Clinical trial results:
HepNet pilot trial: Multicenter trial for the treatment of chronic hepatitis E with sofosbuvir (SofE)

Summary

EudraCT number	2017-000403-24
Trial protocol	DE
Global end of trial date	18 February 2019

Results information

Result version number	v1 (current)
This version publication date	23 September 2022
First version publication date	23 September 2022

Trial information

Trial identification

Sponsor protocol code	HepNet-SofE

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03282474
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 Qualitätsmanagement in der Klinischen Forschung, Hannover Medical School, EudraCT@mh-hannover.de
Scientific contact	Stabsstelle Qualitätsmanagement in der Klinischen Forschung, 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	08 April 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 February 2019
Global end of trial reached?	Yes
Global end of trial date	18 February 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

• To evaluate the antiviral efficacy of sofosbuvir (SOF) against HEV as measured by the proportion of subjects who become HEV RNA negative (HEV RNA undetectable) after 24 weeks of therapy
• To evaluate the safety and tolerability of SOF-containing regimens administered for up to 24 weeks in patients with chronic HEV infection

Protection of trial subjects:

Withdrawal possible when patient´s safety or wellbeing is compromised.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 December 2017
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: 10
Worldwide total number of subjects	10
EEA total number of subjects	10

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)	10
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment between 12/2017 and 02/2019 at 3 sites in Germany (Hannover Medical School, Hannover and University Medical Center Hamburg-Eppendorf, Hamburg and Charité Campus Virchow-Klinikum, Berlin).

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	12[1]
Number of subjects completed	10

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Inclusion/ Exclusion criteria: 2

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 12 patients were screened for enrolment and 10 patients finally were enrolled in the study. 2 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).

Period 1

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

Blinding implementation details:

This was a prospective open-label, single-arm, multicenter, phase II pilot trial of SOF in subjects with chronic HEV infection.

Arms

Arm title	Single Arm

Arm description:

Single Arm Study - Sofosbuvir, 400 mg, film-coated tablets (Sovaldi® 400mg, study-specific labelled

Arm type	Active comparator
Investigational medicinal product name	Sofosbuvir
Investigational medicinal product code	
Other name	Sovaldi
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Sofosbuvir, 400 mg, film-coated tablets (Sovaldi® 400mg, study-specific labelled) once per day

Number of subjects in period 1	Single Arm
Started	10
Completed	9
Not completed	1
Adverse event, serious fatal	1

Baseline characteristics

Reporting groups

Reporting group title	ITT Population

Reporting group description:

The ITT population consisting of all patients who received at least on dose of the study medication.

Reporting group values	ITT Population	Total	
Number of subjects	10	10	
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)	10	10	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	44.5		
standard deviation	± 13.0	-	
Gender categorical Units: Subjects			
Female	3	3	
Male	7	7	
HEV RNA Units: IU/ml			
arithmetic mean	1427667		
standard deviation	± 1878148	-	
ALT Units: U/L			
arithmetic mean	179.0		
standard deviation	± 194.0	-	

Subject analysis sets

Subject analysis set title	PP Population
Subject analysis set type	Per protocol

Subject analysis set description:

One patient was a screening failure who received medication but retesting of screening sample showed negative HEV RNA. The patient stopped intake of study medication after 22 weeks.
One Patient died before completing the study and was excluded from the per protocol analysis.

Subject analysis set title	Efficacy Population
Subject analysis set type	Sub-group analysis

Subject analysis set description:

One patient 01-02 was a screening failure who received medication but retesting of screening sample showed negative HEV RNA. The patient stopped intake of study medication after 22 weeks. Therefore this patient was excluded from the efficacy analyses as the primary endpoint was the proportion of HEV RNA negative patients after 24 weeks of therapy. Including this patient in the efficacy analyses would promote the primary objective of the trial because the patient was not HEV RNA positive at the beginning of treatment, and, in consequence, no clearing of the virus was possible.

Reporting group values	PP Population	Efficacy Population	
Number of subjects	8	9	
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)	8	9	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	46.5	44.0	
standard deviation	± 12.2	± 13.7	
Gender categorical Units: Subjects			
Female	3	3	
Male	5	6	
HEV RNA Units: IU/ml			
arithmetic mean	1427667	1481125	
standard deviation	± 1878148	± 2000491	
ALT Units: U/L			
arithmetic mean	167.4	196.6	
standard deviation	± 188.9	± 197.2	

End points

End points reporting groups

Reporting group title	Single Arm
Reporting group description:	
Single Arm Study - Sofosbuvir, 400 mg, film-coated tablets (Sovaldi® 400mg, study-specific labelled	
Subject analysis set title	PP Population
Subject analysis set type	Per protocol
Subject analysis set description:	
One patient was a screening failure who received medication but retesting of screening sample showed negative HEV RNA. The patient stopped intake of study medication after 22 weeks. One Patient died before completing the study and was excluded from the per protocol analysis.	
Subject analysis set title	Efficacy Population
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
One patient 01-02 was a screening failure who received medication but retesting of screening sample showed negative HEV RNA. The patient stopped intake of study medication after 22 weeks. Therefore this patient was excluded from the efficacy analyses as the primary endpoint was the proportion of HEV RNA negative patients after 24 weeks of therapy. Including this patient in the efficacy analyses would promote the primary objective of the trial because the patient was not HEV RNA positive at the beginning of treatment, and, in consequence, no clearing of the virus was possible.	

Primary: HEV RNA negativity after 24 weeks of therapy

End point title	HEV RNA negativity after 24 weeks of therapy
End point description:	
Proportion of subjects who become HEV RNA negative after 24 weeks of therapy	
End point type	Primary
End point timeframe:	
24 weeks after therapy	

End point values	PP Population	Efficacy Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	8	9		
Units: patients	0	0		

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 after 24 weeks of therapy with SOF will be evaluated. Since it is assumed that 5 out of 10 patients (ITT or PP) will be HEV-RNA negative by that time, the lower limit of the confidence interval is expected to be above 20%. Missing values for the primary endpoint (HEV RNA negativity after 24 weeks of therapy) will be counted as Treatment failures.	
Comparison groups	Efficacy Population v PP Population

Number of subjects included in analysis	17
Analysis specification	Pre-specified
Analysis type	other
P-value	≤ 0.2 [1]
Method	95%Wilson-confidence interval

Notes:

[1] - H0: The proportion of HEV RNA negative patients after 24 weeks of therapy with SOF is lower than or equal to 20%.
H1: The proportion of HEV RNA negative patients after 24 weeks of therapy with SOF is higher than 20%.

Secondary: Proportion of subjects who are HEV RNA negative 12 weeks after discontinuation of therapy

End point title	Proportion of subjects who are HEV RNA negative 12 weeks after discontinuation of therapy

End point description:

End point type	Secondary

End point timeframe:

12 weeks after discontinuation of therapy

End point values	Efficacy Population			
Subject group type	Subject analysis set			
Number of subjects analysed	9			
Units: patients	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Additional efficacy evaluations include HEV RNA change from baseline during therapy

End point title	Additional efficacy evaluations include HEV RNA change from baseline during therapy

End point description:

End point type	Secondary

End point timeframe:

End of Treatment - week 24

End point values	Efficacy Population			
Subject group type	Subject analysis set			
Number of subjects analysed	9			
Units: IU/ml				
median (full range (min-max))	-251500 (-4320000 to 1526000)			

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of subject who reached ALT normalization after 12 weeks of therapy

End point title	Proportion of subject who reached ALT normalization after 12 weeks of therapy

End point description:

End point type	Secondary

End point timeframe:

12 weeks of therapy

End point values	Efficacy Population			
Subject group type	Subject analysis set			
Number of subjects analysed	9			
Units: patients	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of subject who reached ALT normalization after 24 weeks of therapy

End point title	Proportion of subject who reached ALT normalization after 24 weeks of therapy

End point description:

End point type	Secondary

End point timeframe:

24 weeks

End point values	Efficacy Population			
Subject group type	Subject analysis set			
Number of subjects analysed	8[2]			
Units: patients	0			

Notes:

[2] - Patient died before the end of the study

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of subject who reached ALT normalization 12 weeks after discontinuation of therapy (FU12 visit)

End point title	Proportion of subject who reached ALT normalization 12 weeks after discontinuation of therapy (FU12 visit)

End point description:

End point type	Secondary

End point timeframe:

12 after discontinuation of therapy

End point values	Efficacy Population			
Subject group type	Subject analysis set			
Number of subjects analysed	8[3]			
Units: patients	0			

Notes:

[3] - Patient died before the end of the study

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The AE documentation period for this trial begins with informed consent and ends with the 12 weeks post-treatment visit.

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	20.1

Reporting groups

Reporting group title	Sofosbuvir

Reporting group description: -

Serious adverse events	Sofosbuvir		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 10 (30.00%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events			
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombosis			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Eye infection toxoplasmal			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis clostridial			

subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infection			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		

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

Non-serious adverse events	Sofosbuvir		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 10 (100.00%)		
Vascular disorders			
Haematoma			
subjects affected / exposed	3 / 10 (30.00%)		
occurrences (all)	4		
Hypertension			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Thrombosis			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
General disorders and administration site conditions			
Chills			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	2		
Respiratory, thoracic and mediastinal			

disorders			
Dyspnoea			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Nasal dryness			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	2		
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	2		
Blood bilirubin increased			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Blood creatinine increased			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Gamma-glutamyltransferase increased			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	2		
Transaminases increased			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Palpitations			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Nervous system disorders			
Headache			

subjects affected / exposed occurrences (all)	3 / 10 (30.00%) 3		
Ear and labyrinth disorders Tinnitus subjects affected / exposed occurrences (all) Vertigo subjects affected / exposed occurrences (all)	 1 / 10 (10.00%) 1 1 / 10 (10.00%) 2		
Eye disorders Cataract subjects affected / exposed occurrences (all)	 1 / 10 (10.00%) 1		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Dry mouth subjects affected / exposed occurrences (all) Flatulence subjects affected / exposed occurrences (all)	 2 / 10 (20.00%) 3 1 / 10 (10.00%) 1 1 / 10 (10.00%) 1 1 / 10 (10.00%) 1		
Skin and subcutaneous tissue disorders Eczema subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all) Rash pruritic subjects affected / exposed occurrences (all)	 1 / 10 (10.00%) 1 1 / 10 (10.00%) 1 1 / 10 (10.00%) 1		
Musculoskeletal and connective tissue			

disorders			
Muscle spasms			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	2		
Eye infection toxoplasmal			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Gastroenteritis clostridial			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Infection			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Influenza			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	2		
Nasopharyngitis			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	2		
Onychomycosis			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Scrotal abscess			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Oral herpes			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Sepsis			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Urinary tract infection			

subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Metabolism and nutrition disorders Hypokalaemia subjects affected / exposed occurrences (all)	 1 / 10 (10.00%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 December 2017	No. 1.0 (resulting in study protocol version 2.0 of 13.12.2017) covered the following major changes: • Change of coordinating investigator • Addition of an examination during post-treatment visit • Specification of statistical methods
20 September 2018	No. 1.1 (resulting in study protocol version 3.0 of 20.09.2018) covered the following major changes: • Possibility of data collection of diagnosis relevant laboratory values of pre-screening examinations has been included • Update of contact information

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/32624195