

# Single-agent Therapy with Lopinavir/ritonavir Suppresses Plasma HIV-1 Viral Replication in HIV-1 Naïve Subjects: IMANI-2 48-Week Results

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## Background

- A number of pilot trials utilizing Lopinavir/ritonavir (LPV/r) as single-agent therapy have shown good viral suppression.<sup>1-3</sup>
- Data employing the strategy of LPV/r as a single-agent ARV in naive subjects remain limited.<sup>4,7</sup>

## Methods

This is a Phase II, open-label, pilot study in 39 ARV-naïve subjects examining the safety, viral response, and tolerability of Kaletra® single-agent therapy administered 400/100 BID.

Primary end-points:

- Proportion of subjects with plasma HIV-1 RNA <400 c/mL at week 24 and 48
- Proportion of subjects with plasma HIV-1 RNA (branched DNA) <75 c/mL at week 48
- In addition, the IRB required that interim analysis at 24 weeks demonstrate viral suppression not more than 5% lower than LPV/r combination therapy as demonstrated in study M98-863.<sup>8</sup>

Adherence was assessed by returned pill counts.

## Major Inclusion Criteria

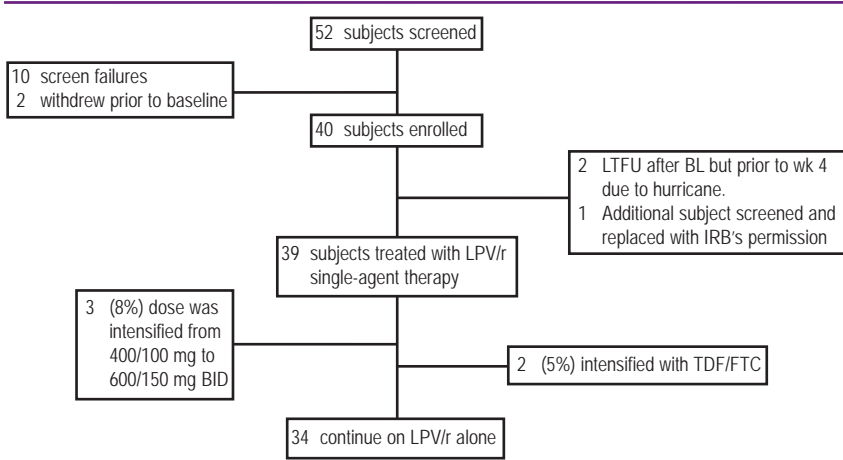
- VL ≥2000 c/mL
- CD4+ <400\*
- ≥18 years of age
- PI-naïve or has <7 days of prior ART with any licensed or investigational compound
- No active opportunistic infection

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

## Major Exclusion Criteria

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

## Subject Disposition through Week 48



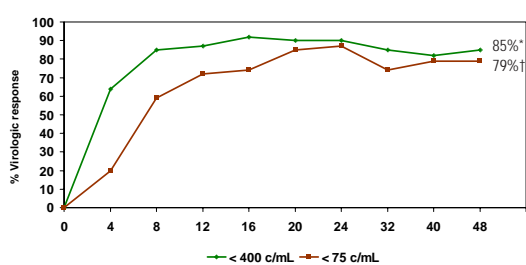
## Results

### 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 c/mL           |
| >100,000 c/mL – n (%)                    | 10 (26)                                |
| CD4+ at baseline – median (range)        | 258 (12 – 1,165) cells/mm <sup>3</sup> |
| >51 – ≤200 cells/mm <sup>3</sup> – n (%) | 10 (26)                                |
| <50 cells/mm <sup>3</sup> – n (%)        | 3 (8)                                  |

### Virologic Response

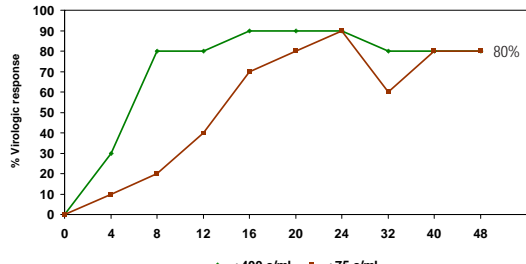
#### Viral Suppression (ITT, M=F)



\*One subject classified as an ITT responder was suppressed <75 c/mL weeks 8 – 40. He returned for 48 week follow-up having run out of LPV/r two weeks previously. VL at week 48 was 2,915 c/mL. Subject was restarted on LPV/r and retested 2 weeks later. At week 50 VL was 126 c/mL. At week 54 VL was <75 c/mL.  
 †Five responding subjects had low level viremia (>75 and <400 c/mL) at one or more follow-up visits after initial suppression to <75 c/mL.

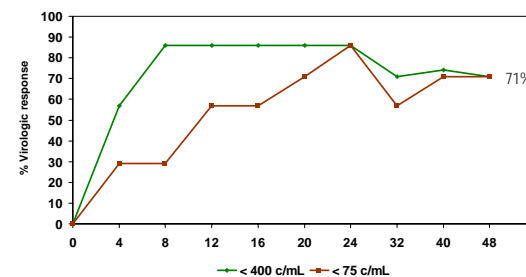
#### Subjects with VL >100,000 c/mL at Baseline (n=10)

#### Viral Suppression (ITT, M=F)

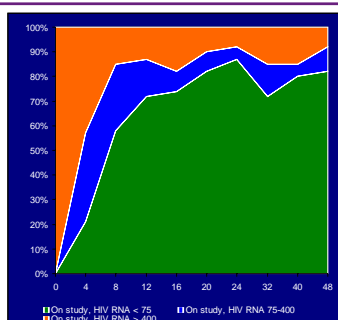


#### Subjects with CD4 <100 cells/mm<sup>3</sup> at Baseline (n=7)

#### Viral Suppression (ITT, M=F)

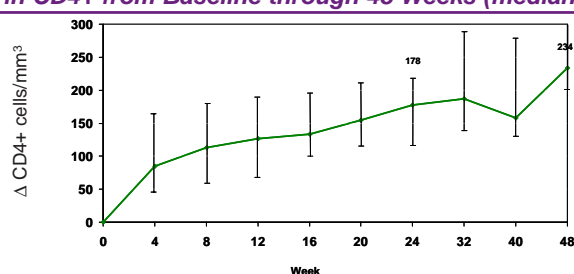


### Point Prevalence of Virologic Response\*



\*No subjects discontinued through week 48.

### Change in CD4+ from Baseline through 48 Weeks (median, IQR)



## Results (continued)

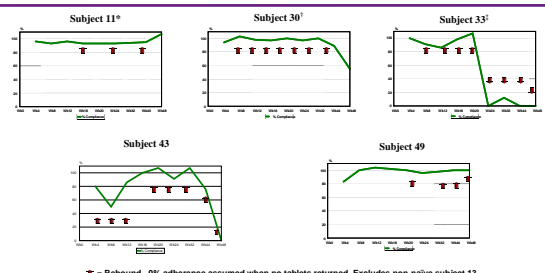
### Genotype/phenotype\* – Subjects who Qualified for Resistance Testing

| 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†  |
| 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                         | 135w/T                | M36I                                     | None                    | Phenotype not done†  |
| 033     | L63P                         | V179D                 | L63P                                     | V179D                   | Phenotype not done†  |
| 043     | L10I, L63P                   | None                  | L10I, L63P, I13V                         | None                    | Lopinavir – 0.89 (sensitive)<br>Ritonavir – 1.59 (sensitive)<br>Atazanavir – 0.96 (sensitive)<br>Darunavir – 1.25 (sensitive)<br>Fosamprenavir – 1.35 (sensitive)<br>Nelfinavir – 1.58 (sensitive)<br>Saquinavir – 1.30 (sensitive)<br>Tipranavir – 1.1 (sensitive)  |
| 049     | L10V, K20I, M36I             | None                  | L10V, K20I, M36I, I13V, H69K, L89M, G16E | None                    | Lopinavir – 0.52 (sensitive)<br>Ritonavir – 0.53 (sensitive)<br>Atazanavir – 0.58 (sensitive)<br>Darunavir – 0.48 (sensitive)<br>Fosamprenavir – 0.34 (sensitive)<br>Nelfinavir – 0.42 (sensitive)<br>Saquinavir – 0.62 (sensitive)<br>Tipranavir – 0.64 (sensitive) |

\*Phenosense – Monogram Biosciences TM

†Phenotype not done due to no recognized change in genotypic resistance.

### Adherence Failures



■ = Rebound. 0% adherence assumed when no tablets returned. Excludes non-naïve subject 13.

\*Documented noncompliant during pharmacist's counseling due to a) avoiding her morning dose to minimize diarrhea if she was going to be out for sometime, b) alcohol intake caused her to forget taking her dose, c) falling asleep and forgetting her dose.  
 †Admitted poor compliance due to chronic diarrhea despite returning no medication.  
 ‡Unannounced LPV/r trough 0.09 ug/mL at week 40.

### Virologic Failures

- Subject
- 011 Rebounded and resuppressed throughout study. Week 40 = VL 1,210 c/mL, week 44 VL = 793 c/mL and 139 c/mL at week 48. Dose intensified at week 48.
  - 013 Dose intensified at week 40. Week 48 VL 139 c/mL. Subject withdrawn. Subject 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".
  - 030 Poor compliance suspected. Adherence counseled. Rebounded throughout study. Intensified with TDF/FTC at week 40. Suppressed to VL <75 c/mL at week 44 and 48.
  - 033 Poor compliance. Adherence counseled. Failure at week 16. Intensified with TDF/FTC. Suppressed below 400 c/mL by week 44 (VL 120 = c/mL), week 48 VL = 19,950 c/mL.
  - 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.
  - 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.

### Cholesterol and Triglycerides Baseline through 48 Weeks

|                                  | Baseline  | Week 24   | Week 48  | % Change from Baseline |
|----------------------------------|-----------|-----------|----------|------------------------|
| <b>Total cholesterol (mg/dL)</b> |           |           |          |                        |
| Median                           | 163       | 210       | 213      | 29%                    |
| Range                            | 115 – 270 | 123 – 349 | 86 – 327 | (-42 – +86%)           |
| <b>HDL-c (mg/dL)</b>             |           |           |          |                        |
| Median                           | 39        | 51        | 51       | 24%                    |
| Range                            | 24 – 71   | 28 – 107  | 24 – 89  | (-19 – +89%)           |
| <b>Non-HDL-c (mg/dL)</b>         |           |           |          |                        |
| Median                           | 124       | 164       | 159      | 29%                    |
| Range                            | 66 – 235  | 67 – 299  | 62 – 276 | (-50 – +114%)          |
| <b>Triglyceride level</b>        |           |           |          |                        |
| Median                           | 116       | 195       | 215      | 45%                    |
| Range                            | 49 – 918  | 35 – 948  | 54 – 741 | (-37 – +598%)          |

### Adverse Events Potentially Related to Study Drug\*

|                           | 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.  
 †10/30 (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.

## Conclusions

- LPV/r single-agent therapy demonstrated sustained virologic response through week 48 with 31/39 (79%) <75 c/mL and 33/39 (85%) <400 c/mL (ITT:M=F).
- When rebound occurred it appeared to be associated with documented or suspected non-adherence.
- 4/6 rebounding subjects resuppressed upon adherence counseling and/or intensification.
- In one subject, a single major PI mutation (IAS-USA mutation score) was selected (I54V). However, upon further investigation, this subject was not ARV naïve.
- 5/39 (13%) of subjects who were responders demonstrated at least one episode of low-level viremia following initial viral suppression. The clinical significance is unclear.
- LPV/r as single therapy was generally well tolerated. The most prevalent adverse event was diarrhea, and was more likely to occur with the soft-gel capsule formulation.
- Cholesterol and triglycerides increased from baseline, consistent with other LPV/r investigation. No subject required lipid lowering agents.

## Discussion

- These results add to the growing body of knowledge on LPV/r single-agent therapy (SAT). While this study is non-comparative, it does provide additional evidence in several key areas:
  - The virologic efficacy (79% <75 c/mL at week 48) and immunologic efficacy (CD4+ cell count increase from baseline = 234 cells/mm<sup>3</sup>) of single-agent LPV/r were comparable to that seen in triple agent HAART<sup>9</sup> in treatment naïve subjects.
  - In this study, phenotypic resistance to protease inhibitor was not observed in naive subjects experiencing viremia suggesting minimal risk of resistance consequences.
  - As seen with LPV/r triple therapy, most subjects experiencing viremia were able to resuppress with adherent counseling or nucleoside intensification.
- The sustained efficacy seen in this study vs. other recent studies with boosted PIs may be due to several unique factors:
  - The coformulation of LPV/r vs. other boosted PIs may confer an efficacy advantage due to the inability to misdose RTV.
  - Effective penetration of LPV into the CNS reservoir resulted in CSF LPV levels greater than the IC<sub>50</sub> of WT virus and virologic control in the CSF.<sup>6</sup>
  - The availability of LPV/r tablet during the study allowed subjects to switch from LPV/r SGC to tablet, providing additional benefits such as reduced PK variability and tolerability.<sup>7</sup>
  - These benefits were not available in earlier studies of LPV/r single-agent therapy.<sup>10-12</sup>
- These results support continued scientific study of LPV/r tablet as SAT and on-going work includes:
  - Assessment of LPV penetration and virologic control in the female genital tract control during SAT
  - Longer term follow-up to assess the durability of the LPV/r tablet SAT strategy
  - Assessment of benefits and risks of simplification of stable subjects from BID to QD LPV/r single-agent therapy
  - Pharmacoeconomic analyses

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