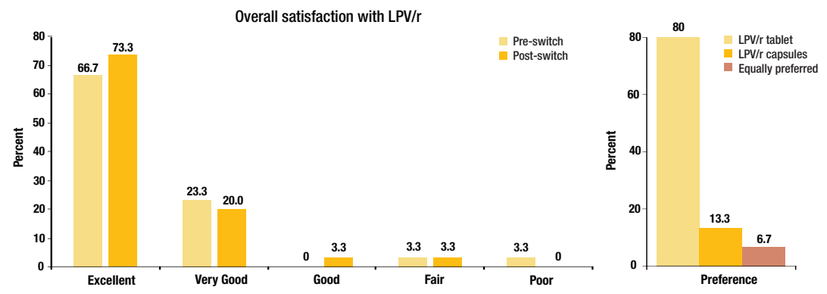
Figure 3: Global Condition Improvement Questionnaire



*Statistically significant change from pre-switch (p = 0.047) – Wilcoxon signed-rank test.

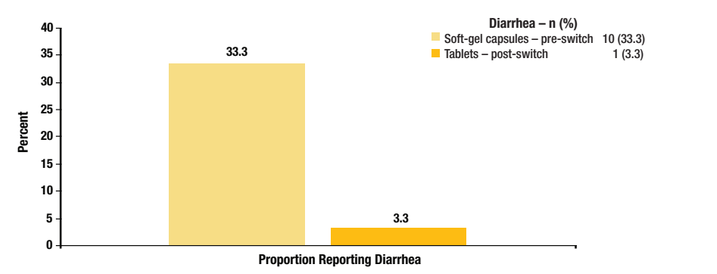
Overall satisfaction with LPV/r therapy was very high with the vast majority of respondents indicating preference for tablet formulation (Figure 4).

Figure 4: Global Condition Improvement Questionnaire, Satisfaction and Preference



Ten patients (33.3%) reported diarrhea of at least Grade 2 at any time of enrollment until switch while receiving soft-gel capsules. One patient* reported diarrhea (Grade 2) following switch to tablet formulation (Figure 5). No patients discontinued trial for diarrhea or AE.

Figure 5: Proportion Reporting Diarrhea Pre- and Post-Tablet Switch



*Patient had diarrhea for 4 months prior to switch from soft-gel capsules to tablets and one report of diarrhea post-switch that was possibly related to drug.

Conclusions

- This study offers the opportunity to examine LPV/r related tolerability without influences of other antiretroviral agents.
- Following switch from LPV/r soft-gel capsules to tablets, subjects reported:
  - Significant reduction/elimination of diarrheal adverse events
  - Significant improved general health and ability to function in role at work or in the home
  - Significantly improved self-reported ease of taking medication
  - High satisfaction and preference for LPV/r in tablet formulation
- The improvements in tolerability and preference for LPV/r tablet formulation may improve adherence and virologic and immunologic outcomes.

References

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