Clinical trial results:
Direct acting antiviral therapy of hepatitis C in Denmark: treatment response, adverse events and resistance associated variants

Summary

EudraCT number	2015-001956-31
Trial protocol	DK
Global end of trial date	01 June 2018

Results information

Result version number	v1 (current)
This version publication date	09 November 2019
First version publication date	09 November 2019
Summary attachment (see zip file)	Published article (Full article published CS.pdf)

Trial information

Trial identification

Sponsor protocol code	2015-001956-31

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Department of Infectious Diseases, Copenhagen University Hospital, Hvidovre.
Sponsor organisation address	Kettegaard Alle´30, Hvidovre, Denmark, 2650
Public contact	Nina Weis, Department of Infectious Diseases, Copenhagen University Hospital, Hvidovre., 0045 38623514, ninaweis@dadlnet.dk
Scientific contact	Nina Weis, Department of Infectious Diseases, Copenhagen University Hospital, Hvidovre., 0045 38623514, ninaweis@dadlnet.dk

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	01 March 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 December 2017
Global end of trial reached?	Yes
Global end of trial date	01 June 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To study the rate of adverse events and sustanied viral response in a randomized study of patients with chronic hepatitis C, genotype 1 patients, treated for 12 weeks with Viekira PAK® and ribavirin versus Harvoni® and ribavirin. Compare the adverse events- and sustanied viral response rates between the two groups of patients in each treatment arm in relation to demographic, biological and genetic factors.

Protection of trial subjects:

Close monitoring during treatment to address any adverse events. Reduction of ribavirin if patient experienced severe anemia. To reduce distress during blood sampling were ultra sound used if the patient had experienced difficulties during previous blood sampling.

Background therapy:

None.

Evidence for comparator:

Clinical trials with direct acting antivirals (DAA) have shown improved cure rates ≥90% with good tolerability, including difficult to treat patient groups (liver cirrhosis and liver transplantation and previous treatment failure) However, this rapid development has led to few systematic comparisons of different DAA regimens, usually evaluated in cohorts of patients randomized with respect to dosage, addition of ribavirin or treatment duration. This design provides limited information about the rate of adverse events across different DAA regimens. Minimizing adverse events is crucial in relation to adherence to treatment and prevention of prematurely treatment termination due to poor tolerability. The chosen DAA drugs in the study were the DAAs available and approved at the time of initiation of the study.

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	Denmark: 72
Worldwide total number of subjects	72
EEA total number of subjects	72

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	66
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were screened from July 1st 2015 to 1st of April 2017 at six screening sites (departments of infectious diseases and department of hepatology) which covered 4 out of 5 regions in Denmark.

Pre-assignment

Screening details:

Eligible patients were 18-70 years and registered with chronic hepatitis C, genotype 1 in the Danish Database for Hepatitis B and C . The patients had to fulfil inclusion criteria defined as: liver biopsy (Metavir score ≥F2), liver stiffness measurement ≥10 kPa, clinical cirrhosis or extra-hepatic manifestations of importance to treat.

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

The study was conducted as non-blinded with randomization lists produced electronically in blocks of 4.

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm 1, genotype 1.

Arm description:

Sofosbuvir/ledipasvir/ribavirin

Arm type	Active comparator
Investigational medicinal product name	Harvoni
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1 tablet ledipasvir 90 mg/sofosbuvir 400 mg and tablets ribavirin (according to weight) in the morning. Tablets ribavirin (according to weight) in the evening.

Investigational medicinal product name	Rebetol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

800-1200 mg depending on weight. Half dose is taken in the morning and half dose is taken in the evening.

Arm title	Arm 2, genotype 1

Arm description:

Paritaprevir/dasabuvir/ombitasvir/ritonavir and ribavirin

Arm type	Active comparator
Investigational medicinal product name	viekira PAK
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

2 tablets of paritaprevir/ombitasvir/ritonavir and 1 tablet of dasabuvir and tablet ribavirin (according to weight) in the morning with food.
1 tablet of dasabuvir tablet ribavirin (according to weight) in the evening with food.

Investigational medicinal product name	Rebetol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

800 - 1400 mg depending on weight. Half dose in the morning and half dose in the evening.

Number of subjects in period 1	Arm 1, genotype 1.	Arm 2, genotype 1
Started	34	38
Completed	32	37
Not completed	2	1
Adverse event, serious fatal	-	1
Adverse event, non-fatal	1	-
Lost to follow-up	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Arm 1, genotype 1.
Reporting group description: Sofosbuvir/ledipasvir/ribavirin	
Reporting group title	Arm 2, genotype 1
Reporting group description: Paritaprevir/dasabuvir/ombitasvir/ritonavir and ribavirin	

Reporting group values	Arm 1, genotype 1.	Arm 2, genotype 1	Total
Number of subjects	34	38	72
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	31	35	66
From 65-84 years	3	3	6
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	54	51	
full range (min-max)	41 to 66	27 to 68	-
Gender categorical Units: Subjects			
Female	10	9	19
Male	24	29	53
Hepatitis C virus subtype Units: Subjects			
1b	9	10	19
1a	25	27	52
unknown	0	1	1
Ethnicity Units: Subjects			
Caucasian	33	37	70
Non-Caucasian	1	1	2
Route of infection Units: Subjects			
Intravenous drug use	20	25	45
Non-intravenous drug use	7	10	17
Unknown	7	3	10
Liver fibrosis Units: Subjects			

Cirrhosis F4, >17 kPa, clinical diagnosed	13	13	26
Severe fibrosis F3/12-16.9 kPa	10	4	14
Mild-moderate fibrosis F1-F2/<11.9 kPa	11	21	32
HIV status Units: Subjects			
Negative	29	31	60
Positive	5	7	12
Hepatitis B status Units: Subjects			
Negative	34	38	72
Previous treatment Units: Subjects			
No	27	31	58
Yes	7	7	14
Previous response to treatment Units: Subjects			
Non-response	1	1	2
Relapse	3	3	6
Viral breakthrough	1	0	1
Termination due to adverse event	2	3	5
No previous treatment	27	31	58
Fatigue at baseline			
The intensity of fatigue was recorded according to the common terminology criteria for adverse events (CTCAE)			
Units: Subjects			
Grade 1	11	5	16
Grade 2	0	2	2
None	23	31	54
Body-mass index Units: numbers			
arithmetic mean	25.7	25.6	
standard deviation	± 3.16	± 4.27	-
HCV RNA level Units: IU/ml			
log mean	2.77	2.35	
standard deviation	± 3.39	± 2.75	-
Alanine transaminase Units: U/L			
median	74	86.5	
inter-quartile range (Q1-Q3)	49 to 124	49 to 137	-
Platelet count			
x 10^9/liter			
Units: x 10^9/liter			
median	187.5	206	
inter-quartile range (Q1-Q3)	126 to 227	161 to 237	-
serum albumin Units: g/liter			
median	39	39	
inter-quartile range (Q1-Q3)	37 to 41	36 to 42	-

End points

End points reporting groups	
Reporting group title	Arm 1, genotype 1.
Reporting group description: Sofosbuvir/ledipasvir/ribavirin	
Reporting group title	Arm 2, genotype 1
Reporting group description: Paritaprevir/dasabuvir/ombitasvir/ritonavir and ribavirin	

Primary: Adverse events	
End point title	Adverse events
End point description:	
End point type	Primary
End point timeframe: 1 July 2015 - 1 December 2018	

End point values	Arm 1, genotype 1.	Arm 2, genotype 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	38		
Units: number of persons				
Experienced Adverse events	33	37		

Attachments (see zip file)	Statistic analysis/Statistic data for adverse events and baseline

Statistical analyses

Statistical analysis title	Adverse events overall
Comparison groups	Arm 2, genotype 1 v Arm 1, genotype 1.
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	≤ 0.05
Method	Fisher exact

Notes:

[1] - A sample size of 50 patients per group with 80% power using 2-sample test for proportions with a 2.sided significance level of 0.05 and the treatment-arm with Viekira PAk/ribavirin set to 30% would detect a difference of 22% giving a proportion of 8% in the other treatment arm. Fisher's exact Test was used.

Statistical analysis title	Changes in laboratory results and liver stiffness

Statistical analysis description:	
The Wilcoxon signed-rank and rank-sum tests were applied to estimate changes in laboratory results and liver stiffness measurement from baseline to the end of treatment for all patients and the comparison of treatment groups, respectively.	
Comparison groups	Arm 2, genotype 1 v Arm 1, genotype 1.
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (net)

Secondary: Proportion of patients with sustanied virologic response after end of treatment

End point title	Proportion of patients with sustanied virologic response after end of treatment
End point description:	
Hepatitis C virus RNA level measured in a blood sample	
End point type	Secondary
End point timeframe:	
1 January 2016 - 1 August 2017.	

End point values	Arm 1, genotype 1.	Arm 2, genotype 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	38		
Units: numbers				
Sustanied viral response	33	37		

Attachments (see zip file)	Flowchart Genotype 1/Figure 1 flowchart GT 1.png

Statistical analyses

Statistical analysis title	Sustanied viral response
Comparison groups	Arm 2, genotype 1 v Arm 1, genotype 1.
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	Fisher exact

Adverse events

Adverse events information

Timeframe for reporting adverse events:

1 July 2015 - 1 December 2018.
Adverse events were recorded at baseline and for all patients at weeks 1, 2, 3, 4, 8 and 12 of the study period, and in the post-treatment period at weeks 4, 12 and 24.

Adverse event reporting additional description:

For all adverse events, start- and end date, intensity (mild, moderate or severe), severity (is recovering, has recovered, recovered with sequelae, still affected), relation to study drug and action taken with study drug was recorded. The severity of adverse events and their relationship to treatment were assessed by the investigator.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4.0

Reporting groups

Reporting group title	Arm 1, genotype 1.

Reporting group description:

Sofosbuvir/ledipasvir/ribavirin

Reporting group title	Arm 2, genotype 1

Reporting group description:

Paritaprevir/dasabuvir/ombitasvir/ritonavir and ribavirin

Serious adverse events	Arm 1, genotype 1.	Arm 2, genotype 1	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 34 (17.65%)	3 / 38 (7.89%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	1	
Cardiac disorders			
Chest pain	Additional description: Occurred during treatment		
subjects affected / exposed	1 / 34 (2.94%)	1 / 38 (2.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Weakened general condition	Additional description: Did not occur during treatment.		
subjects affected / exposed	1 / 34 (2.94%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
gastro-intestinal bleeding	Additional description: Did not occur during treatment		

subjects affected / exposed	1 / 34 (2.94%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Severe stomach pain	Additional description: Occurred during treatment		
subjects affected / exposed	1 / 34 (2.94%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus	Additional description: Occurred during treatment		
subjects affected / exposed	1 / 34 (2.94%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
decompensated liver cirrhosis with ascites	Additional description: Occurred during treatment		
subjects affected / exposed	1 / 34 (2.94%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver failure	Additional description: Suspected Unexpected serious Adverse Reaction (SUSAR).		
subjects affected / exposed	0 / 34 (0.00%)	1 / 38 (2.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory, thoracic and mediastinal disorders			
Shotness of breath	Additional description: Occurred during treatment		
subjects affected / exposed	0 / 34 (0.00%)	1 / 38 (2.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foreign object in throat	Additional description: Occurred during treatment		
subjects affected / exposed	0 / 34 (0.00%)	1 / 38 (2.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back- and hip pain	Additional description: Did not occur during treatment.		

subjects affected / exposed	1 / 34 (2.94%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture	Additional description: Did not occur during treatment		
subjects affected / exposed	1 / 34 (2.94%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Arm 1, genotype 1.	Arm 2, genotype 1	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	33 / 34 (97.06%)	37 / 38 (97.37%)	
Cardiac disorders			
Chest pain			
subjects affected / exposed	1 / 34 (2.94%)	1 / 38 (2.63%)	
occurrences (all)	1	1	
Nervous system disorders			
Headache			
subjects affected / exposed	14 / 34 (41.18%)	19 / 38 (50.00%)	
occurrences (all)	14	19	
Insomnia			
subjects affected / exposed	8 / 34 (23.53%)	9 / 38 (23.68%)	
occurrences (all)	8	9	
Dizziness			
subjects affected / exposed	3 / 34 (8.82%)	5 / 38 (13.16%)	
occurrences (all)	3	5	
Memory impairment/absent minded			
subjects affected / exposed	3 / 34 (8.82%)	1 / 38 (2.63%)	
occurrences (all)	3	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	27 / 34 (79.41%)	29 / 38 (76.32%)	
occurrences (all)	27	29	
General disorders and administration site conditions			

Fatigue			
subjects affected / exposed	26 / 34 (76.47%)	27 / 38 (71.05%)	
occurrences (all)	26	27	
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 34 (0.00%)	3 / 38 (7.89%)	
occurrences (all)	0	3	
Eye disorders			
Affected vision			
subjects affected / exposed	1 / 34 (2.94%)	3 / 38 (7.89%)	
occurrences (all)	1	3	
Gastrointestinal disorders			
Heartburn/abdominal pain/abdominal distention			
subjects affected / exposed	11 / 34 (32.35%)	16 / 38 (42.11%)	
occurrences (all)	11	16	
Nausea/vomiting			
subjects affected / exposed	11 / 34 (32.35%)	14 / 38 (36.84%)	
occurrences (all)	11	14	
Decreased appetite			
subjects affected / exposed	4 / 34 (11.76%)	11 / 38 (28.95%)	
occurrences (all)	4	11	
Diarrhoea			
subjects affected / exposed	6 / 34 (17.65%)	8 / 38 (21.05%)	
occurrences (all)	6	8	
Increased appetite			
subjects affected / exposed	3 / 34 (8.82%)	1 / 38 (2.63%)	
occurrences (all)	3	1	
Constipation			
subjects affected / exposed	1 / 34 (2.94%)	2 / 38 (5.26%)	
occurrences (all)	1	2	
Respiratory, thoracic and mediastinal disorders			
Dyspnea			
subjects affected / exposed	10 / 34 (29.41%)	11 / 38 (28.95%)	
occurrences (all)	10	11	
Skin and subcutaneous tissue disorders			

Pruritus, dry skin or eczema			
subjects affected / exposed	13 / 34 (38.24%)	20 / 38 (52.63%)	
occurrences (all)	13	20	
Psychiatric disorders			
Irritability/mood swings/depression			
subjects affected / exposed	12 / 34 (35.29%)	8 / 38 (21.05%)	
occurrences (all)	12	8	
Musculoskeletal and connective tissue disorders			
Asthenia/malaise/tremor			
subjects affected / exposed	9 / 34 (26.47%)	13 / 38 (34.21%)	
occurrences (all)	9	13	
Arthralgia			
subjects affected / exposed	4 / 34 (11.76%)	3 / 38 (7.89%)	
occurrences (all)	4	3	
muscle spams			
subjects affected / exposed	2 / 34 (5.88%)	3 / 38 (7.89%)	
occurrences (all)	2	3	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	11 / 34 (32.35%)	13 / 38 (34.21%)	
occurrences (all)	11	13	
Herpes outbreak			
subjects affected / exposed	1 / 34 (2.94%)	2 / 38 (5.26%)	
occurrences (all)	1	2	
Fungal infection			
subjects affected / exposed	0 / 34 (0.00%)	2 / 38 (5.26%)	
occurrences (all)	0	2	

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 treatment-arm, enrolling patients with genotype 3 , was prematurely terminated because national treatment guidelines for genotype 3 patients were altered after approval of Epclusa (velpatasvir/sofosbuvir) in Europe.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/29994874