Clinical trial results:
A phase IV open-label, multicentre, international trial of paritaprevir/ritonavir, ombitasvir, dasabuvir with or without ribavirin for people with chronic hepatitis C virus genotype 1 infection and recent injection drug use or receiving opioid substitution therapy.

Summary

EudraCT number	2015-003562-90
Trial protocol	FR
Global end of trial date	31 March 2019

Results information

Result version number	v1 (current)
This version publication date	18 December 2019
First version publication date	18 December 2019

Trial information

Trial identification

Sponsor protocol code	VHCRP1405

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02498015
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of New South Wales Sydney, The Kirby Institute
Sponsor organisation address	UNSW Sydney, Sydney, Australia, 2052
Public contact	Philippa Marks, University of New South Wales Sydney, The Kirby Institute, 61 0293850886, pmarks@kirby.unsw.edu.au
Scientific contact	Gregory Dore, University of New South Wales Sydney, The Kirby Institute, 61 0293850900, gdore@kirby.unsw.edu.au

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	14 June 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	31 March 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to evaluate the proportion of patients with undetectable HCV RNA at 12 weeks post end of treatment (SVR12) following paritaprevir/ritonavir/ombitasvir, dasabuvir and ribavirin therapy for 12 weeks in people with chronic HCV genotype 1 infection and recent injection drug use or receiving opiate substitution therapy.

Protection of trial subjects:

Treatment with paritaprevir/ritonavir, ombitasvir and dasabuvir with or without ribavirin has been shown to be more effective and less toxic that treatment with standard therapy. Clearing the virus significantly reduces the risk of future liver related morbidity and mortality which clearly outweighs the risk of mild or moderate reversible side effects while on treatment.
Patients were monitored closely for adverse events associated with blood collection and the treatment administration.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 June 2016
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	3 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 5
Country: Number of subjects enrolled	Canada: 38
Country: Number of subjects enrolled	New Zealand: 13
Country: Number of subjects enrolled	Switzerland: 20
Country: Number of subjects enrolled	Norway: 4
Country: Number of subjects enrolled	France: 7
Worldwide total number of subjects	87
EEA total number of subjects	11

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)	87
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were recruited from 19 sites, in Australia (4 sites), Canada (6 sites), New Zealand (2 sites), Norway (1 site), Switzerland (4 sites), and France (2 sites). Subjects were recruited from people from 3 drug treatment clinics, 13 hospital clinics, 1 private practice, and 2 community clinics.

Pre-assignment

Screening details:

Participants were 18 years or older, had chronic HCV genotype 1 (confirmed >6 months), had recently injected drugs (self-reported injecting drug use within 6 months of enrolment) or were receiving opioid substitution therapy. participants with HIV infection and/or decompensated liver disease were excluded.

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Not applicable, the study was open-label.

Arms

Arm title	Single arm - open-label

Arm description:

Subjects with HCV genotype 1b enrolled in the study received 2 tablets of co-formulated paritaprevir/ritonavir/ombitasvir (75 mg/50 mg/12.5 mg) once-daily, and 1 tablet of dasabuvir (250 mg) twice-daily administered orally for 12 weeks. Subjects with HCV genotype 1a also received ribavirin administered either 1000 mg or 1200 mg twice-daily according to body weight (<75 kg and >75 kg, respectively). Therapy was administered in weekly electronic blister packs for monitoring of adherence.

Arm type	Experimental
Investigational medicinal product name	ombitasvir/paritaprevir/ritonavir
Investigational medicinal product code	
Other name	Viekirax
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Patients received a fixed-dose combination of 2 tablets of the co-formulated paritaprevir/ritonavir/ombitasvir (75 mg/50 mg/12.5 mg) once-daily administered orally for 12 weeks.

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

Dosage and administration details:

Participants received 1 tablet of dasabuvir (250 mg) twice-daily administered orally for 12 weeks.

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

Dosage and administration details:

Ribavirin administered either 1000 mg or 1200 mg twice-daily according to body weight (<75 kg and >75 kg, respectively) orally for for 12 weeks.

Number of subjects in period 1	Single arm - open-label
Started	87
Completed	84
Not completed	3
Physician decision	1
Incarceration	1
Lost to follow-up	1

Period 2

Period 2 title	Primary endpoint SVR12
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Not applicable, the study was open-label.

Arms

Arm title	Single arm - open-label

Arm description:

Subjects with HCV genotype 1b enrolled in the study received 2 tablets of co-formulated paritaprevir/ritonavir/ombitasvir (75 mg/50 mg/12.5 mg) once-daily, and 1 tablet of dasabuvir (250 mg) twice-daily administered orally for 12 weeks. Subjects with HCV genotype 1a also received ribavirin administered either 1000 mg or 1200 mg twice-daily according to body weight (<75 kg and >75 kg, respectively). Therapy was administered in weekly electronic blister packs for monitoring of adherence.

Arm type	Experimental
Investigational medicinal product name	ombitasvir/paritaprevir/ritonavir
Investigational medicinal product code	
Other name	Viekirax
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Patients received a fixed-dose combination of 2 tablets of the co-formulated paritaprevir/ritonavir/ombitasvir (75 mg/50 mg/12.5 mg) once-daily administered orally for 12 weeks.

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

Dosage and administration details:

Participants received 1 tablet of dasabuvir (250 mg) twice-daily administered orally for 12 weeks.

Investigational medicinal product name	ribavirin
Investigational medicinal product code	
Other name	ribavirin
Pharmaceutical forms	Tablet

Routes of administration	Oral use

Dosage and administration details:

Ribavirin administered either 1000 mg or 1200 mg twice-daily according to body weight (<75 kg and >75 kg, respectively) orally for for 12 weeks.

Number of subjects in period 2	Single arm - open-label
Started	84
Completed	79
Not completed	5
Adverse event, serious fatal	1
Lost to follow-up	1
Lack of efficacy	3

Baseline characteristics

Reporting groups	
Reporting group title	Single arm - open-label

Reporting group description:

Subjects with HCV genotype 1b enrolled in the study received 2 tablets of co-formulated paritaprevir/ritonavir/ombitasvir (75 mg/50 mg/12.5 mg) once-daily, and 1 tablet of dasabuvir (250 mg) twice-daily administered orally for 12 weeks. Subjects with HCV genotype 1a also received ribavirin administered either 1000 mg or 1200 mg twice-daily according to body weight (<75 kg and >75 kg, respectively). Therapy was administered in weekly electronic blister packs for monitoring of adherence.

Reporting group values	Single arm - open-label	Total	
Number of subjects	87	87	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous Units: years			
median	48		
full range (min-max)	43 to 54	-	
Gender categorical Units: Subjects			
Female	20	20	
Male	67	67	
High school or higher education Units: Subjects			
High school or higher education	41	41	
No higher education	46	46	
Any injecting drug use in the previous 6 months Units: Subjects			
Any injecting drug use in the previous 6 months	53	53	
None	32	32	
Not recorded	2	2	
Any injecting drug use in the previous month Units: Subjects			
Heroin	26	26	
Cocaine	10	10	
Methamphetamines	15	15	

Other opioids	10	10	
None	24	24	
Not recorded	2	2	
Injecting drug use frequency in the previous month Units: Subjects			
Never	46	46	
< Daily	26	26	
> Daily	13	13	
Not recorded	2	2	
Any drug use in the previous 6 months Units: Subjects			
Any drug use in the previous 6 months	62	62	
None	23	23	
Not recorded	2	2	
Any non-injecting drug use in the previous month Units: Subjects			
Any non-injecting drug use in the previous month	37	37	
None	48	48	
Not recorded	2	2	
Income Units: Subjects			
Full-time employment	9	9	
Part-time employment	8	8	
Disability/social services	62	62	
Other	6	6	
Not recorded	2	2	
Any alcohol use in the previous month Units: Subjects			
Any alcohol use in the previous month	47	47	
None	38	38	
Not recorded	2	2	
Hazardous alcohol use in the previous month Units: Subjects			
Hazardous alcohol use in the previous month	43	43	
None	42	42	
Not recorded	2	2	
History of OST Units: Subjects			
History of OST	74	74	
None	11	11	
Not recorded	2	2	
Current OST Units: Subjects			
Methadone	51	51	
Buprenorphine	5	5	
Buprenorphine/naloxone	9	9	

None	20	20	
Not recorded	2	2	
OST and had injected in previous month (baseline) Units: Subjects			
No OST, no recent injecting	9	9	
No OST, recent injecting	14	14	
OST, no recent injecting	37	37	
OST, recent injecting	25	25	
Not recorded	2	2	
History of clinically significant psychiatric illness Units: Subjects			
History of clinically significant psychiatric illn	29	29	
None	56	56	
Not recorded	2	2	
HCV genotype Units: Subjects			
1a	78	78	
1b	9	9	
Alanine transaminase, IU/L Units: Subjects			
Alanine transaminase, IU/L	13	13	
None	65	65	
Not recorded	9	9	
Stage of liver disease Units: Subjects			
No or mild fibrosis (F0-F1)	67	67	
Moderate or advanced fibrosis (F2-F3)	11	11	
Cirrhosis (F4)	7	7	
Not recorded	2	2	
Study site distribution Units: Subjects			
Canada	38	38	
Europe	31	31	
Australasia	18	18	

End points

End points reporting groups

Reporting group title	Single arm - open-label

Reporting group description:

Subjects with HCV genotype 1b enrolled in the study received 2 tablets of co-formulated paritaprevir/ritonavir/ombitasvir (75 mg/50 mg/12.5 mg) once-daily, and 1 tablet of dasabuvir (250 mg) twice-daily administered orally for 12 weeks. Subjects with HCV genotype 1a also received ribavirin administered either 1000 mg or 1200 mg twice-daily according to body weight (<75 kg and >75 kg, respectively). Therapy was administered in weekly electronic blister packs for monitoring of adherence.

Reporting group title	Single arm - open-label

Reporting group description:

Subjects with HCV genotype 1b enrolled in the study received 2 tablets of co-formulated paritaprevir/ritonavir/ombitasvir (75 mg/50 mg/12.5 mg) once-daily, and 1 tablet of dasabuvir (250 mg) twice-daily administered orally for 12 weeks. Subjects with HCV genotype 1a also received ribavirin administered either 1000 mg or 1200 mg twice-daily according to body weight (<75 kg and >75 kg, respectively). Therapy was administered in weekly electronic blister packs for monitoring of adherence.

Primary: SVR12

End point title	SVR12

End point description:

The primary efficacy endpoint was the proportion of participants with SVR12, which was defined as a HCV RNA load below the limit of quantification 12 weeks after the end of treatment in all participants who received at least one dose of study medication (ITT).

End point type	Primary

End point timeframe:

12 weeks post-treatment

End point values	Single arm - open-label	Single arm - open-label		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	85	79		
Units: Number of subjects	0	79		

Statistical analyses

Statistical analysis title	Intention to treat
Comparison groups	Single arm - open-label v Single arm - open-label
Number of subjects included in analysis	164
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	90

Confidence interval	
level	95 %
sides	2-sided
lower limit	82
upper limit	95

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment emergent adverse events up to 28 days after last dose of study treatment

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Single arm - open-label

Reporting group description:

The study was open-label. Subjects enrolled in the study received 12 weeks of paritaprevir/ritonavir, ombitasvir, dasabuvir with (G1a) or without (G1b) ribavirin in an oral twice-daily fixed dose combination. Therapy was administered in weekly electronic blister packs for monitoring of adherence.

Serious adverse events	Single arm - open-label		
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 87 (5.75%)		
number of deaths (all causes)	4		
number of deaths resulting from adverse events	0		
Gastrointestinal disorders			
Emesis	Additional description: Abdominal pain, nausea, vomiting		
subjects affected / exposed	2 / 87 (2.30%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Tuberculosis	Additional description: Tuberculosis		
subjects affected / exposed	1 / 87 (1.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Anxiety	Additional description: Increasing anxiety, depression and psychotic decompensation		
subjects affected / exposed	5 / 87 (5.75%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			

Myoclonus	Additional description: Myoclonic jerks		
subjects affected / exposed	1 / 87 (1.15%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Acute lumbosciatalgia	Additional description: Acute lumbosciatalgia		
subjects affected / exposed	1 / 87 (1.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Single arm - open-label		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	53 / 87 (60.92%)		
Nervous system disorders			
Headache			
subjects affected / exposed	12 / 87 (13.79%)		
occurrences (all)	12		
Dizziness			
subjects affected / exposed	7 / 87 (8.05%)		
occurrences (all)	7		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	25 / 87 (28.74%)		
occurrences (all)	25		
Asthenia			
subjects affected / exposed	7 / 87 (8.05%)		
occurrences (all)	7		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	12 / 87 (13.79%)		
occurrences (all)	12		
Low haemoglobin			
subjects affected / exposed	4 / 87 (4.60%)		
occurrences (all)	4		
Low platelets			

subjects affected / exposed occurrences (all)	1 / 87 (1.15%) 1		
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) Decreased appetite subjects affected / exposed occurrences (all)	 20 / 87 (22.99%) 20 11 / 87 (12.64%) 11 7 / 87 (8.05%) 7		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	 11 / 87 (12.64%) 11		
Endocrine disorders Hyperhidrosis subjects affected / exposed occurrences (all)	 7 / 87 (8.05%) 7		

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.

Enrolment closed prematurely at 87/100 due to slower than anticipated recruitment. Participants were recruited from tertiary hospital HCV clinics, drug treatment clinics and community health centres experienced in HCV care in PWID and/or on OST.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/30384028