A single-center, double-blind, randomized, phase I/II dose escalating study to assess the safety, tolerability and immunogenicity of three doses of the therapeutic synthetic long peptide (SLP) vaccine (ISA104) in patients with chronic hepatitis B (cHBV).

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This study has been transitioned to CTIS with ID 2024-518355-36-00 check the CTIS register for the current data. Primary objective:- To determine the safety and optimal dose of three doses of a novel therapeutic vaccine (ISA104) consisting of 12…

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

Summary

ID

NL-OMON51362

Source
ToetsingOnline

Brief title
HEB-PEP

Condition

- Viral infectious disorders

Synonym
cHBV, chronic hepatitis B

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: ISA Therapeutics BV,TKI-LSH financiering en ISA therapeutics

Intervention

Keyword: Hepatitis B, Phase I/II, Synthetic long peptides, Vaccination

Outcome measures

Primary outcome

Safety:

Safety assessments will be performed as specified in the Schedule of

Assessments (Table 1, page ..), and will include monitoring and recording of

AEs, including SAEs; measurement of protocol specified laboratory assessments

and vital signs; and other protocol-specified tests that are deemed critical

for the safety evaluation of the study. NCI-CTCAE version 5.0 will be used.

Secondary outcome

To assess the immunogenicity of ISA104 with the use of additional

non-standardized assays:

In the supernatant of the IFN-y ELISpot assay different cytokines will be

measured (e.g. IFN-y, TNF-α, IL-2) in response to the SLPs by

ELISA/multiplex/Luminex

Serum IgG antibody titers against the vaccine SLP will be measured on patient

serum with the use of a conventional ELISA

By expanding PBMC with a pool of peptides with amino acid sequences contained

within the vaccine, followed by single peptide restimulation and flow cytometry analysis, we will pinpoint the specificity and functionality of vaccine-induced T cells

To determine the quality and define specificity of vaccine-induced HBV-specific T-cells in cHBV patients:
The quality of ISA104 specific T-cells and T-cells recognizing non-vaccine HBV antigens or irrelevant antigens will be assessed.

To study novel HBV disease markers in the study patient population to assist with treatment decisions and/or therapy response monitoring in general:
At different time points plasma levels of HBcrAg and (pg)RNA will be measured.

Study description

Background summary

Despite an effective prophylactic vaccine, chronic Hepatitis B virus infection (cHBV) is a tremendous global health burden with 250 million patients worldwide- amongst these 40.000 in the Netherlands. Many patients suffering from cHBV develop life-threatening liver disease, including cirrhosis and liver cancer. Currently, no effective treatment exists. Available viral replication inhibitors suppress replication but are neither able to abort viral infection (including viral protein synthesis), nor can they reduce cancer risk. There is , therefore, a definite medical need for a therapy that can reinforce effective immunity to the hepatitis B virus. Therapeutic vaccines may fill this position by achieving viral control and clearance through induction of potent anti-viral adaptive immune responses. There are only few disease markers in cHBV and so monitoring of response to therapy and treatment decisions are based on limited information. In that context a panel of novel disease markers will be investigated in the institution*s patient population in order to support clinical treatment decisions and monitor the clinically relevant course of

events.

Study objective

This study has been transitioned to CTIS with ID 2024-518355-36-00 check the CTIS register for the current data.

Primary objective:
- To determine the safety and optimal dose of three doses of a novel therapeutic vaccine (ISA104) consisting of 12 synthetic long peptides, as well as an adjuvant agent (AmplivantTM), in patients with chronic hepatitis B (cHBV), receiving standard of care maintenance anti-viral therapy.

Secondary objectives:
- To assess the immunogenicity of ISA104 with the use of standardized assays
- To assess the efficacy of ISA104 with the use of conventional viral parameters.

Exploratory objectives
- To assess the immunogenicity of ISA104 with the use of additional non-standardized assays.
- To determine the quality and define specificity of vaccine-induced HBV-specific T-cells in cHBV patients.
- To study novel HBV disease markers in the study patient population to assist with treatment decisions, and/or therapy response monitoring in general.

Study design

This is a single-centre, randomized, double-blind, multi-cohort, phase I/II dose escalation study. Patients with cHBV (negative for HBeAg) receiving at least 12 months* standard of care anti-viral maintenance therapy (tenofovir- or entecavir- containing therapy), and showing suppressed virus replication for at least 6 months (no detectable HBV DNA) will be enrolled in 3 cohorts, to include 24 patients in total. If the vaccination is determined to be safe and immunogenicity is found in the majority of patients, after the highest safe and tolerable dose of three doses has been established, an expansion cohort of 12 patients will be included. The intended maximal total treatment duration is 9 weeks. The first 8 patients will be enrolled in cohort 1, the next 8 patients in cohort 2, the next 8 patients in cohort 3. Patients will be treated with either ISA104 (6 patients per dosing cohort) or a saline solution placebo (2 patients per dosing cohort) every three weeks. In total participating patients are to receive three rounds of treatment. The total treatment duration is 9 weeks. The decision to start enrollment at the next dose level will be made after the safety data of the first 6 (out of 8 patients in each dosing cohort) have been analyzed, and no dose limiting toxicities have occurred; this will take place one week after the 6th patient has received 3 doses of

ISA104/placebo in the current dose cohort. If dose limiting toxicities have occurred at most in one of these 6 patients safety data the decision to start enrollment at the next dose level will be made after the safety data of the full cohort of 8 patients have been analyzed and in only 1 out of these 8 patients dose limiting toxicity occurred.
The clinical Principal Investigator (PI) will be given the task to study individual patient data related to baseline characteristics, safety and study medication administered for these patients, summarize findings, and give a recommendation whether or not to endorse the start of enrolment at the next dose level. The summary and recommendation from the PI, including all necessary individual patient background material, will be reviewed and the PI will issue a written approval (or disapproval) regarding the start of enrollment into the next dose cohort.
No dose limiting toxicities (DLTs) are anticipated based on previous clinical studies with synthetic long peptide vaccines.

Intervention

In total 24 patients will be treated with either ISA104 or a normal saline (0.9% saline) placebo. 18 patients will receive ISA104 consisting of 12 SLPs and Amplivant (AV), which will be administered every three weeks for a total of three rounds of vaccination. Six patients in total will receive an intradermally administrated placebo. Patients receive either 10, 20, or 40 µg ISA104 at 3 time points i.e. at baseline (day 0), day 21 and day 42. In addition to the vaccinations, patients will undergo 8 additional blood draws (venapuncture) and two leukaphereses for assessing clinical parameters, viral load, novel biomarkers, and for collection of samples for monitoring immune responses.

Study burden and risks

Currently the only effective drugs in the treatment of HBV are nucleotide/-side analogs (NAs). These drugs suppress viral replication but do not eradicate the virus. Treatment with NAs decreases the risk of cancer- by only 50%. Treatment is lifelong. Because of the increased cancer risk and lifelong treatment, patients need frequent outpatient clinical visits. Therefore, there is high medical need for treatments that can establish full viral immune control. The ultimate therapeutic goal of immunomodulation with ISA104 is complete viral clearance. Viral clearance will not only bring the need for life-long treatment with viral replication inhibitors to an end, but will also do away life-long outpatient appointments. Last but not least it will also reduce the risk of cirrhosis and liver cancer in a meaningful sense. Viral clearance will also diminish the psychosocial burden of patients with chronic HBV.
ISA104 consists of a set of 12 SLP*s that comprise amino acid sequences derived from the hepatitis B virus: these viral sequences are normally not expressed on human cells. However, the peptide vaccine has been designed to induce T-cell

reactivity to the hepatitis B virus and therefore also to hepatitis B infected hepatocytes. Candidates for this first in human trial will be patients who have HBeAg negative disease with long term viral suppression, and consequently have undetectable viral DNA.
It has been demonstrated in clinical trials with an HPV16 directed vaccine (ISA101b) (making use of the same vaccine platform) in cancer patients that peptide vaccination with this (ISA) technology has a very good safety profile in general. Specifically at the dose ranges between 20 and100 µg per peptide per injection there were only treatment emergent injection site reactions/ allergic reactions of NCI-CTC grades <2 (Melief et al, 2020). The majority of adverse reactions in the aforementioned clinical trial in cervical cancer patients were injection site reactions related to the use of the adjuvant Montanide-ISA-51, a mineral oil-based adjuvant very similar to incomplete Freund*s adjuvant; however, that adjuvant will not be used with ISA104 ISA 104 is contains a different adjuvant, called Amplivant, which is a modified version of the TLR-1/2 ligand Pam3Cys. In a rabbit toxicity assay Amplivant was shown to have a much milder local injection site toxicity profile compared to Montanide ISA-51, and this was repeated in a study with a different vaccine with Amplivant as adjuvant (Hespecta trial, data on file- ISA). As with all vaccines, systemic allergic reactions may occasionally occur, which can usually be treated with an anti-histamine.
In this phase I/II clinical trial patients will be asked to report for extra outpatient clinic visits and undergo extra peripheral blood draws and vaccinations specifically for this trial. These are minimally invasive procedures, and the associated risks are limited.
Patients will have adequate and appropriate check-ups during this study to monitor for potential (S)AEs and to minimize risk. The potential risks identified from earlier peptide vaccination studies are judged to be acceptable. Peripheral blood sampling will take place prior to each and after last vaccine administration. The risk of blood withdrawals is negligible.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

• Chronic HBV.
• Receiving treatment at the time of study entry and for greater than or equal to 12 months prior to study entry with HBV-active nucleos(t)ides, with tenofovir- or entecavir-containing therapy: tenofovir disoproxil fumarate (TDF), tenofovir alafenamide (TAF), or entecavir.
• Positive HBsAg for more than 6 months before screening.
• Negative for HBeAg for more than 6 months before screening.
• HBV DNA < limit of quantification (20 IU/ml; CAP-CTM Roche Cobas).
• Available serum ALT values (within 1x ULN) for 2 different time points 14 days apart during the six months before the first dose of study drug with at least one of the determinations obtained during the screening period.
• Available liver biopsy or fibroscan within 12 months before inclusion indicating F0-F1 fibrosis.
• Willing to comply with effective contraception during the study if subject is male or woman of child bearing potential, up to 12 months after the vaccine administration.
• Patients must be >= 18 and <= 55 years of age and must be able to give written informed consent.
• Body mass index (BMI) >= 18.0 and < 32.0 kg/m2.
• Ability to return to the hospital for adequate follow-up as required by this protocol.
• The ability to communicate well with the Investigator in the Dutch or English language.
• Written informed consent according to ICH-GCP.
• Willing to comply with the study restrictions.

Exclusion criteria

• Co-infection with HCV, HIV, HDV, HEV.
• Immune-compromised (known or expected immune deficiency, disease, or use of medication that may affect the immune system).
• History or other evidence of chronic airway or cardiac disease.
• History of a severe seizure disorder or current anticonvulsant use and clinically unstable disease.
• Unstable ongoing severe psychiatric disease, especially depression (stable patients can be included).
• Evidence of an active or suspected cancer or a history of malignancy where the risk of recurrence is >20% within 5 years.
• Current chronic, acute , or recurrent bacterial, fungal, or viral infection that is - in the opinion of the treating MD- serious and requires systemic therapy (within 30 days prior to screening).
• Major organ transplantation.
• Previously received any systemic anti-viral, anti-neoplastic, immunosuppressive or immuno-modulatory treatment other than Tamiflu, acyclovir for herpetic lesions or NUC (including supraphysiologic doses of steroids or radiation) within 3 months prior to inclusion or the expectation that such treatment will be needed at any time during the study.
• History of HDV, HAV, HIV. Determined as positive within 12 months before start of study for anti-HDV, anti-HAV IgM, anti-HIV.
• Patients who are expected to need systemic antiviral therapy other than that provided by the study or Tamiflu at any time during their participation in the study. Exception: patients who have had a limited (<7 day) course of acyclovir for herpetic lesions more than 1 month prior to inclusion are not excluded.
• Evidence of liver cirrhosis (Child Pugh A-B-C).
• Serum total bilirubin > 2xULN at screening.
• History or other evidence of bleeding from oesophageal varices or other conditions consistent with decompensated liver disease.
• History or other evidence of a medical condition associated with chronic liver disease other than HBV (e.g., hemochromatosis, autoimmune hepatitis, metabolic liver diseases including Wilson's disease and alfa1-antitrypsin deficiency, alcoholic liver disease, toxin exposures, thalassemia).
• Hepatic steatosis on ultrasound in the absence of conditions mentioned above and in the absence of liver fibrosis (histology or fibroscan F0-F1) and with elevated serum ALT.
• Women with ongoing pregnancy or who are breast feeding.
• Neutrophil count <1.500 cells/mm3 or platelet count <80.000 cells/mm3 at screening.
• Hemoglobin <7.1 mmol/L (<11.5 g/dL) for females and <7.8 mmol/L (<12.5 g/dL) for men at screening.
• Serum creatinine level >1.5xULN at screening.
• Patients with a value of alfa-fetoprotein >2xULN, unless stability (less than 10% increase) has been documented over at least the previous 3 months.

• Evidence of current hard drug(s) use and/or alcohol abuse (>20g/day for women and >30g/day for men)
• No other routine vaccination, nor booster vaccination, within 14 days before any treatment day or 14 days after a treatment day.
• Participation in an investigational drug, vaccine or device study* within 3 months prior to screening or more than 4 times a year.*Excluding studies comprising donation of body materials for biobanking or research only.
• Documented allergy to the vaccine or one of its components.
• History or other evidence of severe illness or any other conditions which would make the patient, in the opinion of the investigator, unsuitable for the study.
• Clinically significant abnormalities, as judged by the investigator, in laboratory test results (including blood chemistry, haematology and urinalysis). In the case of uncertain or questionable results, tests performed during screening may be repeated before randomization to confirm eligibility or judged to be clinically irrelevant for healthy subjects.
• Evidence of any other active or chronic disease (hematologic, renal, hepatic, cardiovascular, neurologic, endocrinal, gastrointestinal, oncologic, pulmonary, immunologic, or psychiatric disorders) or condition that could interfere with, or for which the treatment might interfere with, the conduct of the study, or that would pose an unacceptable risk to the subject in the opinion of the investigator (following a detailed medical history, physical examination, vital signs (systolic and diastolic blood pressure, and body temperature)). Minor deviations from the normal range may be accepted, if judged by the Investigator to have no clinical relevance.
• Asplenia.
• Loss or donation of blood over 500 mL within 1 month to screening or intention to donate blood or blood products during the study.
• Positive test for drugs or abuse at screening.
• Has body art (e.g. tattoos) or abnormalities that could interfere with the observation of injection site reactions.
• History of bleeding disorder (e.g. factor deficiency, coagulopathy, or platelet disorder requiring special precautions), significant bleeding or bruising following intramuscular injections or vena punctures, or currently receiving anticoagulants.
• Any known factor, condition, or disease that might interfere with treatment compliance, study conduct or interpretation of the results.

Study design

Design

Study type:	Interventional

Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	04-08-2023
Enrollment:	24
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	ISA104
Generic name:	Hepatitis B Virus (HBV) synthetic long peptide vaccine

Ethics review

Approved WMO

Date:	26-09-2022
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO

Date:	20-03-2023
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO

Date:	11-06-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO

Date:	21-06-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-04-2024
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-05-2024
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-08-2024
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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
EU-CTR	CTIS2024-518355-36-00
EU-CTR	CTIS2024-518355-36-01
EudraCT	EUCTR2022-002194-28-NL

Register	ID
CCMO	NL81713.078.22