A randomised study of interferon-free treatment for recently acquired hepatitis C in people who inject drugs and people with HIV coinfection.

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The primary objective is to evaluate the proportion of patients with HCV RNA below the level of quantitation (target not detected [TND] or target detected, not quantifiable [TDnq]) at 12 weeks post end of treatment (SVR12) following sofosbuvir/…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Viral infectious disorders
Study type	Interventional

Summary

ID

NL-OMON45955

Source
ToetsingOnline

Brief title
REACT

Condition

- Viral infectious disorders

Synonym
Inflammation of the liver caused by a virus; viral infection caused by hepatitis C

Research involving
Human

Sponsors and support

Primary sponsor: The Kirby Institute, The University of New South Wales Australia

Source(s) of monetary or material Support: Ministerie van OC&W,Gilead Sciences

Intervention

Keyword: C, Hepatitis, Infection, Recent

Outcome measures

Primary outcome

The primary endpoint is the proportion of participants with HCV RNA below the level of quantitation (target not detected [TND] or target detected, not quantifiable [TDnq]) at 12 weeks post end of treatment (SVR12)

Secondary outcome

Secondary virological endpoints:

1) The proportion of participants with:

- ETR defined as HCV RNA below the level of quantitation at end of therapy

- SVR 4 defined as HCV RNA below the level of quantitation 4 weeks post therapy

- SVR 24 defined as HCV RNA below the level of quantitation 24 weeks post therapy

- HCV RNA below the level of quantitation through 2 years post treatment

Results will be stratified by HCV genotype and HIV-coinfection.

2) 80/80 adherence: Defined as the receipt of >80% of scheduled doses for >80% of the scheduled treatment period.

3) 90/90 adherence: Defined as the receipt of >90% of scheduled doses for >90% of the scheduled treatment period.

4) 100/100 adherence: Defined as the receipt of 100% of scheduled doses for

100% of the scheduled treatment period.

5) On-treatment adherence: Calculated by subtracting the number of missed doses from the total number of doses of scheduled treatment and dividing by the total intended therapy duration. This measures the proportion of doses received from the time that treatment was initiated until treatment was discontinued or completed.

6) Toxicity: Proportion of participants with at least one severe or potentially life threatening (grade 3 or 4) adverse event.

7) Early treatment discontinuation: Discontinuation of therapy prior to the per-protocol planned end of treatment (6 or 12 weeks depending on study arm).

8) Resistance associated variants (RAVs): The proportion of treated subjects with development of RAVs following virological relapse or breakthrough.

9) Reinfection rate: Rates of HCV reinfection will be calculated using person-time of observation during and up to 48 months following end of treatment.

10) Baseline characteristics, on-treatment adherence, risk behaviours and toxicity will be evaluated among subjects withdrawing prior to randomisation.

Study description

Background summary

Globally, 3-4 million new hepatitis C virus (HCV) infections are estimated to occur annually. People who inject drugs (PWID) represent one of the groups at highest risk of transmitting and acquiring infection with the majority of new (60%) and existing (80%) infections in developed countries occur in this population with HCV antibody prevalence estimated at 67% (60-80%). HIV-positive men-who-have-sex-with-men (MSM) are another high risk group for

HCV acquisition.

The advent of DAAs has changed the therapeutic landscape for individuals with chronic HCV infection with IFN-free therapy offering high efficacy and tolerability, even in *difficult-to-treat* populations. Multiple agents in different classes have been approved in Australia by the Therapeutic Goods Administration (TGA), the European Union by the European Medicines Agency (EMA) and the US by the Food and Drug Administration (FDA).

Given the burden of HCV-related disease among PWID and HIV-positive MSM, strategies to enhance HCV assessment, treatment and prevention in these groups are urgently needed. Much of what is known about the timing of treatment initiation, regimen choice and duration of therapy in acute HCV infection comes from small observational studies and randomized controlled trials in selected populations with limited data on treatment in PWID and HIV co-infection. With recent rapid advances in HCV therapeutics, management strategies for acute HCV will evolve rapidly over the next few years.

The REACT study will compare the efficacy and safety of sofosbuvir (SOF)/velpatasvir (VEL) administered for 6 or 12 weeks in individuals with recent HCV infection. The role and activity of potent DAA regimens in acute HCV infection requires evaluation, with the potential to be given as highly efficacious, short course IFN-sparing regimens, maximising acceptability to patients, encouraging uptake of treatment, limiting further transmission and preventing progression to chronic liver disease.

Study objective

The primary objective is to evaluate the proportion of patients with HCV RNA below the level of quantitation (target not detected [TND] or target detected, not quantifiable [TDnq]) at 12 weeks post end of treatment (SVR12) following sofosbuvir/velpatasvir therapy for 6 weeks (short treatment duration) as compared with 12 weeks (standard treatment duration) in people with recent HCV infection (duration of infection <=12 months).

The secondary objectives are as follows:
1 To evaluate the proportion of participants with HCV RNA below the level of quantitation (TND or TDnq) at the end of treatment (ETR), 4 weeks after treatment completion (SVR4) and 24 weeks after treatment completion (SVR24);

2 To evaluate the proportion of participants with undetectable HCV RNA through 2 years post treatment;

3 To evaluate the levels of adherence, factors associated with suboptimal adherence including HIV status, and the impact of suboptimal adherence on therapeutic response;

4 To evaluate the impact of treatment on illicit drug use, injecting behaviour and sexual risk taking behaviour (behavioural survey) during treatment;

5 To evaluate safety and tolerability

6 To evaluate the change in HIV RNA and CD4 (on-treatment and end of treatment);

7 To evaluate the rate and risk factors for reinfection during and up to 2 years following treatment;

8 To evaluate the immunological factors associated with treatment induced clearance and reinfection

Study design

This study will be conducted as a phase III randomised, open-label, non-inferiority multicentre international trial. A total of 250 people with recently acquired hepatitis C will be enrolled.

The study consists of a screening phase (-12 to -4 weeks), treatment commencement from baseline, randomisation between week 5 and 6, treatment for another 6 weeks for those randomised to standard therapy (12 weeks of treatment) or end of treatment for those randomised to shortened treatment (6 weeks of treatment). All participants will then enter the follow-up phase (96 weeks) to evaluate treatment response and reinfection.

Participants will receive six or twelve 12 weeks of open-label sofosbuvir/velpatasvir (400mg/100mg daily) in an oral once-daily fixed dose combination. Dose modifications are prohibited.

Intervention

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Study burden and risks

There are potential risks associated with this study. Participants may experience drug toxicity associated with the use of study medications. The most common adverse events were fatigue, headache, nausea, diarrhoea and insomnia. These symptoms are generally mild and can be managed in a simple standardised fashion and generally resolve on completion of therapy. In clinical trials using the study medications to date, no subject discontinued the study medications due to treatment related side effects.

Participants who receive a shortened duration of study treatment (6 weeks) may potentially have a higher risk of virological relapse. A Data Safety and Monitoring Board (DSMB) will be established in this study to monitor the safety and efficacy data and virological relapse rate. Specifically, a pre-specified high rate of relapse (>20%) in the shortened arm will trigger consideration of terminating the short duration arm. Virological relapse can happen during treatment or up to 6 months after treatment finishes. Participants who experienced virological relapse after an initial response will have the option of receiving re-treatment with current standard of care therapy for chronic HCV infection.
Venepuncture may cause local pain, bruising, occasional light-headedness, fainting, and very rarely, infection at the site of the blood draw. All study staff are experienced in venepuncture to minimise the risk of infection and pain.

There are 15 to 18 study visits (depending on the treatment duration a participant receives). Each visit will take about 30 to 90 minutes depending on the type of visit. A screening visit which involves more study assessments will take about 90 minutes but a treatment follow-up visit may only take about 30 minutes.

Potential benefits arising from this proposed study include the possibility of effective cure of HCV infection at an early stage of infection. Advantages to participants treated at this stage may include a simpler regimen and a shorter treatment duration than that routinely used in the treatment of chronic HCV without loss of efficacy. Shortening duration may result in fewer adverse events, better quality of life, less frequent dose reductions, and increasing the likelihood of optimal adherence.

Contacts

Public
The Kirby Institute, The University of New South Wales Australia

The Kirby Institute, The University of New South Wales Australia Wallace Wurth Building
Sydney, New South Wales 2052
AU
Scientific
The Kirby Institute, The University of New South Wales Australia

The Kirby Institute, The University of New South Wales Australia Wallace Wurth Building
Sydney, New South Wales 2052
AU

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Subjects must meet all of the following inclusion criteria to be eligible to participate in this study. ;1 Participants have voluntarily signed the informed consent form.
2 18 years of age or older.
3 Detectable HCV RNA at screening (>10,000 IU/ml), and in the opinion of the investigator is unlikely to demonstrate spontaneous viral clearance
4 HCV genotypes 1-6.
5 HBsAg negative
6 Negative pregnancy test at baseline (females of childbearing potential only).
7 Male subjects and female subjects of childbearing potential who engage in heterosexual intercourse must agree to use protocol specified method(s) of contraception
8 Medically stable on the basis of physical examination, medical history and vital signs
9 Adequate literacy to provide reliable responses to the study questionnaires
10 All fertile males and females must be using effective contraception during treatment and during the 30 days after treatment end.
11 Recently acquired HCV infection (estimated duration of infection <=12 months)*;Recently acquired HCV infection as defined by:
A)
i) First anti-HCV Ab or HCV RNA positive within the previous 6 months
and
ii) Documented anti-HCV Ab negative within the 12 months prior to anti-HCV antibody positive result ;OR ;B)
i) First anti-HCV Ab or HCV RNA positive within the previous 6 months
and
ii) Acute clinical hepatitis (jaundice or ALT> 10 X ULN) within the previous 6 months prior to first positive HCV antibody or HCV RNA, with no other cause of acute hepatitis identifiable;OR;C) For cases of recent HCV reinfection the following criteria are required: Documented prior HCV antibody positive with HCV RNA negative on at least 2 occasions 6 months apart AND new HCV RNA positive within the previous 6 months ;*Estimated duration

of infection based on midpoint between last antibody negative or HCV RNA and first antibody positive or HCV RNA in the case of seroconversion and 6 weeks prior to date of maximum ALT in the case of acute hepatitis.;If co-infection with HIV is documented, the subject must meet the following criteria:
1. Antiretroviral (ARV) untreated for >8 weeks preceding screening visit with CD4 T cell count >500 cells/mm3
OR
2. On a stable ARV regimen for >8 weeks prior to screening visit, with CD4 T cell count >200 cells/mm3 and an undetectable plasma HIV RNA level.
• Suitable ARV include:
o Nucleos(t)ide reverse transcriptase inhibitors: Tenofovir disoproxil fumarate (TDF), tenofovir alafenamide (TAF), emtricitabine (FTC)Non-nucleoside reverse transcriptase inhibitors: Rilpivirine
o Protease inhibitors: Atazanavir, darunavir, lopinavir, ritonavir
o Integrase inhibitors: Dolutegravir, raltegravir, elvitegravir/cobicistat
• Contraindicated ARV include:
o Efavirenz
* - 50% reduction in velpatasvir (GS-5816) exposure
o Didanosine
o Zidovudine
o Tipranavir
Other ARV agents may be permissible at the time of study commencement pending further drug-drug interaction studies; please discuss with the Medical Monitor.

Exclusion criteria

Subjects who meet any of the exclusion criteria are not to be enrolled in this study.;1 History of any of the following:
a. Clinically significant illness (other than HCV) or any other major medical disorder that may interfere with the participant treatment, assessment or compliance with the protocol; participants currently under evaluation for a potentially clinically significant illness (other than HCV) are also excluded.
b. History of chronic pulmonary disease associated with functional limitation, severe cardiac disease, major organ transplantation or other evidence of severe illness, malignancy, or any other conditions which would make the patient, in the opinion of the investigator, unsuitable for the study
c. Solid organ transplant
d. Malignancy within 5 years prior to screening, with exception of specific cancers that may have been cured by surgical resection (basal cell skin cancer, etc.). Subjects under evaluation for possible malignancy are also excluded.
e. Significant drug allergy (such as anaphylaxis or hepatotoxicity)
2. Subject has a known or documented prior history of cirrhosis
3 Subject shows evidence of significant liver disease in addition to hepatitis C, which may include but is not limited to drug- or alcohol-related cirrhosis, autoimmune hepatitis, hemochromatosis, Wilson*s disease, non-alcoholic steatohepatitis (NASH), or primary biliary

cirrhosis
4 Any of the following lab parameters at screening:
a. Direct bilirubin > 1.5 x ULN
b. Platelets < 50,000/µL
c. Creatinine clearance (CLcr) < 50 mL/min
d. Haemoglobin < 10 g/dL
e. Albumin < 30g/L
f. International Normalised Ratio (INR) >1.5 (unless subject is on a stable anticoagulant regimen or has known coagulopathy)
5 Pregnant or nursing female
6 Use of prohibited concomitant medications as described in the study protocol
7 Chronic use of systemically administered immunosuppressive agents (e.g. prednisone equivalent > 10 mg/day)
8 Known hypersensitivity to velpatasvir, sofosbuvir or formulation excipients.
9 Therapy with any anti-neoplastic or immunomodulatory treatment (including supraphysiologic doses of steroids and radiation) <=6 months prior to the first dose of study drug.
10 Any investigational drug <=6 weeks prior to the first dose of study drug.
11 Previous failure of therapy with sofosbuvir or an NS5A inhibitor prior to the first dose of study drug.
12 Ongoing severe psychiatric disease as judged by the treating physician.
13 Frequent injecting drug use that is judged by the treating physician to compromise treatment safety.
14 Inability or unwillingness to provide informed consent or abide by the requirements of the study.
15. Prior enrolment within this study.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Other
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	29-03-2017
Enrollment:	15
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Epclusa (Sofosbuvir and Velpatasvir)
Generic name:	Velpatasvir
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	25-10-2016
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-11-2016
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	30-03-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-02-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-03-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Approved WMO Date:	25-03-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-04-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-08-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-08-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2015-004243-39-NL
ClinicalTrials.gov	NCT02625909
CCMO	NL55674.018.16

Study results

Date completed:	23-03-2020
Actual enrolment:	28

Summary results
Trial is onging in other countries