Clinical trial results:
Daclatasvir plus Sofosbuvir for chronic HCV-infected renal transplant patients – a pilot study of efficacy and safety

Summary

EudraCT number	2014-004551-32
Trial protocol	DE
Global end of trial date	22 March 2017

Results information

Result version number	v1 (current)
This version publication date	08 September 2022
First version publication date	08 September 2022

Trial information

Trial identification

Sponsor protocol code	AI444-314

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Charité - University Hospital of Berlin
Sponsor organisation address	Charitéplatz 1, Berlin, Germany, 10117
Public contact	Clinical Trial Information, Charité Universitätsmedizin Berlin, +49 030450514001, michael.duerr@charite.de
Scientific contact	Clinical Trial Information, Charité Universitätsmedizin Berlin, +49 030450514001, michael.duerr@charite.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	23 March 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 March 2017
Global end of trial reached?	Yes
Global end of trial date	22 March 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the rate of sustained virologic resonse (SVR) in all treated renal transplant patients at week 12 after the end of treatment.

Protection of trial subjects:

Potential trial participants agreed to participate in the study by providing written informed consent after approval by German health authorities and an independent Ethic committee. The study was conducted according the Declaration of Helsinki, the International Conference on Harmonization and Good Clinical Practice guidelines.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 July 2015
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: 16
Worldwide total number of subjects	16
EEA total number of subjects	16

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)	15
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment started on the 1st of July 2015 at the Department of Nephrology and Medical Intensive Care, Charité
Universitätsmedizin Berlin.

Pre-assignment

Screening details:

1365 Patients were screened.
Drop outs: 1349
Enrolled: 16

Period 1

Period 1 title	Treatment
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	DCV and SOF Arm

Arm description:

In total, 16 KTR with chronic HCV infection received a 12-weeks course of DCV 60 mg and SOF 400 mg orally once daily given

Arm type	Experimental
Investigational medicinal product name	DCV
Investigational medicinal product code	
Other name	Daklinza
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

60mg daily

Investigational medicinal product name	SOF
Investigational medicinal product code	
Other name	Sovaldi
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

400mg daily

Number of subjects in period 1	DCV and SOF Arm
Started	16
Completed	16

Period 2	
Period 2 title	Observation Phase
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms	
Arm title	DCV and SOF
Arm description: observational follow-up period for 24-week	
Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 2	DCV and SOF
Started	16
Completed	15
Not completed	1
Protocol deviation	1

Baseline characteristics

Reporting groups

Reporting group title	Treatment

Reporting group description: -

Reporting group values	Treatment	Total	
Number of subjects	16	16	
Age categorical Units: Subjects			
Age continuous Units: years			
median	51.5		
full range (min-max)	34 to 75	-	
Gender categorical Units: Subjects			
Female	8	8	
Male	8	8	
Number of previous renal transplantations Units: Subjects			
1st	4	4	
2nd	11	11	
3rd	0	0	
4th	1	1	
Cause of end-stage renal disease Units: Subjects			
Chronic Glomerulonephritis	5	5	
Polycystic Kidney Disease	3	3	
Alport-Syndrome	4	4	
Interstitial Nephritis	3	3	
Unknown	1	1	
CMV antibody status			
(Donor (D+/-)/Recipient (R+/-);			
Units: Subjects			
Low-risk (D - / R +)	4	4	
Intermediate risk (D + / R +)	10	10	
High-risk (D + / R -)	2	2	
EBV antibody status Units: Subjects			
(D unknown /R +)	16	16	
HCV genotype Units: Subjects			
Ia	1	1	
Ib	15	15	

Median time since kidney transplantation (range), y Units: years median full range (min-max)	 12.8 2.3 to 25.8	 -	
Renal Transplant function Creatinine Units: mg/dl median full range (min-max)	 1.27 0.95 to 2.3	 -	
Renal Transplant function eGFR			
Median eGFR, ml/min per 1.73 m2			
Units: ml/min median full range (min-max)	 60 25 to 87	 -	
Median body mass index (range) Units: kg/m² median full range (min-max)	 21.47 16.43 to 31.25	 -	

End points

End points reporting groups

Reporting group title	DCV and SOF Arm
Reporting group description:	
In total, 16 KTR with chronic HCV infection received a 12-weeks course of DCV 60 mg and SOF 400 mg orally once daily given	
Reporting group title	DCV and SOF
Reporting group description:	
observational follow-up period for 24-week	
Subject analysis set title	TAC treatment
Subject analysis set type	Safety analysis
Subject analysis set description:	
To further specify the drug metabolism we assessed the C/D ratio of TAC was assesed	
Subject analysis set title	CyA treatment
Subject analysis set type	Safety analysis
Subject analysis set description:	
To further specify the drug metabolism we assessed the C/D ratio of CyA	

Primary: Sustained virological response at SVR 12

End point title	Sustained virological response at SVR 12[1]
End point description:	
these "responders", we noticed early viral response, defined as a rapid virus clearance already after a median of 4 weeks after initiating DCV/SOF therapy. One patient achieved negative HCV PCR at EOT but had early viral relapse 4 weeks after EOT.	
End point type	Primary
End point timeframe:	
12 weeks after EOT	

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: This is an explorative proof of concept study with a calculated sample size of n = 14 patients (power 90% with a type I error of 5% (type II error = 10%) for an estimated efficacy of 79% SVR12. During the course of the study it was decided to enroll 2 additional patients, which even further increases the power of this study to demonstrate adequate efficacy in this population.

End point values	DCV and SOF Arm	DCV and SOF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	16		
Units: Patients	16	15		

Statistical analyses

No statistical analyses for this end point

Secondary: Sustained virological response SVR 4 and 24

End point title	Sustained virological response SVR 4 and 24
End point description:	

End point type	Secondary

End point timeframe:

24 weeks after EOT

End point values	DCV and SOF Arm			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: Patients				
SVR4	15			
SVR24	15			

Statistical analyses

No statistical analyses for this end point

Secondary: Calcineurin inhibitor assessment: C/D Scores

End point title	Calcineurin inhibitor assessment: C/D Scores

End point description:

Metabolism rate of tacrolimus (TAC) or ciclosporin A (CyA) treated patients were determined at predefined study visits by dividing the drug blood trough concentration (C) to the daily TAC or CyA dose (D) respectively. To further specify the drug metabolism we assessed the C/D ratio of TAC-(n = 7) and CyA-(n = 8) treated patients.

End point type	Secondary

End point timeframe:

Screening, baseline, week (w) 1, 2, 4, 6, 8, 10, EOT, SVR4, − 12 and − 24

End point values	TAC treatment	CyA treatment		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	7	8		
Units: ng/ml x 1/mg				
arithmetic mean (standard deviation)				
BL	4.33 (± 1.5)	1.31 (± 0.71)		
EOT	2.85 (± 0.84)	0.89 (± 0.23)		
SVR12	2.49 (± 0.76)	0.79 (± 0.21)		
SVR24	3.12 (± 2.19)	0.57 (± 0.23)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change of the Hepatic function : Liver parameters

End point title	Change of the Hepatic function : Liver parameters

End point description:

End point type	Secondary

End point timeframe:

24 weeks

End point values	DCV and SOF			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: U/l				
arithmetic mean (standard deviation)				
ALT Baseline	48.31 (± 31.71)			
ALT EOT	20.56 (± 10.52)			
ALT SVR12	19.06 (± 7.88)			
AST Baseline	42.06 (± 16.78)			
AST EOT	27.75 (± 12.37)			
AST SVR12	23.0 (± 12.37)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change of the Hepatic function : Ferritin levels

End point title	Change of the Hepatic function : Ferritin levels

End point description:

End point type	Secondary

End point timeframe:

24 weeks

End point values	DCV and SOF			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: µg/l				
arithmetic mean (standard deviation)				
Baseline	253.38 (± 163.37)			
EOT	124.11 (± 64.37)			
SVR12	127.33 (± 6.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change of the Hepatic function: APRI

End point title	Change of the Hepatic function: APRI
End point description: APRI: AST to-platelet ratio index;	
End point type	Secondary
End point timeframe: 32weeks	

End point values	DCV and SOF			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: ratio index U/l x 10^9l				
arithmetic mean (standard deviation)				
Baseline SVR 24	0.47 (± 0.22) 0.25 (± 0.11)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change of the Hepatic function: FIB-4 score

End point title	Change of the Hepatic function: FIB-4 score
End point description:	
End point type	Secondary
End point timeframe: 36 weeks	

End point values	DCV and SOF			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: Score				
arithmetic mean (standard deviation)				
Baseline	1.45 (± 0.63)			
SVR24	1.19 (± 0.53)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change of the Glucose tolerance

End point title	Change of the Glucose tolerance

End point description:

End point type	Secondary

End point timeframe:

24 Weeks

End point values	DCV and SOF			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: mg/dl				
arithmetic mean (standard deviation)				
Baseline	141 (± 77)			
EOT	132 (± 52)			
SVR12	117 (± 77)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 36 Weeks	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18

Reporting groups	
Reporting group title	DCV + SOF

Reporting group description: -

Serious adverse events	DCV + SOF		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 16 (25.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Liverbiopsie (Lymphom)			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pituitary Adenoma			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Urinary tract infections			
subjects affected / exposed	3 / 16 (18.75%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Relapse (HCV-PCR positive after Therapy)			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
C difficile infection			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	DCV + SOF		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 16 (93.75%)		
Nervous system disorders			
Problems with concentration			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	2		
Headache			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	2		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	2		
Edema/swelling foot			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	2		
Nausea			

subjects affected / exposed occurrences (all)	3 / 16 (18.75%) 3		
Gastrointestinal disorders Diarrhoe subjects affected / exposed occurrences (all)	 2 / 16 (12.50%) 2		
Respiratory, thoracic and mediastinal disorders Cold subjects affected / exposed occurrences (all) Dyspnoe/asthma episode subjects affected / exposed occurrences (all)	 5 / 16 (31.25%) 10 3 / 16 (18.75%) 5		
Musculoskeletal and connective tissue disorders Pain shoulder/arm subjects affected / exposed occurrences (all) Lower back pain subjects affected / exposed occurrences (all)	 2 / 16 (12.50%) 2 2 / 16 (12.50%) 2		
Infections and infestations Bronchitis/ pneumonia subjects affected / exposed occurrences (all) Urinary tract infections subjects affected / exposed occurrences (all)	 3 / 16 (18.75%) 2 5 / 16 (31.25%) 7		
Metabolism and nutrition disorders Anemia / iron deficiency subjects affected / exposed occurrences (all)	 3 / 16 (18.75%) 3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The number of 16 treated patients is still relatively small. In addition, further follow-up will have to proof sustained viral clearance and functional improvement. decided to implement an un-controlled open-label design.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/30717681