28 February 2019
EMA/CHMP/105448/2019
Human Medicines Division

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

Exviera

dasabuvir

Procedure no: EMEA/H/C/003837/P46/019

Viekirax

ombitasvir / paritaprevir / ritonavir

Procedure no: EMEA/H/C/003839/P46/021

Note

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

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8613
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

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1. Introduction

On December 8, 2018, the MAH submitted the 12 week primary analysis, paediatric clinical study report for Exviera and 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.

Study M14-748 is an ongoing 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. The study aims to assess 3 drug formulations in the pediatric population, and was designed in accordance with the Pediatric Study Plan (PSP) and Pediatric Investigational Plan (PIP) for OBV/PTV/RTV and DSV for the treatment of HCV infection in pediatric patients 3 to 17 years of age.

2.2. Information on the pharmaceutical formulation used in the study

The approved adult formulation of the 3-DAA (OBV/PTV/RTV and DSV) regimen (for GT1) or the approved adult formulation of the 2-DAA (OBV/PTV/RTV) regimen (for GT4) was administered to subjects in the ≥ 12 to 17 year old age group with weight ≥ 45 kg who were willing to swallow the adult formulations (the formulations of the 3-DAA and 2-DAA regimens are also referred to collectively as the adult formulations).

The pediatric formulation, comprising separate tablets of OBV, PTV, RTV, and DSV, was administered to subjects in the ≥ 3 to 8 year old age group with a weight ≥ 15 to 29 kg and to subjects in the ≥ 9 to 11 year old age group with a weight ≥ 15 kg. The pediatric formulation was designed to allow for dose adjustments on an ongoing basis, based on available PK and clinical data to achieve therapeutic exposures that have been safe and efficacious in adult subjects.

Adult formulations

OBV/PTV/RTV was provided by the sponsor as 12.5 mg/75 mg/50 mg tablets.

OBV/PTV/RTV was taken orally as 2 tablets every morning which corresponded to an OBV 25 mg/PTV 150 mg/RTV 100 mg dose once daily (QD).

DSV was provided by the sponsor as 250 mg tablets. DSV was taken orally as 1 tablet twice daily (BID), which corresponded to a 500 mg daily dose.

Pediatric formulation

OBV, PTV, and RTV were provided by the sponsor as separate tablets. OBV, PTV, and RTV were taken orally and were dosed QD based on body weight.

DSV was also provided by the sponsor as a separate tablet. DSV was taken orally and was dosed BID based on body weight.

RBV

RBV was provided to the investigative sites by the sponsor as 200 mg tablets for subjects who were to be dosed with the adult formulations. For subjects who were to be dosed with the pediatric tablets, RBV was provided as a 40 mg/mL oral solution. RBV was administered as weight-based, with the total daily dose divided into morning and evening doses. Management of RBV in renally-impaired subjects (creatinine clearance [CrCl] < 50 mL/min) was left to the physician's discretion in consultation with the TA MD.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a primary analysis (SVR12) report for:

- 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)

2.3.2. Clinical study M14-748

Description

Study M14-748 is an ongoing 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

Objective(s)

The primary objectives of this study were:

- To assess the PK (non-compartmental analysis) of different OBV, PTV, RTV and DSV formulations with or without RBV in treatment-naïve, non-cirrhotic, GT1 HCV-infected pediatric subjects in Part 1.

- To assess the efficacy (percentage of subjects with sustained virologic response 12 weeks post-treatment [SVR12]) and safety of OBV/PTV/RTV with or without DSV and with or without RBV for 12 or 24 weeks in HCV GT1 or GT4-infected TN and TE pediatric subjects with and without compensated cirrhosis in Part 1 and Part 2.

The secondary objectives of this study were:

- To evaluate the percentage of subjects with SVR12 by formulation, age and weight group and across all subjects on the adult formulations.
- To evaluate the percentage of subjects with sustained virologic response 24 weeks post-treatment (SVR24) and the percentage of subjects with alanine aminotransferase (ALT) normalization by the end of treatment, by formulation, age and weight group, across all subjects, and across all subjects on the adult formulations.

  a. Includes pediatric formulation (3-DAA regimen) and adult formulations.

  b. Adult formulations include the 3-DAA regimen and the 2-DAA regimen

Study design

The study aims to assess 3 drug formulations in the pediatric population. The approved adult formulation of the 3-DAA (OBV/PTV/RTV and DSV) regimen (for GT1) or the approved adult formulation of the 2-DAA (OBV/PTV/RTV) regimen (for GT4) was administered to subjects in the ≥ 12 to 17 year old age group with weight ≥ 45 kg who were willing to swallow the adult formulations (the formulations of the 3-DAA and 2-DAA regimens are also referred to collectively as the adult formulations). The pediatric formulation, comprising separate tablets of OBV, PTV, RTV, and DSV, was administered to subjects in the ≥ 3 to 8 year old age group with a weight ≥ 15 to 29 kg and to subjects in the ≥ 9 to 11 year old age group with a weight ≥ 15 kg.

For Part 1, the PK study, approximately 36 treatment-naïve (TN), noncirrhotic, HCV GT1-infected pediatric subjects were to be enrolled. In the ≥ 12 to 17 year old age group, at least 12 subjects were to receive the 3-DAA adult formulation. In each of the ≥ 3 to 8 and ≥ 9 to 11 year old age group, at least 12 subjects were to receive the pediatric formulation. Up to 12 additional subjects may have been enrolled to receive the pediatric formulation if needed to adequately characterize the PK of a particular age group or subgroup.

Subjects in the ≥ 12 to 17 year old age group began enrollment first. HCV GT1-infected noncirrhotic subjects received 12 weeks of treatment with the 3-DAA adult formulation, with or without RBV depending on the HCV GT1 subtype. Subsequent enrollment into the ≥ 9 to 11 year old age group began with the pediatric formulation when the dosing recommendation for the 3-DAA adult formulation was available and continued with enrollment of the ≥ 3 to 8 year old age group with the pediatric formulation once the dosing recommendation for the ≥ 9 to 11 year old age group was available. HCV GT1-infected noncirrhotic subjects received 12 weeks of treatment with the pediatric formulation of OBV, PTV, RTV and DSV with or without RBV depending on the HCV GT1 subtype.

Table 1. Treatment Regimn and Duration – Part 1

Patient Population	Treatment	Duration
Genotype 1b, without cirrhosis	ombitasvir + paritaprevir + ritonavir + dasabuvir	12 weeks
Genotype 1a,[a] without cirrhosis	ombitasvir + paritaprevir + ritonavir + dasabuvir + ribavirin	12 weeks

a. Follow the genotype 1a dosing recommendations in patients with an unknown genotype 1 subtype or with mixed genotype 1 infection.

Enrollment in Part 2, the safety and efficacy study, began once the doses of the 3-DAA adult formulation for GT1-infected noncirrhotic adolescents were confirmed based on the PK and clinical data from Part 1 of the study. A total of 26 HCV-infected adolescent subjects ≥ 12 to 17 years of age with HCV GT1 or GT4 infection, who were TN or treatment-experienced (TE) with interferon (including standard interferon or pegylated-interferon [pegIFN], with or without RBV) with or without cirrhosis, were enrolled to receive the adult formulations in Part 2. Depending on their genotype, subtype, and cirrhosis status, HCV GT1- and GT4-infected subjects received the 3-DAA or the 2-DAA adult formulations with or without RBV for 12 or 24 weeks.

Table 2. Treatment Regimen and Duration – Part 2 (For Subjects ≥12-17 Years of Age)

Patient Population	Treatment	Duration
Genotype 1b with or without compensated cirrhosis	ombitasvir + paritaprevir + ritonavir + dasabuvir	12 weeks
Genotype 1a,[a] without cirrhosis	ombitasvir + paritaprevir + ritonavir + dasabuvir + ribavirin	12 weeks
Genotype 1a, [a] with compensated cirrhosis	ombitasvir + paritaprevir + ritonavir + dasabuvir + ribavirin	24 weeks
Genotype 4 with or without compensated cirrhosis	ombitasvir + paritaprevir + ritonavir + ribavirin	12 weeks

a. Follow the genotype 1a dosing recommendations in patients with an unknown genotype 1 subtype or with mixed genotype 1 infection.

In Part 3, the long-term follow-up, all subjects who have completed PT Week 24 in either Part 1 or Part 2 of the study will be followed to assess the durability of viral response, the emergence and persistence of resistant viral variants, growth and development outcomes, and serious adverse events (SAEs) related to study drug for an additional 120 weeks until PT Week 144. The results will be reported in a final CSR.

Study population /Sample size

A total of 64 subjects were enrolled at 19 study sites located in the United States (and its territory, Puerto Rico), Belgium, Germany, and Spain. These included 38 subjects in Part 1 and 26 subjects in Part 2 of the study. All subjects in Part 1, including 12 adolescent subjects ≥ 12 to 17 years of age, 12 pediatric subjects ≥ 9 to 11 years of age and 14 pediatric subjects ≥ 3 to 8 years of age, were TN, noncirrhotic, and had HCV GT1 infection. In Part 2, 26 adolescent subjects ≥ 12 to 17 years of age (19 with GT1 and 7 with GT4 infection) were enrolled, of which 13 were TN and 13 were TE with interferon or pegIFN with or without RBV. One subject with compensated cirrhosis who was between 12 to 17 years of age and HCV GT1a infected was enrolled in Part 2. All 64 subjects received at least 1 dose of the study drugs. One subject prematurely discontinued study drug due to noncompliance. Two subjects discontinued from the study after completing study treatment and being followed up for at least 12 weeks in the post-treatment period (1 subject withdrew consent and 1 subject discontinued for other reasons).

Outcomes/endpoints

The primary PK endpoints from Part 1 were:

- Maximum observed plasma concentration (Cmax) and area under the plasma concentration-time curve (AUC) following dosing on Week 2, and trough concentration following dosing on Week 2 and Week 8 for OBV, PTV, DSV, and RTV.

The primary efficacy endpoint was:

- The percentage of subjects with SVR12 among all subjects.

The secondary efficacy endpoints in Parts 1 and 2 were:

- The percentage of subjects with SVR12 by formulation, age and weight group and across all subjects on the adult formulations.
- The percentage of subjects with SVR24 by formulation, age and weight group, across all subjects, and across all subjects on the adult formulations (to be reported in the final CSR).
- The percentage of subjects with ALT normalization during treatment, defined as ALT ≤ upper limit of normal (ULN) at the final treatment visit for subjects with ALT > ULN at baseline by formulation, age and weight group, across all subjects, and across all subjects on the adult formulations.

The following additional efficacy endpoints in Parts 1 and 2 were analyzed by formulation, age and weight group, across all subjects, and across all subjects on the adult formulations:

- The percentage of subjects with virologic failure during treatment.
- The percentage of subjects with Post-Treatment relapse (Relapse12 defined as confirmed HCV RNA ≥ lower limit of quantification [LLOQ] between end of treatment and 12 weeks after last actual dose of active study drug).
- The percentage of subjects who relapsed after achieving SVR12 (Relapse24; to

  be reported in the final CSR).

- The percentage of subjects with HCV RNA < LLOQ at each post baseline visit during the Treatment Period (using data as observed).
- Change from baseline to all postbaseline visits in Fibrotest score.

Results

Baseline data

An overview of genotype distribution, IL-28B genotype and treatment experience is given below.

Table 3. Baseline Characteristics (ITT Population)

	Number (%) of Subjects								
	----- Adult Tablet, ≥ 12 Yr, ≥ 45 Kg -----			---------- Pediatric Tablet ----------					
				---------- 9-11 Yr ---------- Part 1			3-8 Yr Part 1		
Variable	Part 1 (N = 12)	Part 2 (N = 26)	Total (N = 38)	15 to 29 Kg (N = 1)	30 to 44 Kg (N = 9)	≥ 45 Kg (N = 2)	15 to 29 Kg (N = 14)	Total (N = 26)	Total (N = 64)
HCV genotype and subtype									
1a	7 (58.3)	9 (34.6)	16 (42.1)	1 (100)	9 (100)	2 (100)	14 (100)	26 (100)	42 (65.6)
1b	5 (41.7)	10 (38.5)	15 (39.5)	0	0	0	0	0	15 (23.4)
4	0	7 (26.9)	7 (18.4)	0	0	0	0	0	7 (10.9)
IL28B genotype									
CC	2 (16.7)	7 (26.9)	9 (23.7)	1 (100)	4 (44.4)	0	3 (21.4)	8 (30.8)	17 (26.6)
Non-CC	10 (83.3)	19 (73.1)	29 (76.3)	0	5 (55.6)	2 (100)	11 (78.6)	18 (69.2)	47 (73.4)
Prior IFN Treatment history									
Treatment naïve	12 (100)	13 (50.0)	25 (65.8)	1 (100)	9 (100)	2 (100)	14 (100)	26 (100)	51 (79.7)
IFN-based treatment experienced	0	13 (50.0)	13 (34.2)	0	0	0	0	0	13 (20.3)

Pharmacokinetics results

The pharmacokinetic parameters were calculated using non-compartmental analysis.

The primary PK endpoints for Part 1 were the Cmax and AUC following dosing on Week 2 and the trough concentrations following dosing on Week 2 and Week 8 for OBV, PTV, DSV, and RTV. These PK parameters are summarized by weight group in **Table 4** below.

The individual Cmax and AUC values in the present study were also compared with the individual values from historical data from 3 studies in adult HCV-infected subjects that had intensive PK assessment. Figure 1 below shows that the individual Cmax and AUC values from the 3 weight groups of pediatric subjects overlap with the values from adults which have been shown to be safe and efficacious.

Table 4. Summary Statistics of Pharmacokinetic Parameters by Weight Group for Week 2

		Geometric Mean (%CV) and Range				
		Parameter (Unit)				
Weight (kg)	N	C_{max} (ng/mL)	T_{max}[a] (h)	AUC[b] (ng•h/mL)	Week 2 Ctrough (ng/mL)	Week 8 Ctrough (ng/mL)
Ombitasvir						
15 - 29	12	99.6 (27) 63.9 – 154	4.0 4.0 – 4.5	1270 (26) 776 – 1850	24.7 (32) 11.7 – 37.5	29.6 (78)[c] 8.06 – 90.7
30 - 44	9	116 (14) 97.3 – 148	4.0 4.0 – 4.0	1490 (12)[d] 1260 – 1790	28.2 (16)[d] 22.9 – 34.3	30.4 (24)[e] 21.4 – 40.9
≥ 45	13	83.7 (39) 46.1 – 150	4.0 2.0 – 8.0	1060 (43)[f] 664 – 2210	21.8 (39)[f] 14.5 – 42.3	20.9 (58)[g] 0 – 44.5
Paritaprevir						
15 - 29	12	294 (152) 47.4 – 3610	4.0 2.0 – 4.5	2180 (136) 447 – 19100	9.86 (113) 2.89 – 63.9	17.3 (136) 1.00 – 83.9
30 - 44	9	1540 (71) 272 – 4190	4.0 2.0 – 4.0	8640 (90)[d] 1640 – 34900	16.1 (112)[d] 3.15 – 96.9	18.4 (89)[e] 4.16 – 50.8
≥ 45	13	870 (125) 266 – 6590	4.0 4.0 – 8.0	5770 (152)[f] 2020 – 55500	18.0 (78)[f] 5.86 – 63.9	23.5 (86)[g] 0 – 69.2
Ritonavir						
15 - 29	12	1090 (67) 199 – 3050	2.0 2.0 – 4.0	6570 (60) 1520 – 16200	16.1 (72) 8.57 – 54.6	91.8 (268) 0 – 855
30 - 44	9	1830 (42) 851 – 3230	2.4 2.0 – 4.0	14100 (49) 6760 – 29700	32.1 (63) 8.14 – 89.3	38.1 (112)[e] 12.1 – 133
≥ 45	13	1180 (35) 397 – 1940	4.0 2.0 – 8.0	8900 (37)[f] 3640 – 17800	29.8 (54)[f] 12.2 – 81.2	58.2 (138)[g] 0 – 278
Dasabuvir						
15 - 29	12	579 (44) 292 – 1180	4.0 2.0 – 8.0	3960 (44)[h] 1820 – 8630	110 (57) 54.9 – 281	168 (82) 12.3 – 426
30 - 44	9	830 (45) 549 – 1840	4.0 2.0 – 4.0	5960 (47)[i] 4230 – 13700	215 (54) 117 – 518	264 (65)[e] 120 – 621
≥ 45	13	671 (48) 241 – 1470	4.0 2.0 – 8.0	4630 (49) 1820 – 10200	165 (56) 42.0 – 469	191 (60)[g] 11.4 – 361

Table 4. Summary Statistics of Pharmacokinetic Parameters by Weight Group for Week 2 (Continued)

		Geometric Mean (%CV) and Range				
		Parameter (Unit)				
Weight (kg)	N	C_{max} (ng/mL)	T_{max}[a] (h)	AUC[b] (ng•h/mL)	Week 2 C_{trough} (ng/mL)	Week 8 C_{trough} (ng/mL)
Dasabuvir M1 Metabolite						
15 - 29	12	173 (75) 89.7 – 563	4.0 2.0 – 8.0	1140 (72)[h] 689 – 3900	25.4 (77) 11.0 – 97.6	45.5 (135) 0 – 231
30 - 44	9	336 (34) 181 – 525	4.0 4.0 – 4.0	2320 (38)[i] 1130 – 3740	64.8 (53) 23.5 – 131	65.2 (44)[e] 41.8 – 116
≥ 45	13	312 (43) 72.8 – 680	4.0 2.0 – 8.0	2010 (44) 649 – 4020	55.9 (58) 26.4 – 148	54.7 (57)[g] 0 – 89.6
Ribavirin						
15 - 29	12	2100 (28) 1060 – 2790	2.0 2.0 – 4.0	19000 (24)[h] 11200 – 25300	1300 (25) 759 – 1930	1720 (40)[c] 469 – 2560
30 - 44	9	2440 (16) 1940 – 3030	2.0 2.0 – 4.0	24200 (15)[i] 19500 – 29600	1710 (15) 1320 – 2130	2170 (16)[e] 1720 – 2910
≥ 45	9	2320 (26) 1300 – 2970	2.0 2.0 – 4.0	22800 (24) 13800 – 29900	1590 (23) 998 – 2120	2080 (45)[j] 778 – 3090

AUC = area under the plasma concentration-time curve; AUC_{0-12} = area under the plasma concentration-time curve from time zero to 12 hours; AUC_{0-24} = area under the plasma concentration-time curve from time zero to 24 hours; C_{max} = maximum observed plasma concentration; C_{trough} = trough plasma concentration; CV = coefficient of variation; range = minimum – maximum; DSV = dasabuvir; DSV M1 = dasabuvir M1 metabolite; OBV = ombitasvir; PTV = paritaprevir; RBV = ribavirin; RTV = ritonavir; T_{max} = time to maximum observed plasma concentration

a. Median and range.
b. AUC_{0-24} for OBV, PTV, and RTV; AUC_{0-12} for DSV, DSV M1 and RBV.
c. N = 11 (excludes Subject [redacted]).
d. N = 8 (excludes Subject [redacted] for OBV and Subject [redacted] for PTV).
e. N = 7 (excludes Subjects [redacted]).
f. N = 12 (excludes Subject [redacted]).
g. N = 11 (excludes Subjects [redacted]).
h. For Subjects [redacted], the 24 h concentration was used as the 12 h concentration due to the significant sampling time deviation.
i. For Subject [redacted] the 24 h concentration was used as the 12 h concentration due to the significant sampling time deviation.
j. N = 7 (excludes Subjects [redacted]).

Figure 1. Comparison of Individual Cmax and AUC Values between Historical Data in Adults and Pediatric Weight Groups.

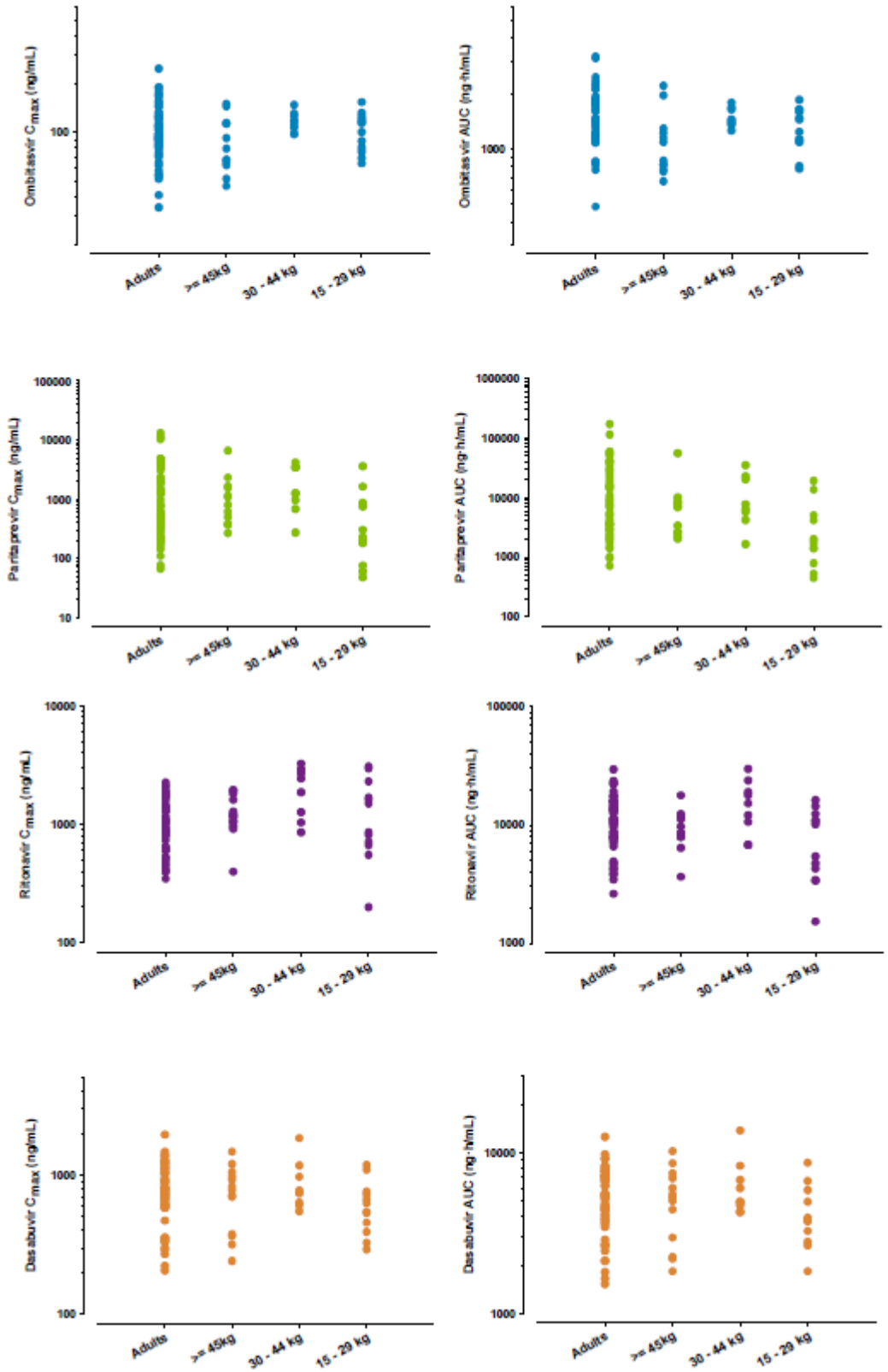
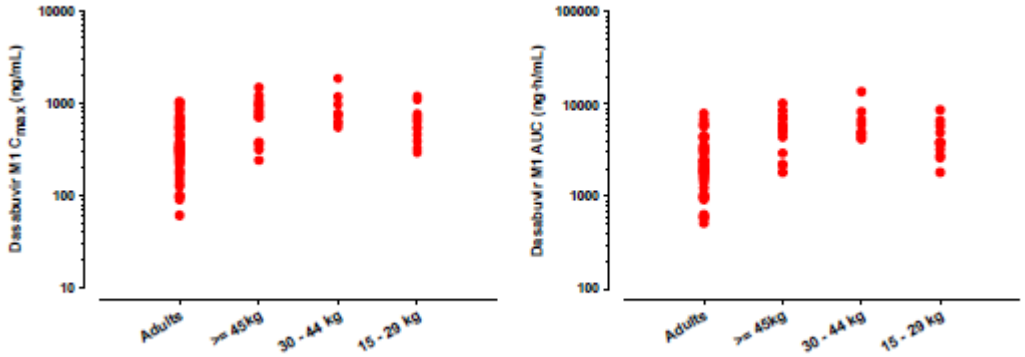


Figure 1 . Comparison of Individual Cmax and AUC Values between Historical Data in Adults and Pediatric Weight Groups (continued)



PK results from the study demonstrated that weight-based pediatric doses 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. The exposures in HCV-infected pediatric subjects were also comparable with those in HCV-infected adults.

CHMP comment:

The PK section is described at an acceptable level and the conclusions made are supported by the presented results.

Efficacy results

An overall SVR12 rate of 98.4% (63/64) with a 2-sided 95% confidence interval (CI) of 91.7% to 99.7% was observed among all subjects in the ITT population.

There were no virologic failures across the ITT population. One subject did not achieve SVR12 due to reasons other than virologic failure, a 3-year-old female with GT1a HCV infection, discontinued study drug prematurely on Study Day 9 due to difficulty in dosing.

CHMP comment:

Given that SVR12 was 98.4% and that no virologic failures were seen, it can be concluded that efficacy seem comparable to that seen in the adult studies and that subgroup analyses are futile.

Safety results

Adverse events

The majority of subjects experienced 1 or more AEs. Most subjects with AEs had events with a maximum severity of Grade 1 (mild). The most frequently reported AEs (≥ 10.0% of subjects overall) were headache, fatigue, nasopharyngitis, pyrexia, upper respiratory tract infection, nausea, and pruritus.

Within the 12 to 17 year age group, headache, fatigue, nasopharyngitis, pruritus, and upper respiratory tract infection were the most common (≥ 10.0%) AEs.

Within the 9 to 11 year age group, headache, fatigue, vomiting, pyrexia, nausea, diarrhea, nasopharyngitis, cough, abdominal pain upper, flatulence, neutropenia, rhinorrhea, and seasonal allergy were the most common AEs.

Within the 3 to 8 year age group, upper respiratory tract infection, headache, pyrexia, cough, and gastroenteritis viral were the most common AEs.

Table 5. Overview of Treatment-Emergent Adverse Events (Safety Population)

	-----Adult Tablet -----	-------- Pediatric Tablet----------			
	12 - 17 Yr	9 - 11 Yr	3 - 8 Yr		
	Total (N = 38) n (%)	Part 1 (N = 12) n (%)	Part 1 (N = 14) n (%)	Total (N = 26) n (%)	Total (N = 64) n (%)
Subjects with:					
Any AE	32 (84.2)	12 (100)	9 (64.3)	21 (80.8)	53 (82.8)
Any AE with a reasonable possibility of being related to DAA[a]	15 (39.5)	6 (50.0)	4 (28.6)	10 (38.5)	25 (39.1)
Any AE with a reasonable possibility of being related to RBV[a]	14 (36.8)	6 (50.0)	4 (28.6)	10 (38.5)	24 (37.5)
Any AE of Grade 3 or higher	0	3 (25.0)	0	3 (11.5)	3 (4.7)
Any AE of Grade 3 or higher with a reasonable possibility of being related to DAA[a]	0	0	0	0	0
Any serious AE	0	1 (8.3)	0	1 (3.8)	1 (1.6)
Any AE leading to discontinuation of study drug	0	0	0	0	0
Any AE leading to interruption of study drug	0	0	1 (7.1)	1 (3.8)	1 (1.6)
Any AE leading to RBV dose modifications	0	1 (8.3)	0	1 (3.8)	1 (1.6)
Any AE leading to death	0	0	0	0	0
Deaths[b]	0	0	0	0	0

AE = adverse event; DAA = direct-acting antiviral agent; RBV = ribavirin; Yr = years old

a. As assessed by investigator.

b. Includes nontreatment-emergent deaths.

No subject experienced a Grade ≥ 3 AE related to DAA, AE leading to discontinuation of study drug, or died during the study. One subject (9 to 11 year age group) experienced SAEs of leukopenia and neutropenia on Study Day 31; both events resolved on Study Day 37 and were considered not related to study drug. One subject (3 to 8 year age group) experienced an AE of viral gastroenteritis on Study Day 31 that led to study drug interruption for 2 days; the event resolved on Study Day 41 and was considered not related to study drug.

Table 6. Treatment-Emergent Adverse Events of Grade ≥3 in Severity (Safety Population)

	---- Adult Tablet ----	---------- Pediatric Tablet ----------			
	12 - 17 Yr	9 - 11 Yr	3 - 8 Yr		
MedDRA 21.0 Preferred Term	Total (N = 38) n (%)	Part 1 (N = 12) n (%)	Part 1 (N = 14) n (%)	Total (N = 26) n (%)	Total (N = 64) n (%)
Any AE	0	3 (25.0)	0	3 (11.5)	3 (4.7)
Depression	0	1 (8.3)	0	1 (3.8)	1 (1.6)
Hyperbilirubinaemia	0	1 (8.3)	0	1 (3.8)	1 (1.6)
Leukopenia	0	1 (8.3)	0	1 (3.8)	1 (1.6)
Neutropenia	0	1 (8.3)	0	1 (3.8)	1 (1.6)

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; Yr = years old

Adverse Events Leading to Premature Discontinuation of Study Drug

No subject had an AE leading to premature discontinuation of study drug.

Adverse Events Leading to Interruption of Study Drug

One subject (3 to 8 year age group) experienced an AE of viral gastroenteritis on Study Day 31 that led to study drug interruption for 2 days; the event resolved on Study Day 41 and was considered not related to study drug.

Adverse Events Leading to RBV Dose Modification

One subject (9 to 11 year age group) experienced AEs of hyperbilirubinemia (Grade 3) and decreased hemoglobin (Grade 2) on Study Day 14 that led to RBV dose modification; the events resolved on Study Days 120 and 28, respectively, and were considered related to RBV.

Haematology

Potentially clinically significant (PCS) hematology values experienced by ≥ 10% of subjects in any age group were low hemoglobin in 12 to 17 year age group females: 11 subjects, 44.0%; 12 to 17 year age group males: 2 subjects, 15.4%; and 3 to 8 year age group: 2 subjects, 15.4%, and low total neutrophils in 9 to 11 year age group: 2 subjects, 16.7%.

Table 7. Number and Percentage of Subjects Meeting Criteria for Potentially Clinically Significant Hematology Values During the Treatment Period (Safety Population)

	---- Adult Tablet ----	---------- Pediatric Tablet ----------			
	12 - 17 Yr	9 - 11 Yr	3 - 8 Yr		
Variable Criteria	Total n/N Obs (%) (N = 38)	Part 1 n/N Obs (%) (N = 12)	Part 1 n/N Obs (%) (N = 14)	Total n/N Obs (%) (N = 26)	Total n/N Obs (%) (N = 64)
Hemoglobin					
3 to 11 yr: < 11.5 g/dL	0/0	1[a]/12 (8.3)	2[b]/13 (15.4)	3/25 (12.0)	3/25 (12.0)
12 to 17 yr female: < 12 g/dL	11[c]/25 (44.0)	0/0	0/0	0/0	11/25 (44.0)
12 to 17 yr male: < 13 g/dL	2[d]/13 (15.4)	0/0	0/0	0/0	2/13 (15.4)
Platelet count					
< 50 × 10^9/L	0/38	0/12	0/13	0/25	0/63
White blood count					
< 2 × 10^9/L	0/38	1[a]/12 (8.3)	0/13	1/25 (4.0)	1/63 (1.6)
> 20 × 10^9/L	0/38	0/12	0/13	0/25	0/63
Total neutrophils					
< 1 × 10^9/L	0/38	2[a,e]/12 (16.7)	0/13	2/25 (8.0)	2/63 (3.2)
Lymphocytes					
< 0.5 × 10^9/L	0/38	0/12	0/13	0/25	0/63
Eosinophils					
> 5 × 10^9/L	0/38	0/12	0/13	0/25	0/63
aPTT					
> 2 × ULN	0/26	0/10	0/7	0/17	0/43
INR					
> 2 × ULN	0/26	0/10	0/7	0/17	0/43

aPTT = activated partial thromboplastin time; INR = international normalized ratio; Obs = observed; SAE = serious adverse event; ULN = upper limit of normal; Yr = years old

a. Subject [redacted] had multiple low hemoglobin values from Study Days 16 through 86, a single low white blood count value on Study Day 29, and low total neutrophil values on Study Days 29 and 31. The tests were performed on Study Days 31 and 37 due to SAEs of leukopenia and neutropenia.

b. Subject [redacted] had multiple low hemoglobin values on Study Days 15, 29, and 113 (28 days after last dose of study drug). Subject [redacted] had a single low hemoglobin value on Study Day 16.

c. Ten of the 11 female subjects had ≥ 2 low hemoglobin values postbaseline.

d. Subject [redacted] had multiple low hemoglobin values on Study Days 1, 15, and 113 (27 days after last dose of study drug). Subject [redacted] had a single low hemoglobin value on Study Day 85.

e. Subject [redacted] had a single low total neutrophil value on Study Day 56.

Note: All values must have also been more extreme than the baseline value.

Chemistry

One subject (2.6%; 12 to 17 year age group) met the PCS criteria for the parameter of high alkaline phosphatase (> 1.5 × ULN) and 4 subjects (1 [2.6%] in 12 to 17 year age group and 3 [25.0%] in 9 to 11 year age group) met the PCS criteria for the parameter for high total bilirubin (≥ 2 × ULN).

Table 8. Number (%) of Subjects Meeting Criteria for Assessment of Hepatic Laboratory Values During the Treatment Period (Safety Population)

	n/N (%) of Subjects				
	---- Adult Tablet ----	---------- Pediatric Tablet ----------			
	12 - 17 Yr	9 - 11 Yr	3 - 8 Yr		
Criteria	Total (N = 38)	Part 1 (N = 12)	Part 1 (N = 14)	Total (N = 26)	Total (N = 64)
Post-nadir ALT > 5 × ULN	0/38	0/12	0/13	0/25	0/63
Total bilirubin ≥ 2 × ULN and > baseline	1/38 (2.6)[a]	3/12 (25.0)[b]	0/13	3/25 (12.0)	4/63 (6.3)
Post-nadir ALT > 3 × ULN and total bilirubin > 2 × ULN	0/38	0/12	0/13	0/25	0/63
Post-nadir ALT > 3 × ULN and total bilirubin ≤ 2 × ULN	1/38 (2.6)[c]	0/12	0/13	0/25	1/63 (1.6)

ALT = alanine aminotransferase; ULN = upper limit of normal; Yr = years old

a. Subject [redacted]

b. Subjects [redacted]

c. Subject [redacted]

Note: For ALT, only post-nadir visits are used. For total bilirubin, only postbaseline visits are used.

CHMP comment:

In this limited dataset, the safety appears comparable to the safety profile established in adults. Most AEs, particular those related to haematologic abnormalities, are likely related to RBV.

2.3.3. **Discussion on clinical aspects**

Pharmacokinetic results from this study demonstrated that weight-based pediatric doses 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. The exposures in HCV-infected pediatric subjects were also comparable with those in HCV-infected adults, based on comparison to historical data in adults. The new formulations are not assessed, as very limited information is presented in the study report.

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 pediatric subjects of ≥ 3 to 17 years of age appear comparable to that in adults.

3. **Rapporteur's CHMP overall conclusion and recommendation**

Pharmacokinetic results from this study demonstrated that weight-based pediatric doses, administered orally, 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.

The MAH has presented results from part 1 and part 2 of the M14-748 study. There are no remaining issues to be resolved within this procedure, but the MAH should provide a final CSR including long-term follow-up data when the study is completed.

Given that these products do not currently have a pediatric indication, and that the MAH does not apply for any, the proposal to leave the SmPC unchanged is endorsed.

☒ **Fulfilled:**

No regulatory action required.