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Nucleos(t)ide withdrawal in Hepatitis B virus infection (NUC-B)

Submission date	Recruitment status	[X] Prospectively registered
07/11/2016	No longer recruiting	[_] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
11/11/2016	Completed	[_] Results
Last Edited	**Condition category**	[_] Individual participant data
31/01/2025	Infections and Infestations	[X] Record updated in last year

Plain English summary of protocol

Background and study aims
Hepatitis B is a type of liver disease, which is caused by the hepatitis C virus (HBV). It can present as either a severe infection with a short duration (acute) or a persistant long term infection (chronic). If a person has a chronic HBV infection, over time the virus causes the liver to become irreversibly scarred (cirrhosis), eventually leading to liver failure. There are two main drug treatments available for treating a chronic HBV infection: interferons or nucleoside/nucleotide analogues. Interferons can have a lot of unpleasant side effects and rarely results in a cure so most patients choose to be treated with nucleoside/nucleotide analogues. Although these daily tablets have no side effects, most people using this treatment will need to continue taking them for the rest of their life. There is evidence from a recent study that if treatment with nucleoside /nucleotide analogues is stopped after a few years of treatment, some patients may be able to eliminate the virus. The aim of this study is to confirm the findings from this earlier study by seeing if stopping nucleoside/nucleotide analogue treatment can be safely stopped and lead to a cure.

Who can participate?
Adults with a long-term Hepatitis B infection who have been undergoing treatment with nucleoside/nucleotide analogues for less than 3 years.

What does the study involve?
Participants are randomly allocated to one of two groups. Those in the first group stop their nucleoside/nucleotide analogue treatment at the start of the study. Those in the second group stop their nucleoside/nucleotide analogue treatment at the start of the study for four weeks, before starting a course of interferon weekly injections for 16 weeks. After this, all treatment is stopped. Participants in both groups attend the clinic at regular intervals over the next three years and provide blood samples to test for signs of HBV.

What are the possible benefits and risks of participating?
There is a chance that stopping nucleoside/nucleotide analogue treatment (with or without interferon treatment) may allow the patient to be cured. There is a risk that participants may experience withdrawal symptoms when stopping their treatment or that they experience a worsening of their hepatitis (hepatitis flare) as the virus starts to replicate again.

Where is the study run from?
Ten NHS hospitals in England (UK)

When is the study starting and how long is it expected to run for?
June 2016 to August 2024

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

Who is the main contact?
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Contact information

Type(s)
Scientific

Contact name
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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
32555

Study information

Scientific Title
Nucleos(t)ide withdrawal in HBeAg negative hepatitis B virus infection to promote HBsAg clearance (NUC-B)

Study objectives

The aim of this trial is to explore whether finite treatment with nucleos(t)ide analogues is feasible in patients with HBeAg (Hepatitis B ‘e’ antigen) negative chronic HBV (Hepatitis B Virus) infection.

Ethics approval required
Old ethics approval format

Ethics approval(s)
London - Central Research Ethics Committee, 26/08/2016, ref: 16/LO/1318

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
Not available in web format, please use the contact details below to request a patient information sheet

Health condition(s) or problem(s) studied
Specialty: Hepatology, Primary sub-specialty: Hepatology; UKCRC code/ Disease: Infection/ Viral hepatitis

Interventions
Patients will be electronically randomised using the InForm eCRF online custom built database to the two management arms in equal proportions using variable block sizes.

Control Arm: Patients will discontinue their nucleos(t)ide analogue treatment at baseline and be followed up for 3 years from randomisation.

Interferon Arm: Patients will discontinue their nucleos(t)ide analogue treatment at randomisation. No treatment will be given for 4 weeks, and then (i.e after the 4 week gap) patients will start pegylated interferon 180 mcg 2a and continue taking it weekly for a total of 16 weeks. They will then stop ALL treatment and be followed up for 3 years from randomisation.

During the follow-up the patients are required to attend the clinic at specified intervals so that their safety can be monitored throughout the study. At each of the visits, patients will have their vital signs checked and give blood samples. The blood samples will be used to measure levels of certain blood chemicals and thus evaluate the patient’s liver function, the levels of HBV in the their body and their body’s ongoing response to the HBV infection. The laboratory tests will

allow us to evaluate the effects, on both the patient and the HBV levels in their body, of withdrawal from treatment and/or introduction of interferon treatment.

Intervention Type
Other

Phase
Phase II

Primary outcome measure
HBsAg (Hepatitis B surface antigen) is measured using standard laboratory ELISA assays at baseline and 3 years.

Secondary outcome measures
1. Efficacy is assessed at various timepoints after randomisation using various laboratory evaluations including immunology, virology and hepatology assessments. Specifically looking at the following:
1.1. The proportion of patients who achieve HBsAg loss who also have undetectable HBV DNA
1.2. The proportion of patients in each group who become inactive HBV carriers; i.e. achieve a sustained virological response (HBV DNA < 2000 IU/ml & normal ALT values) at 3 years
1.3. Magnitude of reduction in quantitative HBsAg levels at 1, 6, 12, 24 and 36 months
1.4. Magnitude of changes in antiviral T cells response at 1, 5, 6, 12, 24 and 36 months
1.5. Magnitude of changes in NK cells response at 1, 5, 6, 12, 24 and 36 months
2. Safety is assessed at various timepoints after randomisation using various laboratory evaluations. Specifically looking at the following:
2.1. The proportion of patients who achieve HBsAg loss who also have undetectable HBV DNA
2.2. The proportion of patients in each group who become inactive HBV carriers; i.e. achieve a sustained virological response (HBV DNA < 2000 IU/ml & normal ALT values) at 3 years
2.3. Magnitude of reduction in quantitative HBsAg levels at 1, 6, 12, 24 and 36 months
2.4. Magnitude of changes in antiviral T cells response at 1, 5, 6, 12, 24 and 36 months
2.5. Magnitude of changes in NK cells response at 1, 5, 6, 12, 24 and 36 months

Overall study start date
01/06/2016

Completion date
31/08/2024

Eligibility

Key inclusion criteria
1. Aged 18 years and over
2. Chronic HBV infection
3. HBeAg negative
4. Nucleos(t)ide analogues treatment for ≥3 years
5. HBV DNA < 400 IU/ml ≥2 years
6. Informed consent

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
Planned Sample Size: 240; UK Sample Size: 240

Key exclusion criteria
1. Cirrhosis at any time
2. HBeAg to anti-HBe seroconversion within the last 3 years
3. Interferon use in the last 3 years
4. Contraindications to interferon use
5. Participation in HBV-specific therapeutic vaccine studies within 12 months
6. HCV, HDV or HIV co-infection
7. Immunosuppressant use
8. Clinically significant comorbidities that, in the opinion of the investigator, render the patient unsuitable

Date of first enrolment
30/11/2016

Date of final enrolment
30/07/2018

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
St Mary's Hospital
Department of Hepatology
10th Floor
QEQM Building
London
United Kingdom
W2 1NY

Study participating centre

Kings College Hospital
Institute of Liver Studies
Denmark Hill
London
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SE5 9RS

Study participating centre
The Royal London Hospital
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Study participating centre
Nottingham Hospital
QMC Campus
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Study participating centre
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Liver Services
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Study participating centre
St George's Hospital
Blackshaw Road
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Study participating centre
Queen Elizabeth Medical Centre
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B15 2TH

Study participating centre
St. James's University Hospital
Beckett Street
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LS9 7TF

Study participating centre
Manchester Royal Infirmary
Oxford Road
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M13 9WL

Study participating centre
Freeman Hospital
Freeman Road
High Heaton
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NE7 7DN

Sponsor information

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Sponsor type
University/education

ROR
https://ror.org/041kmwe10

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
Results will be disseminated at scientific meetings and through publications in relevant scientific journals.

Intention to publish date
28/02/2025

Individual participant data (IPD) sharing plan
The datasets generated and/or analysed during the current study during this study will be included in the subsequent results publication.

IPD sharing plan summary
Other

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			26/07/2023	No	No