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Committee for Medicinal Products for Human Use (CHMP)

Assessment report under article 46

Telzir

International non-proprietary name: Fosamprenavir

Procedure no.: EMA/H/C/0534/P46/0075

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Introduction

On July 2014, the MAH submitted a completed paediatric study for TELZIR, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

TELZIR (fosamprenavir calcium, FPV) film-coated tablets and oral suspension were approved by the European Commission for use in combination with low dose ritonavir (RTV) and other antiretroviral agents for the treatment of HIV infection **in children 6 years and above** on 13 September 2007. Since the time of approval of the paediatric indication for TELZIR, further paediatric data have become available.

Study APV29005 was designed to determine the PK, safety and tolerability, and anti-viral activity of FPV BID in PI-naïve HIV-1 infected children aged 2 to <6 years and FPV/RTV BID in PI-naïve or PI-experienced HIV-1 infected children aged 2 to 18 years. Although the primary endpoint of the study was completed after the last enrolled subject had finished 48 weeks on investigational product, the study remained open so that children already enrolled in the study would continue to have access to the oral FPV formulation until they no longer derived any clinical benefit from FPV, were switched by the investigator to a different PI or were able to transition to the adult tablet formulation in countries where the oral formulation was not yet approved at the recommended dosing or was not commercially available.

This Post Authorisation Measure (PAM) “stand alone” submission therefore provides the current CSR which is the final report with all final data for this completed study.

Specifically:

- The new safety and efficacy data on the six subjects ongoing at the data cut-off date for the 48-week CSR.
- Any changes to the safety and tolerability using data collected post 48 weeks, because despite being planned as a 48-week study, the majority of subjects (65/109; 60%) had >96 weeks of exposure to study treatment, with a median duration of exposure of 138 weeks (range: 2 to 258 weeks).

There is no approved Paediatric Investigation Plan (PIP), and no changes to the paediatric indication or the Product Information for TELZIR are proposed.

Scientific discussion

Information on the development program

Three Phase II studies – Study APV29005, Study APV20003, and Study APV20002 – form the basis of the paediatric development program. Study APV20002 remains ongoing in children enrolled between the ages of 4 weeks to <2 years although recruitment is complete.

While Study APV29005 is considered pivotal, Study APV20003 and Study APV20002 provide supportive safety data with Study APV20003 also contributing to information on resistance. In Study APV29005 and Study APV20003, 158 paediatric subjects 2 to 18 years received at least one dose of FPV/RTV. In Study APV20002, 54 subjects received twice daily FPV/RTV while 5 subjects received only single doses of FPV with or without RTV.

Study APV29005 was designed to evaluate a BID regimen of FPV in PI-naïve subjects 2 to <6 years of age and a BID regimen of FPV/RTV in PI-naïve and -experienced subjects 2 to 18 years of age. This submission contains the post 48-week data from Study APV29005.

Information on the pharmaceutical formulation used in the study

TELZIR was administered as either oral 700 mg tablets or 50 mg/mL oral suspension.

Clinical aspects

1. Introduction

The MAH submitted a final report for study APV29005.

Assessor's comment:

The design, baseline characteristics and Week 48 results of this study have already been discussed as part of the FUM 046 and the variation II/74 of TELZIR. Only post-week 48 results were discussed in this CSR.

2. Clinical study

Study APV29005: A 48 Week, Phase II, Non-Comparative, Open-Label, Multi-Cohort, Multicenter Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Antiviral Activity of Fosamprenavir/Ritonavir BID when Administered to HIV-1 Infected, PI-naive and Experienced, Paediatric Subjects, 2 to 18 Years Old and of Fosamprenavir BID Administered to PI-naive, Paediatric Subjects 2 to < 6 Years Old.

Methods

- Primary objectives

- To define the FPV/RTV BID dosage regimen(s) which provided target steady-state plasma APV exposure to paediatric subjects 2 to 18 years of age.

- To evaluate the safety and tolerability of FPV/RTV BID in combination therapy for 48 weeks in HIV-1 infected, PI-naïve and PI-experienced, paediatric subjects 2 to 18 years of age.

- To define the FPV BID dosage regimen(s) which provided target steady-state plasma APV exposure to paediatric subjects 2 to <6 years of age.

- To evaluate the safety and tolerability of FPV BID in combination therapy for 48 weeks in HIV-1 infected, PI-naive, paediatric subjects 2 to <6 years of age.

- Study design

Enrolment was initially opened to Cohorts 1A, 1B, 2 and 3 and occurred in parallel for paediatric subjects 2 to 18 years of age:

Cohort	Age[a]	Treatment Status	Regimen[b]
1A[c]	2 to <6	PI-naïve	FPV BID
1B[c]	2 to <6	PI-naïve or experienced	FPV/RTV BID
2[c]	6 to 12	PI-naïve or experienced	FPV/RTV BID
3[c]	12 to 18	PI-naïve or experienced	FPV/RTV BID (pill regimen)
4[d]	2 to 18	PI-naïve or experienced	FPV/RTV BID

Each investigational product (FPV or FPV/RTV) was administered with 2 active NRTIs selected by investigator.

Once enrolment in any given age defined cohort was complete, further subjects in that age range may start enrolling in Cohort 4, provided Cohort 4 is open for recruitment for the appropriate age range.

- Study population /Sample size

Subjects from 2 to 18 years old.

Planned: 78 (FPV/RTV: 62; FPV: 16) - Enrolled: 110 - Treated: 109 (FPV/RTV: 89; FPV: 20).

- Treatments

Subjects received FPV BID (Cohort 1A) or FPV/RTV BID (Cohorts 1B, 2, 3 and 4). The dosage regimens were modified by amendments according to the Week 24 interim results:

Cohort	Age	Regimen	Original Dose	Amendment 2	Amendment 3
1A	2 to <6 years	FPV BID	40 mg/kg BID	30 mg/kg BID	
1B	2 to <6 years	FPV/RTV BID	20/4 mg/kg BID		23/3 mg/kg BID
2	6 to <12 years	FPV/RTV BID	15/3 mg/kg BID	18/3 mg/kg BID	
3	12 to 18 years	FPV/RTV BID	15/3 mg/kg BID		18/3 mg/kg BID

For Cohort 3, the majority of subjects in this age group received the standard adult regimen of FPV/RTV 700/100 mg BID regimen whereas, a few received the FPV oral suspension at a dose of FPV/RTV 15/3 mg/kg BID. A dose change for suspension to 18/3 mg/kg BID was implemented in Amendment 3.

To ensure that the paediatric subjects did not maintain concentrations higher than those observed in adults, an upper PK target was defined as a plasma APV AUC(0-τ) value of 61.68 µg.h/mL at the Week 2 visit or a plasma APV C_τ value of 3.52 µg/mL at subsequent visits (where only trough sampling was conducted), representing the 95th percentile observed in adults receiving FPV/RTV 700/100 mg BID.

The doses of each of the drugs given were to be recalculated at each visit and the total daily dose was adjusted according to the child's weight and the recommended dosage regimen. Dose adjustments should have occurred when the dose changed by 10% or more from the subject's prior calculated dose.

A background regimen of 2 active NRTIs was coadministered with FPV or FPV/RTV.

Post-Week 48 Results

This abbreviated clinical study report (CSR) presents the final analysis with all data collected in this study through 29 July 2013. Only 6 subjects continued in the study after the March 31 2011 cut-off date for the Week 48 CSR and therefore the focus for the current abbreviated CSR is any changes in safety and efficacy data that have occurred since that date.

The current analyses of protocol defined virologic failure include all subjects who met the criteria at any point after their Week 48 assessment and therefore contain information from more than just the 6

ongoing subjects. The Week 48 CSR for this study included all data collected by the March 31 2011 data cutoff date for the report with the exception of protocol defined virologic failure analyses which were censored at 48 weeks. At this time, 96 subjects had at least 48 weeks of exposure to study drug, with 77 subjects having evaluable viral load data at Week 60 and an overall median exposure to study drug of 127 weeks.

- Pharmacokinetics results

Table 21 Summary of Steady State Plasma APV PK Parameters and Statistical Comparisons for FPV/RTV BID in Paediatric Subjects 2 to <6 Years Old in APV29005 Week 48 analysis and Historical Adults

Plasma APV PK Parameter	2 to <6 Years[a, c] 23/3 mg/kg BID N=14	3 to <6 Years[a] 23/3 mg/kg BID N=11	Historical Adult 700/100 mg BID[a,c,d] N=159	2 to <6 Years vs. Historical Adult[b,d]
AUC(0-τ) (h.μg/mL)	55.3 (37.9, 80.7) [73]	59.7 (37.1, 96.2) [81]	37.0 (35.1, 38.9) [33]	1.50 (1.27, 1.77)
Cmax (μg/mL)	8.66 (6.08, 12.3) [67]	9.80 (6.51, 14.7) [67]	5.62 (5.35, 5.92) [33]	1.54 (1.30, 1.82)
Cτ (μg/mL)	3.39 (2.51, 4.57) [61]	3.36 (2.44, 4.63) [63]	2.17 (2.05, 2.30) [38]	1.56 (1.28, 1.90)
CL/F (mL/min/kg)	6.06 (4.12, 8.91) [75]	5.64 (3.45, 9.22) [84]	3.52 (3.33, 3.71) [35]	1.72 (1.45, 2.05)
CL/F (mL/min)	91.2 (60.0, 139) [83]	90.9 (52.4, 158) [98]	270 (257, 284) [33]	0.338 (0.280, 0.407)
tmax (h)	1.25 (1.00, 4.00)	1.00 (1.00, 2.05)	1.50 (0.50, 6.00)	ND
t1/2 (h)	5.21 (4.47, 6.08) [27]	5.34 (4.38, 6.52) [30]	ND	ND

Source Data: Table 10.9, Table 10.11, Table 10.13 and Table 10.19
ND = not done
a. Geometric Mean (95% CI) [CVb%], except tmax is presented as median (range)
b. GLS Mean Ratio (90% CI)
c. N=16 for 23/3 mg/kg BID Cτ in subjects 2 to <6 years and N=15 for 23/3 mg/kg BID Cτ in subjects 3 to <6 years, N=158 for historical adult AUC(0-τ) and N=157 for historical adult CL/F
d. Healthy Adults

Table 22 Summary of Steady State Plasma APV PK Parameters and Statistical Comparisons for FPV/RTV BID in Paediatric Subjects 6 to <12 Years Old in APV29005 and Historical Adults

Plasma APV PK Parameter	6 to <12 years[a]			Historical Adult	6 to <12 Years vs. Historical Adult[b,e]		
	15/3 mg/kg BID N=10[c,d]	18/3 mg/kg BID N=12[c,d]	700/100 mg BID N=3[c,d]	700/100 mg BID N=159[a,c,e]	15/3 mg/kg BID	18/3 mg/kg BID	700/100 mg BID
AUC(0-τ) (h.µg/mL)	32.3 (23.0, 45.3) [46]	48.4 (38.1, 61.4) [39]	37.6 (22.2, 63.8) [22]	37.0 (35.1, 38.9) [33]	0.874 (0.712, 1.07)	1.31 (1.09, 1.57)	1.02 (0.717, 1.44)
Cmax (µg/mL)	4.34 (3.16, 5.96) [47]	6.40 (5.02, 8.15) [40]	5.85 (3.94, 8.70) [16]	5.62 (5.35, 5.92) [33]	0.772 (0.635, 0.938	1.14 (0.951, 1.36)	1.04 (0.735, 1.47)
Cτ (µg/mL)	2.24 (1.70, 2.93) [47]	2.42 (1.90, 3.07) [60]	1.81 (0.803, 4.08) [108]	2.17 (2.05, 2.30) [38]	1.03 (0.831, 1.28)	1.12 (0.943, 1.32)	0.835 (0.625, 1.12)
CL/F (mL/min/kg)	6.48 (4.68, 8.98) [44]	5.27 (4.16, 6.68) [39]	5.94 (2.59, 13.6) [34]	3.52 (3.33, 3.71) [35]	1.84 (1.49, 2.28)	1.50 (1.24, 1.81)	1.69 (1.17, 2.43)
CL/F (mL/min)	195 (136, 279) [49]	149 (104, 214) [61]	266 (157, 452) [22]	270 (257, 284) [33]	0.721 (0.574, 0.906)	0.553 (0.453, 0.675)	0.985 (0.668, 1.45)
tmax (h)	2.00 (1.00, 6.00)	1.96 (0.50, 4.00)	3.92 (1.00, 4.02)	1.50 (0.50, 6.00)	ND	ND	ND
t1/2 (h)	10.5 (8.36, 13.1) [25]	8.41 (5.90, 12.0) [53]	7.43 (6.46, 8.55) [20]	ND	ND	ND	ND

Source Data: Table 10.9, Table 10.11, and Table 10.13. ND = not done

a. Geometric Mean (95% CI) [CVb%], except tmax is presented as median (range)
b. GLS Mean Ratio (90% CI)
c. N=9 for 15/3 mg/kg BID AUC(0-τ), CL/F and N=7 for 15/3 mg/kg BID t1/2; N=10 for 18/3 mg/kg BID t1/2; N=2 for 700/100 mg BID t1/2 (shown as Geometric mean (min, max) [CVb%]); N=158 for historical adult AUC(0-τ) and N=157 for historical adult CL/F
d. N=13 for 15/3 mg/kg BID Cτ, N=23 for 18/3 mg/kg BID Cτ,and N=7 for 700/100 mg BID Cτ
e. Healthy Adults

Table 23 Summary of Steady State Plasma APV PK Parameters and Statistical Comparisons for FPV/RTV in Paediatric Subjects 12 to 18 Years Old in APV29005 and Historical Adults

Plasma APV PK Parameter	12 to 18 years[a]			Historical Adult	12 to 18 Years vs. Historical Adult[b,e]		
	15/3 mg/kg BID N=4[c]	18/3 mg/kg BID N=4[c]	700/100 mg BID N=13[c]	700/100 mg BID N=159[a,d,e]	15/3 mg/kg BID	18/3 mg/kg BID	700/100 mg BID
AUC(0-τ) (h.µg/mL)	21.8 (18.0, 26.3) [12]	41.7 (16.2, 108) [40]	35.3 (28.2, 44.1) [38]	37.0 (35.1, 38.9) [33]	0.588 (0.434, 0.797)	1.13 (0.796, 1.60)	0.954 (0.802, 1.13)
Cmax (µg/mL)	3.92 (2.44, 6.29) [30]	4.91 (2.69, 8.97) [39]	4.93 (3.83, 6.34) [44]	5.62 (5.35, 5.92) [33]	0.697 (0.515, 0.943)	0.873 (0.646, 1.18)	0.876 (0.737, 1.04)
Cτ (µg/mL)	1.45 (0.559, 3.74) [89]	1.80 (1.22, 2.67) [59]	2.01 (1.74, 2.32) [47]	2.17 (2.05, 2.30) [38]	0.667 (0.474, 0.938)	0.832 (0.651, 1.06)	0.926 (0.811, 1.07)
CL/F (mL/min/kg)	10.1 (8.35, 12.3) [12]	6.00 (2.37, 15.2) [39]	5.33 (4.26, 6.68) [39]	3.52 (3.33, 3.71) [35]	2.88 (2.10, 3.95)	1.71 (1.19, 2.46)	1.52 (1.27, 1.82)
CL/F (mL/min)	392 (355, 432) [6]	198 (46.7, 838) [63]	284 (227, 354) [38]	270 (257, 284) [33]	1.45 (1.04, 2.03)	0.733 (0.497, 1.08)	1.05 (0.866, 1.27)
tmax (h)	1.00 (1.00, 2.00)	1.50 (0.00, 2.00)	2.00 (0.92, 7.97)	1.50 (0.50, 6.00)	ND	ND	ND
t1/2 (h)	6.12 (3.67, 10.2) [33]	8.76 (2.79, 27.5) [49]	7.64 (4.84, 12.0) [76]	ND	ND	ND	ND

Source Data: Table 10.9, Table 10.11, and Table 10.13
ND = not done

a. Geometric Mean (95% CI) [CVb%], except tmax is presented as median (range)
b. GLS Mean Ratio (90% CI)
c. N=40 for 700/100 mg BID Cτ and N=11 for 700/100 mg BID t1/2; N=10 for 18/3 mg/kg BID Cτ and N=3 for AUC(0-τ) and CL/F; N=6 for 15/3 mg/kg BID Cτ
d. N=158 for historical adult AUC(0-τ) and N=157 for historical adult CL/F
e. Healthy adults

Assessor's comment:

Post-Week 48 PK results did not change the overall conclusion that:

- *plasma APV exposures achieved following FPV/RTV 23/3 mg/kg BID in 2 to <6 year old subjects were ~50% higher than that observed in adults.*
- *plasma APV exposures achieved in 6 to 18 year old subjects were similar than that observed in adults.*

• Efficacy results

The proportions analysis of the observed viral load data were very similar to results reported in the Week 48 CSR. At least 67% of subjects across the treatment groups achieved HIV-1 RNA <400 copies/mL by Week 48 in the Observed analysis. At Week 48, a higher proportion of PI-naïve subjects (78% and 86% in the FPV and FPV/RTV treatment groups, respectively) achieved HIV-1 RNA <400 copies/mL compared to the PI-experienced subjects (67%) in the FPV/RTV treatment group. By Week 144, 88% (14/16) of PI-naïve subjects in the FPV treatment group and 90% (18/20) of PI-naïve subjects in the FPV/RTV treatment group achieved plasma HIV-1 RNA <400 copies/mL compared to 83% (15/18) in the PI-experienced FPV/RTV treatment group. By Week 216, all of the remaining subjects in all groups achieved plasma HIV-1 RNA <400 copies/mL.

Table 46 Summary of Proportion of Subjects with Plasma HIV-1 RNA <400 copies/mL by PI Status and by Visit in APV29005 ITT(E) Population (Observed)

	FPV	FPV/RTV		
Week	**PI-naïve N=20 n/N (%)**	**PI-naïve N=49 n/N (%)**	**PI-exp N=40 n/N (%)**	**FPV/RTV Total N=89 n/N (%)**
Baseline	0/20	0/49	0/39	0/88
Week 24	15/18 (83)	39/44 (89)	24/35 (69)	63/79 (80)
Week 48	14/18 (78)	38/44 (86)	22/34 (65)	60/77 (78)
Week 72	12/17 (71)	23/26 (88)	19/26 (73)	42/52 (81)
Week 96	14/16 (88)	19/21 (90)	15/26 (58)	34/47 (72)
Week 120	12/15 (80)	20/21 (95)	14/22 (64)	34/43 (79)
Week 144	14/16 (88)	18/20 (90)	15/18 (83)	33/38 (87)
Week 168	11/12 (92)	15/15 (100)	8/13 (62)	23/28 (82)
Week 192	11/11 (100)	4/4 (100)	3/4 (75)	7/8 (88)
Week 216	8/8 (100)	3/3 (100)	1/1 (100)	4/4 (100)

Table 47 Summary of Proportion of Subjects with Plasma HIV-1 RNA <50 copies/mL by Visit and PI Status in APV29005 ITT(E) Population (Observed)

	FPV	FPV/RTV		
Week	**PI-naïve N=20 n/N (%)**	**PI-naïve N=49 n/N (%)**	**PI-exp N=40 n/N (%)**	**FPV/RTV Total N=109 n/N (%)**
Baseline	0/20	0/49	0/39	0/88
Week 24	9/18 (50)	27/44 (61)	17/35 (49)	44/79 (56)
Week 48	8/18 (44)	31/44 (70)	19/34 (56)	50/78 (64)
Week 72	11/17 (65)	21/26 (81)	18/26 (69)	39/52 (75)
Week 96	13/16 (81)	17/21 (81)	14/26 (54)	31/47 (66)
Week 120	11/15 (73)	17/21 (81)	10/22 (45)	27/43 (63)
Week 144	13/16 (81)	17/20 (85)	12/18 (67)	29/38 (76)
Week 168	11/12 (92)	15/15 (100)	7/13 (54)	22/28 (79)
Week 192	11/11 (100)	4/4 (100)	3/4 (75)	7/8 (88)
Week 216	8/8 (100)	3/3 (100)	1/1 (100)	4/4 (100)

Table 49 **Median CD4+ Cells/mm^3 Change from Baseline by Visit and PI Status in APV29005 ITT(E) Population (Observed Analysis)**

	CD4+ Cell Count Change from Baseline (cells/mm^3) Median [IQR]							
	FPV		FPV/RTV					
Week	n	PI-naïve N=20	n	PI-naïve N=49	n	PI-exp N=40	n	FPV/RTV Total N=89
Week 24	18	350 [110, 640]	44	184 [53, 367]	34	150 [10, 260]	78	160 [30, 324]
Week 48	17	340 [-30, 470]	42	217 [100, 398]	29	180 [0, 270]	71	190 [50, 350]
Week 72	17	200 [110, 460]	26	325 [240, 550]	24	190 [30, 255]	50	250 [130, 430]
Week 96	15	190 [-30, 510]	22	399 [240, 640]	24	130 [-90, 295]	46	255 [30, 440]
Week 120	14	60 [-170, 530]	19	410 [250, 600]	22	165 [-100, 390]	41	320 [4, 460]
Week 144	15	190 [-90, 510]	19	431 [20, 600]	15	220 [60, 330]	34	275 [60, 490]
Week 168	12	70 [-15, 340]	14	243 [50, 300]	13	30 [-180, 210]	27	140 [10, 290]
Week 192	10	90 [-180, 550]	4	15 [-120, 130]	3	-70 [-320, 260]	7	-30 [-210, 200]
Week 216	8	215 [-65, 555]	3	40 [-60, 410]	1	200 [200, 200]	4	120 [-10, 305]

A total of 33/109 (30%) of subjects met the reporting analysis plan-defined virologic failure (VF) criteria from Day 1 through the end of the study, including 7 subjects on FPV-containing regimens and 26 on FPV/RTV containing regimens. Of those 33 subjects, 25 of these met RAP-defined VF criteria through Week 48 while 8 subjects met VF after Week 48. Of the latter group, 7/8 subjects were receiving FPV/RTV-containing ART regimens while 1 was receiving an FPV-only containing ART regimen. Overall, the majority (25/33; 76%) of the subjects with RAP defined VF were > 5 years or older at study entry. The proportion of VF subjects who were > 6 years or older at study entry was similar through Week 48 (19/25; 76%) and post Week 48 (6/8; 75%).

Paired genotype data was available for analysis of treatment emergent viral mutations and RS from 22/33 subjects with VF. Overall, treatment-emergent NRTI and PI mutations were detected in viruses from 6 subjects at VF by Week 48 and in 5 subjects post Week 48. These included a total of four ART-naïve subjects receiving unboosted FPV-containing regimens, three of whom met VF prior to Week 48. Virus from all 4 subjects selected for the M184V mutation at VF, and virus from 3 of the 4 subjects also developed RS to FPV at VF. The remaining 7 VF subjects with treatment-emergent viral mutations were all on FPV/RTV-containing regimens. Of these, 3 occurred prior to Week 48; and all 3 subjects were heavily treatment-experienced; virus from 2 subjects had treatment-emergent protease mutations and developed FPV RS, while the third had treatment-emergent M184V. Post Week 48, 3 of the 4 subjects with VF on FPV/RTV-containing regimens were treatment-experienced and one was ART-naïve at study start. Virus from the latter subject selected for the RT mutation M184I at VF but did not select any PI mutation and subsequently experienced viral resuppression and remained suppressed for 48 weeks until study withdrawal while for the 3 treatment-experienced VF subjects, virus from 2 subjects had treatment-emergent M184V mutations at V; virus from 2 subjects had treatment-emergent PRO mutations at VF although only virus from one of the subjects developed RS to FPV. Treatment-emergent RS to FPV was detected at VF in virus from 6 subjects; 3 from subjects on FPV-containing regimens and 3 from treatment-experienced subjects on FPV/RTV-containing regimens.

Assessor's comment:

Because of the study discontinuation of many subjects after week 48 (due to insufficient viral load response, protocol violation or patient wish) and the low number of subjects still in treatment, it is difficult to conclude on the long-term efficacy of FPV in these subjects.

Nonetheless, when considering the virologic failure (VF) population, the rate of VF is similar through week 48 and after.

	FPV	FPV/RTV			
	2 - 5 Years	2 - 5 Years	6 - 11 Years	12 - 18 Years	Total
	(N=20)	(N=19)	(N=30)	(N=40)	(N=109)
Total Virology Population, n (%)	18 (90)	10 (53)	27 (90)	38 (95)	93 (85)
VF Population	7 (35)	1 (5%)	12 (40)	13 (33)	33 (30)
VF Population (> Week 24 and ≤ Week 48)	4 (20)	0	1 (3)	2 (5)	7 (6)
VF Population (> Week 48)	1 (5)	1 (5)	3 (10)	3 (8)	8 (7)

Overall, given that current indication of TELZIR includes children from 6 years old, there is no concern about long-term efficacy of FPV in paediatric subjects.

- Safety results

FPV and FPV/RTV were generally well-tolerated when administered to children in this study. No new safety concerns with either the oral suspension or the tablet formulation have emerged since the Week 48 analysis cut-off date, including when treatment was prolonged in many subjects (median 138 weeks; range: 2 to 258 weeks).

Assessor's comment:

Post-Week 48 safety results did not change the safety profile of TELZIR. No death was reported. Change from baseline in the clinical chemistry and hematology parameters were similar at Week 48 and Week 96:

FPV N=20						
Parameters of Special Interest	Median Baseline [IQR]		Median Change [IQR] from Baseline			
	n		n	Week 48	n	Week 96
Triglycerides (mmol/L)	19	0.9 [0.8, 1.2]	17	0.1 [-0.2, 0.3]	--	NA
Total cholesterol (mmol/L)	19	3.1 [2.6, 3.6]	17	1.1 [0.8, 1.5]	--	NA
HDL cholesterol (mmol/L)	19	0.8 [0.6, 1.0]	17	0.4 [0.3, 0.7]	--	NA
LDL cholesterol (mmol/L)	19	1.7 [1.4, 2.3]	17	0.6 [0.3, 1.0]	--	NA
Serum lipase (U/L)	20	18 [15, 27]	18	-2.0 [-5.0, 0.0]	--	NA
Glucose (mmol/L)	20	4.7 [4.3, 4.9]	18	0 [-0.3, 0.6]	16	0.2 [-0.1, 0.6]
ALT (IU/L)	20	19 [12, 37]	18	-3 [-14, 19]	16	4.0 [-7.0, 28]
AST (IU/L)	20	38 [36, 60]	18	-6 [-19, 10]	16	-1.0 [-8.0, 14]
FPV/RTV N=89						
Parameters of Special Interest	Median Baseline [IQR]		Median Change [IQR] from Baseline			
	n		n	Week 48	n	Week 96
Triglycerides (mmol/L)	84	1.1 [0.7, 1.4]	65	0.2 [0.0, 0.8]	5	-0.1 [-0.2, 1.1]
Total cholesterol (mmol/L)	84	3.7 [3.3, 4.2]	65	0.9 [0.2, 1.6]	5	1.0 [0.8, 1.7]
HDL cholesterol (mmol/L)	84	1.0 [0.7, 1.2]	65	0.3 [0.1, 0.4]	5	0.2 [0.2, 0.4]
LDL cholesterol (mmol/L)	84	2.2 [1.8, 2.6]	64	0.5 [-0.1, 1.1]	4	0.6 [0.3, 1.0]
Serum lipase (U/L)	89	19 [15, 28]	69	-1.0 [-7.0, 4.0]	3	-3.0 [-6.0, 0.0]
Glucose (mmol/L)	89	4.7 [4.3, 5.1]	69	0.1 [-0.3, 0.5]	45	0.1 [-0.1, 0.5]
ALT (IU/L)	89	22 [17, 37]	70	-7 [-16, -1]	46	-8.0 [-24, -2.0]
AST (IU/L)	89	35 [26, 47]	70	-9 [-17, -4]	46	-13 [-22, -5.0]

Rapporteur’s overall conclusion and recommendation

Overall conclusion

These long-term results did not provide long-term efficacy or safety concerns. These results did not impact the current paediatric indication and posology, without modification of the safety profile of TELZIR.

Recommendation

☒ **Fulfilled –**

No regulatory action required