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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 At Least 24 Weeks of a 48 Week Study

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Background

- Ideal antimicrobial agents fulfill three key characteristics:
  1) Efficacy in pathogen control
  2) Favorable safety/toxicity profiles
  3) Acceptable cost to ensure product availability
- Triple drug HAART is efficacious in HIV control which has lead to significant declines in morbidity/mortality due to AIDS events in treated subjects. Significant constraints to therapy however exist:
  - Toxicity – the leading cause of treatment discontinuation in the first year.[1]
  - Cost – economic factors ensure millions of eligible subjects do not receive life saving treatment in both developed and underdeveloped countries.
- Effective single drug HAART could decrease therapy cost by at least 2/3 and help to delineate more clearly safety/toxicity issues of an individual drug as compared to its use in combination.
- LPV (r) has ideal characteristics for single drug HAART:
  - Short-term activity comparable to triple drug HAART[2]
  - 24-hour pharmacokinetics significantly above IC_{50} of wild type virus[3]
  - Lack of definable genotypic/phenotypic resistance at time of failure in naïve subjects[4,5]

Methods

- 48 week proof of concept open label study. This is an analysis of subjects completing ≥ 24 weeks.
- Subjects accrued between March 2002 and March 2003 from a single site inner city clinic.
- Study was completely unfunded by any outside revenue source.
- Inclusion criteria
  - Age > 18
  - V_L > 2000
  - ARV naïve
  - No CD_4 criteria

  Exclusion criteria
  - Life threatening active AIDS defining illness
- Primary Endpoints
  - Change in V_L at 12, 24, 48 weeks
  - % of subjects < 400 copies at 48 weeks
  - Incidence of adverse events
- Secondary Endpoints
  - % of subjects < 50 copies at 48 weeks
  - CD_4 count changes
- LPV(r) was dosed 3 caps bid for weight < 70kg and 4 caps bid weight >70 kg.
- Intensification was allowed at any point with either TDF/3TC or SAQ.

Results

Table 1. Patient Baseline Characteristics (n=30)

Gender			
	Female	n=2	6.6%
	Male	n=28	93%
Race			
	White	n=18	60%
	Black	n=6	20%
	Hispanic	n=6	20%
Age			
	Mean		35.8 years old
	Range		20-58 years old
Plasma HIV -1-RNA (log 10 copies/ml)			
	Mean		262,020 copies/ml
	Range		4,161 - > 750,000 copies/ml
CD_4 count			
	Mean		169.5 cell/mm ^{3}
	Range		7 – 425 cell/mm ^{3}
CD_4 < 200		n=21	70%
V_L > 100,000		n=17	57%
CD_4 < 200 ⊕ V_L ≥ 100,000		n=16	54%

Table 2. Subject Disposition at Week 24

Patient Disposition	
LTFU	2
Adverse Events	2
Deported	1
Non Adherent	1
Virologic Failure	1
Hepatitis B	1

* Subject 023 was deported at week 16 and had a VL drop of 2.2 log (259,000 to 1,521)
* Subject 026 & 025 discontinued therapy due to AE's (GI intolerance at W12 & W1)
* Subject 017 was found to have active Hepatitis B and had TDF/3TC added at week 12

Figure 1: V_L Decay Curve of the Only Subject with Virologic Non-Response (Subject 010)

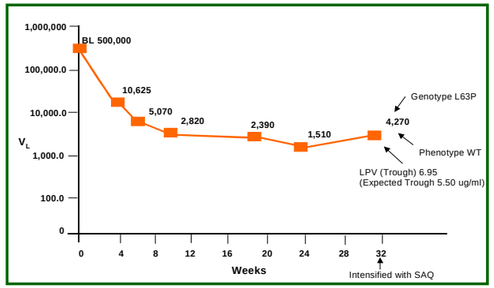


Figure 2: Virologic Response Curve (AT)

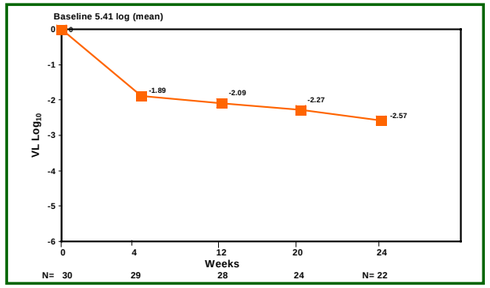


Figure 3: V_L <400 in Subjects ≥ 24 weeks

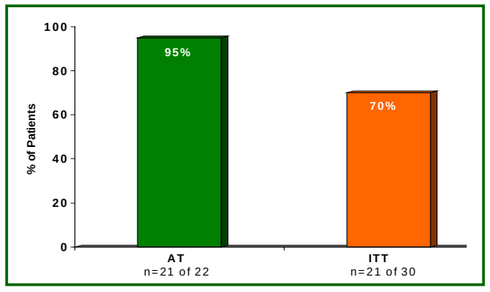


Figure 4: V_L Decay Curve (Subject 009)

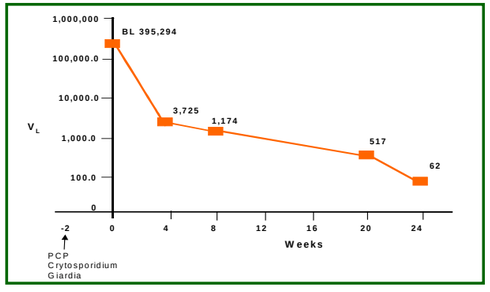


Figure 5. CD_4 Cell Count Change

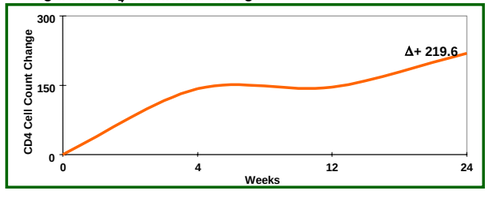


Figure 6: V_L Decay Curve (Subject 016)

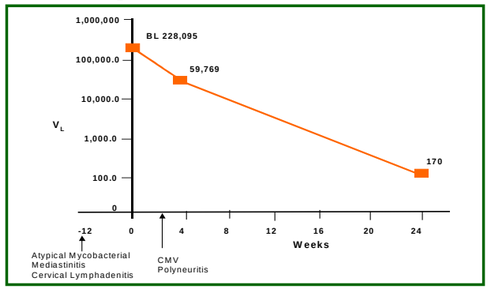
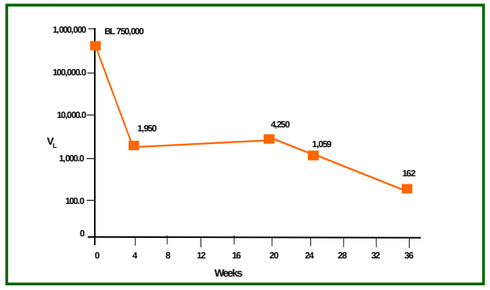


Figure 7: V_L Decay Curve (Subject 004)



Conclusions

- LPV(r) as a Single drug HAART exhibited virologic efficacy comparable to triple therapy.
- Response was not compromised by:
  - High % of advanced disease subjects.
  - Lack of funding of the study
    - LPV(r) was not provided.
    - No dedicated personnel to counsel subjects on adherence, reminder calls, etc.
    - Visits/labs/follow-up constrained by managed care parameters or charitable contributions to our Ryan White free clinic that has not been funded in over 3 years.
- Significant toxicity was not seen.
- Genotypic/phenotypic resistance was not seen.
- Our follow up study, IMANI-2, is a 48 week phase II study with a 48 week extension of LPV(r) as single drug HAART which will begin enrollment November 2003.

References

[1] Monforte, et al. AIDS, 2000; 14:499-507.

[2] Murphy R, et al. 42nd ICAAC, September 2002; Poster #H-165

[3] Bertz R, Lam W, Brun S, et al., Multiple dose pharmacokinitics (PK) of ABT-378/ritonavir (ABT/378/r) in HIV+ subjects [Abstract 0327]. 39th ICCAC, San Francisco, CA, 1999.

[4] Walmsley S., et al., Lopinavir-ritonaivr versus nelfinavir for intial therapy of HIV infection. New England Journal of Medicine, 2002, 346 (26) p.2039-2046.

[5] Stevens, R. et al. 2nd IAS, Paris 2003; Poster #779.