



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

22 July 2021
EMA/92477/2021
Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Exviera

dasabuvir

Procedure no: EMEA/H/C/003837/P46/021

Viekirax

ombitasvir / paritaprevir / ritonavir

Procedure no: EMEA/H/C/003839/P46/023

Note

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



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1. Introduction

On 11 May 2021, the MAH submitted a completed paediatric clinical study report for Exviera/Viekirax, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study M14-748, An Open-Label, Multicenter Study to Evaluate the Pharmacokinetics, Safety, and Efficacy of Ombitasvir (OBV), Paritaprevir (PTV), Ritonavir (RTV) With or Without Dasabuvir (DSV) and With or Without Ribavirin (RBV) in Pediatric Subjects With Genotype 1 or 4 Chronic Hepatitis C Virus (HCV) Infection (ZIRCON), is a stand-alone study.

CHMP comment

The efficacy and on-treatment safety data from this study has already been assessed within procedures EMEA/H/C/003837 and EMEA/H/C/003839. Therefore, this assessment report is limited to the new follow-up data submitted.

2.2. Clinical aspects

2.2.1. Introduction

The MAH submitted a final report for:

- Study M14-748, An Open-Label, Multicenter Study to Evaluate the Pharmacokinetics, Safety, and Efficacy of Ombitasvir (OBV), Paritaprevir (PTV), Ritonavir (RTV) With or Without Dasabuvir (DSV) and With or Without Ribavirin (RBV) in Pediatric Subjects With Genotype 1 or 4 Chronic Hepatitis C Virus (HCV) Infection (ZIRCON)

2.2.2. Clinical study

Study M14-748

Description

Study M14-748 is a completed Phase 2/3, open-label, multicenter study to evaluate the pharmacokinetics (PK), efficacy, and safety of ombitasvir (OBV)/ paritaprevir (PTV)/ ritonavir (RTV) with or without dasabuvir (DSV) and with or without ribavirin (RBV) in hepatitis C virus (HCV) genotype (GT)1 or GT4-infected pediatric subjects of ≥ 3 to 17 years of age.

Methods

See EMEA/H/C/003837 and EMEA/H/C/003839.

Results

Recruitment, numbers analysed and baseline data

See EMEA/H/C/003837 and EMEA/H/C/003839.

Efficacy results

SVR24 results were consistent with the primary efficacy results with 98.4% agreement between SVR12 and SVR24; the overall SVR24 rate in the ITT population was 96.9% with a 2-sided 95% CI of 89.3% to 99.1%. No subject failed to achieve SVR24 due to virologic reasons.

CHMP comment

The high correlation between SVR12 and SVR24 is in line with established knowledge within the field of HCV treatment with DAAs.

Safety results

For on-treatment safety, see EMEA/H/C/003837 and EMEA/H/C/003839.

Growth and Development Outcomes

Height z-scores were calculated at PT visits using WHO published height-for-age z-score tables. No subject had a height z-score below -2, which would indicate evidence of stunted growth, at any visit. Mean change from baseline in height z-score across visits, sexes, and age groups ranged from -0.22 in the male, 12 to 17 year age group at PT Week 144 to 0.63 in the male, 9 to 11 year age group at PT Week 144.

Height Z-score Change from Baseline (ITT Population)

Sex	Age (years)	PT Week 12	PT Week 36	PT Week 96	PT Week144	Final PT Visit
		[N] Mean (SD)	[N] Mean (SD)	[N] Mean (SD)	[N] Mean (SD)	[N] Mean (SD)
Female						
	12 – 17	[N=25] -0.03 (0.197)	[N=21] -0.06 (0.253)	[N=19] -0.15 (0.330)	[N=20] -0.17 (0.325)	[N=25] -0.16 (0.298)
	9 – 11	[N=6] -0.01 (0.139)	[N=6] -0.01 (0.252)	[N=6] 0.09 (0.573)	[N=6] 0.04 (0.744)	[N=6] 0.04 (0.744)
	3 – 8	[N=11] -0.09 (0.424)	[N=11] 0.04 (0.434)	[N=10] 0.04 (0.619)	[N=8] 0.16 (0.538)	[N=11] 0.22 (0.476)
	Total	[N=42] -0.04 (0.264)	[N=38] -0.02 (0.310)	[N=35] -0.05 (0.468)	[N=34] -0.05 (0.476)	[N=42] -0.03 (0.450)
Male						
	12 – 17	[N=12] -0.06 (0.189)	[N=13] -0.12 (0.218)	[N=13] -0.14 (0.338)	[N=12] -0.22 (0.420)	[N=13] -0.17 (0.440)
	9 – 11	[N=6] 0.08 (0.169)	[N=5] 0.21 (0.259)	[N=4] 0.25 (0.101)	[N=4] 0.63 (0.362)	[N=6] 0.49 (0.430)
	3 – 8	[N=2] -0.05 (0.117)	[N=2] 0.06 (0.066)	[N=2] 0.25 (0.132)	[N=2] 0.26 (0.205)	[N=2] 0.26 (0.205)
	Total	[N=20] -0.01 (0.182)	[N=20] -0.02 (0.259)	[N=19] -0.02 (0.337)	[N=18] 0.02 (0.523)	[N=21] 0.06 (0.508)

Height Z-score Change from Baseline (ITT Population) (continued)

Sex	Age (years)	PT Week 12	PT Week 36	PT Week 96	PT Week144	Final PT Visit
		[N] Mean (SD)	[N] Mean (SD)	[N] Mean (SD)	[N] Mean (SD)	[N] Mean (SD)
Overall						
	12 – 17	[N=37] -0.04 (0.192)	[N=34] -0.08 (0.239)	[N=32] -0.15 (0.328)	[N=32] -0.19 (0.358)	[N=38] -0.16 (0.347)
	9 – 11	[N=12] 0.04 (0.156)	[N=11] 0.09 (0.268)	[N=10] 0.15 (0.439)	[N=10] 0.27 (0.665)	[N=12] 0.26 (0.625)
	3 – 8	[N=13] -0.08 (0.389)	[N=13] 0.05 (0.396)	[N=12] 0.08 (0.567)	[N=10] 0.18 (0.481)	[N=13] 0.23 (0.439)
	Total	[N=62] -0.03 (0.240)	[N=58] -0.02 (0.291)	[N=54] -0.04 (0.424)	[N=52] -0.03 (0.489)	[N=63] -0.00 (0.468)

ITT = intention-to-treat; PT = post-treatment; SD = standard deviation

Growth rate was calculated at PT visits as the change in height divided by the change in age from the previous visit. For females, mean growth rate at the Final PT Visit was 27.32 mm/year in the 12 to 17 year age group, 35.14 mm/year in the 9 to 11 year age group, and 73.73 mm/year in the 3 to 8 year age group. For males, mean growth rate at the Final PT Visit was 7.17 mm/year in the 12 to 17 year age group, 89.20 mm/year in the 9 to 11 year age group, and 58.70 mm/year in the 3 to 8 year age group.

Mean change in waist circumference at the Final PT Visit was -0.491 cm in the 12 to 17 year age group.

Tanner pubertal stage subject listings have been provided but not summarized by the Applicant.

2.2.3. Discussion on clinical aspects

The new data assessed within this procedure does not alter the previous conclusion in procedures EMEA/H/C/003837 and EMEA/H/C/003839.

3. Rapporteur's CHMP overall conclusion and recommendation

As concluded in procedures EMEA/H/C/003837 and EMEA/H/C/003839, pharmacokinetic results from this study demonstrated that weight-based paediatric doses, administered orally as tablets, for the DAAs and RTV provided generally comparable exposures across the weight groups of 15 to 29 kg, 30 to 44 kg, and ≥ 45 kg. Also, the efficacy and safety of ombitasvir / paritaprevir / ritonavir with or without dasabuvir and with or without ribavirin in hepatitis C virus GT1 or GT4-infected paediatric subjects of ≥ 3 to 17 years of age appear comparable to that in adults.

The new data assessed within this procedure does not alter the previous conclusion. Given that the Applicant does not intend to pursue a paediatric indication, no further data or clarifications are needed.

The proposal to leave the SmPC unchanged is endorsed.

Fulfilled:

No regulatory action required.