

GSK Medicine: Fosamprenavir
Study No: WWE112880/WEUKSTV2831/EPI40531
Title: An observational multi-cohort study on the use of Fosamprenavir-Ritonavir among HIV-infected children and adolescents in Europe
Rationale: Twice daily fosamprenavir, in combination with low dose ritonavir (FPV/RTV BID), is indicated for the treatment of HIV-infected adults, adolescents and children of 6 years of age and above for use in combination with other anti-HIV medicines. The approved dosing regimen for FPV/RTV is 18/3mg/kg BID up to the adult dosage regimen of 700/100mg BID. Safety data from three Marketing Authorisation Holder (MAH) FPV clinical trials (ongoing study APV29005 involving twice-daily doses of FPV with or without RTV, completed study APV20003 with once daily dosing of FPV/RTV among 2-18 year olds, and ongoing study APV20002 involving twice-daily doses of FPV with RTV among 4 weeks to <2 year olds) indicated that infections and infestation and gastrointestinal events were the most commonly reported adverse events (AEs) (GlaxoSmithKline, personal communication). Treatment-emergent grade 3/4 neutropenia was reported in 20% of children in the APV20003 trial, but was likely to be at least partially confounded by concomitant medications and sample degradation in transit. In the recent 24-week analyses of APV 290005 and APV20002, grade 3/4 neutropenia was reported in 14% and 10% of subjects respectively, but due to the late onset and confounding factors in the majority of cases, these were considered unlikely to be related to FPV (MAH, personal communication). In the risk management plan for fosamprenavir use in the paediatric population, neutropenia was identified as a potential safety concern by the European Medicines Agency (EMA). In addition, the EMA highlighted the need for post-marketing research to further characterise the safety profile of fosamprenavir in children and adolescents.
Objectives: The primary objective was to assess the use and safety of FPV/RTV in HIV-infected children and adolescents aged 6-18 years on the licensed dose in the EU. The secondary objectives were: (1) to provide frequency counts of off-label use in three groups: children <6 years of age (excluding in utero exposure); children aged 6-18 years on unlicensed doses; and children aged <19 years on unboosted doses and (2) to provide biochemistry results for patients treated with the unlicensed dose.
Indication: HIV
Study Investigators/Centers: Six paediatric HIV cohorts participating in the European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC) as follows: Hospital St.Pierre Cohort, Brussels; Italian Register for HIV-infection in Children; Madrid Cohort of HIV-infected Children; Spanish Perinatal Cohort Study [NENEXP], Catalonia, Spain; UK National Study of HIV in Pregnancy and Childhood [NSHPC] & Collaborative HIV Paediatric Study [CHIPS]; and the "Victor Babes" Hospital Cohort, Romania.
Research Methods:
Data Source: Data were collected from the HIV patients cohorts participating in the EPPICC study as described above.
Study Design: Cohort study with retrospective and prospective phase
Study Population: HIV-1 infected children aged ≤ 18 years currently or having ever been exposed to FPV
Study Exposures, Outcomes: Study Exposures <ul style="list-style-type: none"> • Licensed dose of FPV/RTV (18/3mg/kg BID) Study Outcomes <ul style="list-style-type: none"> • Number of children on licensed dose of FPV/RTV • Reason for stopping FPV • Laboratory tests for absolute neutrophil counts (ANC), lipids (total cholesterol [TC] and triglycerides [TG]), and alanine transaminase (ALT) • Off-label use of FPV
Data Analysis Methods: Descriptive analyses only
Limitations: This is an observational study and not a randomized clinical trial. Data on adverse events (AEs) were only collected when of a serious nature and were not collected in a systematic manner across the individual cohorts. There is limited data on dosing information, non-ART medication, clinical data, AEs, and biochemistry/haematology laboratory tests for a number of exposed participants.

Study Results: These results comprise the retrospective analyses i.e. patients exposed to FPV/RTV in the cohorts until the end of 2010 (31/12/2010). In total, the 6 cohorts together provided data on 150 children who had ever taken any dose of FPV, with or without RTV, to the end of 2010, and all were aged ≤18 years when they started FPV. These 150 children together had 213 recorded treatment episodes with any dose of FPV with or without RTV.

Table 1 compares patient characteristics of the 150 children who have ever taken FPV to 92 children who were ever on the licensed dose of FPV (+/- 20% of 18mg/kg BID + RTV; n=92) to those on unlicensed doses also. Between 25-30% of patients on the licensed dose came from each of the Belgian, Italian, and Romanian cohorts. Around half of all the children were male and almost half (45%) were of white ethnicity. The majority of children were infected with HIV through mother-to-child transmission and one quarter (25%) of children on the licensed dose had been infected with HIV parenterally, all from the Romanian cohort. In the licensed dose group, one-third (33%) had an AIDS diagnosis; none died during follow-up. The median age at the start of FPV was 15 years (12-17 years) for those on the licensed dose, and the median duration of exposure to FPV was 37 months (13-50) in these patients. Just over half of these patients (54%) continued on an FPV-containing regimen at last follow-up. Fifteen patients discontinued a FPV-containing regimen for clinical reasons [immunological/virological failure (13), GI tract/liver/abdominal toxicity (2)], and these reasons for stopping may not necessarily have been due to the FPV itself.

Table 1: Characteristics of all children taking FPV

	All children (n=150)	Aged 6-18 years on licensed dose (n=92)	Aged 6-18 years only ever on unlicensed dose (n=15)	Aged <6 years (n=5) ¹
	n (column %) or median [IQR]			
Cohort				
Belgium (Brussels)	31 (21)	28 (30)	2 (13)	0 (0)
Italy	55 (37)	27 (29)	3 (20)	0 (0)
Romania (Bucharest)	27 (18)	23 (25)	3 (20)	0 (0)
Spain (Madrid)	9 (6)	3 (3)	2 (13)	2 (40)
Spain (Catalonia)	17 (11)	8 (9)	0 (0)	1 (20)
UK & Ireland	11 (7)	3 (3)	5 (33)	2 (40)
Male sex	77 (51)	48 (52)	7 (47)	2 (40)
Ethnic group (n)	(n=95)	(n=65)	(n=12)	(n=5)
White	44 (46)	29 (45)	7 (58)	0 (0)
Black African	34 (36)	24 (37)	3 (25)	3 (60)
Other	17 (18)	12 (18)	2 (17)	2 (40)
Mode of infection				
Mother-to-child transmission	113 (75)	85 (71)	12 (80)	5 (100)
Parenteral (non-injecting drug use)	27 (18)	23 (25)	2 (13)	0 (0)
Other	10 (7)	4 (4)	1 (7)	0 (0)
Ever AIDS diagnosis during overall follow-up	51 (34)	30 (33)	7 (47)	2 (40)
Age starting ART (years, excl. pMTC)	5.1 [1.3,9.4]	6.3 [1.4,11.1]	5.5 [0.7,7.8]	1.1 [0.7, 1.1]
Age starting FPV				
<6 years	8 (5)	0 (0)	1 (7)	5 (100)
6-8 years	9 (6)	5 (6)	1 (7)	0 (0)
9-11 years	30 (20)	16 (18)	5 (33)	0 (0)
12-14 years	45 (30)	27 (30)	6 (40)	0 (0)
15-18 years	58 (39)	42 (47)	2 (13)	0 (0)
Est. duration of time on FPV (months)	30 [9, 50]	37 [13, 50]	52 [34, 67]	13 [10, 19]
Not on FPV at last follow-up	69 (46)	42 (46)	3 (23)	1 (20)
Reason for stopping most recent FPV regimen				
Non-compliance	8 (12)	4 (9)	0 (0)	0 (0)
Patient's decision	10 (15)	8 (19)	1 (33)	0 (0)
Immunological or virological failure	20 (27)	13 (30)	0 (0)	0 (0)
GI tract / liver / abdomen toxicity	5 (7)	2 ² (5)	0 (0)	0 (0)
Simplified treatment available	9 (13)	6 (14)	0 (0)	0 (0)
Other	13 (17)	5 ² (12)	2 (67)	1 (1)
Unknown	5 (7)	4 (9)	0 (0)	0 (0)
Died during overall follow-up	2 (1)	0 (0)	0 (0)	0 (0)

¹ 2 of the 5 children starting FPV at age <6 years remained on FPV from age 6 years onwards; 1 at licensed dose and 1 at unlicensed dose only, and so also contributes to the group aged 6-18 years only ever on unlicensed dose.

Safety profile based on biochemical tests while on licensed dose of FPV

Laboratory toxicity data were available for 83 patients aged 6-18 years on licensed dose. Table 2 summarises the number of patients on the licensed FPV dose with each type of test result, the number of tests results available, and Division of AIDS (DAIDS) gradings for paediatric adverse events, which categorise the severity of these events.

Table 2: Biochemistry data for children aged 6-18 years on licensed dose of FPV

Test	Time since start of FPV ¹	No. of tests	No. of patients	No. of patient years on FPV ²	DAIDS grading of test results taken whilst on FPV ³ number (rate per 100 patient years) [95% CI]				No. of patients with maximum normal or 1 (%)	No. of patients with maximum grade 2 (%)	No. patients grade 3/4 (%)
					Normal	Mild (grade 1)	Moderate (grade 2)	Severe or potentially life-threatening (grade 3 or 4)			
ANC	< 12 months	227	75	75	192 (256) [221,295]	18 (24) [14,38]	11 (15) [7,26]	6 (8) [3,17]	64 (85)	6 (8)	5 (7)
	12-24 months	152	55	56	135 (242) [203,287]	11 (20) [10,35]	3 (5) [1,16]	3 (5) [1,16]	51 (93)	1 (2)	3 (5)
	>24 months	248	45	79	226 (287) [251,327]	19 (24) [15,38]	0 (0)	1 (1) [0,7]	44 (98)	0 (0)	1 (2)
	Total	625	82	210	553 (264) [242,287]	48 (23) [17,30]	14 (7) [4,11]	10 (5) [2,9]	68 (83)	6 (7)	8 (10)
TC	< 12 months	143	67	71	72 (101) [79,127]	36 (51) [35,70]	33 (46) [32,65]	2 (3) [0,10]	49 (73)	16 (24)	2 (3)
	12-24 months	109	46	55	55 (101) [76,131]	30 (55) [37,79]	21 (39) [24,59]	3 (6) [1,17]	33 (72)	11 (24)	2 (4)
	>24 months	182	43	103	103 (139) [112,167]	40 (54) [38,73]	36 (48) [34,67]	3 (4) [1,12]	27 (63)	14 (33)	2 (5)
	Total	434	78	201	230 (115) [100,130]	106 (53) [43,64]	90 (45) [36,55]	8 (4) [2,8]	54 (69)	22 (28)	2 (3)
TG	< 12 months	140	66	70	135 (192) [161,228]		4 (6) [2,15]	1 (1) [0,8]	63 (95)	2 (3)	1 (2)
	12-24 months	105	45	54	103 (192) [157,233]		1 (2) [0,10]	1 (2) [0,10]	43 (96)	1 (2)	1 (2)
	>24 months	181	43	75	176 (236) [202,273]		2 (3) [0,10]	3 (4) [1,12]	40 (93)	2 (5)	1 (2)
	Total					N/A ⁴					

Conclusion:

In conclusion, long-term licensed dose FPV-containing regimens appear to be well tolerated in the paediatric population of HIV-infected patients in Europe. Biochemistry and clinical adverse events were reported infrequently, and those that occurred could also be attributed to other drugs within an ART regimen, and differential levels of reporting between cohorts. An indication of higher rates of grade 2 hypercholesterolemia is already described in the literature. The number of patients with off-label use of FPV reported to EPPICC was low, and so it is not possible to make generalisations from such limited data. FPV was prescribed relatively infrequently in the paediatric HIV-infected population in Europe.