Effect of posaconazole on the pharmacokinetics of fosamprenavir and vice versa in healthy volunteers

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Objectives: To manage the interaction between fosamprenavir/ritonavir and posaconazole, we hypothesized that ritonavir can be replaced by posaconazole as an alternative booster of fosamprenavir with no significant influence on posaconazole pharmacokinetics.

Methods: This was an open-label, randomized, three period, cross-over, single-centre trial in 24 healthy volunteers. All subjects received the following three treatments for 10 days, separated by washout periods of 17 days: posaconazole 400 mg twice daily; fosamprenavir/ritonavir 700/100 mg twice daily; posaconazole 400 mg twice daily with fosamprenavir 700 mg twice daily.

Results: Twenty subjects completed the trial. Geometric mean ratios (GMR; +90% confidence interval) of posaconazole AUC and Cmax when taken with fosamprenavir versus posaconazole alone were 0.77 (0.68–0.87) and 0.79 (0.71–0.89), respectively. The GMRs of amprenavir AUC and Cmax when taken as fosamprenavir and posaconazole versus fosamprenavir/ritonavir were 0.35 (0.32–0.39) and 0.64 (0.55–0.76), respectively. No serious adverse events were reported during the trial.

Conclusion: Unboosted fosamprenavir should not be used concomitantly with posaconazole.

Keywords: azole antifungal drugs, antiretroviral drugs, pharmacokinetic, drug–drug interaction, healthy volunteers

Introduction

Infections with fungi and yeasts occur frequently in patients infected with HIV. Since the introduction of combination antiretroviral therapy (cART), the incidence and prevalence of most opportunistic infections has decreased1,2 but they can still pose a problem in, for instance, resource-limited settings or in non-compliant patients. Azole antifungal drugs are first-line therapy in the prophylaxis and treatment of invasive fungal infections. Posaconazole is a second-generation triazole with a broad antifungal spectrum against yeasts and moulds. It has proven to be effective in the prevention and treatment of invasive fungal infections in high-risk patients, including those who are immunosuppressed.3–5 Once absorbed, 76.9% of the administered dose of posaconazole is excreted with faeces. Fourteen per cent of the administered dose is retrieved in the urine as a glucuronide metabolite.6 UDP-glucuronyltransferase 1A4 (UGT1A4) has been identified as the key enzyme responsible for posaconazole glucuronidation.7 Posaconazole is a potent inhibitor of the cytochrome P450 isoform 3A4 (CYP3A4).8

Fosamprenavir is a protease inhibitor prodrug that is used to treat HIV infection.9 Once hydrolysed to amprenavir, this substance is both a substrate and an inhibitor of CYP3A4. Fosamprenavir is given concomitantly with ritonavir, which serves as a booster of the pharmacokinetics of amprenavir.10 Although ritonavir is capable of potent CYP3A4 inhibition, ritonavir induces other metabolic pathways, including glucuronidation and CYP2C19.11–14

The combination of antiretroviral drugs with azole antifungal drugs is not without risk. First, combining fosamprenavir/ritonavir with posaconazole may lead to subtherapeutic posaconazole exposure due to induction of UGT by ritonavir. Second, inhibition of CYP3A4 by posaconazole may (further) increase exposure to amprenavir with an increased risk of fosamprenavir toxicity.

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Subjects were randomized to start with different treatment arms in this cross-over design. Three treatment arms were investigated: study drug and dosing.

Study population

The study population consisted of subjects aged 18–55 years with a body mass index of 18–30 kg/m². Subjects who were included had to be able and willing to sign the Informed Consent Form prior to screening evaluations. Subjects had to be in a good age-appropriate health condition as established by medical history, physical examination, electrocardiography, biochemistry, haematology and urinalysis testing within 4 weeks prior to the first day of dosing. The main exclusion criteria were a history of sensitivity/diosyncrasy to any of the study drugs, a positive HIV test, a positive hepatitis B/C test or therapy with any drug in the 2 weeks preceding dosing, except for acetaminophen. Other exclusion criteria were participation in a drug trial or donation of blood within 60 days prior to the first dose. Pregnant females were also excluded.

Study drug and dosing

In this cross-over design three treatment arms were investigated. Subjects were randomized to start with different treatment arms (six different treatment sequences in total; Table 1). Each period consisted of 10 days of treatment with one of the three regimens. After each treatment period, there was a washout period of 17 days. The interaction arm contained fosamprenavir 700 mg twice daily together with posaconazole. Posaconazole was dose-escalated from 200 mg once daily on day 1 to 200 mg twice daily on day 2 and 400 mg twice daily from day 3 onward. As the first comparator arm, posaconazole was given in a similar fashion as the interaction arm. As the second comparator arm, fosamprenavir 700 mg twice daily with ritonavir 100 mg twice daily was given. The dose escalation for posaconazole, which is not listed in the label, was chosen to minimize toxicity since this regimen had never been tested.

Table 1. Study design

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POS, posaconazole; FPV, fosamprenavir; RTV, ritonavir.

To manage the interaction between fosamprenavir/ritonavir and posaconazole, we hypothesized that ritonavir can be replaced by posaconazole as an alternative booster of the pharmacokinetics of fosamprenavir, with the additional advantage of eliminating the potential negative effect of ritonavir on posaconazole. Based on these theoretical considerations, we performed a trial to determine the effect of unboosted fosamprenavir on posaconazole and vice versa.

Patients and methods

Study design

This open-label, three period, cross-over, single-centre, Phase I, multiple-dose trial was conducted from March to May 2009 in the Clinical Research Centre of the Radboud University Nijmegen Medical Centre, The Netherlands. The study was designed to examine the effect of fosamprenavir on the pharmacokinetics of posaconazole, and vice versa by intrasubject comparison. The secondary objective of this trial was to evaluate the safety of combined administration of posaconazole and fosamprenavir.

The trial (ClinicalTrials.gov Identifier NCT00817765) was approved by the review board of the Radboud University Nijmegen Medical Centre and conducted according to the Declaration of Helsinki.

Study population

This trial was conducted in healthy male and female volunteers, aged 18–55 years with a body mass index of 18–30 kg/m². Subjects who were included had to be able and willing to sign the Informed Consent Form prior to screening evaluations. Subjects had to be in a good age-appropriate health condition as established by medical history, physical examination, electrocardiography, biochemistry, haematology and urinalysis testing within 4 weeks prior to the first day of dosing. The main exclusion criteria were a history of sensitivity/diosyncrasy to any of the study drugs, a positive HIV test, a positive hepatitis B/C test or therapy with any drug in the 2 weeks preceding dosing, except for acetaminophen. Other exclusion criteria were participation in a drug trial or donation of blood within 60 days prior to the first dose. Pregnant females were also excluded.

Study drug and dosing

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Fosamprenavir, ritonavir and posaconazole were taken with food at ~8 AM and 8 PM. Subjects visited the trial centre approximately every other day during the treatment periods for supervised dosing and blood sampling. On every visit day of each treatment period, subjects received a standardized breakfast at around 8 AM followed by the supervised intake of an oral dose of posaconazole, fosamprenavir/ritonavir or fosamprenavir/posaconazole (depending on the treatment arm). Fosamprenavir tablets and ritonavir capsules were swallowed whole with 200 mL of water. The posaconazole suspension was swallowed with 200 mL water. The breakfast consisted of two slices of wheat bread with 48 g fat (one slice with 48+ cheese (full fat) and one with luncheon meat or cervelat) and one glass of full milk or full chocolate milk. This breakfast contained, depending on the choice of topping and milk, 488–553 kcal and 26–28 g fat (43%–50% fat).

Pharmacokinetic sampling and safety assessments

Blood samples for pharmacokinetics were collected throughout a 12 h period at 11 pre-defined timepoints (0, 1, 2, 3, 4, 5, 6, 7, 8, 10 and 12 h after dosing) at day 10 of every treatment period to characterize drug absorption and elimination. Trough concentrations, just before the intake of the drugs, were collected on study days 1, 3, 5 and 8 of each treatment period.

Serum biochemistry and haematology were checked at screening and on days 1, 3, 5, 8 and 10 of each treatment period. Adverse events assessment, blood glucose and urinalysis were performed at screening and on days 1 and 5 of each treatment period. A pregnancy test for women was conducted at screening and a screening for drugs of abuse was conducted before the dosing on day 1 of each treatment period. The electrocardiogram and blood pressure/pulse rate (supine) were checked at screening and on days 1 and 5 of each treatment period.
Compliance

Study personnel supervised all medication intake at the clinical trial unit on visit days. The times of dosing were recorded. Drug intake of subjects at home was monitored by the use of MEMS caps (Aardex, Zug, Switzerland), which record the opening of the medication bottle. Furthermore, subjects were asked to write down the exact times of medication intake in a diary.

Pharmacokinetic analysis

Pharmacokinetic parameters for posaconazole, amprenavir and ritonavir were calculated by non-compartmental methods using the WinNonLin software package (version 5.2.1; Pharsight, Mountain View, CA) and the log-linear trapezoidal rule. On the basis of the individual plasma concentration–time data, the following pharmacokinetic parameters were determined: the area under the plasma concentration–time curve from 0 to 12 h after intake (AUC0–12; in mg·h/L), the maximum plasma concentration of the drug (Cmax; in mg/L), the time to reach Cmax (Tmax in h), the apparent clearance after oral administration (CL/F; in L), the apparent volume of distribution (V/F; in L), the trough concentration in plasma (C12 (12 h after intake)) and the apparent elimination half-life (t1/2; in h).

Analytical procedure

All plasma samples were analysed at the Department of Clinical Pharmacy, Radboud University Nijmegen Medical Centre.

Amprenavir and ritonavir were determined by a validated HPLC method with UV detection.15 Samples were pretreated using liquid/liquid extraction from plasma. The dynamic range of the amprenavir assay was 0.10–30 mg/L and that of the ritonavir assay 0.045–30 mg/L. The assay had an accuracy range (five replicates of three concentrations of quality control samples), dependent on the concentration, of 102%–105% for amprenavir and 101%–104% for ritonavir. Intraday precision (n=15) for amprenavir was 2.55%–4.05% and that for ritonavir 0.89%–3.22%. Interday precision (n=3) for amprenavir was 1.18%–5.04% and that for ritonavir 1.10%–3.64%.

Posaconazole samples (total and free fraction) were measured by a validated HPLC method with fluorescence detection. Samples were pretreated using a protein precipitation procedure. The dynamic range of the assay was 0.05–10 mg/L. The assay had an accuracy range (five replicates of three concentrations of quality control samples), dependent on the concentration, of 97.9% to 104.1%. Intraday precision varied between 1.56% and 3.03% and interday precision was between 1.37% and 4.11%.

To determine the free fraction of posaconazole, we used plasma samples drawn at or around Tmax. This plasma was then transferred into Centrifree Centrifuge tubes (30 KDa). Samples were centrifuged for 10 min at 2000 relative centrifugal force (3310 rpm) (Rotante 46 R, radius 164 mm, angle 45 degrees, temperature 25°C). The analysis was modified to be able to determine very low concentrations of unbound posaconazole and had a lower limit of quantification of 0.01 mg/L without loss of accuracy and precision. Both assays are externally validated by an international proficiency testing programme.16–18

Sample size calculation and statistical analysis

To determine bioequivalence with sufficient power, the sample size calculation was performed on posaconazole since this drug has the highest estimated degree of intrasubject variation.19–21 The study was powered (power of 80%) to detect a 20% difference in posaconazole AUC. The required number of participants was 16 and, to compensate for drop-outs, 24 subjects were included.

For the identification of a clinically relevant drug interaction, we used the bioequivalence approach described in ‘Guidance for Industry: Statistical Approaches to Establishing Bioequivalence’.22 Geometric mean ratios (GMRs) with 90% confidence intervals (CIs) were calculated for AUC0–12 and Cmax after log transformation of within-subject ratios. GMRs with 90% CIs falling entirely within the range 0.80–1.25 were considered to indicate no significant interaction.

To assess the carry-over and period effects of concomitant administration of posaconazole on the pharmacokinetics of fosamprenavir, linear mixed model analyses were performed on the log(AUC0–12) of amprenavir. Similar analyses were performed for fosamprenavir. In this approach, treatment, period and a carry-over variable were treated as fixed factors and patient effects as random.

Statistical evaluations were carried out using SPSS for Windows, version 16.0.1 (SPSS, Chicago, IL, 1989–2005).

Results

Baseline characteristics

Twenty-four healthy volunteers (10 females and 14 males) were included. The mean (range) age, body weight and body mass index were 36 (18–54) years, 73 (44–104) kg and 23 (18–29) kg/m2, respectively. Twenty-one participants were Caucasian and three were Hispanic. Three subjects prematurely withdrew from the study due to adverse events and a fourth subject withdrew at own request, not related to treatment. Twenty participants completed the trial (9 female and 11 male) and were available for pharmacokinetic analyses.

Compliance

The compliance of all participants was good, as indicated by their statements about the intake of the drug, the number of tablets in the returned vials, the trough drug concentrations and the MEMS caps (data not shown).

Pharmacokinetics

The mean pharmacokinetic parameters of posaconazole are described in Table 2. Fosamprenavir reduced the exposure to posaconazole in a statistically significant manner. For posaconazole co-administered with fosamprenavir relative to posaconazole alone, the GMR (90% CI) was 0.77 (0.68–0.87) for AUC0–12 and 0.79 (0.71–0.89) for Cmax (Table 2; Figures 1 and 2).

Geometric mean free posaconazole concentration in the posaconazole arm was 0.029 mg/L (95% CI 0.023–0.036) and 0.029 mg/L (95% CI 0.022–0.038) in the combination arm. There was no statistically significant difference in geometric mean (range) free fractions of posaconazole (n=20) in the posaconazole arm alone versus the combination arm: 0.988% (0.63%–1.64%) versus 1.10% (0.63%–1.74%) (P=0.177, paired samples t-test).

The mean pharmacokinetic parameters of amprenavir are presented in Table 2. For fosamprenavir with posaconazole relative to fosamprenavir with ritonavir, the GMR (90% CI) was 0.35 (0.32–0.39) for AUC0–12 and 0.64 (0.55–0.76) for Cmax (Table 2, Figures 2 and 3).

The mean pharmacokinetic parameters of amprenavir are presented in Table 2. For fosamprenavir with posaconazole relative to fosamprenavir with ritonavir, the GMR (90% CI) was 0.35 (0.32–0.39) for AUC0–12 and 0.64 (0.55–0.76) for Cmax (Table 2, Figures 2 and 3).

There was no carry-over effect of fosamprenavir on posaconazole as assessed by the contribution of the variable defined to be 1 and 0 if a treatment with fosamprenavir preceded and did not precede the treatment with posaconazole, respectively (P=0.9).

For the identification of a clinically relevant drug interaction, we used the bioequivalence approach described in ‘Guidance for Industry: Statistical Approaches to Establishing Bioequivalence’. Geometric mean ratios (GMRs) with 90% confidence intervals (CIs) were calculated for AUC0–12 and Cmax after log transformation of within-subject ratios. GMRs with 90% CIs falling entirely within the range 0.80–1.25 were considered to indicate no significant interaction.

To assess the carry-over and period effects of concomitant administration of posaconazole on the pharmacokinetics of fosamprenavir, linear mixed model analyses were performed on the log(AUC0–12) of amprenavir. Similar analyses were performed for fosamprenavir. In this approach, treatment, period and a carry-over variable were treated as fixed factors and patient effects as random.

Statistical evaluations were carried out using SPSS for Windows, version 16.0.1 (SPSS, Chicago, IL, 1989–2005).
Likewise, there was no carry-over effect of posaconazole on fosamprenavir \( (P = 0.6) \). For both outcome variables there was no indication of a period effect \( (P = 0.5 \text{ for posaconazole and } P = 0.9 \text{ for fosamprenavir}) \).

A regression analysis was performed to determine if there was a concentration-dependent inhibition of amprenavir metabolism by posaconazole. No significant correlation was found between posaconazole exposure and amprenavir exposure \( (P = 0.099; r^2 = 0.144) \).

Adverse events and safety assessments

A total of 141 adverse events were reported by a total of 23 subjects. The severity of 28 adverse events was grade 2; two adverse events were grade 3 and two grade 4 (three occasions of increased creatine kinase (CK) in one subject and one grade 4 occasion of increased CK in a second subject; all were judged not to be related to the study medication); all other (109) adverse events were grade 1. No serious adverse events were reported. There was no notable difference in adverse events among the different treatment arms.

The relation to the study drug was judged to be definite on eight occasions reported by three subjects: a grade 2 rash occurred in two subjects (one on fosamprenavir/ritonavir and one on posaconazole/fosamprenavir) and one subject experienced a grade 3 rash on posaconazole/fosamprenavir treatment. All three subjects discontinued treatment, after which they recovered from the rash. Other side effects definitely related to the study drug were reported by a single subject: loose stool (two occasions), flatulence (two occasions) and pruritis. Seventeen adverse events were judged to be probably related and 36 possibly related.

**Discussion**

This trial showed a significant, bidirectional pharmacokinetic interaction of posaconazole and fosamprenavir. Exposures to both posaconazole (−23%) and fosamprenavir (−65%) were significantly lower than in the comparator arms.

We could think of four possible explanations for the decrease in exposure of posaconazole caused by fosamprenavir: (i) induction of UGT1A4; (ii) induction of P-glycoprotein; (iii) decreased absorption of posaconazole; and (iv) protein displacement of posaconazole.

It is generally thought that ritonavir is responsible for the induction of glucuronidation,\(^ {12,13} \) although an effect of the boosted protease inhibitor cannot be ruled out.\(^ {12,13,23} \) Fosamprenavir has been shown to significantly reduce plasma raltegravir exposure, likely through UGT1A1 induction;\(^ {16} \) however, the effect on UGT1A4 remains unknown.\(^ {10,25} \) Based on the average

**Table 2. Steady-state pharmacokinetic parameters as determined on day 10 of treatment: geometric mean ratios of area under the concentration–time curve and maximum concentrations of posaconazole and amprenavir**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>POS</th>
<th>POS + FPV</th>
<th>FPV/RTV</th>
<th>FPV + POS</th>
<th>POS + FPV vs POS alone</th>
<th>FPV + POS vs FPV/RTV</th>
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<tbody>
<tr>
<td>AUC(_{0–12}) (mg.h/L)</td>
<td>30.4 (25.2–36.7)</td>
<td>23.5 (19.7–27.9)</td>
<td>42.0 (36.7–47.9)</td>
<td>14.8 (12.4–17.7)</td>
<td>0.77 (0.68–0.87)</td>
<td>0.35 (0.32–0.39)</td>
</tr>
<tr>
<td>C(_{\text{max}}) (mg/L)</td>
<td>3.0 (2.5–3.6)</td>
<td>2.4 (2.0–2.8)</td>
<td>5.8 (5.0–6.6)</td>
<td>3.7 (3.0–4.5)</td>
<td>0.79 (0.71–0.89)</td>
<td>0.64 (0.55–0.76)</td>
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<tr>
<td>T(_{\text{max}}) (h)(^ {a} )</td>
<td>5 (4–5)</td>
<td>5 (4–5)</td>
<td>3 (2–4)</td>
<td>2 (1–3)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>C(_{\text{min}}) (mg/L)</td>
<td>2.2 (1.8–2.7)</td>
<td>1.6 (1.4–2.0)</td>
<td>2.1 (1.8–2.5)</td>
<td>0.3 (0.2–0.4)</td>
<td>—</td>
<td>—</td>
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<tr>
<td>CL/F (L/h)</td>
<td>13.2 (10.9–15.9)</td>
<td>17.1 (14.4–20.3)</td>
<td>16.7 (14.6–19.1)</td>
<td>47.2 (39.5–56.4)</td>
<td>—</td>
<td>—</td>
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<tr>
<td>t(_{1/2}) (h)</td>
<td>32.1 (26.0–39.7)</td>
<td>19.1 (16.3–22.5)</td>
<td>7.2 (6.1–8.5)</td>
<td>3.5 (2.7–4.7)</td>
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</table>

POS, posaconazole; FPV, fosamprenavir; RTV, ritonavir; AUC, area under the plasma concentration–time curve over the 12 h dosing interval; C\(_{\text{max}}\), peak plasma concentration; T\(_{\text{max}}\), time to reach C\(_{\text{max}}\); C\(_{\text{min}}\), plasma concentration 12 h after intake of study drug; CL/F, apparent clearance after oral administration; V/F, volume of distribution; t\(_{1/2}\), elimination half-life; CI, confidence interval.

\(^ {a} \)For T\(_{\text{max}}\), median + interquartile range is reported.

**Figure 1.** Arithmetic mean plasma posaconazole concentration profile following the administration of multiple doses of 400 mg posaconazole twice daily alone versus posaconazole 400 mg twice daily with fosamprenavir 700 mg twice daily. Error bars represent the SD.
23% decrease in posaconazole exposure, fosamprenavir may be a less potent UGT1A4 inducer than efavirenz and phenytoin, which have shown a reduction of 50% in exposure to posaconazole.26,27

Posaconazole is a substrate for P-glycoprotein. Fosamprenavir has been shown to induce intestinal expression of P-glycoprotein in rats.28 This mechanism could be an additional explanation for an increase in intestinal efflux of posaconazole with subsequent lowered exposure.

An effect of fosamprenavir on the absorption of drugs by, for instance, alterations in gastric pH, is not supported by the literature. Although posaconazole absorption is significantly influenced by gastric pH, the prandial state and the timing of intake relative to the meal,29 the $T_{\text{max}}$ of posaconazole was not changed after addition of fosamprenavir, indicating that at least the rate of absorption was not influenced.

In general, an increased free fraction due to protein displacement will result in a lower total plasma concentration.30 Posaconazole is >98% bound to serum albumin,27 while amprenavir is 90% bound to alpha-1-acid glycoprotein and albumin;31 hence, an interaction based on protein displacement is possible. In our study the posaconazole free drug fraction was unaltered and thus protein displacement can be ruled out as an explanation.

In a recent study the AUC and $C_{\text{max}}$ of atazanavir combined with posaconazole were comparable to the AUC and $C_{\text{max}}$ of atazanavir boosted with ritonavir (33.4 mg·h/L and 3.57 mg/L versus 35.4 mg·h/L and 3.93 mg/L, respectively).26 This suggests that posaconazole may be an equipotent inhibitor of CYP3A4 when compared with ritonavir.

In our study, the AUC and $C_{\text{max}}$ of amprenavir after intake of fosamprenavir with posaconazole were 2.9- and 1.6-fold lower compared with administration of fosamprenavir with ritonavir. Yet, when compared with a historical control group published in the literature an effect on the pharmacokinetics of fosamprenavir by posaconazole compared with unboosted fosamprenavir 700 mg twice daily can be noted: AUC$_{0-12}$ 14.82 mg·h/L (95% CI 12.41–17.70; this study) versus AUC$_{0-12}$ 9.51 mg·h/L (95% CI 7.81–11.6).32 The extent of boosting of fosamprenavir by posaconazole is an indication that there might be a moderate effect of posaconazole on fosamprenavir pharmacokinetics, but clearly not to an extent similar to ritonavir. In addition, the exposure to amprenavir given as fosamprenavir 700 mg twice daily with posaconazole approximates that to unboosted fosamprenavir 1400 mg twice daily, which is a dose licensed by the FDA for treatment of therapy-naive patients.10,33 However, this
1400 mg fosamprenavir twice daily dose is considered a non-favourable regimen according to the Panel on Antiretroviral Guidelines for Adults and Adolescents.9

No serious adverse events were reported during this trial and none of the included subjects experienced irreversible damage due to the use of the trial medication. Three subjects dropped out because of a rash, but the other adverse events during this trial were mild or moderate. We expected rash to be an adverse event of fosamprenavir, as it is described as ‘common’ in the Safety Product Characteristics (SPC) of fosamprenavir.10

Once again our study demonstrates the complexity of combined use of antiretroviral and antifungal drugs. From the results of our study we conclude that combined use of fosamprenavir with posaconazole results in subtherapeutic amnaprenavir concentrations compared with ritonavir-boosted fosamprenavir and therefore unboasted fosamprenavir 700 mg twice daily must not be used in combination with posaconazole. Future studies must reveal whether ritonavir-boosted fosamprenavir can be safely combined with posaconazole. With regard to posaconazole, concentrations must be monitored by means of therapeutic drug monitoring to assure adequate exposure in order to warrant efficacy.

Acknowledgements
We thank the healthy volunteers for participating in this trial. The technicians at the Department of Clinical Pharmacy, Radboud University Nijmegen Medical Centre, The Netherlands, are kindly acknowledged for processing and analysing the plasma samples of posaconazole, fosamprenavir and ritonavir. Ton Feuth is kindly acknowledged for his assistance in the statistical analysis. This work was presented in part at the 17th Conference on Retroviruses and Opportunistic Infections, San Francisco, February 16–19, 2010 (Abstract no. 621).

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Transparency declarations
D. M. B. has received honoraria for serving on advisory boards, speaker’s fees, and educational grants for clinical research from GlaxoSmithKline, the manufacturer of fosamprenavir. C. P. is employed by GlaxoSmithKline. All other authors have no conflicts of interest to declare.

R. B., M. vL., E. C. and D. B. designed the study, R. B., M. vL., D. B., E. C. and B. S. conducted it, R. B. and E. C. collated the data, and R. B. analysed it, M. vD. assayed the drugs, R. B. performed the pharmacokinetic analysis, and all authors contributed to and approved the manuscript.

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