A Phase 2 Study to Evaluate Efficacy, Safety and Tolerability of VIR-2218 and VIR-3434 in Participants with Chronic Hepatitis D Virus Infection (SOLSTICE)

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This study has been transitioned to CTIS with ID 2024-512203-40-00 check the CTIS register for the current data. The purpose of the study is to evaluate (1) the efficacy of monotherapy and combination VIR-2218 and VIR-3434 therapy in suppressing HDV...

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

Summary

ID

NL-OMON53856

Source
ToetsingOnline

Brief title
SOLSTICE

Condition

- Viral infectious disorders

Synonym
Chronic Hepatitis D Virus (HDV) Infection, Hepatitis D

Research involving
Human

Sponsors and support

Primary sponsor: Vir Biotechnology, Inc.

Source(s) of monetary or material Support: Vir Biotechnology;Inc

Intervention

Keyword: Chronic Hepatitis D Virus (HDV) Infection

Outcome measures

Primary outcome

Primary endpoints

- Proportion of participants with undetectable HDV RNA (< LOD) or >= 2 log10 decrease in HDV RNA from baseline and alanine aminotransferase (ALT) normalization (ALT < upper limit of normal [ULN]) at Week 24 (Cohorts 2 and 3 only)

- Treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs)

Secondary outcome

Secondary endpoints:

- Proportion of participants with undetectable HDV RNA (< LOD) or >= 2 log10 decrease in HDV RNA from baseline and ALT normalization at Week 12, Week 48, Week 72, Week 96, Week 144 and Week 192

- Proportion of participants with undetectable HDV RNA (< LOD) or >= 2 log10 decrease in HDV RNA from baseline at Week 12, Week 24, Week 48, Week 72, Week 96, Week 144 and Week 192

- Proportion of participants with undetectable HDV RNA (< LOD) at Week 12, Week 24, Week 48, Week 72, Week 96, Week 144 and Week 192

- Proportion of participants with HDV RNA < lower limit of quantitation (LLOQ) at Week 12, Week 24, Week 48, Week 72, Week 96, Week 144 and Week 192

- Change from baseline in HDV RNA at Week 12, Week 24, Week 48, Week 72, Week

96, Week 144 and Week 192

- Proportion of participants with ALT normalization at Week 12, Week 24, Week 48, Week 72, Week 96, Week 144 and Week 192

- Incidence of anti-drug antibodies (ADA) and titers of ADA to VIR-3434 at specified study visits up to Week 192 (for cohorts with VIR-3434)

- Change from baseline in liver fibrosis at Week 48, Week 96, Week 144, and Week 192

- Change from baseline in Model for End Stage Liver Disease (MELD) score at Week 12, Week 24, Week 36, Week 48, Week 60, Week 72, Week 84, Week 96, Week 144, and Week 192

- Change from baseline in Child-Pugh-Turcotte (CPT) score at Week 24, Week 48, Week 72, Week 96, Week 144, and Week 192

Study description

Background summary

Treatment options for HDV infection are limited to pegylated interferon alfa (PEG-IFNα) and, in some regions of the world, buleviritide (BLV). Limitations and poor efficacy of current agents highlights an unmet need for patients with chronic HDV infection in all stages of the disease.

This study aims to evaluate whether the combination of investigational therapies VIR-2218 and VIR-3434 in comparison to monotherapy treatment of each can achieve durable suppression of HDV in patients with chronic HBV/HDV infection. VIR-2218 is a small interfering ribonucleic acid (siRNA) associated with substantial reductions in HBsAg in patients with chronic HBV infection. VIR-3434 is a monoclonal antibody (mAb) targeting HBsAg with multiple potential mechanisms of action, including strong neutralizing activity to HDV and HBV and enhanced immunologic activity due to Fc domain engineering. Coadministration of VIR-2218+VIR-3434 has the potential to durably suppress HDV viremia, normalize liver inflammation, reverse or halt the progression of liver fibrosis and hepatic impairment, and improve the quality of life of persons with chronic HDV

infection.

Study objective

This study has been transitioned to CTIS with ID 2024-512203-40-00 check the CTIS register for the current data.

The purpose of the study is to evaluate (1) the efficacy of monotherapy and combination VIR-2218 and VIR-3434 therapy in suppressing HDV viremia and normalizing ALT in participants with varying degrees of liver fibrosis and compensated cirrhosis and (2) the safety of VIR-2218 and VIR-3434 in this population.

Primary objectives
- To evaluate the efficacy of VIR-2218 and VIR-3434 in participants with chronic HDV infection in Cohorts 2 and 3 only
- To evaluate the safety of VIR-2218 and VIR-3434 in participants with chronic HDV infection in each cohort

Secondary objectives
- To evaluate the efficacy of VIR-2218 and VIR-3434 in participants with chronic HDV infection on HDV RNA and ALT normalization in each cohort
- To assess the immunogenicity of VIR-3434 (for cohorts with VIR-3434)
- To assess the effects of VIR-2218 and VIR-3434 on liver fibrosis and hepatic function in each cohort

Study design

This is a Phase 2, multicenter, randomized, open-label study designed to evaluate the efficacy, safety and tolerability of VIR-2218 and VIR-3434 in noncirrhotic and cirrhotic CPT-A adult participants with chronic HDV infection on NRTI therapy.

The study will consist of cohorts receiving either VIR-2218 or VIR-3434 monotherapy or combination therapy. For Cohorts 1a and 1b, the study intervention treatment period with VIR-2218 and VIR-3434 is composed of 2 periods: Induction (12 weeks) and Maintenance (up to 84 weeks). For Cohorts 2a, 2b1, 2b2, and 2c, 3, and 5 the intervention period with VIR-2218 and VIR-3434 consists of the study intervention treatment period (up to 192 weeks). The study also includes two optional sub-studies collecting (1) liver tissue and (2) blood samples for PK studies.

Intervention

The research study includes 2 groups (or cohorts), and each group will contain participants with different levels of liver disease and will evaluate different

dosing schedules of the study drugs VIR-2218 and VIR-3434. Please refer to the protocol for a detailed table with information on Intervention groups and duration.

Study burden and risks

BURDEN:
Physical examination
ECG
Blood sampling
Urine sampling
Liver scan
Questionnaires
Pregnancy test
Liver biopsy

When participants experience ALT elevation meeting ECI criteria:
- Abdominal ultrasound, including doppler flow if available (CT or MRI is acceptable in place of ultrasound if clinically indicated)

RISK:
VIR-2218
Possible side effects of VIR-2218 include, but are not limited to:
• Changes in liver function/liver related blood tests: Since VIR-2218 targets the liver, there is a potential for liver injury. You will be carefully monitored throughout the research study for any signs of liver injury, including liver blood tests, and other potential symptoms of liver injury. Changes in liver related blood tests could be short term or may require research study discontinuation and possibly additional medical care. In an ongoing research study, 2 of 5 participants with chronic HDV had an increase in their liver function blood test results after receiving VIR-2218 as a single therapy (treatment for their HDV). These liver function blood test results returned to normal over time and did not result in permanent changes in their liver function.
• Immunogenicity: Is the creation of antibodies against which may affect VIR-2218. This means that if antibodies (products of the body's defense) against VIR-2218 are present, VIR-2218 may not work as well as expected and/or there may be unknown side effects.
• Injection site reactions: Pain or a local immune reaction (i.e., redness and/or swelling, at the injection site which can vary in severity) has occurred in participants with chronic HBV who have received VIR-2218 alone. These reactions were considered mild to moderate. If you experience a reaction, the injection site may be photographed to monitor the reaction over time. The photographs will not identify you and they will not include your face, only the injection site.
• Allergic reaction, which may or may not occur with any drug. Some symptoms of allergic reactions are:

• Rash
• Itching
• Wheezing, or difficulty breathing
• Dizziness or fainting
• Swelling around the mouth, tongue, throat or eyes
• A fast pulse and/or a drop in blood pressure
• Sweating

VIR-3434
Possible side effects of VIR-3434 include, but are not limited to:
• Changes in liver function/liver related blood tests: Since VIR-3434 targets a virus in the liver, there is a potential for liver injury. You will be carefully monitored throughout the research study for any signs of liver injury, including liver blood tests, and other potential symptoms of liver injury. Changes in liver related blood tests could be short term or may require additional medical care.
• Immune complex disease: Immune complexes are formed when antibodies (which are proteins that help the body fight infections) combine with antigens (which are foreign substances in the body). When a large amount of immune complexes are formed, they can be deposited throughout the body and cause problems with your organs. This may result in a variety of conditions, including but not limited to rash, joint pain, kidney injury, and stomach pain.
• Immunogenicity: Is the generation of antibodies against VIR-3434 which may affect VIR-3434. This means that if antibodies are present the drug may not work as well as expected and/or there may be unknown side effects.
• Hypersensitivity reactions: injection site reactions (pain, redness, itching and/or swelling, at the injection site which can vary in severity), and serious allergic reactions, which may be severe or life-threatening.
o These are potential risks associated with antibody treatments. The risk of developing such conditions after receiving VIR-3434 is unknown.
o Serious allergic reactions including anaphylaxis, which may or may not occur with any new experimental study drug. Some symptoms of allergic reactions are:
* Rash
* Itching
* Wheezing, or difficulty breathing
* Dizziness or fainting
* Swelling around the mouth, tongue, throat, or eyes
* A fast pulse and/or a drop in blood pressure
* Sweating

Possible risks of study procedures:
- Blood Draws and Injections: Having a drug injected or blood taken may cause some discomfort, bruising, minor infection, or bleeding.
- Ultrasound Scan: Gel from this procedure may be sticky but the test should not cause any pain or discomfort
- Magnetic Resonance Imaging (MRI): During this test, the patient will lie in a small, closed area inside a large magnetic tube. Some people are scared or

anxious in small places (claustrophobic). The MRI scanner makes loud banging noises while taking a measurement, so either ear plugs, or specially designed headphones may be used to reduce the noise. It is possible the that the MRI will be done with contrast (dye) to help them see the images from the scan more clearly. Possible risks of contrast can be found below.
- Contrast Dye (with MRI): If contrast (dye) is ordered with the MRI scan, it is given by injection into a vein (IV). The most commonly used contrast agent contains a material called gadolinium. About 1 in 100 people may notice discomfort, tingling or warmth in the lips, metallic taste in the mouth, tingling in the arm, nausea, or headache. These symptoms go away quickly. There is a small risk of an allergic reaction to gadolinium. However, a severe allergic reaction occurs in less than one in 300,000 people. The placement of the needle to give the contrast may cause minor pain, bruising and/or infection at the injection site.
- Computerized Tomography (CT) Scan: The cumulative radiation exposure from these tests is considered small and is not likely to adversely affect the patient or disease. However, the effects of radiation add up over a lifetime. It is possible that having several of these tests may add to your risk of injury or disease. It is possible to have the CT scan with contrast (dye) to help them see the images from the scan more clearly. Possible risks of contrast can be found below.
- Contrast Dye (with CT): If contrast (dye) is ordered with the CT scan, it is given by injection into a vein (IV) or the patient may be asked to drink oral contrast. Most CT contrast reactions (approximately 95%) are mild to moderate and most resolve themselves without treatment. There is a chance of developing an allergic reaction from the contrast material, which may cause symptoms ranging from mild itching or a rash to severe difficulty breathing, shock or rarely, death. The contrast material may also cause kidney problems.
For IV contrast: Patient may feel discomfort when the contrast material is injected. Patient may feel warm, flushed, get a metallic taste in the mouth or, rarely, may make them vomit or feel sick to the stomach. The placement of the needle to give you the contrast may cause minor pain, bruising and/or infection at the injection site.
For oral contrast: Patient may experience vomiting, nausea, cramping, bloating, constipation, or diarrhea after taking the contrast.

Genetic Testing: There is a risk that information about taking part in a genetic research study may influence insurance companies or employers regarding the patient's health. To further safeguard the privacy, genetic information obtained in this research study will not be placed in the medical record.

Taking part in a research study involving genetic research may also have a negative impact on family or other relationships.

The genetic testing could show the patient may be at risk for certain diseases. If others found out, it could lead to discrimination or other problems. However, it is very unlikely for patient or others to know the test results

from the genetic testing. The results are not part of the research study records and are not given to patient or study doctor.

HIV and hepatitis testing: The HIV t

Contacts

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Vir Biotechnology, Inc.

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Scientific
Vir Biotechnology, Inc.

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Age 1. Age >= 18 (or age of legal consent, whichever is older) to < 70 years at the time of screening Type of Participant and Disease Characteristics 2. Chronic HBV infection defined as a positive serum HBsAg, HBV DNA, or HBeAg on 2 occasions at least 6 months apart based on previous (within the past 12 months) or current laboratory documentation (any combination of these tests performed 6 months apart is acceptable) 3. On locally approved NRTI therapy for at least 12

weeks prior to Day 1 4. HBsAg > 0.05 IU/mL at screening 5. Positive HDV antibody for at least 6 months prior to screening and HDV RNA >= 500 IU/mL at screening 6. Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) > ULN and < 5 x ULN Weight 7. Body Mass Index (BMI) >= 18 kg/m2 to <= 40 kg/m2 Sex and Contraceptive/Barrier Requirements 8. Female participants must have a negative pregnancy test or confirmation of postmenopausal status. Postmenopausal status is defined as 12 months with no menses without an alternative medical cause (see Section 10.7 for additional details). Women of childbearing potential (WOCBP) must have a negative blood pregnancy test at screening and a negative urine pregnancy test on Day 1, cannot be breast feeding, and must be willing to use highly effective methods of contraception (Section 10.7) 14 days before study intervention administration through 48 weeks after the last dose of VIR-2218 or VIR-3434. Female participants must also agree to refrain from egg donation and in vitro fertilization from the time of study intervention administration through 48 weeks after the last dose of VIR-2218 or VIR-3434. 9. Male participants with female partners of childbearing potential must agree to meet 1 of the following contraception requirements from the time of study intervention administration through 48 weeks after the last dose of VIR-2218 or VIR-3434: documentation of vasectomy or azoospermia, or male condom use plus partner use of 1 of the contraceptive options listed for contraception for WOCBP (Section 10.7). Male participants must also agree to not donate sperm from the time of first study intervention administration through 48 weeks after the last dose of VIR-2218 or VIR-3434. Informed Consent 10. Capable of giving signed informed consent as described in Section 10.1.3, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol Other Inclusion Criteria 11. 12-lead electrocardiogram (ECG) within normal limits; or, with no clinically significant abnormalities at screening, as determined by the investigator. 12. Agrees not to donate blood during the duration of the study and for an additional 3 months after the last dose of study intervention. Cohort Specific Inclusion Criteria 13. Cohort 1 specific inclusion criteria • Noncirrhotic * Liver biopsy with METAVIR F0-F3 or Liver elastography (eg, Fibroscan®) < 12 kilopascal (kPa) within the 12 months prior to screening * Creatinine clearance (CLcr) >= 30 mL/min as calculated by the Cockcroft-Gault formula at screening * Platelet count > 150,000 cells/mm3 (/µL) • Cirrhotic * Liver biopsy with METAVIR F4 or Liver elastography (Fibroscan®) >= 12 kPa (Cohort 2) within the 12 months prior to screening * CLcr >= 60 mL/min as calculated by the Cockcroft-Gault formula at screening * CPT score of 5 or 6, inclusive at screening and at start of study 14. Cohorts 2a, 2b1, 2b2, 2c, 3 & 4 specific inclusion criteria • Noncirrhotic -Liver biopsy with METAVIR F0-F3 or Liver elastography (eg, Fibroscan®) < 12 kPa within the 12 months prior to screening -CLcr >= 30 mL/min as calculated by the Cockcroft-Gault formula at screening -Platelet count > 150,000 cells/mm3 (/µL) • CPT-A Cirrhotic -Liver biopsy with METAVIR F4 or Liver elastography (eg, Fibroscan®) >= 12 kPa within the 12 months prior to screening -CLcr >= 60 mL/min as calculated by the Cockcroft-Gault formula at screening -Platelet count > 90,000 cells/mm3 (/µL) -CPT score of 5 or 6, inclusive at screening and at start of study

*Alternatives to Fibroscan, eg, 2D-Shear Wave Elastography, can be allowed following approval of the sponsor
15. Cohort 5 specific inclusion criteria
• Noncirrhotic
* Liver biopsy with METAVIR F0-F3 or Liver elastography (eg, Fibroscan®)
< 8 kilopascal (kPa) within the 12 months prior to screening
* Creatinine clearance (CLcr) >= 30 mL/min as calculated by the Cockcroft-Gault formula at screening
* Platelet count > 150,000 cells/mm3 (/µL)
* HBsAg < 10,000 IU/mL

Exclusion criteria

Medical Conditions 1. History of clinically significant liver disease from non-HBV and non-HDV etiology as determined by the investigator 2. History of clinically significant immune complex disease as determined by the investigator 3. History of clinically significant autoimmune disorder as determined by the investigator 4. History of HBV-related extrahepatic disease, including but not limited to HBV-related rash, arthritis, or glomerulonephritis 5. History of allergic reactions, hypersensitivity, or intolerance to study intervention, its metabolites or excipients 6. Anti-HBs >10 mIU/L at screening 7. Corrected QT interval (QTc) > 450 milliseconds 8. ALT or AST >= 5x ULN 9. Total bilirubin > 2.0 mg/dL 10. Serum albumin < 30 g/L 11. Absolute neutrophil count < 1,000/mm3 (/µL) 12. International normalized ratio (INR) > 1.5 13. Hemoglobin < 8 g/dL 14. History of anaphylaxis 15. History of malignancy diagnosed or treated within 5 years (localized treatment of squamous or noninvasive basal cell skin cancers is permitted; cervical carcinoma in situ is allowed if appropriately treated prior to screening); participants under evaluation for malignancy are not eligible 16. History of or listed for bone marrow or solid organ transplant 17. Known active infection other than chronic HBV and HDV infection or any clinically significant acute condition such as fever (> 38° C) or acute respiratory illness within 7 days prior to Day 1 18. Coinfection with human immunodeficiency virus (HIV), hepatitis A virus (HAV), hepatitis C virus (HCV) or hepatitis E virus (HEV). Participants who are HCV antibody positive and HCV RNA negative are eligible. Participants who are HAV or HEV immunoglobulin M antibody (IgM) positive are not eligible. Participants who are asymptomatic and HAV or HEV immunoglobulin G antibody (IgG) positive are eligible. 19. Any clinically significant medical or psychiatric condition that may interfere with study intervention, assessment, or compliance with the protocol or otherwise makes the participant unsuitable for participation in the study, as determined by the investigator. Participants with controlled Diabetes Mellitus are eligible. 20. Acute or worsening chronic hepatitis, fluctuating or rapidly deteriorating hepatic function or use of any therapy known to exacerbate hepatic dysfunction in the opinion of the investigator. Prior/Concomitant

Therapy 21. Therapy with an immunomodulatory agent, IFN-α (eg, IFN-alfa-2a or IFN-alfa-2b, or pegylated IFN-alfa-2a or alfa 2b), immunosuppressants (eg, disease-modifying antirheumatic drugs), cytotoxic or chemotherapeutic agent, or chronic systemic corticosteroids within 6 months of screening. 22. Received an HDV active agent (including lonafarnib and bulevirtide) within 90 days or 5 half-lives (if known), whichever is longer, before study drug administration or are active in the Follow-Up period of another clinical study involving interventional treatment. Participants must also agree not to take part in any other interventional study at any time during their participation in this study, inclusive of the Follow-Up Period. 23. Receipt of an oligonucleotide (eg, siRNA, antisense oligonucleotide) with activity against HBV within 48 weeks before study drug administration 24. Receipt of VIR-3434 or any antibody targeting HBV or HDV within 24 weeks of first study drug administration Additional Exclusions 25. History or clinical evidence of alcohol or drug abuse within the 12 months before screening or a positive drug screen at screening unless it can be explained by a prescribed medication (the diagnosis and prescription must be approved by the investigator). Cannabis use is permitted. Additional Exclusions Criteria for Hepatically Impaired Participants 26. Participants requiring paracentesis > 1 time per month. 27. Participants with refractory encephalopathy or significant Central Nervous System disease as judged by the investigator. 28. History of gastric or esophageal variceal bleeding within the past 6 months. 29. Participants with Transjugular Intrahepatic Portosystemic Shunt (TIPS) placement. 30. Presence of hepatopulmonary or hepatorenal syndrome. 31. Presence of primary cholestatic liver diseases. 32. Inability or unwillingness to comply with dietary recommendations for liver cirrhosis and hepatic impairment as advised by the investigator and lifestyle considerations outlined in this protocol.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL
Recruitment status: Recruiting

Start date (anticipated):	01-11-2023
Enrollment:	4
Type:	Actual

Medical products/devices used

Registration:	No

Ethics review

Approved WMO Date:	19-10-2022
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	12-04-2023
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	11-07-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	30-08-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	26-02-2024
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	20-03-2024
Application type:	Amendment

Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	29-05-2024
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	17-07-2024
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

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	CTIS2024-512203-40-00
EudraCT	EUCTR2022-001993-78-NL
ClinicalTrials.gov	NCT05461170
CCMO	NL82432.000.22