The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

| Study No: APV10020
| Title: A Phase I, Open Label, Two Period, Single-Sequence, Drug-Drug Interaction Study Comparing Steady-State Plasma Ethinyl Estradiol and Norethisterone Pharmacokinetics following Administration of Brevinor for 21 Days with and without Fosamprenavir 700 mg Twice Daily (BID) and Ritonavir 100 mg BID for 21 Days in Healthy Adult Female Subjects
| Rationale: Fosamprenavir (FPV) is a human immunodeficiency virus type 1 (HIV-1) protease inhibitor (PI). FPV is converted to the active metabolite amprenavir (APV) in vivo. Ritonavir (RTV), also an HIV-1 PI, is co-administered with FPV at sub-therapeutic doses to increase plasma APV concentrations via inhibition of cytochrome P450 (CYP) 3A4 metabolism.

Previous studies have shown that HIV-1 PIs have variable effects on the plasma pharmacokinetics (PK) of ethinyl estradiol (EE) and norethisterone (NE), which are common components of oral contraceptives. The effects of FPV and RTV on the plasma PK of EE and NE were unknown. Study APV10020 was designed to compare steady-state plasma EE and NE PK following co-administration of EE 0.035 mg/NE 0.5 mg (Brevinor®) once daily (QD) with and without FPV 700 mg BID + RTV 100 mg BID. This study also evaluated the impact of EE 0.035 mg/NE 0.5 mg QD on steady-state plasma APV and RTV PK following co-administration with FPV 700mg BID + RTV 100mg BID; APV and RTV comparisons were made to historical control data.

| Phase: I
| Study Period: 18 April 2005 - 20 December 2005
| Study Design: Open-label, two-period, single-sequence
| Centres: One centre in United Kingdom.
| Indication: None (healthy female volunteers)
| Treatment: Run-in: Brevinor (EE 0.035 mg/NE 0.5 mg) QD for 21-49 days.
| Period 1: Treatment A: Brevinor QD for 21 days.
| Period 2: Treatment B: Brevinor QD co-administered with FPV 700 mg BID + RTV 100 mg BID) for 21 days.
| Objectives: To demonstrate equivalence in steady-state plasma EE and NE PK following administration of Brevinor® (EE 0.035 mg/NE 0.5 mg) QD with and without concurrent FPV 700 mg BID + RTV 100 mg BID.
| Statistical Methods: Plasma PK parameters were calculated using non-compartmental methods. The primary PK endpoints were plasma EE and NE steady-state AUC(0-τ). The secondary PK endpoints were plasma EE and NE maximum observed concentration (Cmax) at steady-state and concentration at the end of dosing interval (Cτ) at steady-state, and plasma APV and RTV AUC(0-τ), Cmax, and Cτ.

This study was designed to demonstrate no interaction in steady-state plasma EE and NE PK following administration of Brevinor (EE 0.035 mg/NE 0.5 mg) with and without concurrent FPV 700 mg BID + RTV 100 mg BID administration. The statistical criteria to conclude no interaction was that the 90% CI for the ratio of geometric least squares (GLS) means for the Brevinor-FPV/RTV combination versus Brevinor alone fell in the range of 0.80-1.25 for both EE and NE.

Analysis of variance (ANOVA), considering treatment as a fixed effect and subject as a random effect, was performed to evaluate the impact of FPV 700 mg BID + RTV 100 mg BID on plasma EE and NE PK using SAS™ (Version 8.2) Mixed Linear Models procedure. The ratio of GLS means and associated 90% confidence intervals (CIs) were estimated for plasma EE and NE PK parameters. PK parameters were log-transformed prior to analyses and treatment comparisons were expressed as ratios on the original scale. A separate model was used to compare plasma APV and RTV PK to historical female healthy adult data. ANOVA, considering study population (APV10020 vs historical) as a fixed effect, was used to evaluate the impact of oral contraceptive on plasma APV and RTV PK. The ratio of GLS means and associated 90% CI were estimated for plasma APV and RTV PK parameters.

For pharmacodynamic (PD) data, for each subject, the difference in maximum leutinizing hormone (LH), maximum follicle stimulating hormone (FSH), Day 14 LH, Day 14 change from baseline (Day 1) in LH, and progesterone (PGS) for the two treatments (Treatment B minus Treatment A) was calculated. A descriptive summary of these differences was produced.

Analysis populations:
Study Population: Healthy female subjects, aged ≥18 and ≤45 years; body weight ≤45.0 kg (99 lbs) and body mass index (BMI) of 18.5 to 29.9 kg/m² inclusive. Subjects of child-bearing potential had to be willing to use one of the protocol-specified additional contraceptive methods during the study.

The subject must have received monophasic oral contraceptives, triphasic oral contraceptives, extended cycle oral contraceptive (i.e. >21 days of active hormone/cycle) or transdermal contraceptive containing or delivering ≤0.035 mg ethinyl estradiol/day for at least three months prior to receiving investigational product in this study (Day 1 of the Run-in Period).

<table>
<thead>
<tr>
<th>Number of Subjects:</th>
<th>Run-in</th>
<th>Period 1</th>
<th>Period 2</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Planned, N</td>
<td>50</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dosed, N</td>
<td>41</td>
<td>41</td>
<td>38</td>
<td>41</td>
</tr>
<tr>
<td>Completed, n (%)</td>
<td>41 (100)</td>
<td>38 (93)</td>
<td>25 (66)</td>
<td>25 (61)</td>
</tr>
<tr>
<td>Total Number Subjects Withdrawn, n (%)</td>
<td>0 (0)</td>
<td>3 (7)</td>
<td>13 (34)</td>
<td>16 (39)</td>
</tr>
<tr>
<td>Withdrawn due to Adverse Events, n (%)</td>
<td>0 (0)</td>
<td>2 (5)</td>
<td>13 (34)</td>
<td>15 (37)</td>
</tr>
<tr>
<td>Withdrawn for Other Reasons, n (%)</td>
<td>0 (0)</td>
<td>1 (2)</td>
<td>0 (0)</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

Demographics

<table>
<thead>
<tr>
<th>Females : Males</th>
<th>41 : 0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age in Years (SD)</td>
<td>26.8 (3.70)</td>
</tr>
<tr>
<td>Mean Weight in kg (SD)</td>
<td>61.3 (8.64)</td>
</tr>
<tr>
<td>Mean BMI in kg/m² (SD)</td>
<td>22.8 (2.61)</td>
</tr>
<tr>
<td>White - White/Caucasian/European Heritage, n (%)</td>
<td>35 (85)</td>
</tr>
</tbody>
</table>

Pharmacokinetics (PK) and Pharmacodynamics (PD):
### Plasma EE and NE PK Parameters: PK Summary Population

<table>
<thead>
<tr>
<th>Plasma PK Parameter</th>
<th>Treatment A</th>
<th>Treatment B</th>
<th>Treatment A</th>
<th>Treatment B</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC(0-(\tau))</td>
<td>1028</td>
<td>653</td>
<td>95.3</td>
<td>63.3</td>
</tr>
<tr>
<td></td>
<td>(993, 131)</td>
<td>(883, 1198)</td>
<td>(84.4, 108)</td>
<td>(56.1, 71.3)</td>
</tr>
<tr>
<td>Cmax</td>
<td>114</td>
<td>82.0</td>
<td>11.8</td>
<td>7.26</td>
</tr>
<tr>
<td></td>
<td>(99.3, 131)</td>
<td>(71.1, 94.6)</td>
<td>(10.6, 13.1)</td>
<td>(6.29, 8.38)</td>
</tr>
<tr>
<td>C(\tau)</td>
<td>22.5</td>
<td>ND</td>
<td>1.32</td>
<td>0.98</td>
</tr>
<tr>
<td></td>
<td>(19.0, 26.7)</td>
<td>(ND)</td>
<td>(1.14, 1.55)</td>
<td>(0.85, 1.13)</td>
</tr>
</tbody>
</table>

**Treatment A:** Brevinor (EE 0.035 mg/NE 0.5 mg) QD for 21 days.

**Treatment B:** Brevinor (EE 0.035 mg/NE 0.5 mg) QD plus FPV 700 mg BID + RTV 100 mg BID for 21 days.

ND: not determined (13/25 values were non-quantifiable [NQ]).

1. Concentration units are pg/mL for EE and ng/mL for NE; AUC units are pg.h/mL for EE and ng.h/mL for NE.

### Plasma APV and RTV PK Parameters: PK Summary Population and Historical Control Population

<table>
<thead>
<tr>
<th>Plasma PK Parameter</th>
<th>Treatment A</th>
<th>Treatment B</th>
<th>Treatment A</th>
<th>Treatment B</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC(0-(\tau))</td>
<td>40.3</td>
<td>38.6</td>
<td>5.40</td>
<td>7.85</td>
</tr>
<tr>
<td></td>
<td>(35.1, 46.2)</td>
<td>(35.2, 42.5)</td>
<td>(3.78, 7.72)</td>
<td>(6.50, 9.49)</td>
</tr>
<tr>
<td>Cmax</td>
<td>6.10</td>
<td>6.00</td>
<td>1.26</td>
<td>2.05</td>
</tr>
<tr>
<td></td>
<td>(5.42, 6.86)</td>
<td>(5.54, 6.50)</td>
<td>(0.84, 1.89)</td>
<td>(1.69, 2.48)</td>
</tr>
<tr>
<td>C(\tau)</td>
<td>2.33</td>
<td>2.43</td>
<td>0.17</td>
<td>0.19</td>
</tr>
<tr>
<td></td>
<td>(1.99, 2.72)</td>
<td>(2.03, 2.90)</td>
<td>(0.12, 0.25)</td>
<td>(0.12, 0.31)</td>
</tr>
</tbody>
</table>

**Treatment B:** Brevinor (EE 0.035 mg/NE 0.5 mg) QD plus FPV 700 mg BID + RTV 100 mg BID for 21 days.

1. Historical control plasma APV PK data from female subjects dosed with FPV/RTV alone from studies APV10010, APV10011, APV10012, APV10022, APV10002, APV10026, and APV10031.

2. Historical control plasma RTV PK data from female subjects dosed with FPV/RTV alone from studies APV10010, APV10026, and APV10028.

### Statistical Comparisons of Steady-State Plasma EE and NE: PK Summary Population

<table>
<thead>
<tr>
<th>Plasma PK Parameter</th>
<th>Treatment B/Treatment A (N=25/25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC(0-(\tau))</td>
<td>Ethinyl Estradiol</td>
</tr>
<tr>
<td></td>
<td>0.63 (0.58, 0.70)</td>
</tr>
<tr>
<td>Cmax</td>
<td>0.72 (0.65, 0.79)</td>
</tr>
<tr>
<td>C(\tau)</td>
<td>ND</td>
</tr>
</tbody>
</table>

**Treatment A:** Brevinor (EE 0.035 mg/NE 0.5 mg) QD for 21 days.

**Treatment B:** Brevinor (EE 0.035 mg/NE 0.5 mg) QD plus FPV 700 mg BID + RTV 100 mg BID for 21 days.

ND: not determined (13/25 values were non-quantifiable [NQ] for Treatment B).
Statistical Comparisons of Steady-State Plasma APV and RTV: PK Summary Population vs Historical Control Population

<table>
<thead>
<tr>
<th>Plasma PK Parameter</th>
<th>Ratio of Geometric Least Squares Means (90% CI)</th>
<th>Treatment B/Historical Control1,2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Amprenavir N=25/28</td>
<td>Ritonavir N=25/12</td>
</tr>
<tr>
<td>AUC(0-τ)</td>
<td>0.96 (0.83, 1.10)</td>
<td>1.45 (1.08, 1.95)</td>
</tr>
<tr>
<td>Cmax</td>
<td>0.98 (0.87, 1.11)</td>
<td>1.63 (1.19, 2.22)</td>
</tr>
<tr>
<td>Ct</td>
<td>1.04 (0.86, 1.26)</td>
<td>1.13 (0.64, 2.00)</td>
</tr>
</tbody>
</table>

Treatment B: Brevinor (EE 0.035 mg/NE 0.5 mg) QD plus FPV 700mg BID + RTV 100mg BID for 21 days.
1. Historical control plasma APV PK data from female subjects dosed with FPV/RTV alone from studies APV10010, APV10011, APV10012, APV10013, APV10022, APV10026, APV10028, and APV10031.
2. Historical control plasma RTV PK data from female subjects dosed with FPV/RTV alone from studies APV10010, APV10026, and APV10028.

Summary of the Difference (Treatment B versus Treatment A) in PD Parameters: PD Population

<table>
<thead>
<tr>
<th>Parameter</th>
<th>n</th>
<th>Mean Difference</th>
<th>95% CI of Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum LH (Days 11-14) (mIU/mL)</td>
<td>30</td>
<td>1.032</td>
<td>(0.284, 1.780)</td>
</tr>
<tr>
<td>Day 14 LH (mIU/mL)</td>
<td>24</td>
<td>0.678</td>
<td>(-0.021, 1.377)</td>
</tr>
<tr>
<td>Day 14 LH Change from Baseline (mIU/mL)</td>
<td>24</td>
<td>-0.098</td>
<td>(-0.876, 0.679)</td>
</tr>
<tr>
<td>Maximum FSH (Days 11-14) (mIU/mL)</td>
<td>30</td>
<td>1.495</td>
<td>(0.869, 2.121)</td>
</tr>
<tr>
<td>PGS (Day 21) (ng/mL)</td>
<td>25</td>
<td>0.0059</td>
<td>(-0.0336, 0.0454)</td>
</tr>
</tbody>
</table>

Treatment A = Brevinor (EE 0.035 mg + NE 0.5 mg) QD.
Treatment B = Brevinor (EE 0.035 mg + NE 0.5 mg) QD + FPV 700 mg BID + RTV 100 mg BID.

Safety Results: Adverse events (AEs) were collected during the study period. The most commonly reported AEs (reported by >1 subject for either treatment), by system organ class (SOC) and by preferred term, are shown in the following table:
### Adverse Events

<table>
<thead>
<tr>
<th>Adverse Events:</th>
<th>Run-in</th>
<th>Treatment A</th>
<th>Treatment B</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (Safety Population)</td>
<td>41</td>
<td>41</td>
<td>38</td>
</tr>
<tr>
<td>Subjects with AEs, n (%)</td>
<td>18 (44)</td>
<td>25 (61)</td>
<td>37 (97)</td>
</tr>
</tbody>
</table>

#### Most Frequent AEs: Reported by >1 Subject in Any Study Period, n (%)

| Gastrointestinal disorders, any event | 1 (2)  | 6 (15)      | 33 (87)     |
| Diarrhoea                             | 0      | 1 (2)       | 22 (58)     |
| Nausea                                | 0      | 4 (10)      | 19 (50)     |
| Vomiting                              | 1 (2)  | 3 (7)       | 9 (24)      |
| Hypoaesthesia oral                    | 0      | 0           | 5 (13)      |
| Abdominal pain                        | 0      | 2 (5)       | 4 (11)      |
| Abdominal discomfort                  | 0      | 0           | 3 (8)       |
| Mouth ulceration                      | 0      | 0           | 3 (8)       |
| Nervous system disorders, any event   | 5 (12) | 14 (34)     | 21 (55)     |
| Headache                              | 5 (12) | 13 (32)     | 14 (37)     |
| Somnolence                            | 0      | 0           | 5 (13)      |
| Dysgeusia                             | 0      | 0           | 2 (5)       |
| Hypoaesthesia                         | 0      | 0           | 2 (5)       |
| Dizziness                             | 0      | 2 (5)       | 0           |
| Skin & subcutaneous tissue disorders, any event | 1 (2)  | 1 (2)       | 17 (45)     |
| Rash generalised                      | 0      | 0           | 8 (21)      |
| Rash                                  | 0      | 1 (2)       | 4 (11)      |
| Rash maculo-papular                   | 0      | 0           | 3 (8)       |
| Infections & infestations, any event  | 3 (7)  | 4 (10)      | 4 (11)      |
| Herpes simplex                        | 0      | 1 (2)       | 2 (5)       |
| Upper respiratory tract infection      | 2 (5)  | 2 (5)       | 1 (3)       |
| Reproductive system & breast disorders, any event | 7 (17) | 3 (7)       | 4 (11)     |
| Metrorrhagia                          | 5 (12) | 2 (5)       | 4 (11)      |
| Respiratory, thoracic and mediastinal disorders, any event | 4 (10) | 5 (12)     | 3 (8)       |
| Pharyngolaryngeal pain                | 1 (2)  | 3 (7)       | 3 (8)       |
| Rhinorrhoea                           | 0      | 2 (5)       | 0           |
| Metabolism and nutrition disorders, any event | 0      | 0           | 7 (18)     |
| Decreased appetite                    | 0      | 0           | 5 (13)      |
| Anorexia                              | 0      | 0           | 2 (5)       |
| Investigations, any event             | 0      | 0           | 4 (11)      |
| Transaminases increased               | 0      | 0           | 4 (11)      |
| Immune system disorders, any event    | 0      | 2 (5)       | 0           |

**Run-in: Brevinor (EE 0.035 mg/NE 0.5 mg) QD.**

**Treatment A: Brevinor (EE 0.035 mg/NE 0.5 mg) QD.**

**Treatment B: Brevinor (EE 0.035 mg/NE 0.5 mg) QD co-administered with FPV 700 mg BID + RTV 100 mg BID.**

### Serious Adverse Events

<table>
<thead>
<tr>
<th>Serious Adverse Events (SAEs):</th>
<th>Run-in</th>
<th>Treatment A</th>
<th>Treatment B</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (Safety Population)</td>
<td>41</td>
<td>41</td>
<td>38</td>
</tr>
<tr>
<td>Subjects with SAEs, n (%) [considered by the investigator to be related, possibly related, or probably related to study medication]</td>
<td>0 (0) [0]</td>
<td>0 (0) [0]</td>
<td>0 (0) [0]</td>
</tr>
</tbody>
</table>

**Run-in: Brevinor (EE 0.035 mg/NE 0.5 mg) QD.**

**Treatment A: Brevinor (EE 0.035 mg/NE 0.5 mg) QD.**

**Treatment B: Brevinor (EE 0.035 mg/NE 0.5 mg) QD co-administered with FPV 700 mg BID + RTV 100 mg BID.**

**Publications:**

No Publication
Date Updated: 18-Aug-2006