

GSK Medicine: Fosamprenavir
Study No.: WWE111949 / WEUKSTV2430 / EPI40537
Title: Using observational cohorts to monitor safety of fosamprenavir in patients with hepatic impairment: Telzir/Ritonavir in Hepatically Impaired Subjects
Rationale: Two regimens of fosamprenavir/ritonavir (FPV/RTV) have are approved by the EMEA and FDA for use in patients with mild/moderate hepatic impairment; FPV 700mg BID/RTV 100mg QD for those with mild HI (Child-Pugh score 4-6) and FPV 450mg BID/RTV 100mg QD for those will moderate HI (Child Pugh score 7-9). This observational study was undertaken to assess safety of these regimens using routinely collected data from three HIV patient cohorts with a high proportion of hepatitis co-infected individuals.
Objectives: The primary objective of this analysis was to assess the safety and tolerability of FPV/RTV-based ART in subjects with mild to severe hepatic impairment. The secondary objectives were to: i) compare the safety and tolerability of FPV/RTV-based ART in subjects with hepatic impairment when compared to FPV/RTV-based ART in HBV or HCV co-infected subjects with normal hepatic function, and ii) compare the safety and tolerability of FPV/RTV-based ART to lopinavir/ritonavir (LPV/RTV)-based ART in subjects with hepatic impairment.
Indication: HIV
Study Investigators/Centers: 1). ICONA cohort: Icona Foundation Study, Milan, Italy. 2). MASTER cohort: Infectious Disease and International Health Foundation, Brescia, Italy. 3). HEPAVIH cohort: Unité des Maladies Infectieuses, Hôpital Cochin, Paris, France.
Research Methods:
Data Source: Data were collected from 3 European HIV cohorts (ICONA and MASTER [Italy] and HEPAVIH [France]).
Study Population: Patients included in the study were HIV-positive individuals from the three cohorts who started FPV/RTV-based therapy on or after January 1, 2008; these patients were compared to those exposed to LPV/RTV-based therapy on or after January 1, 2007 (this is a deviation from protocol, see below). Patients were stratified into groups according to their degree of baseline hepatic impairment, defined by FPV/RTV dose received, as follows: <ul style="list-style-type: none"> • subjects with HBV or HCV co-infection but normal hepatic function, defined by exposure to the standard dose of FPV 700mg BID/RTV 100mg BID and a 'baseline' APRI [APRI score is the AST to platelet ratio index] score of <2.0 • subjects with mild hepatic impairment, defined by exposure to the reduced FPV/RTV dose 700mg BID/100mg QD • subjects with moderate/severe hepatic impairment, defined by exposure to the to the standard dose of FPV 700mg BID/RTV 100mg BID and a 'baseline' APRI of >2.0. Two other groups were planned according to the protocol (subjects with moderate hepatic impairment, defined by exposure to the reduced FPV/RTV dose [450mg BID/100mg QD] and subjects with severe hepatic impairment, defined by exposure to the reduced FPV/RTV dose [300mg BID/100mg QD]) could not be created due to insufficient patient numbers. As such, a fourth group was created as an alternative to include patients exposed to all other FPV doses other than the standard or reduced dose. These doses were FPV 700mg QD + RTV 100mg QD or FPV 1400mg QD and this group is referred to as "Other FPV dose".
Study Exposures, Outcomes:
Study Exposures Different dosing regimes of FPV/RTV-therapy
Study Outcomes <ol style="list-style-type: none"> 1. ALT elevation/flare after baseline; 2. First discontinuation of FPV/RTV or LPV/RTV alone; 3. First discontinuation of one or more drugs included in the FPV/RTV or LPV/RTV-based regimen 4. Severe hepatic events: treatment-emergent hepatic decompensation [defined as onset/progression of ascites, encephalopathy, jaundice, gastrointestinal bleeding, serious bacterial infection (spontaneous bacterial peritonitis, pneumonia, bacteremia), or hepatorenal syndrome]; 5. Occurrence of death/hospitalisation.
Data Analysis Methods: Descriptive analysis of patients at baseline and assessment of incidence rates of events

and study-defined endpoint in the different FPV/RTV and LPV/RTV groups. Kaplan-Meier curves and Cox proportional hazards regression were used to compare the hazard rates in the groups.

Limitations: This is an observational study and not a randomized clinical trial. The major limitations of this analysis are the small number of events, the short follow-up and potential bias due to unmeasured confounding.

Study Design: Retrospective cohort analysis of a multi-cohort study. These results represent the second interim set of data from the study.

Study Results:

The results reported here are the second set of interim results for this study and are comprised of patients exposed to FPV/RTV in these cohorts until the end of March 2010. The study will continue to collect data until 2011 and the final report will be available in Q3 2011.

There were several deviations from the protocol as follows:

1. As specified in the study population section above, the groups for analyses were different than specified in the protocol due to low/insufficient numbers, and hence were modified as stated above.
2. The variable "race" was not collected and was replaced by "origin". Six patients showed hepatic de-compensation pre-baseline, one person developed it over follow-up. Alcohol units intake was collected only in a minority of patients (and in ICONA, units were estimated on the basis of two variables, one indicating the frequency and another type of alcohol usage) and therefore were not included in the descriptive tables.
3. Inclusion criteria for LPV/r were extended from those starting therapy in 2008 to include patients starting over the year 2007 to include a larger control group. A 1:3 ratio between FPV/r- and LPV/r-recipients was reached, however in order to maintain this ratio, LPV/r recipients were not matched by APRI score or any other variable and confounding was controlled by means of multivariable analysis. APRI score and variables showing a significant imbalance between treatment groups (when possible) were included in the multivariable models.
4. Only n=18 patients experienced ALT elevation using the definition of two consecutive values >200 IU/l (or 50% increase from baseline if already >200 IU/l at baseline). This was changed to a single value for this report, resulting in a total of 39 events.

A total of 424 patients were included in the analysis. Key baseline characteristics are shown in the table below.

Characteristics	Treatment groups					p-value*
	FPV/r			LPV/r		
	700mg BID/RTV 100mg BID, APRI<2.0	700mg BID/RTV 100mg QD	Other dose**	700mg BID/RTV 100mg BID, APRI>=2.0	Standard dose	
	N= 54	N= 25	N= 11	N= 12	N= 322	
Age, years						0.298
Median (IQR)	45 (41, 49)	45 (41, 49)	45 (42, 47)	44 (41, 49)	44 (40, 47)	
Gender, n(%)						0.274
Female	17 (31.5%)	7 (28.0%)	3 (27.3%)	0 (0.0%)	95 (29.5%)	
Cohort, n(%)						<.001
Master	34 (63.0%)	20 (80.0%)	6 (54.5%)	8 (66.7%)	162 (50.3%)	
Hepaviih	4 (7.4%)	5 (20.0%)	2 (18.2%)	0 (0.0%)	98 (30.4%)	
Icna	16 (29.6%)	0 (0.0%)	3 (27.3%)	4 (33.3%)	62 (19.3%)	
Length of follow-up, years						0.092
Median (IQR)	1.11 (0.79, 1.68)	0.95 (0.35, 1.42)	1.57 (0.44, 1.94)	0.53 (0.16, 0.82)	1.06 (0.53, 1.62)	
ART-naive at baseline, n(%)	18 (33.3%)	7 (28.0%)	3 (27.3%)	3 (25.0%)	105 (32.6%)	0.956
AIDS before baseline, n(%)	14 (25.9%)	1 (4.0%)	4 (36.4%)	1 (8.3%)	88 (27.3%)	0.057
CD4 count, cells/mm³						<.001
Median (IQR)	351 (282, 525)	356 (231, 529)	348 (229, 427)	292 (231, 464)	258 (131, 406)	
Time on ART, years						0.810
Median (IQR)	2 (0, 9)	6 (0, 9)	4 (0, 11)	2 (0, 8)	3 (0, 9)	
HCV-Ab positive, n(%)	46 (85.2%)	24 (96.0%)	11 (100.0%)	12 (100.0%)	259 (80.4%)	0.052
HBs-Ag positive, n(%)	6 (11.1%)	4 (16.0%)	3 (27.3%)	1 (8.3%)	38 (11.8%)	0.571
Baseline ALT, n(%)						0.012
<=200 IU/L	48 (88.9%)	22 (88.0%)	7 (63.6%)	10 (83.3%)	242 (75.2%)	
>200 IU/L	0 (0.0%)	2 (8.0%)	2 (18.2%)	2 (16.7%)	15 (4.7%)	
Unknown	6 (11.1%)	1 (4.0%)	2 (18.2%)	0 (0.0%)	65 (20.2%)	
APRI score						<.001
Median (range)	0.57 (0.14, 1.80)	0.82 (0.14, 17.90)	0.92 (0.31, 3.93)	2.86 (2.05, 6.02)	0.72 (0.00, 12.73)	
FIB score						<.001
Median (IQR)	0.50 (0.32, 1.25)	0.48 (0.29, 1.50)	0.96 (0.37, 2.88)	2.04 (0.67, 5.90)	1.14 (0.49, 2.03)	
Meld score						0.009
Median (IQR)	5.15 (4.15, 8.08)	4.59 (4.04, 15.00)	6.04 (5.06, 7.01)	9.83 (1.25, 11.00)	2.47 (1.00, 3.91)	

* Chi-square or Fisher exact test as appropriate (for categorical variables) or Kruskal-Wallis test (for continuous variables)

**either - FPV 700mg QD + RTV 100mg QD (n=5) or FPV 1400mg QD (n=6)

1. ALT elevations/flare after baseline:

Thirty-nine patients experienced an elevation in ALT as by our revised definition (using a single value >200 IU/l) over a total of 422 PYFU for an overall incidence rate of 9.2 per 100 person years (95% CI: 6.7-12.4). The events per treatment groups were distributed as follows: FPV 700mg BID/ RTV100mg BID and APRI<2 (n=7), FPV 700mg BID/ RTV100mg BID and APRI>2 (n=0), FPV 700mg BID/ RTV 100mg QD (n=1), FPV other dose (n=0) and LPV/r (n=31).

The relative hazards of the risk of experiencing ALT elevation from fitting a multivariable Cox regression model for treatment group (no significant differences between the treatment groups) and variables that were significant in the model are as follows:

	Adjusted RH (95% CI)	p-value
Treatment group		
LPV/r	1.0	
FPV 700mg BID/ RTV100mg BID and APRI<2	1.33 (0.52, 3.38)	0.550
FPV 700mg BID/ RTV 100mg QD	0.24 (0.03, 2.02)	0.189
ART-naïve		
No	1.0	
Yes	2.49 (1.06, 5.83)	0.036

*Adjusted for the APRI score and also the following variables which were non-significantly associated with the outcome: gender, mode of HIV transmission, baseline values of CD4, APRI-score, platelets, bilirubin, use of anti-HBV/HCV drugs at baseline

2. Discontinuation of FPV/RTV- or LPV/RTV alone:

A total number of 129 discontinuations of FPV/r or LPV/r were observed over a total of 367 person-years of follow-up (PYFU) for an overall incidence rate of 35 per 100 PYFU (95% CI:30-40).

Multivariate Cox regression modelling indicated those exposed to “FPV other doses” were at significantly higher risk of discontinuing FPV/r compared to the risk of stopping LPV/r (see below).

Treatment group	APRI-Adjusted RH (95% CI)*	p-value
LPV/r	1.0	
FPV 700mg BID/ RTV100mg BID and APRI<2	1.27 (0.71, 2.29)	0.421
FPV 700mg BID/ RTV 100mg QD	0.94 (0.41, 2.14)	0.889
FPV other dose	4.04 (1.55, 10.50)	0.004

* Variables included in the model but were not significantly associated with the outcome: gender, mode of HIV transmission, ART-naïve, baseline values of CD4, APRI, platelets, bilirubin, and use anti HBV/HCV drugs at baseline

As per protocol, we also performed this analysis by restricting to discontinuations due to adverse events alone and using a competing risk approach to analysis. In summary, there were 42 discontinuations of FPV/r or LPV/r due to adverse events (5 for dyslipidaemia, 4 hypersensitivity reactions, 17 toxicity of abdomen and GI tract, 2 toxicity of CNS, 1 kidneys, and 13 other unspecified side effects). In the Cox regression analyses, the only independent predictor was starting FPV 700mg BID/ RTV100mg BID when patients’ APRI was <2; these patients were at >2-fold higher risk of discontinuing FPV/r (RH = 2.64, 95% 1.06, 6.54) because of toxicity than were patients starting LPV/r of stopping LPV/r due to adverse events. (full data not shown).

3. Discontinuation of ≥1 drugs included in the FPV/RTV- or LPV/RTV-based regimen

One hundred and sixty-nine patients discontinued ≥1 drugs of those used at baseline over a total of 338 PYFU for an overall incidence rate of 50 per 100 PYFU (95% CI: 45-55). Among those exposed to FPV, the most commonly discontinued drug was ritonavir (63% among 700mg BID / RTV 100mg BID APRI <2.0; 54% among 700mg BID / RTV 100mg QD; 17% among other FPV dose, and 33% among 700mg BID / RTV 100mg BID APRI >2.0). For 63/169 (37%) of patients, the major reason for drug discontinuation was listed as “other” or “unknown causes” (so excludes

stated causes including virologic failure, hypersensitivity reaction, toxicity, side effects, comorbidity, simplified treatment, structured treatment interruption, patient/physician wish or non-compliance). The results of a multivariable Cox regression model indicated that the relative hazards of the risk of discontinuing ≥ 1 drugs in the FPV/r-containing regimen compared to the risk of stopping ≥ 1 drugs in the LPV/r-containing regimen was significantly increased for those exposed to other FPV doses (see below).

	APRI Adjusted* RH (95% CI)	p-value
Treatment group		
LPV/r	1.0	
FPV 700mg BID/ RTV100mg BID and APRI<2	1.42 (0.84, 2.42)	0.192
FPV 70□mg BID/ RTV 100mg QD	1.21 (0.63, 2.34)	0.565
FPV other dose	3.34 (1.30, 8.53)	0.012
Baseline CD4 count		
per 100 cells/mm ³ higher	1.08 (1.00, 1.17)	0.046

* Variables included in the model but were not significantly associated with the outcome: gender, mode of HIV transmission, ART naive, baseline values of APRI score, platelets, bilirubin and use of anti HBV/HCV drugs at baseline

As per protocol, we also restricted the analysis to drug(s) that were discontinued because of adverse events alone and using a competing risk approach to analysis. In summary, there were 56 discontinuations of ≥ 1 drugs due to adverse events (1 for abnormal fat redistribution, 5 dyslipidaemia, 4 hypersensitivity reactions, 20 toxicity of abdomen and GI tract, 4 toxicity of CNS, 2 kidneys, 1 haematological and 19 other unspecified side effects). The adjusted RH indicated that those exposed to FPV 700mg BID/ RTV100mg BID and APRI<2 were significantly more likely to discontinue ≥ 1 drug due to adverse events compared to patients exposed to LPV/r (RH=3.55 95%1.66, 7.59).

4. Severe hepatic events

Six events of hepatic de-compensation were reported at baseline (1 in 700mg BID/RTV 100mg BID, APRI<2.0 recipients, 1 in 700mg BID/RTV 100mg BID, APRI \geq 2.0 recipients, and 4 in patients who initiated LPV/r). Only one event of treatment-emergent hepatic de-compensation was observed after baseline over a total clinical follow-up of 464 person years. The patient started LPV/r. The 95% confidence interval around this estimate of 0.2/100 person years is [0.005-1.19] /100 PYFU.

5. Death and hospitalization

There were 11 deaths which all occurred in patients who started LPV/r. The corresponding estimated incidence rate is 2.4 per 100 PYFU with 95% CI:1.2-4.2. Causes of deaths were: Complication due to hepatitis (n=1), invasive bacterial infection (n=1), other not specified (n=1), accidental (n=1), non AIDS malignancies (n=2) and unknown (n=5). Hospitalizations are not recorded in the Master cohort and therefore this endpoint was not analysed.

Conclusion:

It is concluded that compared to the control group of LPV/r-recipients, the risk of observing ALT elevation seemed to be elevated in patients receiving the standard dose of FPV/r although the association was not statistically significant (Adjusted RH=1.33, 95% CI 0.52, 3.38, p=0.55), whilst patients receiving the reduced dose did not appear to show an excess in risk (RH=0.24, 95% CI 0.03, 2.02, p=0.19). Of note, there were no ALT elevations in the patients who received FPV "other dose" or those on the standard dose with APRI >2.0. Compared to the previous interim analysis (including data up to the end of March 2009) patients who started the standard dose of FPV/r were estimated to be at a significantly 4-fold increased risk of ALT elevation compared to LPV/r recipients. The current analyses as described above, suggests a much smaller and statistically non-significant difference in risk.

In the first interim analyses, it was previously reported that there was a higher rate of discontinuations of any drugs used at baseline in people who started FPV/r (regardless of the dose) compared to those who started LPV/r. In this updated analysis there was a clear difference between "FPV other dose" (rate of discontinuation 65% by 8 months) and patients on LPV/r (23% by 8 months, log rank p=0.01) but less difference between FPV/r 700mg BID/RTV

100mg QD (40% by 8 months) and LPV/r, at least over the first 18 months from starting the study drugs . The interpretation of these findings is not clear, although it suggests that the initiation of non-standard doses of FPV/r (mainly 1400 mg QD) as compared to LPV/r may create an unstable regimen that quickly requires modification by the clinician.

In keeping with the interim report when assessing the rate of specific discontinuations of FPV/r or LPV/r, this again indicated that the “FPV/r other dose” group was the only treatment group associated with an increased risk of stopping FPV compared to the control group of LPV/r recipients. There were 8 interruptions in the 25 patients receiving FPV/r of 700mg BID/RTV 100mg QD and the most common reasons reported by the treating clinician were “non compliance” and “other causes” although GI-tract toxicity and side effects were also reported. Both the FPV 700mg BID/ RTV 100mg QD dose and the FPV/r standard dose did not show significant differences when compared to LPV/r for most of the examined outcomes. However, when the rate of discontinuation due to adverse events (AE) was analysed, there was a significant difference between FPV standard dose and LPV/r but only a tendency for a difference between the reduced dose and LPV/r supporting the hypothesis that the new dosage would lead to a reduction of toxicity-induced discontinuations. However, the sample size of patients receiving the reduced dose was smaller than that of patients receiving the standard dose and lack of significance may be due to reduced power.

During the study period, 11 deaths were observed and only one of these appeared to be liver-related. Furthermore, all deaths occurred in the control group of patients who started LPV/r.

In conclusion, this analysis does not show any evidence that, in patients with mild hepatic impairment, the use of the reduced dose of FPV/r is associated with a higher 1-year risk of drug discontinuation, ALT elevation, hepatic de-compensation or death than patients using the standard dose or a control group of patients who started LPV/r. However, the power of the analysis remains low and further data accumulation would be needed to increase the precision of our estimates and draw firmer conclusions, especially among patients with moderate and severe hepatic impaired. In addition, because patients were not randomised to the study treatments, unmeasured confounding cannot be ruled out.