#431 DUAL HIV PROTEASE INHIBITOR (PI) THERAPY OF CHILDREN

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BACKGROUND
Combination therapy that includes two protease inhibitors is currently under investigation in HIV-infected adults. In a phase I study in adults combining saquinavir with nelfinavir, saquinavir levels increased 392% following the addition of a single dose of saquinavir to a 4 day regimen of nelfinavir 750 mg tid. Continued combination dosing of SQV-SGC + NFV was shown to be efficacious and well tolerated with little or no change in toxicity profile or incidence for either drug. This metabolic interaction may benefit children with intrinsically high rates of drug metabolism by enabling increased saquinavir drug levels leading to greater viral suppression and delayed development of resistance compared to when saquinavir is administered alone.

OBJECTIVE
To evaluate the pharmacokinetics (PK), tolerance, safety and antiviral effect of saquinavir soft gelatin capsules (SQV-SGC) given in combination with nelfinavir (NFV) and nucleoside reverse transcriptase inhibitors (NRTIs) in HIV-infected children.

DESIGN
The study is being conducted in two parts with up to 14 children per part. Part 1 evaluates the PK, tolerance, safety and antiviral effect of SQV-SGC combined with NRTIs. Part 1 patients that did not meet the saquinavir pharmacologic target were offered the opportunity to add NFV to their existing treatment regimen. Part 2 evaluates the PK, tolerance, safety and antiviral effect of SQV-SGC combined with NFV and one or more NRTIs.

Seventeen children (5 from Part 1 and 12 from Part 2) with HIV infection, ages 3-16 years and able to swallow adult capsules, are being treated orally with SQV-SGC (initial dose, 33 mg/kg tid; subsequent dosing adjustments based on PK), NFV (30 mg/kg tid) and NRTI(s) of choice. Patients have been followed for a minimum of 24 weeks with intensive PK assessments occurring at day 0 (single dose profile), week 4 (steady state) and as necessary thereafter. Sparse sampling for PK is scheduled at every study visit after week 4. CD_4+ lymphocyte counts, plasma HIV RNA concentrations, weight and adverse events are assessed at each scheduled study visit.

RESULTS
This is an informal analysis on the 24 week safety and activity data collected on children from Parts 1 and 2 that took SQV-SGC + NFV + NRTI(s).

Seventeen children were enrolled: median age is 5 years, 59% are female and 82% are non-white. All but one child acquired HIV through vertical transmission. All but one child have a history of prior NRTI therapy and one child has a history of greater than one year of prior Indinavir therapy. NRTIs selected for use with SQV-SGC are 3TC, d4T, AZT and ddI.

At week 4, the median (and range) PK parameters for SQV-SGC were: oral clearance (CL/F), 9.9 L/h/kg (2-55); elimination half-life, 2.4 hours (1.6-3.7); maximum concentration, 1280 ng/mL (217-4670); 8-hour concentration, 314 ng/mL (30-4540); and 24 hour area-under-the-curve (AUC24), 9555 ng*h/mL (1560-57690). When compared with the week 4 saquinavir PK parameters in children from part 1 that did not receive NFV, the addition of NFV resulted in a 57% decrease in CL/F and a 53% increase in AUC24.

Saquinavir-SGC in combination with NFV and NRTIs was generally well tolerated. No serious adverse events or deaths were reported. One patient withdrew consent within the first week of therapy and one patient discontinued treatment on day 149 because of difficulty swallowing the capsules.

The mean baseline CD4+ count and plasma HIV RNA concentration were 600 cells/μL (range 10 – 1651) and 4.0 log_{10} copies/mL, respectively (range 2.6 – 5.2). The low baseline viral load can be explained, at least in part, by the inclusion of 5 children from Part 1 that added NFV to their treatment regimen due to the inability to achieve the SQV-SGC pharmacologic target. At the time these patients added NFV (crossover baseline) 4/5 children had less than 400 copies/mL of HIV RNA and 1/5 had less than 50 copies/mL.

Activity was evaluated on an intent-to-treat basis. By week 24, 11/17 (65%) children had less than 400 copies/mL of plasma HIV RNA by the Amplicor assay and 8/17 (47%) had less than 50 copies/mL of plasma HIV RNA by the UltraSensitive assay. The mean decrease in HIV RNA by the Amplicor assay was –0.85 log_{10} copies/mL (range: -2.6 to 0.6) and –1.3 log_{10} copies/mL (range: -3.5 to 0.5) by the UltraSensitive assay. The mean CD_4+ count increased from baseline by 159 cells/μL.

CONCLUSIONS
Consistent with data obtained in adults that have received the combination of SQV-SGC plus NFV, the addition of NFV increased the systemic exposure of SQV. The median CL/F was approximately 2.5 fold less than that seen in children in part 1 that were not taking NFV. These findings may be due to an increase in the bioavailability (F) or a reduction in the systemic clearance (CL) or a combination of the two. The combination of SQV-SGC + NFV + NRTI(s) was well tolerated. The changes observed in CD4+ cell counts and plasma HIV RNA indicate good antiviral activity.

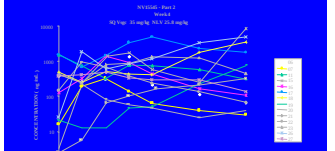
Objectives

- Part 1
  To evaluate SQV-SGC given in combination with two nucleoside agents
- **Part 2**
  To evaluate the pharmacokinetics, tolerance, safety and antiviral effect of saquinavir-SGC (SQV-SGC, FORTOVASE®)given in combination with nelfinavir and nucleoside agent(s)

Dose Selection

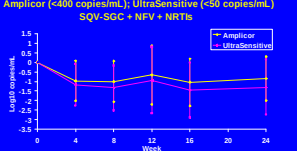
- Starting doses
  - Saquinavir: 33 mg/kg TID
  - Nelfinavir: 30 mg/kg TID
- Saquinavir Pharmacologic target
  - AUC-24 of >10,000 ng•h/mL
  - C8h of 25-50 ng/mL
- Individual doses of saquinavir adjusted as per day 0 and week 4 concentrations

Saquinavir Concentrations



Mean RNA Change (+/- Std Deviation) from Baseline

Amplicor (<400 copies/mL); UltraSensitive (<50 copies/mL)
SQV-SGC + NFV + NRTIs



Week	0	4	8	12	16	20	24
SQV-SGC + NFV + nRTIs	17	17	15	13	15	15	16

Methods

- Entry Criteria
  - 3 to 16 years old / able to swallow adult capsules
  - HIV-infected
  - CDC category 2 or 3, or symptomatic disease (category A, B, or C)
  - protease inhibitor naive
  - naive to at least one NRTI
- 24 week treatment duration + extension

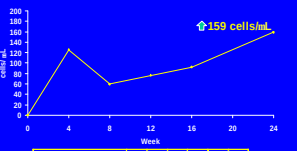
Baseline Demographics

- N = 17
- Sex: 59% female
- Race: 82% non-white
- Age range: 3 - 13yrs; median 5yrs
- Mean CD_4: 600 cells/μL (10-1651)
- Mean RNA: 4.0 log_{10} copies/mL (2.6-5.2)
- Vertically acquired: 16/17
- Protease inhibitor naïve: 16/17
- Prior NRTI therapy: 16/17

Safety

- Well tolerated in combination with NFV and nRTIs
- No serious adverse events or deaths
- One child discontinued study therapy due to moderate difficulty swallowing capsules

Part 2 Mean CD4+ Change from Baseline



Week	0	4	8	12	16	20	24
SQV-SGC + NFV + nRTIs	17	16	15	13	15	15	16

Methods

- Treatment Evaluations
  - Clinical and routine laboratory
    Days 0 and 7; weeks 4, 8, 12, 16 and every 8 weeks thereafter
  - Virologic/Immunologic
    HIV-RNA PCR and CD4 at every visit
  - Pharmacokinetics
    Intensive assessments at day 0 and week 4; sparse sampling at weeks 8, 12, 16, and every 8 weeks thereafter

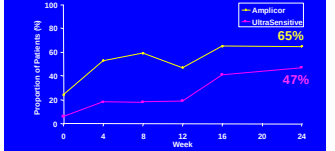
Saquinavir Pharmacokinetic Parameters

Parameter	SQV-SGC + nRTIs (n=14)	SQV + NFV + nRTI(s) (n=16)*
	median and range	
Dose (mg/kg/d)	118 (88-157)	100 (62-162)
CL/F (L/h/kg)	22.7 (6.5-54)	9.9 (2-55)
T1/2 (h)	1.6 (0.9-2.8)	2.4 (1.6-3.7)
Cmax (ng/mL)	572 (267-1830)	1280 (217-4670)
C8h (ng/mL)	65 (7-381)	314 (30-4540)
AUC24 (ng*h/mL)	6210 (1770-21480)	9555 (1560-57690)

*Includes patients that added NFV to existing SQV + nRTIs regimen.

Plasma HIV RNA Below Limit of Quantification

Amplicor (<400 copies/mL); UltraSensitive (<50 copies/mL)
SQV-SGC + NFV +nRTIs



Conclusions

- The addition of NFV increased the exposure to SQV. This change is due to an increase in the bioavailability (F) or a reduction in the systemic clearance (CL) or a combination of both.
- The variability of SQV PK in children is large.
- Excellent short-term tolerance and safety
- Short-term antiviral activity demonstrated
  - 65% with HIV RNA below 400 copies/mL
  - 47% with HIV RNA below 50 copies/mL
  - Mean CD4 increase of 159 cells/μL

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