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Abstract S29e

## Comparative pharmacokinetics and short-term safety of Fortovase®/ritonavir and Invirase®/ritonavir 1000mg/100mg BID

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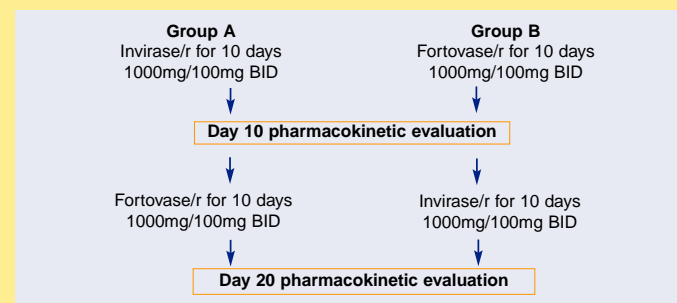
### Background

- The two formulations of saquinavir (SQV) are Invirase® (hard gelatin capsules) and Fortovase® (soft gelatin capsules). Both capsules contain 200mg of SQV
- When used without a booster drug, the bioavailability of Fortovase is greater than Invirase. This is mainly due to the glyceride excipient, capmul (medium chain mono- and di-glycerides), which allows SQV to dissolve and disperse rapidly once administered<sup>1</sup>
- A pilot study in HIV-1 infected patients showed that Fortovase/ritonavir (r) and Invirase/r 1000mg/100mg twice-daily (BID) dosages led to similar SQV plasma levels<sup>2</sup>
- Some adverse events of drugs are specifically related to the levels of the active drug substance – for example, nephrolithiasis is associated with high plasma indinavir drug levels<sup>3</sup>. However, other substances used in HIV treatment formulations may also affect tolerability. For example, Fortovase capsules contain capmul<sup>1</sup>, lopinavir/r (Kaletra®) capsules contain castor oil<sup>4</sup>, amprenavir (Agenerase®) capsules contain polyethylene glycol<sup>5</sup>, and the liquid formulation of ritonavir (Norvir®) contains alcohol<sup>6</sup> all of which have characterized toxicity profiles<sup>7</sup>. It is unknown whether the quantities of these additional substances in HIV drug formulations can affect tolerability, relative to the effects of the active drug substance
- Saquinavir/ritonavir (SQV/r) 1000mg/100mg BID is under evaluation in two large comparative randomized clinical trials versus indinavir/r 800mg/100mg BID (MaxCmin I trial) or lopinavir/r 400mg/100mg BID (MaxCmin II trial)

### Objective

- To determine the comparative pharmacokinetics of SQV/r 1000mg/100mg BID at steady state when SQV is administered using Invirase or Fortovase in healthy volunteers

Figure 1: Study design



### Methods

- In this single centre, open-label, prospective, cross-over study, 24 healthy male volunteers (mean age 26 years) received SQV/r 1000mg/100mg BID for a total of 20 days (SQV as Invirase, n=12; SQV as Fortovase, n=12)
- Subjects were randomized to Group A or Group B (Figure 1). On day 10, subjects attended hospital in the morning after an overnight fast. The pharmacokinetic profile of SQV was then determined over a 24-hour period
- Subjects then switched to the alternative formulation and the pharmacokinetic profile of SQV was again determined 10 days later (day 20). All study medications were taken at 0 and 12 hours. Meals were taken at 0 and 12 hours, with snacks permitted at any time

### Evaluations

- SQV was isolated from human plasma by solid-phase extraction and determined by LC-tandem-mass spectrometry using deuterated SQV as an internal standard
- A SQV concentration/time profile was constructed from which 24-hour pharmacokinetic parameters were determined by non-compartmental methods
- Data on adverse events were collected from subjects each day after the morning drug administration

### Statistical analysis

- The trial was designed to determine equivalence of the two boosted SQV formulations, within a  $\pm 30\%$  range. Mean differences between Invirase and Fortovase for Group A and Group B were compared in terms of all pharmacokinetic variables
- The incidence of adverse events was examined using logistic regression on drug type (Invirase versus Fortovase) and plasma drug levels ( $AUC_{0-24}$ )

### Results

- The mean SQV plasma concentration/time profiles for subjects receiving Invirase/r or Fortovase/r 1000mg/100mg BID are presented in Figure 2, and pharmacokinetic data are summarized in Table 1
- Invirase/r led to significantly higher SQV plasma levels than Fortovase/r, for all the pharmacokinetic variables evaluated

Figure 2: Twenty-four hour pharmacokinetic profile (mean and standard deviation)

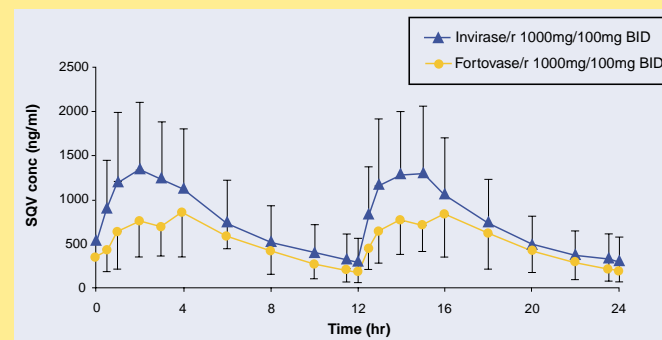


Table 1: Comparison of 24-hour SQV pharmacokinetic parameters following Invirase/r or Fortovase/r (both 1000mg/100mg BID)

Parameter	Invirase/r	Fortovase/r	Mean % difference* (95% CI)	P value (t-test)
$C_{min12}$ (ng/ml)	217	153	+41.9	0.0147
Geom. mean (95% CI)	(153, 308)	(122, 192)	(7.83, 86.6)	
$C_{min24}$ (ng/ml)	232	166	+40.0	0.0143
Geom. mean (95% CI)	(172, 314)	(134, 206)	(7.67, 82.1)	
$C_{max0-12}$ (ng/ml)	1318	1001	+35.0	0.0023
Geom. mean (95% CI)	(1052, 1653)	(836, 1199)	(12.6, 61.9)	
$C_{max12-24}$ (ng/ml)	1228	983	+28.8	0.0087
Geom. mean (95% CI)	(965, 1562)	(825, 1172)	(7.31, 54.6)	
$AUC_{0-12}$ (ng.h/ml)	7979	5745	+38.9	0.0020
Geom. mean (95% CI)	(6175, 10123)	(4883, 6759)	(14.3, 68.8)	
$AUC_{12-24}$ (ng.h/ml)	7792	5894	+35.6	0.0112
Geom. mean (95% CI)	(5998, 10123)	(5047, 6884)	(7.2, 63.0)	
$AUC_{0-24}$ (ng.h/ml)	15798	11655	+35.0	0.0043
Geom. mean (95% CI)	(12212, 20437)	(9961, 13637)	(11.1, 65.3)	

\*Invirase/r versus Fortovase/r, t-test on log transformed data; CI = confidence interval

### Adverse events

- These were classified as occurring either during the Invirase/r phase of treatment, the Fortovase/r phase, or both phases. The most frequently reported adverse events were attributable to the gastrointestinal (GI) system (Table 2)
- All of the GI adverse events were mild or moderate with no severe adverse events reported
- During the Invirase/r treatment phase, the number of subjects reporting GI system disorders was lower compared with the Fortovase/r treatment phase (eight subjects versus 23 subjects,  $p < 0.05$ ). Diarrhoea, abdominal distension, and vomiting were most frequently reported during the Fortovase/r treatment phase

- The incidence of diarrhoea was significantly higher with Fortovase/r (15/24 subjects) compared with Invirase/r (4/24 subjects) ( $p < 0.01$ )
- There was no significant correlation between SQV AUC drug levels and the incidence of either diarrhoea or abdominal symptoms ( $p > 0.05$  for both comparisons)

Table 2: Summary of adverse events by body system – all subjects

Body system	Invirase/r phase only	Fortovase/r phase only	Both phases
GI system:			
Abdominal distension	0	4	14
Abdominal pain	4	2	8
Diarrhoea	1	12	3
Nausea	3	2	1
Vomiting	0	3	0
Light abdominal discomfort	0	0	1
CNS:			
Headache	1	4	0
Dizziness	0	1	0
Other:			
Weakness/tiredness/muscle aches	1	1	4

GI = gastrointestinal; CNS = central nervous system

### Conclusions

- Invirase/r led to significantly higher plasma SQV levels than Fortovase/r, for all the pharmacokinetic variables evaluated
- The combination of Invirase/r was better tolerated than Fortovase/r, with diarrhoea and abdominal distension occurring less frequently during the Invirase/r treatment period. This difference may be related to capmul<sup>1</sup>, the glyceride excipient component of Fortovase, which is not present in Invirase
- For patients taking Fortovase/r at 1000mg/100mg BID (or other dosages) who have GI side effects, a switch to Invirase/r at the same dosage may be an additional treatment option, allowing continuation of SQV treatment with the potential for better tolerability
- Invirase/r 1000mg/100mg BID may have a better pharmacokinetic profile because the Invirase capsules dissolve slowly, providing time for ritonavir to dissolve and inhibit CYP3A4 metabolism and p-glycoprotein function before SQV is released

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