Clinical trial results:
A Phase 2, Open-label Study to Investigate the Efficacy and Safety of Ledipasvir/Sofosbuvir Fixed Dose Combination in the Treatment of Hepatitis C Virus (HCV) Infection in Pediatric Subjects Undergoing Cancer Chemotherapy

Summary

EudraCT number	2018-003741-42
Trial protocol	Outside EU/EEA
Global end of trial date	03 February 2019

Results information

Result version number	v1 (current)
This version publication date	14 August 2019
First version publication date	14 August 2019

Trial information

Trial identification

Sponsor protocol code	GS-US-337-1904

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02868242
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)	No
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	03 February 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 November 2018
Global end of trial reached?	Yes
Global end of trial date	03 February 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objectives of this study were to evaluate the efficacy, safety, and tolerability of ledipasvir/sofosbuvir (LDV/SOF) in treating hepatitis C virus (HCV) infection in pediatric participants who are undergoing cancer chemotherapy.

Protection of trial subjects:

The protocol and consent/assent form was 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 August 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Egypt: 19
Worldwide total number of subjects	19
EEA total number of subjects	0

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)	19
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 one study site in Egypt. The first participant was screened on 28 August 2016. The last study visit occurred on 03 February 2019.

Pre-assignment

Screening details:

24 participants were screened.

Period 1

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

Arms

Arm title	LDV/SOF

Arm description:

LDV/SOF 90/400 mg fixed dose combination (FDC) orally once daily for 12 weeks

Arm type	Experimental
Investigational medicinal product name	Ledipasvir/Sofosbuvir
Investigational medicinal product code	
Other name	LDV/SOF; Harvoni®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

90/400 mg FDC orally once daily for 12 weeks

Number of subjects in period 1	LDV/SOF
Started	19
Completed	19

Baseline characteristics

Reporting groups	
Reporting group title	LDV/SOF
Reporting group description:	
LDV/SOF 90/400 mg fixed dose combination (FDC) orally once daily for 12 weeks	

Reporting group values	LDV/SOF	Total	
Number of subjects	19	19	
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	14		
standard deviation	± 1.8	-	
Gender categorical Units: Subjects			
Female	3	3	
Male	16	16	
Ethinicity Units: Subjects			
Not Hispanic or Latino	19	19	
Race Units: Subjects			
White	19	19	
IL28B			
The CC, CT, and TT alleles are different forms of the IL28b gene.			
Units: Subjects			
CC	6	6	
CT	12	12	
TT	1	1	
HCV RNA Category Units: Subjects			
< 800,000 IU/mL	12	12	
≥ 800,000 IU/mL	7	7	
HCV RNA Units: log10 IU/mL			
arithmetic mean	5.3		
standard deviation	± 1.65	-	

End points

End points reporting groups

Reporting group title	LDV/SOF
Reporting group description:	
LDV/SOF 90/400 mg fixed dose combination (FDC) orally once daily for 12 weeks	

Primary: 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)[1]
End point description:	
SVR12 was defined as HCV RNA < the lower limit of quantitation (LLOQ; ie, 50 IU/mL) at 12 weeks after stopping study treatment. Full Analysis Set included participants who took at least 1 dose of study drug.	
End point type	Primary
End point timeframe:	
Posttreatment Week 12	

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	LDV/SOF			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: Percentage of participants				
number (confidence interval 95%)	100.0 (82.4 to 100.0)			

Statistical analyses

No statistical analyses for this end point

Primary: 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[2]
End point description:	
Safety Analysis Set included participants who took at least 1 dose of study drug.	
End point type	Primary
End point timeframe:	
First dose date up to Week 12	

Notes:

[2] - 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	LDV/SOF			
Subject group type	Reporting group			
Number of subjects analysed	19			
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 at 4 Weeks After Discontinuation of Therapy (SVR4)

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

End point description:

SVR4 was defined as HCV RNA < LLOQ at 4 weeks after stopping study treatment. Participants in the Full Analysis Set were analyzed.

End point type	Secondary

End point timeframe:

Posttreatment Week 4

End point values	LDV/SOF			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: Percentage of participants				
number (confidence interval 95%)	100.0 (82.4 to 100.0)			

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

SVR24 was defined as HCV RNA < LLOQ at 24 weeks after stopping study treatment. Participants in the Full Analysis Set were analyzed.

End point type	Secondary

End point timeframe:

Posttreatment Week 24

End point values	LDV/SOF			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: Percentage of participants				
number (confidence interval 95%)	100.0 (82.4 to 100.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With HCV RNA < LLOQ While on Treatment

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

End point description:

Participants in the Full Analysis Set were analyzed.

End point type	Secondary

End point timeframe:

Weeks 1, 4, 8 and 12

End point values	LDV/SOF			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: Percentage of Participants				
number (confidence interval 95%)				
Week 1	89.5 (66.9 to 98.7)			
Week 4	100.0 (82.4 to 100.0)			
Week 8	94.7 (74.0 to 99.9)			
Week 12	100.0 (82.4 to 100.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: HCV RNA Change From Baseline/Day 1

End point title	HCV RNA Change From Baseline/Day 1

End point description:

Participants in the Full Analysis Set were analyzed.

End point type	Secondary

End point timeframe:

Baseline; Weeks 1, 4, 8, 12

End point values	LDV/SOF			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: log10 IU/mL				
arithmetic mean (standard deviation)				
Change at Week 1	-3.34 (± 1.730)			
Change at Week 4	-3.62 (± 1.653)			
Change at Week 8	-3.36 (± 1.526)			
Change at Week 12	-3.62 (± 1.653)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Virologic Failure

End point title	Percentage of Participants With Virologic Failure

End point description:

Participants in the Full Analysis Set were analyzed.
Virologic failure was defined as:
- On-treatment virologic failure:
-- Breakthrough (confirmed HCV RNA ≥ LLOQ after having previously had HCV RNA < LLOQ while on treatment), or
-- Rebound (confirmed > 1 log10 IU/mL increase in HCV RNA from nadir while on treatment), or
-- Non-response (HCV RNA persistently ≥ LLOQ through 8 weeks of treatment)
- Virologic relapse:
-- Confirmed HCV RNA ≥ LLOQ during the posttreatment period having achieved HCV RNA < LLOQ at last on-treatment visit

End point type	Secondary

End point timeframe:

Baseline up to Posttreatment Week 24

End point values	LDV/SOF			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: Percentage of participants				
number (not applicable)	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events: First dose date up to Week 12 plus 30 days; All-Cause Mortality: First dose date up to Posttreatment Week 24

Adverse event reporting additional description:

Safety Analysis Set included participants who took at least 1 dose of study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	LDV/SOF

Reporting group description:

LDV/SOF 90/400 mg FDC orally once daily for 12 weeks

Serious adverse events	LDV/SOF		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 19 (15.79%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	LDV/SOF		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 19 (78.95%)		
Investigations			
Neutrophil count decreased			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 19 (21.05%)		
occurrences (all)	4		
Blood and lymphatic system disorders			
Diarrhoea			
subjects affected / exposed	3 / 19 (15.79%)		
occurrences (all)	4		
Anaemia			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	5 / 19 (26.32%)		
occurrences (all)	5		
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	3 / 19 (15.79%)		
occurrences (all)	4		
Abdominal pain			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Lip ulceration			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Mouth ulceration			

subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Tongue ulceration			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Rhinorrhoea			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Productive cough			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Pruritus generalised			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Skin lesion			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Skin Ulcer			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Joint effusion			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Osteonecrosis			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		

Ear infection subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		
Oral candidiasis subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		
Pneumonia subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		
Metabolism and nutrition disorders Hypophagia subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 June 2017	• Added: HBcAb, HBsAb on Screening visit • Added text regarding sample collection for HBV DNA testing at Day 1, Weeks 4, 8, and 12, or Early Termination, and all post-treatment visits and that HBV DNA will only be tested in subjects who are HBcAb+ at screening. • Clarified timing of Fibrotest (Screening, Baseline, Week 12, Post Treatment Week 12, Post Treatment Week 24, and ESDD as applicable) and APRI (Screening, Week 12, and Post Treatment Week 4, and ESDD as applicable) • Changed APRI calculation at Post Treatment Week 24 to Week 12 and Post Treatment Week 4 • Changed the Inclusion Criteria from Weight ≥ 45 kg to Weight ≥ 35 kg • Clarified HBV Infection in Exclusion Criteria: Hepatitis B surface antigen positive (HBsAg+) at screening

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported