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.

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| Study No.: APV102002 |
| Title: A Phase III, Randomized, Controlled, Open-label, Multicentre, Three Arm Study to Compare the Efficacy and Safety of a Dual-boosted HIV-1 Protease Inhibitor (PI) regimen of Fosamprenavir (FPV)/ Lopinavir (LPV)/Ritonavir (RTV) 1400mg/533mg/133mg Twice Daily (BID) and an Increased Dosage Regimen of FPV/RTV 1400mg/100mg BID Versus the Standard Dosage Regimen of FPV/RTV 700mg/100mg BID for 24 Weeks in Multiple-PI Experienced, HIV-infected Adults Experiencing Virological Failure. |
| Rationale: The aim of the study was to compare the efficacy and safety of a Dual-boosted HIV-1 PI regimen of FPV/LPV/RTV 1400mg/533mg/133mg BID and an Increased Dosage Regimen of FPV/RTV 1400mg/100mg BID Versus the Standard Dosage Regimen of FPV/RTV 700mg/100mg BID in Multiple-PI Experienced, HIV-infected Adults Experiencing Virological Failure.<br>The FPV/RTV 700mg/100mg BID regimen is approved for the treatment of PI-experienced subjects, in combination with other antiretroviral agents, based on the demonstration of safety and efficacy in this population. The FPV/RTV 1400mg/100mg BID regimen was selected for administration in this study based on its association with the highest plasma APV exposure and lower frequency of Grade 2/3 transaminase elevations (compared to FPV 1400 mg BID+RTV 200 mg BID). It was expected that subjects with a multi-drug resistant virus would benefit from an increase in plasma APV exposure through increasing the FPV/RTV dose to 1400 mg/100 mg BID, while being closely monitored for liver enzyme changes.<br>The dual-boosted HIV-1 PI combination of FPV/LPV/RTV 1400mg/533mg/133mg BID selected for administration in this study was based on previous experience of the combination of APV (delivered by AGENERASE) with LPV/RTV in heavily treatment-experienced subjects and the combination of these 2 potent PIs was considered to be beneficial for PI-experienced subjects. |
| Phase: Phase III |
| Study Period: 25 January 2005 to 15 May 2007 |
| Study Design: A Phase III, randomised, controlled, open-label, 3-arm, multicentre study. |
| Centres: This was a multicentre GSK-sponsored clinical study, involving study centres in Spain, UK, France, Germany, Italy and Canada. |
| Indication: Human Immunodeficiency Virus |
| Treatment: Subjects were randomised, in a 1:1:1 ratio, to 1 of the following treatment groups:<br>Group A (STD-FPV/RTV) : 700 mg FPV/100 mg RTV BID<br>Group B (HD-FPV/RTV) : 1400 mg FPV/100 mg RTV BID<br>Group C (FPV/LPV/RTV) : 1400 mg FPV/533 mg LPV/133mg RTV BID.<br>Trial medications were administered orally for a period of at least 24 weeks. Subjects randomised to Group A who met the criteria for virological failure were permitted to switch to receive either the increased dose FPV/RTV regimen (1400 mg FPV/100 mg RTV BID) or the FPV/LPV/RTV (1400 mg FPV/533 mg LPV/133 mg RTV BID) regimen. |
| Objectives: The primary objective of this study was to test the superiority of the increased FPV dose (FPV/RTV 1400 mg/100 mg BID; Group B) and the dual boosted PI combination FPV/LPV/RTV (1400 mg/533 mg/133 mg BID) based therapy (Group C) over the standard FPV/RTV (700 mg/100 mg BID) based therapy (Group A), as measured by the average area under the curve minus Baseline [AAUCMB] in plasma HIV-1 ribonucleic acid (RNA) at 24 weeks when each are administered in combination with an optimised background therapy, in a multiple PI-experienced population experiencing virological failure. |
| Primary Outcome/Efficacy Variable: The average area under the curve minus Baseline (AAUCMB) in $log_{10}$ plasma HIV-1 RNA at Week 24. |

Secondary Outcome/Efficacy Variable(s):

- AAUCMB in $log_{10}$ plasma HIV-1 RNA at Week 48
- Proportion of subjects with plasma HIV-1 RNA levels <50 copies/mL, <400 copies/mL or a ≥$log_{10}$ decrease in plasma HIV-1 RNA from Baseline at Weeks 24 and 48
- Time to virological failure
- Time to treatment failure
- Absolute values and changes from Baseline in plasma HIV-1 RNA and helper-inducer T-lymphocyte surface antigen (CD4+) lymphocyte count at Weeks 24 and 48
- Incidence and nature of AEs and laboratory abnormalities in study subjects
- Proportion of subjects who permanently discontinued randomised PI due to AEs
- Steady-state plasma APV and LPV trough concentrations
- Genotypic analysis of selected viral isolates
- Values of GIQ for FPV and LPV
- Virological outcome at Week 24 by GIQ for FPV and LPV

Statistical Methods: The planned sample size for this study was 150 subjects randomised in a 1:1:1 ratio to STD-FPV/RTV, HD-FPV/RTV or FPV/LPV/RTV; however, with agreement of regulatory agencies, study recruitment was stopped early at Week 24 before the planned sample size of 150 subjects was achieved and all final analyses were performed at Week 24. The primary analysis of the study analysed the superiority of HD-FPV/RTV and FPV/LPV/RTV treatment over STD-FPV/RTV treatment as measured by the plasma HIV-1 RNA AAUCMB at Week 24.

The primary efficacy population was the Intent-to-Treat (Exposed) (ITT[E]), which consisted of randomised subjects with documented evidence of having received at least 1 dose of treatment. The primary population for the safety analyses was the Safety Population, which consisted of randomised subjects with documented evidence of having received at least 1 dose of treatment.

Efficacy evaluations were planned for the ITT(E) Population subjects through 24 weeks. Analyses included the plasma HIV-1 RNA AAUCMB; the proportion of subjects with <400 copies/mL, <50 copies/mL and >1 $log_{10}$ copies/mL HIV-1 RNA decrease by visit; and actual values and changes from Baseline in $log_{10}$ plasma HIV-1 RNA levels and helper-inducer T-lymphocyte surface antigen (CD4+) cell counts by visit.

Safety analyses included clinical AEs, SAEs, AEs leading to permanent discontinuation of investigational product and Grade 3/4 clinical AEs. Clinical chemistry and haematological toxicities were also summarised.

Study Population: Adult male or female PI-experienced HIV-infected subjects were recruited into this study with the following main inclusion criteria:

- Three antiretroviral class (Nucleotide or Non-Nucleotide Reverse Transcriptase Inhibitor [NtRTI/NNRTI] and PI) therapy-experienced subjects
- ≥2 prior PI-based regimens with a documented history of virological failure (a confirmed plasma HIV-1 RNA concentration of ≥400 copies/mL)
- Documented evidence, in either the Screening genotype and/or in any historical resistance genotype tests taken in the previous 12 months, of at least 1 primary/major PRO mutation other than the D30N
- HIV-1 RNA assay ≥1000 copies/mL at Screening.

The study was terminated early with agreement from the EMEA, after 50% of the planned subjects had been enrolled, due to slow recruitment into the study. After the decision to terminate the study, all subjects enrolled in the study continued to receive treatment until the last subject had completed 24 weeks of study medication and the final analyses were conducted at Week 24.

| | Group A<br>STD-FPV/RTV | Group B<br>HD-FPV/RTV | Group C<br>FPV/LPV/RTV |
|---|---|---|---|
| Number of Subjects: | | | |
| Planned, N | 50 | 50 | 50 |
| Randomised, N | 24 | 25 | 25 |
| Completed, n (%) | 7 (29) | 13 (52) | 11 (44) |
| Total Number Subjects Withdrawn[1], N (%) | 17 (71) | 12 (48) | 14 (56) |

| | | | |
|---|---|---|---|
| Withdrawn due to Adverse Events n (%) | 1 (4) | 1 (4) | 3 (12) |
| Withdrawn due to Lack of Efficacy n (%) | 12 (50) | 8 (32) | 4 (16) |
| Withdrawn for other reasons n (%) | 4 (17) | 3 (12) | 7 (28) |

1. Total number of subjects discontinuing randomised treatment

Demographics:

| | Group A STD-FPV/RTV | Group B HD-FPV/RTV | Group C FPV/LPV/RTV |
|---|---|---|---|
| N (ITT[E]) | 24 | 25 | 25 |
| Females: Males | 4:20 | 4:21 | 7:18 |
| Median Age, years (range) | 42.5 (35, 69) | 42.0 (36, 61) | 44.0 (32, 79) |
| Race, n (%) | | | |
| White – Caucasian/European Heritage | 23 (96) | 21 (84) | 21 (84) |
| African American/African Heritage | 0 | 2 (8) | 2 (8) |
| American Indian/ Alaska Native | 0 | 0 | 1 (4) |
| White – Arabic/North African Heritage | 1 (4) | 1 (4) | 1 (4) |
| East Asian Heritage | 0 | 1 (4) | 0 |

Primary Efficacy Results at Week 24 (Randomised Period):

Plasma HIV-1 RNA AAUCMB ($log_{10}$ copies/mL)

| | Group A STD-FPV/RTV | Group B HD-FPV/RTV | Group C FPV/LPV/RTV |
|---|---|---|---|
| Mean (SD) | -0.98 (1.071) | -1.00 (0.837) | -1.05 (0.977) |

Statistical Results of HIV-1 RNA AAUCMB (log10 copies/ml)

| | HD-FPV/RTV vs. STD-FPV/RTV | | | LPV/FPV/RTV vs. STD-FPV/RTV | | |
|---|---|---|---|---|---|---|
| Analysis Type | Diff. | 97.5% CI | p-value | Diff. | 97.5% CI | p-value |
| LACF[1] | -0.066 | -0.714, 0.582 | 0.816 | -0.073 | -0.709, 0.563 | 0.794 |
| Per-protocol | -0.014 | -0.835, 0.806 | 0.968 | -0.005 | -0.846, 0.836 | 0.989 |
| Discontinuation=Baseline | -0.123 | -0.773, 0.526 | 0.665 | -0.065 | -0.703, 0.573 | 0.816 |
| LVLCF[2] | -0.078 | -0.746, 0.589 | 0.789 | -0.108 | -0.764, 0.547 | 0.706 |

[1]Last AAUCMB carried forward
[2]Last viral load carried forward
Note: Analysis adjusted for baseline viral load and T20 use

Secondary Outcome Variable(s) (Randomised Period):

Proportion of Subjects at Week 24, (TLOVR Analysis)

| | Group A STD-FPV/RTV n (%) | Group B HD-FPV/RTV n (%) | Group C FPV/LPV/RTV n (%) |
|---|---|---|---|
| <400 copies/mL Plasma HIV-1 RNA | 5 (21) | 6 (24) | 5 (20) |
| <50 copies/mL Plasma HIV-1 RNA | 5 (21) | 6 (24) | 5 (20) |
| ≥1.0 $Log_{10}$ copies/mL Plasma HIV-1 RNA | 5 (21) | 7 (28) | 6 (24) |

| Proportion of Subjects at Week 24 (Observed Analysis), | | | |
|---|---|---|---|
| | Group A<br>STD-FPV/RTV<br>n/N (%) | Group B<br>HD-FPV/RTV<br>n/N (%) | Group C<br>FPV/LPV/RTV<br>n/N (%) |
| <400 copies/mL Plasma HIV-1 RNA | 5/9 (56) | 6/17 (35) | 5/17 (29) |
| <50 copies/mL Plasma HIV-1 RNA | 4/9 (44) | 6/17 (35) | 5/17 (29) |
| ≥1.0 $Log_{10}$ copies/mL Plasma HIV-1 RNA | 5/9 (56) | 6/17 (35) | 6/17 (35) |
| Median CD4+ Cells/$mm^3$ by Visit at Week 24 (Observed Analysis) | | | |
| | Group A<br>STD-FPV/RTV<br>[n] Median (IQR) | Group B<br>HD-FPV/RTV<br>[n] Median (IQR) | Group C<br>FPV/LPV/RTV<br>[n] Median (IQR) |
| Median CD4+ Cells/$mm^3$ | [9]<br>307 (269, 513) | [18]<br>310 (198, 467) | [17]<br>244 (153, 390) |
| Plasma Amprenavir $C\tau$ for the Week 24 Overall Analysis | | | |
| | Group A<br>STD-FPV/RTV<br>N=24 | Group B<br>HD-FPV/RTV<br>N=20 | Group C<br>FPV/LPV/RTV<br>N=20 |
| Geometric Mean<br>(95% CI)<br>[CVb%] | 1.96<br>(1.49, 2.59)<br>[74] | 2.93<br>(2.39, 3.60)<br>[46] | 1.80<br>(1.26, 2.59)<br>[91] |
| Plasma Amprenavir $C\tau$ Treatment Comparisons for the Week 24 Overall Analysis | | | |
| | HD-FPV/RTV<br>vs<br>STD-FPV/RTV | | FPV/LPV/RTV<br>vs<br>STD-FPV/RTV |
| GLS Mean Ratio (90% CI) | 1.49<br>(1.08, 2.06) | | 0.919<br>(0.665, 1.27) |
| Plasma LPV overall $C\tau$ values for the Week 24 | | | |
| | Group C<br>FPV/LPV/RTV<br>N=20 | | |
| Geometric mean (95% CI)<br>[CVb%] | 7.99 (6.97, 9.15) [30], | | |
| Safety Results (Randomised Period) A treatment-emergent adverse event (AE) was defined as an AE with onset on or after the start date of study medication but not later than one day after the last date of study medication. A treatment-emergent serious adverse event (SAE) was defined as a SAE with onset on or after the start date of study medication and up to the final analysis (Week 24). | | | |
| | Group A<br>STD-FPV/RTV<br>(N=25)[1] | Group B<br>HD-FPV/RTV<br>(N=25) | Group C<br>FPV/LPV/RTV<br>(N=24) |
| Total number of all treatment-emergent AEs | 45 | 52 | 45 |
| Number of subjects with ≥1 treatment-emergent AEs | 15 (60) | 19 (76) | 20 (83) |
| Diarrhoea | 3 (12) | 9 (36) | 9 (38) |
| Bronchitis | 2 (8) | 3 (12) | 2 (8) |
| Cough | 3 (12) | 3 (12) | 1 (4) |
| Hypertriglyceridaemia[2] | 2 (8) | 0 | 5 (21) |
| Headache | 3 (12) | 2 (8) | 1 (4) |
| Nasopharyngitis | 2 (8) | 1 (4) | 3 (13) |
| Dizziness | 4 (16) | 1 (4) | 0 |
| Nausea | 3 (12) | 2 (8) | 0 |
| Asthenia | 0 | 2 (8) | 2 (8) |
| Myalgia | 2 (8) | 0 | 2 (8) |

| | | | |
|---|---|---|---|
| Pharyngitis | 1 (4) | 2 (8) | 1 (4) |
| Fatigue | 4 (16) | 0 | 0 |
| Vomiting | 1 (4) | 2 (8) | 0 |
| Neuropathy | 0 | 2 (8) | 0 |
| Insomnia | 0 | 0 | 2 (8) |
| Serious Adverse Events – Treatment-Emergent | | | |
| | Group A STD-FPV/RTV (N=25)1 n (%) [n considered "related"] | Group B HD-FPV/RTV (N=25) n (%) [n considered "related"] | Group C FPV/LPV/RTV (N=24) n (%) [n considered "related"] |
| Subjects with non-fatal SAEs | 0 | 2 (8) | 4 (17) |
| Diarrhoea | 0 | 1 (4) [1] | 1 (4) [0] |
| Glomerulonephropathy | 0 | 0 | 1 (4) [0] |
| Renal failure acute | 0 | 0 | 1 (4) [1] |
| Anaemia | 0 | 0 | 1 (4) [0] |
| Pyrexia | 0 | 0 | 1 (4) [0] |
| Pneumonia | 0 | 0 | 1 (4) [0] |
| Tibia fracture | 0 | 1 (4) [0] | 0 |
| Hyponatraemia | 0 | 1 (4) [0] | 0 |
| Leiomyosarcoma | 0 | 0 | 1 (4) [0] |
| Depression | 0 | 1 (4) [0] | 0 |
| Neuropathy peripheral | 0 | 1 (4) [0] | 0 |
| Lung disorder | 0 | 0 | 1 (4) [0] |
| Hypertension | 0 | 0 | 1 (4) [0] |
| Subjects with fatal SAEs | 0 | 0 | 0 |
| Treatment-Emergent Grade 3 or 4 Laboratory Abnormalities | Group A STD-FPV/RTV (N=25)1 n (%) | Group B HD-FPV/RTV (N=25) n (%) | Group C FPV/LPV/RTV (N=24) n (%) |
| Parameters of Special Interest | 4 (16) | 2 (8) | 5 (21) |
| ALT (U/L) | 0 | 1 (4) | 0 |
| AST (U/L) | 0 | 0 | 0 |
| Cholesterol (mg/dL) | 2 (8) | 0 | 1 (4) |
| LDL Cholesterol (mg/dL) | 1 (4) | 0 | 0 |
| Hyperglycaemia (mmol/L) | 0 | 0 | 1 (4) |
| Triglycerides | 3 (12) | 1 (4) | 4 (17) |

1. Subject 355 was randomised to the FPV/LPV/RTV group but took STD-FPV/RTV and hence is included in the STD-FPV/RTV group for the Safety Population

Conclusion: Antiviral responses were observed in all 3 treatment groups; however, there was no evidence for a statistical difference in efficacy of HD-FPV/RTV or FPV/LPV/RTV compared to STD-FPV/RTV in this population of highly treatment-experienced subjects with a high level of Baseline resistance to PIs and N(t)RTIs. Plasma APV $C\tau$ values were approximately 49% higher for the HD-FPV/RTV group compared to the STD-FPV/RTV group, and similar between the FPV/LPV/RTV and STD-FPV/RTV groups. Plasma LPV overall $C\tau$ values through Week 24 were similar to values historically observed for the LPV/RTV 400/100 mg BID regimen.There was no significant correlation between log-transformed plasma APV $C\tau$ or plasma APV $C\tau$ and AAUCMB and the percentage of subjects with Week 24 plasma HIV-1 RNA concentrations <400 copies/mL for any treatment, nor was there when the HD-FPV/RTV and STD-FPV/RTV groups were combined. No new serious safety concerns were identified with any of the study groups and there were no deaths during the study; however, the HD-FPV/RTV and FPV/LPV/RTV regimens appeared to be associated with higher incidence of gastrointestinal AEs and elevations in triglycerides.

Publications: No Publication

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