Clinical trial results:
A Phase 2, Open-Label, Multicenter, Multi-cohort Study to Investigate the Pharmacokinetics, Safety and Efficacy of Sofosbuvir/Velpatasvir/Voxilaprevir Fixed Dose Combination in Adolescents and Children with Chronic HCV Infection

Summary

EudraCT number	2018-000480-87
Trial protocol	DE GB PL IT
Global end of trial date	19 February 2020

Results information

Result version number	v2 (current)
This version publication date	14 October 2020
First version publication date	29 August 2020
Version creation reason	• Correction of full data set Updated the text in the Screening field and slightly updated the description for the last 4 secondary endpoints regarding neuropsychiatric assessments.

Trial information

Trial identification

Sponsor protocol code	GS-US-367-1175

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Gilead Sciences
Sponsor organisation address	333 Lakeside Drive, Foster City, CA, United States, 94404
Public contact	Gilead Clinical Study Information Center, Gilead Sciences, GileadClinicalTrials@gilead.com
Scientific contact	Gilead Clinical Study Information Center, Gilead Sciences, GileadClinicalTrials@gilead.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001822-PIP01-15
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	19 February 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 December 2019
Global end of trial reached?	Yes
Global end of trial date	19 February 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the steady-state pharmacokinetics (PK) and confirm the age-appropriate dose of sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) fixed-dose combination (FDC) in pediatric participants with chronic hepatitis C virus (HCV) infection.

Protection of trial subjects:

The protocol and consent/assent forms were submitted by each investigator to a duly constituted Independent Ethics Committee (IEC) or Institutional Review Board (IRB) for review and approval before study initiation. All revisions to the consent/assent forms (if applicable) after initial IEC/IRB approval were submitted by the investigator to the IEC/IRB for review and approval before implementation in accordance with regulatory requirements.

This study was conducted in accordance with recognized international scientific and ethical standards, including but not limited to the International Conference on Harmonization guideline for Good Clinical Practice (ICH GCP) and the original principles embodied in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 January 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Italy: 13
Country: Number of subjects enrolled	Poland: 4
Country: Number of subjects enrolled	United Kingdom: 4
Worldwide total number of subjects	21
EEA total number of subjects	21

Notes:

Subjects enrolled per age group

In utero	0

Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	21
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at study sites in Europe. The first participant was screened on 28 January 2019. The last study visit occurred on 19 February 2020.

Pre-assignment

Screening details:

The study was terminated because EMA granted Gilead a waiver for SOF/VEL/VOX in children less than 12 years old. Cohorts 2 and 3 were not enrolled. As per the protocol, participants could have received 8 or 12 weeks of treatment, depending on their prior treatment and disease status, however all participants received treatment for 8 weeks.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	SOF/VEL/VOX FDC

Arm description:

Direct-acting antiviral (DAA) - naive participants without cirrhosis (12 to < 18 years old) received sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) fixed-dose (FDC) combination (400/100/100 mg tablet) orally once daily in nonfasting state for 8 weeks. A single placebo to match tablet was administered during screening until Day 1 to confirm the participant was able to swallow SOF/VEL/VOX 400/100/100 mg tablets.

Arm type	Experimental
Investigational medicinal product name	SOF/VEL/VOX FDC
Investigational medicinal product code	
Other name	Vosevi ®
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

400/100/100 mg administered once daily

Number of subjects in period 1	SOF/VEL/VOX FDC
Started	21
Completed	21

Baseline characteristics

Reporting groups	
Reporting group title	SOF/VEL/VOX FDC

Reporting group description:

Direct-acting antiviral (DAA) - naive participants without cirrhosis (12 to < 18 years old) received sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) fixed-dose (FDC) combination (400/100/100 mg tablet) orally once daily in nonfasting state for 8 weeks. A single placebo to match tablet was administered during screening until Day 1 to confirm the participant was able to swallow SOF/VEL/VOX 400/100/100 mg tablets.

Reporting group values	SOF/VEL/VOX FDC	Total	
Number of subjects	21	21	
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	14		
standard deviation	± 1.2	-	
Gender categorical Units: Subjects			
Female	13	13	
Male	8	8	
Race Units: Subjects			
White	16	16	
Black or African American	1	1	
Asian	2	2	
Other	2	2	
American Indian or Alaska Native	0	0	
Native Hawaiian or Pacific Islander	0	0	
Ethnicity Units: Subjects			
Hispanic or Latino	2	2	
Not Hispanic or Latino	19	19	
Unknown or Not Reported	0	0	
Cirrhosis Units: Subjects			
Yes	0	0	
No	21	21	
Baseline Alanine aminotransferase (ALT) Category Units: Subjects			
≤ 1.5 x (Upper Limit of Normal) ULN	16	16	
> 1.5 x ULN	5	5	

Baseline HCV Ribonucleic acid (RNA) Units: log10 IU/mL arithmetic mean standard deviation	 5.9 ± 0.70	 -	

End points

End points reporting groups

Reporting group title	SOF/VEL/VOX FDC

Reporting group description:

Direct-acting antiviral (DAA) - naive participants without cirrhosis (12 to < 18 years old) received sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) fixed-dose (FDC) combination (400/100/100 mg tablet) orally once daily in nonfasting state for 8 weeks. A single placebo to match tablet was administered during screening until Day 1 to confirm the participant was able to swallow SOF/VEL/VOX 400/100/100 mg tablets.

Primary: Pharmacokinetic (PK) Parameter: AUCtau of SOF, GS-331007 (Metabolite of SOF), VEL, and VOX

End point title	Pharmacokinetic (PK) Parameter: AUCtau of SOF, GS-331007 (Metabolite of SOF), VEL, and VOX[1]

End point description:

AUCtau was defined as concentration of drug over time (the area under the concentration verses time curve over the dosing interval). For participants with separate consent to participate in the optional intensive PK substudy, intensive serial PK blood samples were collected at Week 2 or Week 4. Sparse PK samples were collected from all participants at Weeks 1, 2, 4, and end of treatment/Week 8. Plasma concentration data from all PK samples (intensive and sparse) were combined and used to generate PK parameters of SOF, GS-331007, VEL, and VOX for all participants using a population PK modeling approach.

End point type	Primary

End point timeframe:

Sparse PK Sample (all participants): At Weeks 1 and 8 at any time, Weeks 2 and 4 (predose and between 15 minutes and 4 hours postdose). Intensive PK Sample [PK Substudy (N=14)]: Week 2 or Week 4 (0 (predose), 0.5, 1, 2, 3, 4, 6, 8, and 12 hours postdose).

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical comparison was planned or performed.

End point values	SOF/VEL/VOX FDC			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: hours•nanogram/milliliter				
arithmetic mean (standard deviation)				
SOF	2474.8 (± 1247.28)			
GS-331007 (metabolite of SOF)	14890.2 (± 3126.35)			
VEL	6773.0 (± 2367.30)			
VOX	2205.8 (± 1403.45)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Permanently Discontinued Study Drug Due to an Adverse Event

End point title	Percentage of Participants Who Permanently Discontinued Study Drug Due to an Adverse Event

End point description:

Treatment-emergent Adverse Events (TEAE) were defined as events that met 1 or both of the following criteria as any AEs with onset dates on or after the study drug start date and no later than 30 days after the permanent discontinuation of study drug. It also includes the AEs that leads to premature discontinuation of study drug. The Safety Analysis Set included participants who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

First dose date up to the last dose date (maximum: 8 Weeks) plus 30 days

End point values	SOF/VEL/VOX FDC			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: percentage of participants				
number (not applicable)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Sustained Virologic Response (SVR) 12 Weeks After Discontinuation of Therapy (SVR12)

End point title	Percentage of Participants With Sustained Virologic Response (SVR) 12 Weeks After Discontinuation of Therapy (SVR12)

End point description:

SVR was defined as hepatitis C virus (HCV RNA) < Lower limit of quantification (LLOQ) (ie, < 15 IU/mL) 12 weeks after discontinuation of the study drug. The Full Analysis Set included all adolescent participants 12 to < 18 years old who were enrolled into the study and took at least 1 dose of study drug (SOF/VEL/VOX FDC).

End point type	Secondary

End point timeframe:

Posttreatment Week 12

End point values	SOF/VEL/VOX FDC			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: percentage of participants				
number (confidence interval 95%)	100.0 (83.9 to 100.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With HCV RNA < LLOQ 4 Weeks After Discontinuation of Therapy (SVR4)

End point title	Percentage of Participants With HCV RNA < LLOQ 4 Weeks After Discontinuation of Therapy (SVR4)

End point description:

SVR is defined was HCV RNA < LLOQ (ie, < 15 IU/mL) 4 weeks after discontinuation of the study drug. Participants in the Full Analysis Set were analysed.

End point type	Secondary

End point timeframe:

Posttreatment Week 4

End point values	SOF/VEL/VOX FDC			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: percentage of participants				
number (confidence interval 95%)	100.0 (83.9 to 100.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With HCV RNA < LLOQ 24 Weeks After Discontinuation of Therapy (SVR24)

End point title	Percentage of Participants With HCV RNA < LLOQ 24 Weeks After Discontinuation of Therapy (SVR24)

End point description:

SVR is defined was HCV RNA < LLOQ (ie, < 15 IU/mL) 24 weeks after discontinuation of the study drug. Participants in the Full Analysis Set were analysed.

End point type	Secondary

End point timeframe:

Posttreatment Week 24

End point values	SOF/VEL/VOX FDC			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: percentage of participants				
number (confidence interval 95%)	100.0 (83.9 to 100.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Overall Virologic Failure

End point title	Percentage of Participants With Overall Virologic Failure

End point description:

Overall Virologic Failure comprises of on-treatment virologic failure and relapse. On-treatment virologic failure (breakthrough, rebound, and nonresponse) and relapse were defined as follows: Breakthrough (confirmed HCV RNA ≥ LLOQ after having previously had HCV RNA < LLOQ while on treatment), Rebound (confirmed > 1 log10IU/mL increase in HCV RNA from nadir while on treatment), or Nonresponse (HCV RNA persistently ≥ LLOQ through 8 weeks of treatment) and Relapse (confirmed HCV RNA ≥ LLOQ during the posttreatment period having achieved HCV RNA < LLOQ at last on treatment visit). Participants in the Full Analysis Set were analysed.

End point type	Secondary

End point timeframe:

Up to Posttreatment Week 24

End point values	SOF/VEL/VOX FDC			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: percentage of participants				
number (not applicable)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with HCV RNA < LLOQ on Treatment

End point title	Percentage of Participants with HCV RNA < LLOQ on Treatment

End point description:

Percentage of participants with HCV RNA < LLOQ (15 IU/mL) while on treatment by analysis visit. Participants in the Full Analysis Set were analysed.

End point type	Secondary

End point timeframe:

Weeks 1, 2, 4, and 8

End point values	SOF/VEL/VOX FDC			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: percentage of participants				
number (confidence interval 95%)				
Week 1	52.4 (29.8 to 74.3)			
Week 2	81.0 (58.1 to 94.6)			
Week 4	90.5 (69.6 to 98.8)			
Week 8	100.0 (83.9 to 100.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Developed Viral Resistance to SOF, VEL, and/or VOX During Treatment

End point title	Percentage of Participants Who Developed Viral Resistance to SOF, VEL, and/or VOX During Treatment

End point description:

Plasma samples were collected and stored for potential HCV sequencing. Impact on the treatment outcomes of SVR12 and SVR24 were observed during the study. Baseline nonstructural protein (NS)3, NS5A, and NS5B deep sequencing analysis was performed for all participants. Sequencing for the HCV NS5A and NS5B regions was performed for all enrolled participants at baseline and for participants with virologic failure. Resistance Analysis Population was defined as all participants in the Safety Analysis Set with a virologic outcome. No on-treatment virologic breakthrough or relapse was observed. Therefore, no participants qualified for resistance testing.

End point type	Secondary

End point timeframe:

Up to End of Treatment (Week 8)

End point values	SOF/VEL/VOX FDC			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: percentage of participants				
number (not applicable)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Developed Viral Resistance to SOF, VEL, and/or VOX When Treatment is Discontinued

End point title	Percentage of Participants Who Developed Viral Resistance to SOF, VEL, and/or VOX When Treatment is Discontinued

End point description:

Plasma samples were collected and stored for potential HCV sequencing. Impact on the treatment outcomes of SVR12 and SVR24 were observed during the study. Baseline nonstructural protein (NS)3, NS5A, and NS5B deep sequencing analysis was performed for all participants. Sequencing for the HCV NS5A and NS5B regions was performed for all enrolled participants at baseline and for participants with virologic failure. Resistance Analysis Population was defined as all participants in the Safety Analysis Set with a virologic outcome. No on-treatment virologic breakthrough or relapse was observed through posttreatment Week 12 or posttreatment Week 24.

End point type	Secondary

End point timeframe:

Up to Posttreatment Week 24

End point values	SOF/VEL/VOX FDC			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: percentage of participants				
number (not applicable)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in HCV RNA from Day 1 Through End of Treatment

End point title	Change in HCV RNA from Day 1 Through End of Treatment

End point description:

Participants in the Full Analysis Set with available data were analysed.

End point type	Secondary

End point timeframe:

Baseline (Day 1); Weeks 1, 2 ,4, and 8

End point values	SOF/VEL/VOX FDC			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: log10 IU/mL				
arithmetic mean (standard deviation)				
Change at Week 1 (N = 20)	-4.55 (± 0.525)			
Change at Week 2	-4.65 (± 0.621)			
Change at Week 4 (N = 20)	-4.71 (± 0.661)			
Change at Week 8	-4.77 (± 0.698)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Alanine Aminotransferase (ALT) Normalization

End point title	Percentage of Participants with Alanine Aminotransferase (ALT) Normalization

End point description:

ALT normalization was defined as ALT > upper limit of normal (ULN) at baseline and ALT ≤ ULN at each visit. Participants in the Full Analysis Set with available data were analysed. It includes participants with ALT >ULN at Baseline.

End point type	Secondary

End point timeframe:

Baseline (Day 1); Week 1, 2, 4, 8, and Posttreatment/Follow-up Week 4 (FU-4)

End point values	SOF/VEL/VOX FDC			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: percentage of participants				
number (not applicable)				
Week 1 (N = 4)	50.0			
Week 2 (N = 4)	75.0			
Week 4	100.0			
Week 8	100.0			
FU - 4 (N = 4)	100.0			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Height Percentiles as a Measurement of Growth and Development

End point title	Change from Baseline in Height Percentiles as a Measurement of Growth and Development

End point description:

An age- and sex-specific percentile was derived for each weight, height, and body mass index (BMI) measurement according to the statistical analysis system (SAS) program available on the Centers for Disease Control and Prevention (CDC) website using the year 2000 growth charts. Participants in the Safety Analysis Set with available data were analysed.

End point type	Secondary

End point timeframe:

Baseline (Day 1); Weeks 1, 2, 4, 8, FU - 4, Posttreatment/Follow-up Week 12 (FU-12), and Posttreatment/Follow-up Week 24 (FU-24)

End point values	SOF/VEL/VOX FDC			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: percentile				
median (inter-quartile range (Q1-Q3))				
Baseline	47.9 (32.4 to 63.2)			
Change at Week 8	0.0 (-3.0 to 1.3)			
Change at FU-12	0.0 (-2.2 to 3.8)			
Change at FU-24	-0.2 (-3.1 to 4.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Weight Percentiles as a Measurement of Growth and Development

End point title	Change From Baseline in Weight Percentiles as a Measurement of Growth and Development

End point description:

An age- and sex-specific percentile was derived for each weight, height, and body mass index (BMI) measurement according to the statistical analysis system (SAS) program available on the Centers for Disease Control and Prevention (CDC) website using the year 2000 growth charts. Participants in the Safety Analysis Set with available data were analysed.

End point type	Secondary

End point timeframe:

Baseline (Day 1); Weeks 1, 2, 4, 8, FU-4, FU-12, and FU-24

End point values	SOF/VEL/VOX FDC			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: percentile				
median (inter-quartile range (Q1-Q3))				
Baseline	54.0 (30.9 to 75.9)			
Change at Week 8	-2.5 (-3.5 to -1.2)			
Change at FU-12	-2.7 (-7.1 to 0.3)			
Change at FU-24	-1.6 (-5.2 to 4.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants by Tanner Stage Assessment as a Measurement of Growth and Development

End point title	Number of Participants by Tanner Stage Assessment as a Measurement of Growth and Development

End point description:

Tanner Pubertal Staging were assessed for pubic hair growth and genitalia development (males) and for pubic hair growth and breast development (females) in stages 1 to 5. It was used to evaluate the onset and progression of pubertal changes from stage 1 (pre-pubertal) to stage 5 (adult). If a participant had reached Tanner stage 5, no further assessments were done. Pubic hair growth: Tanner stages (1: No hair, 2: Downy hair, 3: Coarse and curly hair, 4: Adult-like hair quality; 5: Hair extends to medial surface of the thighs); Breast development: Tanner stages (1: No glandular tissue, 2: Breast bud forms,3: More elevated, outside areola, 4: Increased breast size,5: Final adult-size breasts); Genitalia development: Tanner stages (1: Testes, scrotum, and penis about same size, 2: Enlargement of scrotum and testes, Penis (10.5-12.5); 3: Enlargement of penis (11.5-14); 4: Penis size (13.5-15); 5: Genitalia adult in size and shape). Participants in the Safety Analysis Set were analysed.

End point type	Secondary

End point timeframe:

Baseline (Day 1); Weeks 8, FU-12, and FU-24

End point values	SOF/VEL/VOX FDC			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: participants				
number (not applicable)				
Pubic Hair (Male); Baseline; Stage 1 (N=8)	1			
Pubic Hair (Male); Baseline; Stage 2 (N=8)	1			

Pubic Hair (Male); Baseline; Stage 3 (N=8)	0			
Pubic Hair (Male); Baseline; Stage 4 (N=8)	4			
Pubic Hair (Male); Baseline; Stage 5 (N=8)	2			
Pubic Hair (Male); Week 8; Stage 1 (N=8)	0			
Pubic Hair (Male); Week 8; Stage 2 (N=8)	2			
Pubic Hair (Male); Week 8; Stage 3 (N=8)	0			
Pubic Hair (Male); Week 8; Stage 4 (N=8)	4			
Pubic Hair (Male); Week 8; Stage 5 (N=8)	2			
Pubic Hair (Male); FU-12; Stage 1 (N=8)	0			
Pubic Hair (Male); FU-12; Stage 2 (N=8)	2			
Pubic Hair (Male); FU-12; Stage 3 (N=8)	0			
Pubic Hair (Male); FU-12; Stage 4 (N=8)	3			
Pubic Hair (Male); FU-12; Stage 5 (N=8)	3			
Pubic Hair (Male); FU-24; Stage 1 (N=8)	0			
Pubic Hair (Male); FU-24; Stage 2 (N=8)	1			
Pubic Hair (Male); FU-24; Stage 3 (N=8)	1			
Pubic Hair (Male); FU-24; Stage 4 (N=8)	2			
Pubic Hair (Male); FU-24; Stage 5 (N=8)	4			
Genitalia (Male); Baseline; Stage 1 (N=8)	1			
Genitalia (Male); Baseline; Stage 2 (N=8)	1			
Genitalia (Male); Baseline; Stage 3 (N=8)	0			
Genitalia (Male); Baseline; Stage 4 (N=8)	4			
Genitalia (Male); Baseline; Stage 5 (N=8)	2			
Genitalia (Male); Week 8; Stage 1 (N=8)	0			
Genitalia (Male); Week 8; Stage 2 (N=8)	2			
Genitalia (Male); Week 8; Stage 3 (N=8)	0			
Genitalia (Male); Week 8; Stage 4 (N=8)	4			
Genitalia (Male); Week 8; Stage 5 (N=8)	2			
Genitalia (Male); FU-12; Stage 1 (N=8)	0			
Genitalia (Male); FU-12; Stage 2 (N=8)	2			
Genitalia (Male); FU-12; Stage 3 (N=8)	0			
Genitalia (Male); FU-12; Stage 4 (N=8)	3			
Genitalia (Male); FU-12; Stage 5 (N=8)	3			

Genitalia (Male); FU-24; Stage 1 (N=8)	0			
Genitalia (Male); FU-24; Stage 2 (N=8)	1			
Genitalia (Male); FU-24; Stage 3 (N=8)	1			
Genitalia (Male); FU-24; Stage 4 (N=8)	2			
Genitalia (Male); FU-24; Stage 5 (N=8)	4			
Pubic Hair (Female); Baseline; Stage 1 (N=13)	0			
Pubic Hair (Female); Baseline; Stage 2 (N=13)	2			
Pubic Hair (Female); Baseline; Stage 3 (N=13)	2			
Pubic Hair (Female); Baseline; Stage 4 (N=13)	5			
Pubic Hair (Female); Baseline; Stage 5 (N=13)	4			
Pubic Hair (Female); Week 8; Stage 1 (N=13)	0			
Pubic Hair (Female); Week 8; Stage 2 (N=13)	2			
Pubic Hair (Female); Week 8; Stage 3 (N=13)	1			
Pubic Hair (Female); Week 8; Stage 4 (N=13)	5			
Pubic Hair (Female); Week 8; Stage 5 (N=13)	5			
Pubic Hair (Female); FU-12; Stage 1 (N=13)	0			
Pubic Hair (Female); FU-12; Stage 2 (N=13)	2			
Pubic Hair (Female); FU-12; Stage 3 (N=13)	1			
Pubic Hair (Female); FU-12; Stage 4 (N=13)	5			
Pubic Hair (Female); FU-12; Stage 5 (N=13)	5			
Pubic Hair (Female); FU-24; Stage 1 (N=13)	0			
Pubic Hair (Female); FU-24; Stage 2 (N=13)	1			
Pubic Hair (Female); FU-24; Stage 3 (N=13)	2			
Pubic Hair (Female); FU-24; Stage 4 (N=13)	4			
Pubic Hair (Female); FU-24; Stage 5 (N=13)	6			
Breasts (Female); Baseline; Stage 1 (N=13)	0			
Breasts (Female); Baseline; Stage 2 (N=13)	2			
Breasts (Female); Baseline; Stage 3 (N=13)	2			
Breasts (Female); Baseline; Stage 4 (N=13)	4			
Breasts (Female); Baseline; Stage 5 (N=13)	5			
Breasts (Female); Week 8; Stage 1 (N=13)	0			
Breasts (Female); Week 8; Stage 2 (N=13)	2			
Breasts (Female); Week 8; Stage 3 (N=13)	1			

Breasts (Female); Week 8; Stage 4 (N=13)	5			
Breasts (Female); Week 8; Stage 5 (N=13)	5			
Breasts (Female); FU-12; Stage 1 (N=13)	0			
Breasts (Female); FU-12; Stage 2 (N=13)	2			
Breasts (Female); FU-12; Stage 3 (N=13)	1			
Breasts (Female); FU-12; Stage 4 (N=13)	5			
Breasts (Female); FU-12; Stage 5 (N=13)	5			
Breasts (Female); FU-24; Stage 1 (N=13)	0			
Breasts (Female); FU-24; Stage 2 (N=13)	1			
Breasts (Female); FU-24; Stage 3 (N=13)	2			
Breasts (Female); FU-24; Stage 4 (N=13)	4			
Breasts (Female); FU-24; Stage 5 (N=13)	6			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Radiographic Bone Age Assessment as a Measurement of Growth and Development

End point title	Change from Baseline in Radiographic Bone Age Assessment as a Measurement of Growth and Development

End point description:

For radiographic bone age assessment, a single x-ray of the left wrist, hand, and fingers was performed and assessed by changes from baseline through end of treatment period. Participants in the Safety Analysis Set were analysed.

End point type	Secondary

End point timeframe:

Baseline (Day 1); Week 8

End point values	SOF/VEL/VOX FDC			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: years				
median (inter-quartile range (Q1-Q3))				
Baseline	14.5 (13.7 to 16.0)			
Change at Week 8	0.0 (0.0 to 0.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in C-Type Collagen Sequence (CTX) Bone Turn-Over Biochemical Marker as a Measurement of Growth and Development

End point title	Change from Baseline in C-Type Collagen Sequence (CTX) Bone Turn-Over Biochemical Marker as a Measurement of Growth and Development

End point description:

Fasting blood samples for baseline values for bone age biomarkers CTX and change from baseline were recorded. Participants in the Safety Analysis Set were analysed.

End point type	Secondary

End point timeframe:

Baseline (Day 1); FU-24

End point values	SOF/VEL/VOX FDC			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: ng/mL				
median (inter-quartile range (Q1-Q3))				
Baseline	1.35 (1.05 to 2.35)			
Change at FU - 24	-0.22 (-0.55 to -0.04)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Procollagen Type 1 N-Terminal Propeptide (P1NP) Bone Turn-Over Biochemical Marker as a Measurement of Growth and Development

End point title	Change from Baseline in Procollagen Type 1 N-Terminal Propeptide (P1NP) Bone Turn-Over Biochemical Marker as a Measurement of Growth and Development

End point description:

Fasting blood samples for baseline values for bone age biomarkers P1NP and change from baseline were recorded. Participants in the Safety Analysis Set with available data were analysed.

End point type	Secondary

End point timeframe:

Baseline (Day 1); FU-24

End point values	SOF/VEL/VOX FDC			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: ng/mL				
median (inter-quartile range (Q1-Q3))				
Baseline	383.25 (175.00 to 944.20)			
Change at FU-24	-101.50 (-359.00 to -24.98)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants in Each Swallowability Category of Able to Swallow or Unable to Swallow SOF/VEL/VOX 400/100/100 mg Size Tablets

End point title	Percentage of Participants in Each Swallowability Category of Able to Swallow or Unable to Swallow SOF/VEL/VOX 400/100/100 mg Size Tablets

End point description:

Swallowability for SOF/VEL/VOX FDC placebo to match (PTM) tablets was summarized based on the participants present in each swallowability category of Able to Swallow or Unable to Swallow a placebo tablet on one occasion during screening until Day 1. Participants in the Safety Analysis Set were analysed.

End point type	Secondary

End point timeframe:

Baseline (Day 1)

End point values	SOF/VEL/VOX FDC			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: percentage of participants				
number (not applicable)				
Able to Swallow PTM Tablet	100.0			
Unable to Swallow PTM Tablet	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Acceptability Questionnaire Responses as assessed by the Study Participant

End point title	Percentage of Participants With Acceptability Questionnaire Responses as assessed by the Study Participant

End point description:

A questionnaire was administered to participants to assess acceptability, including palatability, of the formulation. Acceptability and palatability were assessed by questions about how the study drug tasted, how easy it was to swallow the study drug, and also at the end of treatment about how it was to take the study drug and, as they all received a single tablet daily, how they felt about the number of tablets they had to swallow.

End point type	Secondary

End point timeframe:

Baseline (Day 1); Week 8

End point values	SOF/VEL/VOX FDC			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: percentage of participants				
number (not applicable)				
Did Not Taste Study Drug; Day 1	23.8			
Taste (Very Bad); Day 1	9.5			
Taste (Bad); Day 1	9.5			
Taste (Maybe Bad/ Maybe Good); Day 1	38.1			
Taste (Good); Day 1	19.0			
Taste (Very Good); Day 1	0			
Swallow (Very Hard); Day 1	9.5			
Swallow (Hard); Day 1	9.5			
Swallow (Maybe Hard/ Maybe Easy); Day 1	9.5			
Swallow (Easy); Day 1	23.8			
Swallow (Very Easy); Day 1	47.6			
Did Not Taste Study Drug; Week 8 (N=20))	25.0			
Taste (Very Bad); Week 8 (N=20)	0			
Taste (Bad); Week 8 (N=20)	25.0			
Taste (Maybe Bad/ Maybe Good); Week 8 (N=20)	40.0			
Taste (Good); Week 8 (N=20)	5.0			
Taste (Very Good); Week 8 (N=20)	5.0			
Swallow (Very Hard); Week 8 (N=20)	0			
Swallow (Hard); Week 8 (N=20)	5.0			
Swallow (Maybe Hard/ Maybe Easy); Week 8 (N=20)	20.0			
Swallow (Easy); Week 8 (N=20)	25.0			
Swallow (Very Easy); Week 8 (N=20)	50.0			
Take (Very Hard); Week 8 (N=20)	0			
Take (Hard); Week 8 (N=20)	0			
Take (Maybe Hard/Maybe Easy); Week 8 (N=20)	25.0			
Take (Easy); Week 8 (N=20)	50.0			
Take (Very Easy); Week 8 (N=20)	25.0			

Number of Tablets(Very Hard); Week 8 (N=20)	0			
Number of Tablets(Hard); Week 8 (N=20)	0			
NumberofTablets(Maybe Hard/Maybe Easy);Week8(N=20)	45.0			
Number of Tablets(Easy); Week 8 (N=20)	25.0			
Number of Tablets (Easy); Week 8 (N=20)	30.0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Acceptability Questionnaire Responses as assessed by the Parent/Legal Guardian

End point title	Percentage of Participants With Acceptability Questionnaire Responses as assessed by the Parent/Legal Guardian

End point description:

A questionnaire was administered to the parent/legal guardian of participants to assess acceptability, including palatability, of the formulation. Acceptability and palatability were assessed by questions about how the study drug tasted, how easy it was to swallow the study drug, about how it was to take the study drug and, as they all received a single tablet daily, how they felt about the number of tablets they had to swallow.

End point type	Secondary

End point timeframe:

Week 8

End point values	SOF/VEL/VOX FDC			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: percentage of participants				
number (not applicable)				
Did Not Taste Study Drug	61.9			
Taste (Very Bad)	0			
Taste (Bad)	23.8			
Taste (Maybe Bad/ Maybe Good)	9.5			
Taste (Good)	4.8			
Taste (Very Good)	0			
Swallow (Very Hard)	4.8			
Swallow (Hard)	9.5			
Swallow (Maybe Hard/ Maybe Easy)	14.3			
Swallow (Easy)	33.3			
Swallow (Very Easy)	38.1			
Take (Very Hard)	0			
Take (Hard)	9.5			
Take (Maybe Hard/ Maybe Easy)	19.0			
Take (Easy)	47.6			

Take (Very Easy)	23.8			
Number of Tablets (Very Hard)	0			
Number of Tablets (Hard)	4.8			
Number of Tablets (Maybe Hard/Maybe Easy)	28.6			
Number of Tablets (Easy)	47.6			
Number of Tablets (Very Easy)	19.0			

Statistical analyses

No statistical analyses for this end point

Secondary: Neuropsychiatric Assessments Based on Questionnaire as Completed by Participant

End point title	Neuropsychiatric Assessments Based on Questionnaire as Completed by Participant

End point description:

Neuropsychiatric safety assessment was done using the Pediatric Quality of Life (PedsQL™ 4.0 SF15). The PedsQL™ 4.0 SF15 Questionnaires was completed by all participants. It is a comprehensive and widely used patient-reported outcome survey designed to measure health-related quality of life in healthy children and adolescents. It is presented for each of the 4 domains of the SF-15 (physical functioning, emotional functioning, social functioning, and school functioning), the psychosocial health summary (emotional, social, and school functioning domains), physical health summary and the Total Score. Total scores as well as each of the subscale scores are transformed on a scale from 0 to 100. Higher scores in each case indicate better health-related quality of life (HRQOL). A positive change from end of treatment period indicates improvement. Participants in the Full Analysis Set with available data were analysed.

End point type	Secondary

End point timeframe:

Weeks 8, FU-12, and FU-24

End point values	SOF/VEL/VOX FDC			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: score on a scale				
arithmetic mean (standard deviation)				
Physical Functioning; Week 8	88.1 (± 17.06)			
Physical Functioning; Change at FU-12	-0.7 (± 7.29)			
Physical Functioning; Change at FU-24	-0.9 (± 6.40)			
Emotional Functioning; Week 8	78.0 (± 19.33)			
Emotional Functioning; Change at FU-12	-3.0 (± 21.43)			
Emotional Functioning; Change at FU-24	-1.8 (± 18.56)			
Social Functioning; Week 8 (N=20)	95.0 (± 10.95)			
Social Functioning; Change at FU-12 (N=20)	-2.9 (± 8.67)			
Social Functioning; Change at FU-24 (N=20)	-0.4 (± 6.88)			
School Functioning; Week 8	80.2 (± 22.89)			
School Functioning; Change at FU-12	-4.8 (± 18.37)			
School Functioning; Change at FU-24	-3.6 (± 16.15)			

Physical Health; Week 8	88.1 (± 17.06)			
Physical Health ; Change at FU-12	-0.7 (± 7.29)			
Physical Health; Change at FU-24	-0.9 (± 6.40)			
Psychosocial Health; Week 8	83.6 (± 15.04)			
Psychosocial Health; Change at FU-12	-3.6 (± 12.38)			
Psychosocial Health; Change at FU-24	-2.4 (± 11.51)			
Total Score; Week 8	85.1 (± 14.13)			
Total Score; Change at FU-12	-2.6 (± 9.32)			
Total Score; Change at FU-24	-1.9 (± 8.83)			

Statistical analyses

No statistical analyses for this end point

Secondary: Neuropsychiatric Assessments Based on Questionnaire as Completed by Parent/Legal Guardian

End point title	Neuropsychiatric Assessments Based on Questionnaire as Completed by Parent/Legal Guardian

End point description:

Neuropsychiatric safety assessment was done using the Pediatric Quality of Life (PedsQL™ 4.0 SF15). The PedsQL™ 4.0 SF15 Questionnaires was completed by the parent/ legal guardian of the participants. It is a comprehensive and widely used patient-reported outcome survey designed to measure health-related quality of life in healthy children and adolescents. It is presented for each of the 4 domains of the SF-15 (physical functioning, emotional functioning, social functioning, and school functioning), the psychosocial health summary (emotional, social, and school functioning domains), physical health summary and the Total Score. Total scores as well as each of the subscale scores are transformed on a scale from 0 to 100. Higher scores in each case indicate better HRQOL. A positive change from end of treatment period indicates improvement. Participants in the Full Analysis Set were analysed.

End point type	Secondary

End point timeframe:

Weeks 8, FU-12, and FU-24

End point values	SOF/VEL/VOX FDC			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: score on a scale				
arithmetic mean (standard deviation)				
Physical Functioning; Week 8	87.4 (± 17.29)			
Physical Functioning; Change at FU-12 (N=20)	-2.5 (± 9.39)			
Physical Functioning; Change at FU-24	-1.7 (± 12.97)			
Emotional Functioning; Week 8	78.6 (± 21.06)			
Emotional Functioning; Change at FU-12 (N=20)	-0.3 (± 22.53)			
Emotional Functioning; Change at FU-24	-2.4 (± 17.95)			
Social Functioning; Week 8	87.7 (± 17.80)			
Social Functioning; Change at FU-12 (N=20)	4.2 (± 18.04)			
Social Functioning; Change at FU-24	0.8 (± 14.41)			

School Functioning; Week 8	74.2 (± 27.63)			
School Functioning; Change at FU-12 (N=20)	3.3 (± 20.84)			
School Functioning; Change at FU-24	3.2 (± 16.77)			
Physical Health; Week 8	87.4 (± 17.29)			
Physical Health ; Change at FU-12 (N=20)	-2.5 (± 9.39)			
Physical Health; Change at FU-24	-1.7 (± 12.97)			
Psychosocial Health; Week 8	80.0 (± 17.46)			
Psychosocial Health; Change at FU-12 (N=20)	2.1 (± 15.82)			
Psychosocial Health; Change at FU-24	0.2 (± 9.61)			
Total Score; Week 8	82.5 (± 16.10)			
Total Score; Change at FU-12 (N=20)	0.6 (± 12.67)			
Total Score; Change at FU-24	-0.4 (± 7.87)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Neuropsychiatric Assessments as Completed by Participant

End point title	Change from Baseline in Neuropsychiatric Assessments as Completed by Participant

End point description:

Neuropsychiatric safety assessment was done using the Pediatric Quality of Life (PedsQL™ 4.0 SF15). The PedsQL™ 4.0 SF15 Questionnaires was completed by all the participants. It is a comprehensive and widely used patient-reported outcome survey designed to measure health-related quality of life in healthy children and adolescents. It was presented for each of the 4 domains of the SF-15 (physical functioning, emotional functioning, social functioning, and school functioning), the psychosocial health summary (emotional, social, and school functioning domains), physical health summary and the Total Score. Total scores as well as each of the subscale scores are transformed on a scale from 0 to 100. Higher scores in each case indicate better HRQOL. A positive change from baseline indicates improvement. Participants in the Full Analysis Set with available data were analysed.

End point type	Secondary

End point timeframe:

Baseline (Day 1); Weeks 8, FU-12, and FU-24

End point values	SOF/VEL/VOX FDC			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: Score on a scale				
arithmetic mean (standard deviation)				
Physical Functioning; Baseline	90.7 (± 13.81)			
Physical Functioning; Change at Week 8	-2.6 (± 10.20)			
Physical Functioning; Change at FU-12	-3.3 (± 11.87)			
Physical Functioning; Change at FU-24	-3.5 (± 12.72)			
Emotional Functioning; Baseline	73.2 (± 20.07)			
Emotional Functioning; Change at Week 8	4.8 (± 10.63)			

Emotional Functioning; Change at FU-12	1.8 (± 19.78)			
Emotional Functioning; Change at FU-24	3.0 (± 15.64)			
Social Functioning; Baseline	93.3 (± 12.53)			
Social Functioning; Change at Week 8 (N=20)	0.4 (± 9.16)			
Social Functioning; Change at FU-12	-2.0 (± 10.17)			
Social Functioning; Change at FU-24	-0.8 (± 8.70)			
School Functioning; Baseline	75.0 (± 24.58)			
School Functioning; Change at Week 8	5.2 (± 17.97)			
School Functioning; Change at FU-12	0.4 (± 12.21)			
School Functioning; Change at FU-24	1.6 (± 11.06)			
Physical Health; Baseline	90.7 (± 13.81)			
Physical Health; Change at Week 8	-2.6 (± 10.20)			
Physical Health; Change at FU-12	-3.3 (± 11.87)			
Physical Health, Change at FU-24	-3.5 (± 12.72)			
Psychosocial Health; Baseline	79.8 (± 14.16)			
Psychosocial Health; Change at Week 8	3.8 (± 7.47)			
Psychosocial Health; Change at FU-12	0.2 (± 9.74)			
Psychosocial Health; Change at FU-24	1.4 (± 8.81)			
Total Score; Baseline	83.4 (± 12.40)			
Total Score; Change at Week 8	1.7 (± 5.30)			
Total Score; Change at FU-12	-1.0 (± 8.83)			
Total Score; Change at FU-24	-0.2 (± 8.58)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Neuropsychiatric Assessments as Completed by Parent/Legal Guardian

End point title	Change from Baseline in Neuropsychiatric Assessments as Completed by Parent/Legal Guardian

End point description:

Neuropsychiatric safety assessment was done using the Pediatric Quality of Life (PedsQL™ 4.0 SF15). The PedsQL™ 4.0 SF15 Questionnaires was completed by the parent/ legal guardian of the participants. It is a comprehensive and widely used patient-reported outcome survey designed to measure health-related quality of life in healthy children and adolescents. It is presented for each of the 4 domains of the SF-15 (physical functioning, emotional functioning, social functioning, and school functioning), the psychosocial health summary (emotional, social, and school functioning domains), physical health summary and the Total Score. Total scores as well as each of the subscale scores are transformed on a scale from 0 to 100. Higher scores in each case indicate better HRQOL. A positive change from baseline indicates improvement. Participants in the Full Analysis Set with available data were analysed.

End point type	Secondary

End point timeframe:

Baseline (Day 1); Weeks 8, FU-12, and FU-24

End point values	SOF/VEL/VOX FDC			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: score on a scale				
arithmetic mean (standard deviation)				
Physical Functioning; Baseline	85.3 (± 22.56)			
Physical Functioning; Change at Week 8	3.5 (± 20.97)			
Physical Functioning; Change at FU-12 (N=19)	2.1 (± 20.90)			
Physical Functioning; Change at FU-24	4.0 (± 19.97)			
Emotional Functioning; Baseline	73.4 (± 18.57)			
Emotional Functioning; Change at Week 8	7.8 (± 18.57)			
Emotional Functioning; Change at FU-12 (N=19)	6.6 (± 14.50)			
Emotional Functioning; Change at FU-24	4.7 (± 12.80)			
Social Functioning; Baseline	85.8 (± 18.36)			
Social Functioning; Change at Week 8	1.3 (± 21.84)			
Social Functioning; Change at FU-12 (N=19)	6.1 (± 18.39)			
Social Functioning; Change at FU-24	2.1 (± 21.27)			
School Functioning; Baseline	72.5 (± 27.59)			
School Functioning; Change at Week 8	0.4 (± 23.64)			
School Functioning; Change at FU-12 (N=19)	3.9 (± 22.80)			
School Functioning; Change at FU-24	3.8 (± 20.50)			
Physical Health; Baseline	85.3 (± 22.56)			
Physical Health; Change at Week 8	3.5 (± 20.97)			
Physical Health; Change at FU-12 (N=19)	2.1 (± 20.90)			
Physical Health, Change at FU-24	4.0 (± 19.97)			
Psychosocial Health; Baseline	76.8 (± 17.34)			
Psychosocial Health; Change at Week 8	3.7 (± 17.39)			
Psychosocial Health; Change at FU-12 (N=19)	5.7 (± 15.31)			
Psychosocial Health; Change at FU-24	3.7 (± 15.52)			
Total Score; Baseline	79.7 (± 15.40)			
Total Score; Change at Week 8	3.6 (± 15.84)			
Total Score; Change at FU-12 (N=19)	4.5 (± 14.37)			
Total Score; Change at FU-24	3.8 (± 14.89)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
First dose date up to the last dose date (maximum: 8 Weeks) plus 30 days.	
Adverse event reporting additional description:	
The Safety Analysis Set included participants who received at least 1 dose of study drug.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups	
Reporting group title	SOF/VEL/VOX FDC
Reporting group description:	
Direct-acting antiviral (DAA) - naive participants without cirrhosis (12 to < 18 years old) received sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) fixed-dose (FDC) combination (400/100/100 mg tablet) orally once daily in nonfasting state for 8 weeks. A single placebo to match tablet was administered during screening until Day 1 to confirm the participant was able to swallow SOF/VEL/VOX 400/100/100 mg tablets.	

Serious adverse events	SOF/VEL/VOX FDC		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 21 (4.76%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	SOF/VEL/VOX FDC		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 21 (61.90%)		
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 21 (23.81%)		
occurrences (all)	9		
Dizziness			

subjects affected / exposed occurrences (all)	2 / 21 (9.52%) 2		
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all) Asthenia subjects affected / exposed occurrences (all)	 3 / 21 (14.29%) 5 2 / 21 (9.52%) 2		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all)	 5 / 21 (23.81%) 5 4 / 21 (19.05%) 10 3 / 21 (14.29%) 13		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	 2 / 21 (9.52%) 2		
Infections and infestations Rhinitis subjects affected / exposed occurrences (all)	 3 / 21 (14.29%) 4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 March 2019	- The approximate amount of blood drawn at each visit was reduced to align with the pediatric EMA guidance "Guideline on the Investigation of Medicinal Products in the Term and Preterm Neonate" dated 25 June 2009. - Weight related inclusion criteria were added for the PK substudy to align with the pediatric EMA guidance "Guideline on the Investigation of Medicinal Products in the Term and Preterm Neonate" dated 25 June 2009. - Clarification was provided regarding the possible impact of the study drug on P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and organic anion-transporting polypeptide (OATP)1B1, OATP1B3, or OATP2B1 substrates, as described in the Investigator Brochure. - Details regarding dose calculations for Cohorts 2 and 3 (aged 3 to < 12 years old) were added. - Changes to the list of disallowed medications and concomitant medications to be used with caution were made to align with Vosevi EU summary of product characteristics.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported