Selecting treatment duration based on early response to Epclusa in patients with type 3 hepatitis C virus infection – is longer therapy worthwhile?

Submission date	Recruitment status No longer recruiting	[X] Prospectively registered		
13/03/2017		[X] Protocol		
Registration date	Overall study status Completed	Statistical analysis plan		
16/03/2017		[X] Results		
Last Edited 06/10/2022	Condition category Infections and Infestations	Individual participant data		

Plain English summary of protocol

Background and study aims

Hepatitis C is a type of liver disease, which is caused by the hepatitis C virus (HCV). Over time, the virus causes the liver to become irreversibly scarred (cirrhosis), eventually leading to liver failure. Treatment for long-term (chronic) HCV has evolved rapidly in the last few years, with licensing of new oral treatments (pills) which are highly successful at clearing the virus and enabling a cure. Despite this however, some patients remain relatively more difficult to cure. These include patients infected with type 3 HCV and with advanced liver disease. In the UK, up to half of all people infected with HCV have type 3 virus. Standard treatment in the UK for patients with type 3 HCV and advanced liver disease is a 12 week course of sofosbuvir/velpatasvir (trade name Epclusa). It is known that such patients may require an additional drug, ribavirin, to improve cure rates. However, ribavirin is associated with many unpleasant side effects such as anaemia (low blood count), tiredness, and cough. International guidelines recommend extending Epclusa treatment to 24 weeks in order to avoid ribavirin in patients who may not tolerate such side effects. Given the high costs of Epclusa it is important to have ways to identify which patients are best treated with the extended 24 weeks rather than standard 12 weeks. There is increasing evidence that early response on treatment predicts the likelihood of cure for some HCV therapies in type 3 virus infected patients – patients who clear the virus slowly during therapy are more likely to fail treatment. The aim of this study is to find out whether 24 weeks of Epclusa treatment improves cure rates compared to the standard duration of 12 weeks in patients who are slow responders to Epclusa treatment.

Who can participate?

Adults with genotype 3 HCV cirrhosis and a slow early response to Epclusa.

What does the study involve?

Patients who agree to participate are randomly allocated (by computer programme) to receive standard treatment (12 weeks of Epclusa) or extended treatment (24 weeks of Epclusa). The study looks at which treatment leads to a higher proportion of HCV cure. Participants are

reviewed monthly with blood tests monitoring, until three months after end of treatment, to determine through blood tests if HCV cure has been achieved.

What are the possible benefits and risks of participating?

Participants allocated to the extension treatment may benefit from an improved chance of cure, however this is not known for sure. There is a small risk of pain or bruising from blood testing.

Where is the study run from?

- 1. Royal London Hospital (UK)
- 2. King's College Hospital (UK)
- 3. St George's Hospital (UK)
- 4. Royal Free Hospital (UK)
- 5. North Manchester General Hospital (UK)
- 6. Chelsea & Westminster Hospital (UK)

When is the study starting and how long is it expected to run for? January 2015 to July 2019 (as of 08/10/2018)

Who is funding the study? National Institute for Health Research (UK)

Who is the main contact?
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Contact information

Type(s)

Public

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Additional identifiers

EudraCT/CTIS number

2016-000599-87

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers

33488

Study information

Scientific Title

Response guided therapy with sofosbuvir and velpatasvir for 12 or 24 weeks in patients with genotype 3 chronic hepatitis C virus: is longer therapy worthwhile?

Acronym

Extend-3

Study objectives

The aim of this study is to evaluate cure rates in patients with genotype 3 HCV cirrhosis and a slow early response to Epclusa, to evaluate if 24 weeks is better than 12 weeks of treatment.

Ethics approval required

Old ethics approval format

Ethics approval(s)

London-West London & GTAC REC, 22/11/2016, ref: 16/LO/0879

Study design

Randomised; Interventional; Design type: Treatment, Drug

Primary study design

Interventional

Secondary study design

Randomised controlled trial

Study setting(s)

Hospital

Study type(s)

Treatment

Participant information sheet

See additional files

Health condition(s) or problem(s) studied

Specialty: Hepatology, Primary sub-specialty: Hepatology; UKCRC code/ Disease: Infection/ Sequelae of infectious and parasitic diseases, Infection/ Viral hepatitis

Interventions

A total of 60 patients will be randomized (between weeks 8-12) to receive a total of 12 weeks of sofosbuvir/velpatasvir treatment (standard therapy) or 24 weeks of sofosbuvir/velpatasvir (extended therapy which is being studied in the trial). There will be 30 patients in each treatment group (1:1). Block randomization will be performed and participants stratified by compensated or decompensated cirrhosis at baseline.

Follow up is the same for both treatment groups – patients will be seen once/ month until 3 months after treatment end. At this point, SVR rates will indicate if the patient has been cured of hepatitis C virus infection.

Intervention Type

Drug

Phase

Not Applicable

Drug/device/biological/vaccine name(s)

Sofosbuvir, velpatasvir

Primary outcome measure

Proportion of patients in each group (12 or 24 weeks of sofosbuvir/velpatasvir) with undetectable HCV RNA (below limit of quantification up to 15 IU/mL) in serum at 12 weeks (+ 4 weeks) after end of treatment (SVR12).

Secondary outcome measures

- 1. Proportion of patients in each group requiring premature treatment discontinuation, reported in patient notes, throughout the treatment period
- 2. Proportion of patients in each group who developed serious adverse events, reported in patient notes, throughout the trial period
- 3. Quality of life, measured as SF36 questionnaire scores, in each treatment group at end of study treatment and end of study follow-up (12 weeks post-treatment end)

Overall study start date

01/01/2015

Completion date

04/07/2019

Eligibility

Key inclusion criteria

- 1. Voluntarily signed informed consent form
- 2. Aged 18 years or older
- 3. Chronic HCV infection, defined by anti-HCV antibody or HCV RNA detection for greater than 6 months
- 4. Infected with genotype 3 HCV (identified by referring hospital)
- 5. Meets NHS England treatment criteria to commence sofosbuvir/velpatasvir
- 6. Pre-treatment HCV RNA >10,000 iu/mL (can be any time before treatment week 0)
- 7. HCV RNA > or equal to 30 iu/mL at treatment week 2 (+/- 3 days)
- 8. Has cirrhosis defined by: evidence of portal hypertension, OR APRI >2 plus AST:ALT ratio >1, OR radiological evidence of cirrhosis, OR fibroscan score >11.5kPa, OR liver biopsy showing cirrhosis
- 9. Patients with decompensated cirrhosis (variceal bleeding, ascites and encephalopathy) can be included
- 10. Patients with malignancy including hepatocellular carcinoma can be included
- 11. Patients with liver transplant can be included
- 12. Patients coinfected with chronic hepatitis B virus or human immunodeficiency virus can be included
- 13. Female subjects of childbearing potential must have documented negative pregnancy test prior to enrolment (negative urinary pregnancy test), and if engaged in heterosexual intercourse must use protocol specified method of contraception (see below) during study drug treatment and for 30 days after last dose
- 14. Male subjects engaged in heterosexual intercourse with a female of childbearing potential should protocol specified method of contraception during study drug treatment and for 30 days after last dose

Participant type(s)

Patient

Age group

Adult

Lower age limit

18 Years

Sex

Both

Target number of participants

Planned Sample Size: 60; UK Sample Size: 60

Total final enrolment

25

Key exclusion criteria

- 1. Any of the above inclusion criteria not met
- 2. Any of the following criteria excludes a subject from enrolling into this study
- 3. Clinically-significant medical or psychiatric illness (other than chronic HCV) in the past, present, or being evaluated, that may interfere with participant treatment, safety, assessment or compliance with the protocol.
- 4. Severe renal impairment with eGFR <30 mL/min/1.73m2 or requiring dialysis
- 5. Alcohol consumption or illicit drug abuse likely to interfere with participant treatment, safety, assessment or compliance with protocol, as deemed by the investigator
- 6. Previous exposure to sofosbuvir (or other NS5B inhibitor) or NS5A inhibitor
- 7. Severe allergy to study drugs, its metabolites or formulation excipient (see SmPC for details)
- 8. Any investigational medicinal product ≤ 6 weeks prior to treatment start
- 9. Pregnant or nursing female, or males wishing to conceive during the period of study treatment + 30 days after
- 10. Patients who adhered to less than 90% of prescribed sofosbuvir/velpatasvir at screening
- 11. In accordance with the SmPC of sofosbuvir/velpatasvir concomitant use of the following medications are contraindicated:
- 11.1. Anticonvulsants carbamazepine, phenytoin, phenobarbital, oxcarbazepine
- 11.2. Antimycobacterials rifampicin, rifabutin, rifapentine
- 11.3. Antiretrovirals efavirenz
- 11.4. St John's wort
- 11.5. Modafinil
- 11.6. Proton-pump inhibitors should be avoided and if necessary, should be administered 4 hours after at maximum doses equivalent to 20mg omeprazole per day
- 11.7. Amiodarone should be avoided and if necessary, close monitoring is required
- 12. Using effective contraception if of child-bearing potential

Date of first enrolment

05/04/2017

Date of final enrolment

01/10/2018

Locations

Countries of recruitment

England

United Kingdom

Study participating centre Royal London Hospital

Whitechapel Road London United Kingdom E1 1BB

King's College Hospital

Denmark Hill London United Kingdom SE5 9RS

Study participating centre St George's Hospital

Blackshaw Road London United Kingdom SW17 0QT

Study participating centre Royal Free Hospital

Pond Street London United Kingdom NW3 2QG

Study participating centre North Manchester General Hospital

Delaunays Road Crumpsall Manchester United Kingdom M8 5RB

Study participating centre Chelsea & Westminster Hospital

369 Fulham Road Chelsea London United Kingdom SW10 9NH

Sponsor information

Organisation

Queen Mary University of London

Sponsor details

Joint Research Management Office QM Innovation Building 5 Walden Street London England United Kingdom E1 2EF +44 (0)20 7882 7260 sponsorsrep@bartshealth.nhs.uk

Sponsor type

University/education

ROR

https://ror.org/026zzn846

Funder(s)

Funder type

Government

Funder Name

National Institute for Health Research

Alternative Name(s)

National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type

Government organisation

Funding Body Subtype

National government

Location

United Kingdom

Results and Publications

Publication and dissemination plan

Planned publication in a high-impact peer reviewed journal, around 1 year after trial end.

Intention to publish date

04/07/2020

Individual participant data (IPD) sharing plan

The datasets generated during and/or analysed during the current study will be stored in a non-publically available repository: Discovere (available at www.discoverecert.cerner.co.uk). Access can be granted to representatives from the Sponsor, host institution and regulatory authorities.

IPD sharing plan summary

Stored in non-publicly available repository

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	version v1.4	23/11/2016	16/03/2017	No	Yes
Basic results		05/07/2020	18/01/2021	No	No
Protocol file	version 2.9.3	13/11/2016	05/10/2022	No	No
HRA research summary			28/06/2023	No	No