

Pilot study of the safety and antiviral activity of Saquinavir 1000_{mg} twice daily and Lopinavir/Ritonavir (Kaletra) Combination Therapy in HIV Positive Individuals

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Background

Successful regimens are limited by tolerance, adverse events, adherence, and the development of viral resistance. Development of new antiretroviral's (ART) are needed to overcome the above factors. Equally important is the investigation of dosing regimens from combinations of licensed ART's. High levels of 2 protease inhibitors (PIs) may be critical for successful ART treatment of HIV+ patients with multiclass drug resistance. When given with either the soft gel (SGC) or hard gel capsule (HGC) 1000 mg formulation of saquinavir (SQV)®, 100 mg ritonavir (RTV) boosts peak and AUC of SQV, resulting in elevated and sustained levels. The mean Cmin values at 12 hr post dose are significantly higher for Invirase® than Fortovase® p-value equal to 0.017. (Ref: 432-W, "Comparative PK and Short Term Safety of Twice Daily (BID) Fortovase/Ritonavir and Invirase/Ritonavir" M. Kurowski et.al., 9th ROI Feb 2002). The pharmacokinetics of coformulated LPV/RTV (Kaletra)® with (SQV) has not been reported. In this study, we document the 24 week safety and HIV antiviral activity of RTV- boosted SQV, RTV - boosted LPV in combination with nucleosides.

Methods

Open label, single arm, 48 week study of safety and antiviral activity of SQV + LPV/r in PI experienced, LPV-naïve subjects. NRTI choices guided by virtual phenotype (vPT). Tenofovir was allowed. All initiated with SQV 1000 mg BID. The distribution between Normalized Inhibitory Quotient (NIQ) values above and below the median for SQV and LPV were tabulated by week 12 and week 24 suppression below 50 c/mL

Results

28 enrolled. Female 29%, Male 71%; Risk Factors: Het 25%, IDU 14%, MSM 57%, BL/O 4%; Age: mean 41 years. Log median baseline plasma HIV-RNA 4.44; 94,933c/ml; CD4=216 cells/µl. Prior PI use: mean 2.89, 71% SQV experienced. vPT predicted resistance to SQV in 31% and LPV in 42%. 53% were off antivirals at the time of resistance testing. 14 required initial SQV dose reduction to 600 mg primarily due to gastrointestinal intolerance, and then dose escalated to 1000 mg. 3 discontinued prematurely for adverse events. A trend toward higher NIQ in suppressed subjects is evident for each PI and for a combined NIQ. Variability in these results is due to the small sample size, use of intent to treat analysis including subjects non-adherent to medication, and lack of HAART use in large numbers at baseline, resulting in the wild type overgrowth detected in the virtual phenotype of individuals with substantial background PI resistance.

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Baseline Data			
Gender	n=28		
	Male	20 (71%)	
	Female	8 (29%)	
HIV Risk Factor	MSM	16 (57%)	
	Heterosexual	7 (25%)	
	IDU	4 (14%)	
	Blood / Organ	1 (4%)	
Age Mean	41 yrs		
Ethnicity	Caucasian	15 (54%)	
	Hispanic	8 (29%)	
	African American	5 (18%)	

Baseline Data (con't)		
Baseline		
CD4 median (range 2 - 469 cells/uL)	216 cells/uL	
HIV-RNA (bDNA) mean	94,933 copies/ml	
median	31,100 copies/ml	
Log VL	4.44	
HIV Medication Exposure:		
Mean # prior use of PIs	2.89	
Prior saquinavir	71%	
Mean # prior nucs	3.3	
Tenofovir	4%	
NNRTI exposure	70%	

Subject disposition at week 24		Total No (%)
STATUS		
Initiated Tx		28
Initiated, permanently discontinued (23%)		7
Reasons for discontinuation:		
Virological failure		1
Death		0
Clinical adverse event		3
Laboratory abnormality		0
Non adherence		2
Lost to follow up		1
Still on treatment		21

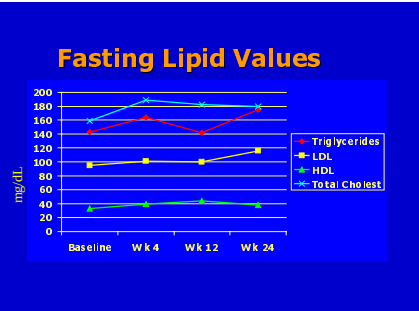
Subject Disposition - cont'd	
Dose adjustments:	
N=28	
Maintain full dose	17/28 (61%)
Dose escalation	11/28 (39%)
N=6 Switched to Invirase	
N=2 Intolerant to Invirase	

FTV Dose reduction	
All subjects initiated FTV 1000 mg BID	
GI intolerance -- primarily nausea, managed with reduction to FTV 600 BID plus anti-nausea and anti-diarrheal medications if needed	
Escalation to 800 mg BID, 1000 mg BID over 3 - 10 days	
Intolerance managed with 1-2 wk interruption, substitution with INV (n=6)	

Adverse Events	
AE most commonly reported during med initiation:	
	First 4 weeks
Nausea	23 (82%)
Diarrhea	12 (43%)
Vomiting	8 (29%)
Bloating or gas	6 (21%)
Abdominal pain or cramping	3 (11%)
Indigestion	2 (7%)

GI Adverse Events	
Mean number of days to onset	1.1±0.4
Mean number of days to resolution	21.7±29.3
Range of number of days to resolution	1-90

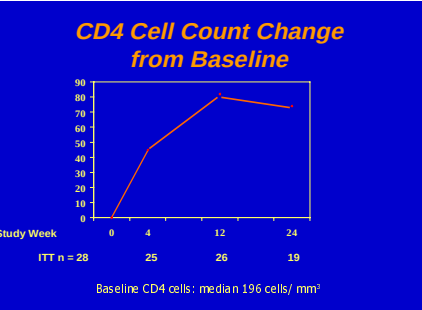
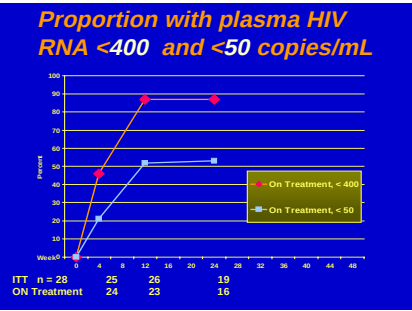
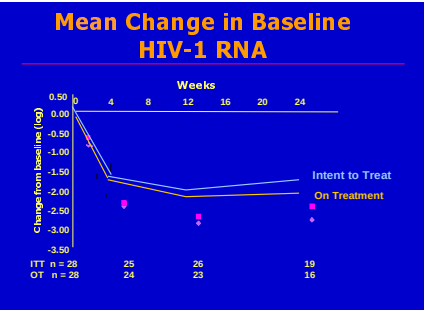
24 Week Safety*	
Grade 3/4 Adverse Events	
Diarrhea	5 (18%)
Nausea	2 (7%)
Abdominal Pain	1 (4%)
Abdominal bloating/gas	0
Vomiting	0
Asthenia	3 (11%)
Dizziness	1 (4%)
Myalgia/arthritis	2 (8%)
Most common grade 3/4 Laboratory Abnormalities	
Cholesterol (>300mg/dL)	2
Triglycerides (>750mg/dL)	1
* (C considered related to the ART)	



Previous Protease Inhibitor Use	
Saquinavir	20 (71%)
Fortovase	17 (63%)
Invirase	5 (16%)
Ritonavir	19 (68%)
Indinavir	16 (57%)
Nelfinavir	16 (57%)
Amprevir	16 (57%)

Baseline Virtual Phenotype*	
Frequency of Medication resistance	
> 4-fold PI resistance	
IDV	77%
RTV	77%
NFV	85 %
SQV	62%
APV	54%
LPV	85%
* In 13 subjects taking HAART with mean ABT Mutation Count 2.6	

Antiretrovirals used with FTV/ Kaletra	
ABC	75%
Tenofovir	47%
ddI	42%
AZT	21%
d4T	14%



Cmin Protease Inhibitor Levels		
	Week 4	Week 12
	Median Cmin ug/ml	Cmin ug/ml
Saquinavir	1.1	1.0
Lopinavir	7.1	6.9
Ritonavir	0.15	0.18
Modest inpatient variability between wks 4-12		
Substantial inter-patient variability		

Individual and Combined NIQ for SQV and LPV in relation to HIV suppression		
n (% below 50 copies/ml)	Week 12	Week 24
LPV NIQ <= 5.4	1/5 (20%)	2/5 (40%)
LPV NIQ > 5.4	4/8 (50%)	3/7 (43%)
SQV NIQ <= 4.7	4/9 (44%)	2/8 (25%)
SQV NIQ > 4.7	5/9 (56%)	4/8 (50%)
LPV NIQ <= 5.4 & SQV NIQ <= 4.7	0/4 (0%)	1/4 (25%)
LPV NIQ <= 5.4 & SQV NIQ > 4.7	1/1 (100%)	1/1 (100%)
LPV NIQ > 5.4 & SQV NIQ <= 4.7	1/1 (100%)	0/1 (0%)
LPV NIQ > 5.4 & SQV NIQ > 4.7	3/7 (43%)	3/6 (50%)

Normalized Inhibitory Quotient (NIQ)*	
IQ Ref value =	Cmin / Fold change in IC 50 (cutoff)
SQV IQ Ref value =	0.120 ug/mL / 2.5 fold change in cutoff
LPV IQ Ref value =	0.5 ug/mL / 2.5 fold change in cutoff
Virtual IQ Vs. Normalized IQ	
Both are based on that IQ= Trough / Susceptibility	
Virco 's definition - Corrected factor is based on population trough values and virtual phenotype cutoff for susceptibility	
Difference exists only in method to correct for the protein binding	
*Ref: S. Piscitelli et. al. Poster # 164, ECCM, Athens, Greece 2001	

Preliminary themes: Fortovase - Kaletra	
FTV dose escalation may be required - Invirase switch is option	
Encouraging viral suppression and CD4 response to week 24	
SQV and LPV drug levels are stable over 12 wks	
Planned: virtual IQ=Cmin / vIC50, Normalized IQ, and combined NIQ as predictors of viral suppression	

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Conclusions

SQV 1000 mg BID with LPV/r + nucleosides achieves high Ctrough levels of both SQV and LPV, active against highly PI resistant virus. SQV required dose escalation in 50%. Additional statistical analysis of NIQ for each protease inhibitor, combined NIQ for both SQV and LPV, and other predictors of viral suppression are planned.