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A first-in-human study of HMB-001 in patients with Glanzmann thrombasthenia

Submission date
24/09/2022

Recruitment status
No longer recruiting

Registration date
28/07/2023

Overall study status
Completed

Last Edited
28/07/2023

Condition category
Other

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[ ] Record updated in last year

Plain English summary of protocol

Background and study aims
Glanzmann thrombasthenia (GT) is a rare bleeding disorder, in which patients' bodies cannot properly form blood clots to stop bleeding. This leads to frequent bleeding, with many patients experiencing a bleed every day. This is a very serious disorder that, whilst rare (there are only around 150 patients in the UK), leads to regular and potentially life-threatening bleeding. These frequent bleeds also have a significant impact on an individual's ability to lead a normal life, often having to miss school or work.
While there are drugs currently available to help stop bleeding once it has occurred, there are no drugs currently available to effectively prevent bleeding from occurring. Hemab Therapeutics ApS is funding this research to evaluate the ability of a new drug, HMB-001, to help patients with GT. HMB-001 is a medicine intended to prevent and reduce bleeding events in patients with GT. This will be the first time HMB-001 will be given to humans, and the main goal of this trial is to look at the safety of the drug. In addition to determining how safe and well tolerated it is in humans, this clinical trial will also look at how long the drug will remain in the body (pharmacokinetics), how it affects the body (pharmacodynamics), and whether it works for preventing bleeding (efficacy).

Who can participate?
Adults with GT

What does the study involve?
This is a multicenter clinical trial conducted in the UK and can have up to 15 research sites. This trial plans to enrol a maximum of 57 male and female participants. The trial is comprised of two parts (Part A and Part B). Part A will include up to 21 participants and will evaluate a single dose of HMB-001. Part B will include up to 36 participants and will evaluate multiple doses of HMB-001. If a participant is recruited into Part A, they may also be able to enter into Part B of the study once they have completed Part A. Participants will be in the trial for approximately one and half years.

What are the possible benefits and risks of participating?
At the moment there are no treatments to prevent the bleeds caused by Glanzmanns thrombasthenia, only ways to manage them when they happen. Whilst there are expected to be

risks associated with taking part in the trial for HMB-001, everything possible has been done to control them. Participants in this trial will all have GT and so the benefit to them from finding better ways to treat the illness is expected to outweigh these risks.
Groups that represent individuals with GT have been important to the decisions made about this trial, particularly the advocacy organisation and patient community forum called Haemnet. Along with specialist doctors, they have already helped to design an approved trial that will gather the information needed for potential participants to take part in the HMB-001 trial.
The main risk expected from HMB-001 is that, rather than the blood being too slow to clot, it may cause participants to form a clot too easily. The potential impact of this could range from relatively minor changes that the participant would suffer no harm from, all the way through to clots in the heart, lungs, or brain that could potentially lead to death.
The risk of people forming these clots is thought to be minimal. HMB-001 will work in a similar way to a treatment called rFVIIa that is already used for people with GT and other, more common bleeding problems. RFVIIa is a well-understood medicine and has not been seen to frequently cause dangerous clots. In the rare cases where clots have been reported, they have been in patients who have had additional risks, like those undergoing major surgery.
To minimise the unlikely chance of a clot occurring, every potential participant will be reviewed by trained doctors to look for factors that increase their risk of forming a clot. If any are present, they will not be able to take part in the trial.
HMB-001 belongs to a type of medicines called monoclonal antibodies, these medicines work by mimicking the part of our immune system that recognises things that can do us harm. Over time, the participant's immune system may start to react to this by forming its own antibodies that attack HMB-001. This can cause the medicine to become less effective or to behave differently. To monitor for this, participants in all parts of the trial will have samples taken to check for these antibodies.
Finally, there are the risks associated with trial procedures. In particular, the trial for HMB-001 will involve a bleeding time assessment, this requires a small cut to be made on the individual's forearm with the help of local anaesthetic to numb the area. In people with a bleeding disorder such as GT, this can lead to prolonged bleeding and potentially the formation of a small scar. All bleeding time assessments will be conducted in a clinical setting by trained professionals. If the participant prefers not to undergo this specific test, they are able to opt-out. In addition to this, anyone with a history of allergy to local anaesthetic, or who has a tendency to form larger, troublesome scars will not have this test performed.
Participants will have the opportunity to individually discuss the risks and benefits involved in HMB-001 with a doctor familiar with the trial, this will take place during the informed consent process.
With regard to the burden of taking part in the trial for HMB-001, participants will be expected to attend seven visits to a clinic alongside a stay of five consecutive days. The trial has been designed to minimise the number of visits required, and where possible the exact day participants need to attend is made flexible by allowing their scheduled visit to occur between one and three days either side of it.
COVID-19 continues to pose a significant risk to certain individuals, and those with GT may be at a higher risk. To keep potential participants and other visitors safe, a lateral flow test will be performed before entering the clinic. If an individual tested positive, they would not be given HMB-001 and their involvement in the trial would be deferred. This is because COVID-19 is known to increase the risk from clots forming in the blood.
If any significant changes to the risks, benefits, or burden involved in the trial for HMB-001 emerge after participants enrol, they will be informed in a timely manner and asked whether they continue to consent to take part.

Where is the study run from?
Richmond Pharmacology Ltd (UK)

When is the study starting and how long is it expected to run for?
September 2022 to December 2023

Who is funding the study?
Hemab Therapeutics ApS (Denmark)

Who is the main contact?
Dr Ulrike Lorch, u.lorch@richmondpharmacology.com

Contact information

Type(s)
Principal investigator

Contact name
Dr Ulrike Lorch

Contact details
1a Newcomen Street
London Bridge
London
United Kingdom
SE1 1YR
+44 (0)2070425800
u.lorch@richmondpharmacology.com

Type(s)
Scientific

Contact name
Dr Catherine Rea

Contact details
Ole Maaløes Vej 3
Copenhagen
Denmark
2200
+44 (0)7974270125
catherine@hemab.com

Additional identifiers

Clinical Trials Information System (CTIS)
2022-001583-10

Integrated Research Application System (IRAS)
1006088

Protocol serial number

HMB001-CL101

Study information

Scientific Title
A Phase I/II, first-in-human, single and multiple ascending dose study to investigate the safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy of HMB-001 in participants With Glanzmann thrombasthenia

Study objectives
1. To evaluate how safe and well-tolerated single doses of HMB-001 are when given to participants with Glanzmann thrombasthenia
2. To evaluate how safe and well tolerated multiple doses of HMB-001 are when given to participants with Glanzmann thrombasthenia
3. To evaluate whether HMB-001 works for preventing bleeding (efficacy)
4. To characterise how long HMB-001 remains in the body (pharmacokinetics), how it affects the body (pharmacodynamics), if the human body reacts to HMB-001 (immunogenicity), and whether it works for preventing bleeding (efficacy) when single doses are given to participants with Glanzmann thrombasthenia
5. To characterise how long HMB-001 remains in the body (pharmacokinetics) and if the human body reacts to HMB-001 (immunogenicity) when multiple doses of HMB-001 are given to participants with Glanzmann thrombasthenia

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 02/11/2022, London Bridge REC (Skipton House, 80 London Road, London, SE1 6LH, UK; +44 (0)2071048387; londonbridge.rec@hra.nhs.uk), ref: 22/LO/0615

Primary study design
Interventional

Study design
First-in-human single-dose multiple-ascending-dose study

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Glanzmann thrombasthenia

Interventions
The clinical trial is made up of the following parts:

Screening visit: Participants will be required to attend a screening visit scheduled within 28 days before the start of the clinical trial. Screening will be conducted over 1 day or may be divided into more than 1 day.

Run-in Observation Period or Historical Bleeding Data: In order to determine how often they usually experience bleeds, participants will be asked to either participate in an observation period lasting up to 3 months where the researchers will record information on bleeding symptoms in an electronic diary and come in for 3 study visits or they will be asked to provide an estimate of how often they have bled and how severe these bleeds have been over the past 3 months. Participants who already participated in Hemab's Natural History study (A Prospective, Observational Study of Bleeding and Quality of Life in Patients with Glanzmann Thrombasthenia in the United Kingdom Clinical) will not be required to do either.

Treatment Period: Participation in Part A of the study requires an in-patient period of 5 days and 4 nights. The in-patient stay may be extended if necessary for your safety. In Part A, participants receive a single dose of HMB-001 on the 2nd day of the in-patient stay.

Follow-up Period: In Part A, after you complete the in-patient stay, you will be required to return to the study site for six additional follow-up visits.

Standard safety assessments will be conducted during the clinical trial, including safety blood and urine laboratory tests, vital signs, physical examinations, ECG (electrocardiogram – electrical heart recording), telemetry/Holter (real-time heart monitoring), pharmacokinetics (measurement of medicine levels in the blood), pharmacodynamics (biological effects of the medicine) and observations of any adverse events (side effects).

The Research Doctor will be contactable 24 hours a day during the entire clinical trial in case you do not feel well or need any medical advice.
During participation in this clinical trial including follow-up visits, participants will be asked to not travel outside the UK without consent as the researchers may need to get in touch with them to attend additional visits that may need to be done at short notice.

Intervention Type
Drug

Phase
Phase I/II

Drug/device/biological/vaccine name(s)
HMB-001

Primary outcome(s)
Part A:
1. Safety assessed by the incidence of treatment-emergent adverse events (AEs) and changes in physical examinations, vital signs, clinical laboratory assessments, and ECG parameters.

Part B:
2. Safety assessed by the incidence of treatment-emergent AEs and changes in physical examinations, vital signs, clinical laboratory assessments, and ECG parameters
3. Preliminary prophylactic effect of HMB-001 as assessed via:
3.1. Frequency of major bleeds (defined as bleeding events requiring pharmacological treatment, transfusion, or surgical/interventional radiology intervention)
3.2. Frequency of minor bleeds (all other bleeding and bruising events)
3.3. Transfusion product use: Red blood cell, platelets, fresh frozen plasma, cryoprecipitate
3.4. Mean change in hemoglobin from baseline

3.5. Iron replacement therapy requirements: intravenous or oral
3.6. Factor Concentrate Use: Recombinant FVIIa
3.7. Tranexamic acid use

On Day 1 of their in-clinic stay, participants of Part A will receive a single dose of HMB-001 treatment and will then be monitored for safety by AE reporting, physical examinations, vital signs, laboratory tests, and ECGs. Blood samples for systemic PK and PD biomarkers will be collected. All AEs and SAEs will be recorded. Bleeding events will be recorded continuously using a custom-designed electronic application. Safety will be evaluated on an ongoing basis throughout the study. From the signing of informed consent, all SAEs and study procedure-related AEs will be recorded.

Key secondary outcome(s)

Part A:
1. Plasma concentrations of HMB-001
2. PK parameters including, but not limited to:
3. Maximum observed plasma concentration (Cmax)
3.1. Area under the curve from time zero to last quantifiable concentration (AUClast)
3.2. Incremental recovery (IncRec)
3.3. Area under the curve from time zero to extrapolated infinite time (AUCinf)
3.4. Time to reach maximum observed plasma concentration (Tmax)
4. Pharmacodynamic parameters including, but not limited to:
4.1. Maximum mean increase in FVII from baseline
4.2. Maximum mean decrease from baseline in prothrombin time (PT)
4.3. Maximum mean decrease from baseline in activated partial thromboplastin time (aPTT)
5. Preliminary prophylactic effect of HMB-001 as assessed via:
5.1 Frequency of major bleeds (defined as bleeding events requiring pharmacological treatment, transfusion, or surgical/interventional radiology intervention)
5.2 Frequency of minor bleeds (all other bleeding and bruising events)
5.3 Transfusion product use: Red blood cells, platelets, fresh frozen plasma, cryoprecipitate
5.4 Mean change in hemoglobin from baseline
5.5 Factor Concentrate Use: Recombinant FVIIa
5.6 Tranexamic acid use
6. Anti-drug antibody (ADA) formation

Part B:
7. Plasma concentrations of HMB-001
8. PK parameters including, but not limited to:
8.1. Cmax
8.2. AUClast
8.3. IncRec
8.4. AUCinf
8.5. Volume of distribution at steady state (Vss)
8.6. Tmax
9. ADA formation
10. Changes from Baseline in QOL assessment scores

Participants in Part B will receive multiple doses of HMB-001 treatment at intervals defined in Part A for a 3-month period beginning on Day 1 and will be monitored for safety by AE reporting, physical examinations, vital signs, laboratory tests, and ECGs. Blood samples for systemic PK and PD biomarkers will be collected. All AEs and SAEs will be recorded. Bleeding events will be recorded continuously using a custom-designed electronic application.

Completion date
17/12/2023

Eligibility

Key inclusion criteria
1. Male or female, aged 18 to 65 years, inclusive, at the time of signing informed consent
2. Glanzmann thrombocythemia:
2.1. Documented abnormal, diagnostic platelet aggregometry plus deficiency of the αIIbβ3 (GPIIb/GPIIIa) receptor via flow cytometry
2.2. Genetic diagnosis
3. Has not received a COVID-19 vaccine dose in the last 28 days. Has not received any live vaccine within 4 weeks of enrollment and is not planning to have a live vaccine during the study period.
4. Agrees to not receive COVID-19 vaccination throughout the dosing period and for 4 weeks after the final dose.
5. Has the ability to provide written, personally signed and dated informed consent to participate in the trial, in accordance with the International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guideline E6 (R2) (2016) and applicable regulations, before completing any trial-related procedures.
6. Has an understanding, ability, and willingness to fully comply with trial procedures and restrictions.
7. Women of child-bearing potential have a negative serum pregnancy test within 72 hours prior to the first dose of HMB-001.
8. Women of child-bearing potential agree to use highly effective contraceptive methods (excluding estrogen containing combined oral contraceptive pill as per exclusion criteria) and avoid egg donation for 14 days prior to Day 1, during the study treatment, and for 6 months after the last dose of HMB-001. A woman is considered to be of child-bearing potential unless she:
8.1. Has had a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy;
8.2. Is aged 50 years old and over and has been amenorrhoeic for ≥ 12 months (including no irregular menses or spotting) in the absence of any medication which induces a menopausal state and has documented ovarian failure by serum estradiol and follicle-stimulating hormone levels within the institutional laboratory postmenopausal range).
9. Men of child-producing potential agree to use highly effective contraceptive methods and avoid sperm donation for 14 days prior to Day 1, during the study treatment, and for 6 months after the last dose of HMB-001. A man is considered to be of child-producing potential unless he has had a bilateral vasectomy with documented aspermia or a bilateral orchiectomy.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Upper age limit
65 Years

Sex
All

Key exclusion criteria
1. Severe infection or inflammation at the time of Screening
2. History of clinically significant hypersensitivity associated with monoclonal antibody therapies
3. Personal history of venous or arterial thrombosis or thromboembolic disease
4. Known severe congenital or acquired thrombophilia
5. Has vital signs outside of the following normal range at Screening:
5.1 Supine heart rate <100 bpm (after at least 5 minutes of supine rest)
5.2. Blood pressure (BP): Supine BP (after at least 5 minutes of supine rest):
5.3. Systolic blood pressure: 90 - 140 mmHg
5.4. Diastolic blood pressure: 40 - 90 mmHg
6. Has a positive test for Hepatitis B surface antigen (HBsAg), Hepatitis C antibody (HCV Ab), or human immunodeficiency virus antibody (HIV Ab) at Screening
7. Is currently positive for COVID-19 based on lateral flow
8. Is within 6 weeks of COVID-19 infection
9. Other conditions that substantially increase risk of thrombosis by the discretion of the investigator including, but not limited to: significant family history, BMI >30 kg/m2 (moderately obese, adjusted for ethnicity), reduced mobility, active malignancy, major surgery within 6 weeks preceding first dose of study drug, post-partum within 12 weeks preceding first dose of study drug
10. Women who are using estrogen-containing medication or hormone modulators (within 8 weeks pre dose to 8 weeks post dose of study drug) including:
10.1. Combined oral contraception pill
10.2. Hormone replacement therapy (excluding transdermal patches)
10.3. Oestrogen receptor modulators (eg, Tamoxifen)
10.4. Gonadotropin releasing hormone receptor (GnRH receptor) agonist
11. Clinically significant cardiovascular disease including, but not limited to: New York Heart Association Class III or IV heart failure, coronary artery disease, uncontrolled arrythmia, moderate to severe valvular heart disease, peripheral vascular disease, and ischaemic stroke.
12. Other conditions that substantially increase risk of cardiovascular events by the discretion of the Investigator including, but not limited to: smoking, cocaine use, and uncontrolled hypertension.
13. Congenital or acquired bleeding disorders other than Glanzmann thrombocythemia.
14. Concurrent disease, treatment, medication, or abnormality in clinical laboratory tests that may pose additional risk in the opinion of the investigator and preclude the participant’s safe participation in and completion of the study.
15. Addiction or other diseases that prevent the participant from appropriately assessing the nature and scope of the clinical study or participating in study procedures by the discretion of the Investigator.
16. Received investigational medication in another clinical study within 5 half-lives before administration of the study drug.
17. Female participants who are pregnant (including a positive serum pregnancy test at Screening) or breastfeeding.

Date of first enrolment
02/11/2022

Date of final enrolment
17/12/2023

Locations

Countries of recruitment
United Kingdom

France

Netherlands

Study participating centre
Not provided at time of registration
United Kingdom
-

Sponsor information

Organisation
Richmond Pharmacology Ltd

Funder(s)

Funder type
Industry

Funder Name
Hemab Therapeutics ApS

Results and Publications

Individual participant data (IPD) sharing plan
The data-sharing plans for the current study are unknown and will be made available at a later date

IPD sharing plan summary
Data sharing statement to be made available at a later date