Background: An open-label, randomized, crossover study was performed to investigate the effect of multiple doses of darunavir co-administered with low-dose ritonavir (DRV/r) on the steady-state pharmacokinetics of the oral contraceptives ethinyl estradiol (EE) and norethindrone (NE) (commercial name of the combined drug Ortho-Novum 1/35) in 19 HIV-negative healthy women.

Methods: In session 1, participants received 35 μg EE and 1.0 mg NE from days 1 to 21. In session 2, participants received the same oral contraceptive treatment as in session 1 on days 1 to 21 plus DRV/r (600 mg/100 mg twice daily) on days 1 to 14. Pharmacokinetic assessments were performed on day 14 for each session.

Results: Steady-state systemic exposure to EE and NE decreased when DRV/r was co-administered, based on the ratio of least square means of the minimum plasma concentration (Cmin), the maximum plasma concentration (Cmax), and the area under the curve (AUC 24h) of EE (which decreased by 62%, 32% and 44%, respectively) and NE (which decreased by 30%, 10% and 14%, respectively) compared with administration of EE and NE alone. Five participants discontinued the study due to grade 2 cutaneous events, as required per protocol, during treatment with EE and NE in combination with DRV/r. There were no clinically relevant findings for laboratory and cardiovascular parameters.

Conclusions: The pharmacokinetic interaction observed here is considered to be clinically relevant as EE concentrations are considerably reduced when DRV/r is co-administered with EE and NE. Alternative or additional contraceptive measures should be used when oestrogen-based contraceptives are co-administered with DRV/r.

Original article
Pharmacokinetic interaction between ethinyl estradiol, norethindrone and darunavir with low-dose ritonavir in healthy women
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Introduction
Oral contraceptives (OCs) are one of the most commonly used contraceptive methods worldwide and are used by both HIV-1-negative and HIV-1-infected women [1]. OCs most commonly comprise a fixed combination of ethinyl estradiol (EE) and norethindrone (NE) [2]. As guidelines for the treatment of HIV-infected, antiretroviral-naive individuals recommend the first-line use of two nucleoside reverse transcriptase inhibitors (NRTIs) with either a protease inhibitor (PI; generally boosted) or a non-nucleoside reverse transcriptase inhibitor (NNRTI) [3–5], PIs and OCs are likely to be combined in HIV-1-infected women. Both PIs and OCs are metabolized by the cytochrome P450 3A4 isoenzyme (CYP3A4) and EE is also metabolized by glucuronidation [5–7]. Darunavir (DRV) and ritonavir (RTV) inhibit CYP3A4, while RTV also induces CYP3A4 and other enzymes, including glucuronosyl transferase [8,9]. Therefore, as a result of drug–drug interactions, there is the potential for an alteration of drug exposure for OCs.

DRV (TMC114, Prezista®) is a novel PI administered in combination with low-dose ritonavir (DRV/r). DRV binds to the HIV protease and is highly active against both wild-type and resistant HIV-1 strains [8,10]. DRV has received its first regulatory approval for the treatment of HIV infection in treatment-experienced adult patients, such as those with HIV-1 strains resistant to more than one PI [8].

Drug–drug interaction studies with PIs and OCs have shown changes (both increases and decreases) in
pharmacokinetic parameters of EE and NE [5,11]. Co-administration with atazanavir (ATV) and indinavir (IDV) led to plasma area under the curve (AUC) increases of EE (48% and 24%, respectively) and NE (110% and 26%, respectively). Co-administration with fosamprenavir (FPV) resulted in increases in the minimum plasma concentration (C_{min}) of EE and NE (32% to 45%), but no significant changes in the AUC of EE and NE. This co-administration also affected the pharmacokinetic parameters of amprenavir (APV): a decrease in AUC of 22% and a decrease in C_{min} of 20% was observed. Decreases in the AUC of both EE (42–47%) and NE (17–18%) have been observed with co-administration of lopinavir/ritonavir (LPV/r) and nelfinavir (NFV) and decreases in the AUC of EE (40–50%) have been observed with co-administration of RTV and tipranavir/ritonavir (TPV/r). For patients who use one of these four PIs and, more importantly, ritonavir-boosted PIs, which decrease the plasma concentrations of EE and NE (LPV, NFV, RTV and TPV), the use of alternative or an additional method of contraception is recommended.

In the present study, the effect of multiple doses of DRV/r was investigated on the steady-state pharmacokinetics of EE and NE in HIV-negative healthy women. Short-term safety and tolerability of the co-administration of DRV/r with EE and NE was also assessed.

Methods

Study population and study design

This was an open-label, single centre, randomized, crossover trial to investigate the effect of multiple doses of DRV/r on the steady-state pharmacokinetics of EE and NE. The study participants were 19 HIV-negative, healthy, non-smoking women, aged 18 to 43 years with normal weight (body mass index 18–30 kg/m², extremes included) receiving oral contraceptives EE 35 μg/NE 1.0 mg for at least 2 weeks before screening and until 1 month after receiving the last dose of DRV/r. Study participants consented to use a double barrier method of birth control (that is, condom plus diaphragm or cervical cap) from screening until 1 month after the last study medication intake.

Individuals were randomized to two panels to receive two consecutive 28-day sessions (each session is a full menstrual cycle): session 1 followed by session 2 (panel I; n=10) or session 2 followed by session 1 (panel II; n=9). During session 1, participants received EE 35 μg/NE 1.0 mg (capsule) from day 1 to day 15, there was no OC treatment on days 22–28. In session 2, participants received the same OC treatment (from day 1 to day 21) as in session 1, but in addition from day 1 to day 14 DRV/r 600 mg/100 mg twice daily was co-administered (DRV was taken as two 300 mg tablets; RTV as a 100 mg capsule). Intake of DRV/r was within 15 min after completing a meal. When DRV, RTV, EE and NE were co-administered (session 2), the order of intake was: first EE/NE, then RTV, followed by DRV. During session 1, participants were admitted to the study unit from day 13 to day 15; during session 2, participants were admitted to the study unit from day 1 to day 15. On day 14 (pharmacokinetic sampling day) of both sessions 1 and 2, participants received a standard breakfast in the testing facility (a standard breakfast consisted of four slices of bread, two slices of ham or cheese, butter, jelly and two cups of decaffeinated coffee or tea with milk and/or sugar). The time of each intake of study medication and start and stop times of meals served in the testing facility were recorded in the case report forms.

The study protocol was reviewed and approved by the appropriate Institutional Review Board (IRB) and health authorities, and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all volunteers.

Pharmacokinetic assessments

Serial venous blood samples were drawn over the dosing interval for EE, NE, DRV and RTV. Exact times of blood sampling for pharmacokinetics were recorded and plasma samples were stored at ≤18°C until analysis. Plasma concentrations of EE, DRV and RTV were determined by validated liquid chromatography tandem mass spectrometry (LC-MS/MS) methods. The lower limit of quantification was 3.00 pg/ml for EE, 10.0 ng/ml for DRV, and 5.00 ng/ml for RTV. Plasma concentrations of NE were determined using a validated gas chromatography mass spectrometry (GC-MS) method. The lower limit of quantification was 0.0500 ng/ml. The precision and accuracy of the analytical method for plasma DRV and RTV was within the acceptable limit of 15%: coefficients of variation for the low-, medium- and high-quality control samples were <13% [12]. The precision and accuracy of the analytical method for plasma EE and NE was within the acceptable limit of 20%: coefficients of variation for the low-, medium- and high-quality control samples were <18%.

In session 1, plasma samples were taken on day 1 (pre-dose) and on day 14 at pre-dose and 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 20 and 24 h post-dose for the measurement of plasma concentrations of EE and NE. In session 2, samples for the measurement of plasma concentrations of EE and NE were taken on day 1 (pre-dose), days 11 to 13 (pre-dose), and on day 14 at pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 20 and 24 h post-dose. In session 2, samples for the measurement of plasma concentrations of DRV and RTV were taken on day 1 (pre-dose), days 11 to 13 (pre-dose), and on day 14 at pre-dose, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 10 and 12 h post-dose.
Pharmacokinetic interaction of oral contraceptives and darunavir/r

Safety and pharmacodynamic evaluations

Safety and tolerability were assessed throughout the study by adverse events (AEs), clinical laboratory evaluations, physical examinations, vital signs, and 12-lead electrocardiograms (ECG). All safety evaluations were graded according to the Division of AIDS (DAIDS) grading scale [13].

Pharmacodynamic assessments of OC efficacy, that is, serum concentrations of progesterone, luteinising hormone (LH) and follicle-stimulating hormone (FSH), were determined before drug administration on day 1 and day 14 of each session. For these assessments, no formal statistical analysis was performed as this analysis was only exploratory in nature.

Pharmacokinetic and statistical methods

Pharmacokinetic analysis was done using WinNonlin Professional™ (version 4.1; Pharsight Corporation, Mountain View, CA, USA). Noncompartmental analysis model 200 (extravascular input, plasma data) was applied for the pharmacokinetic analysis. Descriptive statistics were calculated for the plasma concentrations of EE, NE, DRV and RTV, and the derived pharmacokinetic parameters. Furthermore, Microsoft Excel® (version 2000; Microsoft, Redmond, WA, USA) and/or SAS (version 9.1.3, SAS Institute Inc., Cary, NC, USA) were used for statistical analyses.

Statistical analysis was performed comparing session 2 (test) versus session 1 (reference) for EE and NE. The primary pharmacokinetic parameters were C_{\text{min}}, maximum plasma concentration (C_{\text{max}}) and AUC_{24h} for EE and NE. The least square (LS) means of the primary parameters for each treatment group were estimated with a linear mixed effects model, controlling the primary parameters for each treatment group were AUC_{24h} for EE and NE. The primary pharmacokinetic parameters were determined before drug administration on day 1 and day 14 of each session. For these assessments, no formal statistical analysis was performed as this analysis was only exploratory in nature.

Results

In total, 19 healthy women were assigned to treatment. Eleven participants completed both sessions and 8 participants prematurely discontinued the study before completing session 1 of panel I (2 participants were lost to follow up and 1 participant withdrew consent) and 5 participants discontinued owing to AEs during session 2 of panel II (for details, see results for safety and tolerability below). Full pharmacokinetic profiles of EE and NE were available for 13 participants in session 1 and for 11 participants in session 2; full pharmacokinetic profiles of DRV and RTV were available for 11 participants (in session 2). The median age was 34 years (range 18–43).

Pharmacokinetic analysis

The linear mean plasma concentration–time curves of EE and NE are shown in Figures 1A and 1B, respectively. Visual inspection of the mean plasma concentration–time curves of EE and NE revealed that at steady-state, co-administration of EE/NE and DRV/r (session 2, day 14) resulted in lower mean plasma concentrations of EE and NE than following administration of EE/NE alone (session 1, day 14) in the entire dosing interval. Mean pharmacokinetic parameters determined for EE and NE are shown in Table 1.

Individual pre-dose plasma concentrations of EE and NE for days 11, 12, 13 and 14 of session 2 showed that steady-state conditions were achieved prior to full pharmacokinetic blood sampling on day 14.

When DRV/r was added to treatment with EE/NE, systemic exposure to EE decreased. The ratios of the LS means (90% CI) of EE were 0.38 (0.27–0.53), 0.68 (0.61–0.74) and 0.56 (0.50–0.63), for C_{\text{max}}, and AUC_{24h}, respectively, comparing administration of EE/NE in the presence of DRV/r 600 mg/100 mg twice daily to administration of EE/NE alone. The median time to reach maximum plasma concentrations of EE was 2.0 to 3.0 h after dosing.

Systemic exposure to NE also decreased when DRV/r was added to treatment with EE/NE. The ratios of the LS mean (90% CI) of NE were 0.70 (0.51–0.97), 0.90 (0.83–0.97) and 0.86 (0.75–0.98) for C_{\text{max}}, C_{\text{max}} and AUC_{24h}, respectively, comparing administration of EE/NE in the presence of DRV/r to administration of EE/NE alone. The median time to reach maximum plasma concentrations of NE was 2.0 h after dosing for both treatments (Table 1).

The mean ± SD values of C_{\text{max}}, C_{\text{min}} and AUC_{12h} of DRV (8,073 ± 988 ng/ml, 2,594 ± 1,090 ng/ml and 55,920 ± 129,290 ng h/ml) and ritonavir (1,780 ± 864 ng/ml, 285 ± 129 ng/ml and 8,548 ± 3,112 ng h/ml) were compared with those obtained in previously performed Phase I studies (TMC114-C138 [15] and TMC114-C130 [16] see Table 2; and interaction trials between DRV/r and, respectively, saquinavir and digoxin). Overall, there is no indication that the presence of EE and NE had an influence on DRV or RTV pharmacokinetics.
Safety, tolerability and pharmacodynamic assessments
No serious adverse events (SAEs) or grade 3 or 4 AEs were reported. Nine participants (47%) reported at least one AE during the trial, all during treatment with EE/NE co-administered with DRV/r 600 mg/100 mg twice daily. No AEs were reported when EE/NE was administered alone. AEs reported in more than 1 participant during combined treatment were drug eruption (reported by 3 participants), and headache, diarrhoea and nausea (all reported by 2 participants). AEs reported by 1 participant only were vomiting, drug hypersensitivity, pain in extremity and papular rash. Five participants prematurely discontinued treatment due to an AE (all during session 2 of Panel II). All 5 participants discontinued the trial due to grade 2 cutaneous events, as required per protocol (3 participants)

Table 1. Pharmacokinetic results for ethinyl estradiol and norethindrone after oral administration alone (session 1; day 14) and in combination with ritonavir-boosted darunavir 600 mg/100 mg twice daily (session 2; day 14)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>EE and NE</th>
<th>EE and NE plus DRV/r</th>
<th>LS means ratio (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethinyl estradiol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Participants, n</td>
<td>13</td>
<td>11</td>
<td>–</td>
</tr>
<tr>
<td>Median Tmax, h (range)</td>
<td>2.0 (1.0–4.0)</td>
<td>3.0 (1.0–4.0)</td>
<td>–</td>
</tr>
<tr>
<td>Mean C0h, pg/ml (±SD)</td>
<td>23.66 (±11.91)</td>
<td>9.628 (±4.683)</td>
<td>–</td>
</tr>
<tr>
<td>Mean Cmin, pg/ml (±SD)</td>
<td>22.27 (±11.11)</td>
<td>8.082 (±3.856)</td>
<td>0.38 (0.27–0.53)</td>
</tr>
<tr>
<td>Mean Cmax, pg/ml (±SD)</td>
<td>104.7 (±29.01)</td>
<td>73.74 (±16.96)</td>
<td>0.68 (0.61–0.74)</td>
</tr>
<tr>
<td>Mean AUC0–24h, pg h/ml (±SD)</td>
<td>1,095 (±400.4)</td>
<td>608.7 (±151.0)</td>
<td>0.56 (0.50–0.63)</td>
</tr>
<tr>
<td>Norethindrone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Participants, n</td>
<td>13</td>
<td>11</td>
<td>–</td>
</tr>
<tr>
<td>Median Tmax, h (range)</td>
<td>2.0 (1.0–3.0)</td>
<td>2.0 (1.0–4.0)</td>
<td>–</td>
</tr>
<tr>
<td>Mean C0h, ng/ml (±SD)</td>
<td>2.381 (±1.254)</td>
<td>1.578 (±0.9786)</td>
<td>–</td>
</tr>
<tr>
<td>Mean Cmin, ng/ml (±SD)</td>
<td>2.241 (±1.267)</td>
<td>1.419 (±0.9034)</td>
<td>0.70 (0.51–0.97)</td>
</tr>
<tr>
<td>Mean Cmax, ng/ml (±SD)</td>
<td>17.16 (±4.718)</td>
<td>15.36 (±3.845)</td>
<td>0.90 (0.83–0.97)</td>
</tr>
<tr>
<td>Mean AUC0–24h, ng h/ml (±SD)</td>
<td>144.2 (±54.57)</td>
<td>112.5 (±33.73)</td>
<td>0.86 (0.75–0.98)</td>
</tr>
</tbody>
</table>

AUC, area under plasma concentration–time curve; C0h, pre-dose plasma concentration; Cmin, minimum plasma concentration; Cmax, maximum plasma concentration; CI, confidence interval; DRV/r, darunavir with low-dose ritonavir; EE, ethinyl estradiol; LS, least square; NE, norethindrone; Tmax, time to maximum plasma concentration.
had drug eruption [2 of these participants used hydrocortisone butyrate propionate as concomitant medication]; 1 participant had drug hypersensitivity; and 1 participant had papular rash). All other AEs were grade 1. With the exception of one unrelated AE, all AEs were considered at least possibly related to DRV/r.

No clinically relevant changes over time in laboratory parameters were noted. Except for increased low-density lipoprotein (reported in 3 participants during combined treatment: grade 3 in 1 participant and grade 1 in 2 participants), all other treatment-emergent abnormalities during combined treatment were reported in 1 or 2 participants and were grade 1 or 2 in severity.

For pharmacodynamic assessments, FSH and LH concentrations decreased versus pre-dose after 14 days of treatment with EE/NE, as expected. The median decreases were less when DRV/r was co-administered (Table 3).

The fluctuations in median vital sign and ECG parameter values noted during the trial were generally small. There were no clinically relevant changes in vital sign or ECG parameters at any time point during any treatment and no AEs related to vital signs or ECG parameters were reported.

**Discussion**

The main pathways of metabolism for OCs, including EE and NE, occur via the cytochrome P450 enzyme system, predominantly in the gastrointestinal tract and liver, and through glucuronidation. In particular, CYP3A4 is the dominant enzyme involved in the metabolism of OCs [7]. There is potential for significant drug–drug interactions in the use of OCs and antiretroviral medications, because NNRTIs and PIs also undergo metabolism via the CYP3A4 enzyme [5,6]. NRTIs do not undergo metabolism via the cytochrome P450 system, therefore, there is less of a concern for drug–drug interactions between OCs and NRTIs [5].

### Table 2. Comparison of darunavir and ritonavir PK parameters obtained in this study with historical data

<table>
<thead>
<tr>
<th></th>
<th>Clinical study*</th>
<th>TMC114-C131</th>
<th>TMC114-C138</th>
<th>TMC114-C150</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DRV/r plus EE and NE</td>
<td>DRV/r alone†</td>
<td>DRV/r with digoxin</td>
<td></td>
</tr>
<tr>
<td>PK darunavir 600 mg twice daily</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Participants, n</td>
<td>11</td>
<td>14</td>
<td>14‡</td>
<td></td>
</tr>
<tr>
<td>Mean C_{min}, ng/ml (±SD)</td>
<td>2,594 (±1,090)</td>
<td>3,017 (±1,064)</td>
<td>3,426 (±900)</td>
<td></td>
</tr>
<tr>
<td>Mean C_{max}, ng/ml (±SD)</td>
<td>8,073 (±988)</td>
<td>7,283 (±2,030)</td>
<td>7,729 (±1,072)</td>
<td></td>
</tr>
<tr>
<td>Mean AUC_{12h}, ng h/ml (±SD)</td>
<td>55,920 (±11,290)</td>
<td>56,288 (±16,395)</td>
<td>63,830 (±10,830)</td>
<td></td>
</tr>
<tr>
<td>PK ritonavir 100 mg twice daily</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Participants, n</td>
<td>11</td>
<td>14</td>
<td>14§</td>
<td></td>
</tr>
<tr>
<td>Mean C_{min}, ng/ml (±SD)</td>
<td>285 (±129)</td>
<td>221 (±87.9)</td>
<td>372 (±282)</td>
<td></td>
</tr>
<tr>
<td>Mean C_{max}, ng/ml (±SD)</td>
<td>1,780 (±864)</td>
<td>1,099 (±468)</td>
<td>1,436 (±682)</td>
<td></td>
</tr>
<tr>
<td>Mean AUC_{12h}, ng h/ml (±SD)</td>
<td>8,548 (±3,712)</td>
<td>6,362 (±3,147)</td>
<td>8,582 (±4,486)</td>
<td></td>
</tr>
</tbody>
</table>

* C131, this study (that is, ritonavir-boosted darunavir [DRV/r] and oral contraceptive study); C138, trial number for the DRV/r saquinavir interaction study; C150, trial number for the DRV/r digoxin study. † 400 mg darunavir administered, pharmacokinetic (PK) parameters were dose-normalized to 600 mg. ‡ n=13 for AUC_{12h}. § n=13 for AUC_{12h}. AUC_{12h}, area under plasma concentration–time curve after 12 h; C_{min}, minimum plasma concentration; C_{max}, maximum plasma concentration.

### Table 3. Median values and changes from reference for contraceptive efficacy parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>EE and NE alone</th>
<th>EE and NE plus DRV/r</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 1 pre-dose</td>
<td>Day 14 pre-dose</td>
</tr>
<tr>
<td></td>
<td>Actual values (n=14)</td>
<td>Actual values (n=13)</td>
</tr>
<tr>
<td>Median 17-OH-progesterone, nmol (range)</td>
<td>3.0 (1.1–46.1)</td>
<td>2.1 (0.5–26.2)</td>
</tr>
<tr>
<td>Median FSH, U/l (range)</td>
<td>6.1 (1.8–8.3)</td>
<td>1.6 (0.9–6.1)</td>
</tr>
<tr>
<td>Median LH, U/l (range)</td>
<td>5.0 (1.2–13.7)</td>
<td>4.1 (0.5–9.5)</td>
</tr>
</tbody>
</table>
| Reference: day 1 pre-dose in the same session as the reassessments. n, number of participants at the scheduled timepoints with available data; i, decrease. FSH, follicle-stimulating hormone; LH, luteinising hormone.
Like all PIs, DRV is a substrate for CYP3A4 metabolism [8]. DRV is co-administered with low-dose RTV, because DRV/r has an improved pharmacokinetic profile compared with DRV alone [8]. RTV is a potent inhibitor of both CYP3A4 and CYP2C9 and is also an inducer of both CYP3A4 and glucuronidation [9]. Therefore, drug–drug interactions between OCs and DRV/r are likely. The present study was designed to investigate the effect of multiple doses of DRV co-administered with low-dose RTV (DRV/r 600 mg/100 mg twice daily) on the steady-state pharmacokinetics of EE and NE. Steady-state plasma concentrations of EE, NE, DRV and RTV were achieved prior to full pharmacokinetic blood sampling on day 14 of combined treatment.

In the presence of DRV/r and based on the ratio of LS means, $C_{\text{max}}$, $C_{\text{min}}$ and AUC$_{24\text{h}}$ of EE decreased by 62%, 32% and 44%, respectively, and $C_{\text{max}}$, $C_{\text{min}}$ and the AUC$_{24\text{h}}$ of NE decreased by 30%, 10% and 14%, respectively, compared with administration of EE/NE alone. This pharmacokinetic interaction is considered to be clinically relevant as EE concentrations are considerably reduced when DRV/r is co-administered with Ortho-Novum® (the commercially available combined form of EE/NE).

The effect of DRV/r on the pharmacokinetics of EE and NE is consistent with what has been observed for other RTV-boosted PIs. For example, an interaction study between LPV/r 400 mg/100 mg twice daily and EE/NE showed that for EE the AUC decreased by 42%, $C_{\text{max}}$ decreased by 41% and $C_{\text{min}}$ decreased by 58% upon co-administration, whereas for NE the AUC decreased by 17%, $C_{\text{max}}$ decreased by 16% and $C_{\text{min}}$ decreased by 32% [17]. The observed decrease in the exposure to EE and NE in this study may be a result of metabolic enzyme induction by RTV [18]. The clinical relevance of these decreases depends on their effects on the hormone levels of FSH and LH, as discussed below.

The presence of EE and NE did not seem to have a clinically relevant influence on the pharmacokinetics of DRV or RTV, as the PK parameters of both compounds were generally comparable to those observed in other trials with DRV/r in healthy volunteers.

Owing to AES, 5 out of the 19 healthy female participants (26%) discontinued treatment with DRV/r 600 mg/100 mg twice daily in combination with EE and NE. These discontinuations were attributable to grade 2 cutaneous events, as required per protocol. Although results of other Phase I (pooled Phase I repeated dose trials) trials with DRV/r performed in healthy volunteers showed that women were more likely to develop rash-related events than men [19], this observation was not found in HIV-infected participants participating in large-scale clinical trials [8]. In Phase III trials of DRV/r, there was a small proportion of HIV-infected women taking DRV/r and OCs: 12 TITAN patients (4%) and 31 ARTEMIS patients (9%) [19]. However, in the ARTEMIS trial, for example, rash (all types) was observed with a comparable incidence in HIV-infected men (14%) and women (15%) (unpublished data). There have been very few publications on the incidence of rash in women receiving other PIs and OCs, although it has been suggested that women receiving oestrogen and TPV/r could have an increased risk of non-serious rash [20]. The incidence of laboratory, vital signs and ECG abnormalities was generally low. No laboratory, vital signs or ECG abnormalities were reported as AEs. None of the women presented dysfunctional bleeding during the trial. Concentrations of FSH and LH decreased between pre-dose at day 1 and day 14 in patients receiving EE/NE alone and also in those receiving EE/NE and DRV/r, indicating reliable intake of OCs via a negative feedback loop and as demonstrated elsewhere [21]. Comparison of FSH and LH between those receiving EE/NE and those receiving EE/NE and DRV/r revealed a decrease in these hormone levels. This change is thought to be attributed to metabolic enzyme induction by RTV, which in turn increases the metabolism of OCs and lessens the extent of the negative feedback mechanism responsible for the secretion of FSH and LH.

In conclusion, the results of this trial demonstrated that plasma exposures of EE and NE were decreased when DRV/r 600 mg/100 mg twice daily was co-administered. These decreases in EE and NE exposure are considered clinically relevant, as they could be associated with an increased risk of pregnancy in HIV-infected women of childbearing age. Alternative or additional contraceptive measures are recommended when oestrogen-based contraceptives are co-administered with DRV/r.

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Pharmacokinetic interaction of oral contraceptives and darunavir/r


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