Clinical trial results:
Interferon-free Treatment of Acute Genotype 1 Hepatitis C Virus Infection with Ledipasvir/Sofosbuvir Fixed-Dose Combination - The HepNet Acute HCV IV Study

Summary

EudraCT number	2013-001081-42
Trial protocol	DE
Global end of trial date	13 June 2016

Results information

Result version number	v1 (current)
This version publication date	31 December 2023
First version publication date	31 December 2023

Trial information

Trial identification

Sponsor protocol code	HepNet-aHCV-IV

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02309918
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Hannover Medical School
Sponsor organisation address	Carl-Neuberg-Str. 1, Hannover, Germany, 30625
Public contact	Stabsstelle Zentrum für Klinische Studien, Hannover Medical School, EudraCT@mh-hannover.de
Scientific contact	Stabsstelle Zentrum für Klinische Studien, Hannover Medical School, EudraCT@mh-hannover.de

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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	29 March 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 June 2016
Global end of trial reached?	Yes
Global end of trial date	13 June 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objectives of this study are as follows:
• To evaluate the efficacy of treatment with ledipasvir (LDV)/sofosbuvir (SOF) FDC for 6 weeks in patients with acute genotype 1 HCV infection as measured by the proportion of subjects with sustained viral response (HCV RNA < LLOQ TND) 12 weeks after discontinuation of therapy (SVR12)
• To evaluate the safety and tolerability of LDV/SOF FDC -containing regimens administered for up to 6 weeks in patients with acute genotype 1 HCV infection

Protection of trial subjects:

Before study enrolment all subjects got detailed information about study procedures, potential risks and benefits as well as alternative treatment options. The study was approved by regulatory authorities and independent monitoring was conducted to ensure subjects safety. The IMP is an approved drug with extensive data from clinical trials and favorable risk-benefit profile.
Safety was assessed throughout the treatment and follow-up periods based on the AEs. Adverse events were documented within one week on the respective AE forms in the (e)CRF. The same documentation responsibilities as described for AEs applied to SAEs. In addition, SAEs were documented on a paper SAE-form and reported to the sponsor. Documentation of SAE was done as complete and detailed as possible. Safety Laboratory assessments were conducted at each single visit. The investigator had the right to withdraw a patient from the study if the patient’s safety or wellbeing was compromised by further study participation.

Background therapy:

-

Evidence for comparator:

-

Actual start date of recruitment	05 November 2014
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	Germany: 26
Worldwide total number of subjects	26
EEA total number of subjects	26

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)	0
Adults (18-64 years)	26
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patints were screened in 10 study centers in Germany. Overall 26 patients were screened for elegibility and signed informed consent. Six patients were ineligible at screening. Recruitment period was between 11/2014 and 11/2015.

Pre-assignment

Screening details:

Adults (≥18 years) with acute HCV genotype 1 monoinfection. Leading inclusion criteria: HCV RNA > 10.000 IU/mL and documented HCV antibody seroconversion, or known exposure with ALT > 10 ULN within 4 month.
Leading exclusion criteria: Liver cirrhosis, hepatic decompensation, systemic drug usage, contraindications against IMP.

Pre-assignment period milestones

Number of subjects started	26
Number of subjects completed	20

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Screening Failure: 6

Period 1

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

Arms

Arm title	Single-Arm

Arm description:

Single-arm study

Arm type	Experimental
Investigational medicinal product name	Ledipasvir/ Sofosbuvir
Investigational medicinal product code	
Other name	Harvoni
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Ledipasvir/ Sofosbuvir fixed dose combination. Film-coated tablets containing 90 mg of Ledipasvir (LDV) and 400 mg of Sofosbuvir (SOF). LDV/SOF FDC tablet was administered once daily.

Number of subjects in period 1[1]	Single-Arm
Started	20
End of treatment	20
Follow up week 12	20

Completed	19
Not completed	1
Consent withdrawn by subject	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 26 patients were screened for enrolment and 20 patients finally were enrolled in the study. 11 patients dit not met inclusion-/ exclusion criteria and thus must be excluded as screening failure. The number of patients in the baseline period reflects the number of patients who received at least one dose of study medication (ITT).

Baseline characteristics

Reporting groups	
Reporting group title	Study period
Reporting group description:	
Single Arm study	

Reporting group values	Study period	Total	
Number of subjects	20	20	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	20	20	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
median	49		
inter-quartile range (Q1-Q3)	36 to 54	-	
Gender categorical Units: Subjects			
Female	8	8	
Male	12	12	
HCV Genotype Units: Subjects			
1a	11	11	
1b	9	9	
HCV RNA Units: Subjects			
<= 50.000 IU/ml	12	12	
< 15 IU/ml	1	1	
> 50.000 IU/ml	7	7	
Risk factors for infection Units: Subjects			
Sexual transmission	11	11	
Medical procedures/needle stick injury	5	5	
Nail treatment	1	1	
Unspecified	3	3	
HCV RNA Units: IU/ml			
median	11000		
inter-quartile range (Q1-Q3)	140 to 190000	-	

Alanine Aminotransferase Units: U/l median inter-quartile range (Q1-Q3)	 225 71 to 722	 -	
Bilirubin Units: µmol/l median inter-quartile range (Q1-Q3)	 13.7 10.2 to 25.1	 -	
Aspartate aminotransferase Units: U/l median inter-quartile range (Q1-Q3)	 76.5 34.5 to 286.5	 -	
Gamma GT Units: U/l median inter-quartile range (Q1-Q3)	 134 71 to 292	 -	
Alkaline phosphatase Units: U/l median inter-quartile range (Q1-Q3)	 104 80 to 138	 -	

Subject analysis sets	
Subject analysis set title	IIT-Analysis
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The overall population is an ITT population and consists of all patients who received at least one dose ofthe study medication.

Subject analysis set title	Per Protocol Analysis
Subject analysis set type	Per protocol

Subject analysis set description:

The PP population comprises of all patients that were complying with the studyprotocol until the end of the observational period, particularly all patients that attended all study visits and have fully observed data for the primary endpoint.

Reporting group values	IIT-Analysis	Per Protocol Analysis	
Number of subjects	20	19	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	20	19	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years median	 49	 49	

inter-quartile range (Q1-Q3)	36 to 54	35 to 54	

Gender categorical Units: Subjects			
Female	8	7	
Male	12	12	
HCV Genotype Units: Subjects			
1a	11	11	
1b	9	8	
HCV RNA Units: Subjects			
<= 50.000 IU/ml	12	12	
< 15 IU/ml	1	1	
> 50.000 IU/ml	7	6	
Risk factors for infection Units: Subjects			
Sexual transmission	11	11	
Medical procedures/needle stick injury	5	4	
Nail treatment	1	1	
Unspecified	3	3	
HCV RNA Units: IU/ml			
median	11000	6750	
inter-quartile range (Q1-Q3)	140 to 190000	138 to 250000	
Alanine Aminotransferase Units: U/l			
median	225	269	
inter-quartile range (Q1-Q3)	71 to 722	68 to 766	
Bilirubin Units: µmol/l			
median	13.7	15.4	
inter-quartile range (Q1-Q3)	10.2 to 25.1	10.1 to 27.4	
Aspartate aminotransferase Units: U/l			
median	77	72	
inter-quartile range (Q1-Q3)	35 to 287	32 to 294	
Gamma GT Units: U/l			
median	134	135	
inter-quartile range (Q1-Q3)	71 to 292	75 to 292	
Alkaline phosphatase Units: U/l			
median	104	108	
inter-quartile range (Q1-Q3)	80 to 138	84 to 139	

End points

End points reporting groups

Reporting group title	Single-Arm
Reporting group description:	
Single-arm study	
Subject analysis set title	IIT-Analysis
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The overall population is an ITT population and consists of all patients who received at least one dose ofthe study medication.	
Subject analysis set title	Per Protocol Analysis
Subject analysis set type	Per protocol
Subject analysis set description:	
The PP population comprises of all patients that were complying with the studyprotocol until the end of the observational period, particularly all patients that attended all study visits and have fully observed data for the primary endpoint.	

Primary: sustained virological response (SVR 12)

End point title	sustained virological response (SVR 12)
End point description:	
Proportion of subjects with sustained virological response (SVR 12) 12 weeks after discontinuation of therapy	
End point type	Primary
End point timeframe:	
Follow up visit 12	

End point values	Single-Arm	IIT-Analysis	Per Protocol Analysis	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	20	20	19	
Units: Patients				
sustained virological response (SVR 12) week 12	20	20	19	

Statistical analyses

Statistical analysis title	two-sided 95%-Wilson-confidence interval
Statistical analysis description:	
The two-sided 95%-Wilson-confidence interval for the proportion of subjects with sustained viral response 12 weeks after discontinuation of therapy (SVR 12) was evaluated. Since all patients (ITT or PP) were expected to be HCV-RNA negative, the lower limit of the confidence interval was expected to be above 80%.	
Comparison groups	Single-Arm v IIT-Analysis v Per Protocol Analysis

Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	< 0.05 [2]
Method	95%Wilson-confidence interval

Notes:

[1] - 95%Wilson-confidence interval

[2] - H0: pSVR12 < 0.83 and H1: pSVR12 ≥ 0.83.

Secondary: sustained virological response (SVR 24)

End point title	sustained virological response (SVR 24)

End point description:

Proportion of subjects with durability of sustained virological response (SVR 24) 24 weeks after discontinuation of therapy

End point type	Secondary

End point timeframe:

Follow up week 24

End point values	Single-Arm	IIT-Analysis	Per Protocol Analysis	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	20	20	19[3]	
Units: patients				
Patients sustained virological response (SVR 24)	19	19	19	

Notes:

[3] - FU24 data were available for 19 patients, 1 patient was lost to follow up

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The adverse event documentation period for this trial begins upon first administration of the IMPs and ends with the end-of-trial visit of the respective patient.

Adverse event reporting additional description:

Numbers in the non-serious adverse events section reflect all adverse events occurring during the study (non-serious and serious).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	LDV/SOF FDC

Reporting group description: -

Serious adverse events	LDV/SOF FDC		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 20 (5.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Ligament rupture			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	LDV/SOF FDC		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 20 (95.00%)		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	4 / 20 (20.00%)		
occurrences (all)	5		
Performance status decreased			

subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Psychiatric disorders			
Mood altered			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Irritability			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Sleep disorder			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Investigations			
Blood uric acid increased			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Meniscus injury			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Ligament rupture			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Wrist fracture			

subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Multiple sclerosis			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Transient global amnesia			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Transient ischemic attack			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Eye disorders			
Blepharospasm			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	2		
Abdominal pain			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	3		
Constipation			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Diarrhea			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Dyspepsia			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Feces discolored			

subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Flatulence subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Nausea subjects affected / exposed occurrences (all)	4 / 20 (20.00%) 4		
Oral discomfort subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Vomiting subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Hepatobiliary disorders			
Hepatic pain subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Hepatic steatosis subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Skin and subcutaneous tissue disorders			
Alopecia subjects affected / exposed occurrences (all)	3 / 20 (15.00%) 3		
Rash subjects affected / exposed occurrences (all)	2 / 20 (10.00%) 2		
Skin reaction subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Musculoskeletal and connective tissue disorders			
Back pain subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Arthralgia			

subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Musculoskeletal pain			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Musculoskeletal discomfort			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Myalgia			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	3		
Oral herpes			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Otitis media			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 February 2015	Inclusion criterium changed and inclusion of a prohibited concomitant medication
12 June 2015	secondary objectives were defined more precisely and shipping of samples for the cytokine analysis was changed to the end of the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/28029529

http://www.ncbi.nlm.nih.gov/pubmed/33517457

http://www.ncbi.nlm.nih.gov/pubmed/30548086

http://www.ncbi.nlm.nih.gov/pubmed/34843107