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A two-period study to investigate the safety, tolerability and effect of WVE-006 in healthy volunteers

Submission date
18/12/2023

Recruitment status
No longer recruiting

Registration date
18/12/2023

Overall study status
Completed

Last Edited
27/01/2026

Condition category
Other

[_] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
The purpose of this study was to investigate the study drug WVE-006. The overall objectives of this study were to determine the safety, tolerability (degree to which side effects of a drug can be tolerated) and amount of WVE-006 in the blood and urine when it was administered in different conditions, i.e. one versus many doses and at different dose strengths.

Who can participate?
A total of 47 participants were enrolled in this study with 46 fully completing. Participants were healthy adult males or females aged between 18 and 65 years.

What does the study involve?
The study had two Periods; Period 1 looked at a single dose of WVE-006 at increasing dose strengths and Period 2 selected a dose of WVE-006 from Period 1 that was given multiple times. The purpose of Period 1 was to evaluate WVE-006 when it was administered as a single dose at increasing dose strengths. Period 1 consisted of 4 groups of 8 participants and one group of 7 participants: each group evaluated a different dose of WVE-006 starting at the lowest dose and gradually increasing the dose level in each group. This is known as a single ascending dose (SAD) study. Each group received WVE-006 or a placebo (which contains no active drug) in the form of subcutaneous injection(s), which is a type of injection(s) into the tissue layer between the skin and muscle. Period 1 of the study consisted of a screening visit, one in-house stay (consisting of 4 days with 3 overnight stays) and up to 12 weekly return visits up to Day 85.
The purpose of Period 2 was to evaluate WVE-006 when it was administered at a selected dose strength once every other week for a period of 4 weeks (for a total of 3 doses). Period 2 consisted of 8 participants and the dose selected for administration in Period 2 was selected from a dose evaluated in Period 1 (evaluating different dose strengths of WVE-006 administered as a single dose on one occasion) which was considered to be safe and well tolerated. In Period 2, participants received WVE-006 or a placebo (which contains no active drug) in the form of subcutaneous injection(s) which is a type of injection(s) into the tissue layer between the skin and muscle. Period 2 of the study consisted of a screening visit, two in-house stays (consisting of 4 days with 3 overnight stays for the first in-house stay and 3 days with 2 overnight stays. This

period of the study also included 11 return visits up to Day 113.
Blood and urine samples were taken at set timepoints throughout each period of the study in order to measure the levels of WVE-006 in the blood and urine. The results from each of the dosing groups and each study period have been analysed in order to understand how WVE-006 works in the body (including impact from single and multiple doses, and different dose strengths).

What are the possible benefits and risks of participating?
Taking part in this study was not expected to provide participants with any direct medical benefit. However, the information we get from this study may help improve the treatment of alpha-1 antitrypsin deficiency.

Possible risks included the following:
Blood sampling:
During the course of the study, the volume of blood to be taken did not exceed 750 ml (equivalent to 1.5 pints). This is more than is given during a standard blood donation (approximately 470 mL). The volume taken was spread over a period of time (up to 85 and 113 days in each period) and participants were monitored for any potential side effects following blood sampling. The procedure for blood collection either by direct puncture or indwelling cannula may cause mild pain and bruising at the collection site. Placement of an indwelling cannula was proposed in order to minimise these effects for rapid PK sampling. Very rarely, a blockage of a vein or a small nerve injury can occur, resulting in numbness and pain. If this occurs, it will resolve with time. However, this was not observed in this study.

Blood pressure and pulse rate:
The participant's blood pressure and pulse were measured using an inflatable cuff which was placed on the arm. They may have experienced mild discomfort in the arm whilst the cuff was inflated.

Electrocardiogram (ECG):
Small sticky pads were placed on the participants' upper bodies before the ECG and an ECG machine measured the electrical activity of the participant's heart. Before the pads were applied, the skin was cleaned. Trained staff may have needed to shave/clip small patches of the participant's hair in these areas. Like Elastoplast® these sticky pads were uncomfortable to remove.

Holter recording:
This procedure may cause mild irritation, slight redness, and itching at the areas on the skin where the recording patches are placed. There is a possibility that the analysis of ECG measurements taken throughout the study may detect clinically significant abnormalities. If this is the case, then participants may be withdrawn from the study (if deemed appropriate by the Investigator) and referred for appropriate follow-up.

COVID-19 risks:
Participants were aware of the risks of exposure to COVID-19. When participants attended the clinical unit at each visit, they were asked to complete a self-declaration form and temperature check to confirm that they were not showing any early signs of COVID-19 infection and that they did not have any contact with individuals who were currently self-isolating or tested positive (dependent on risk mitigation measures employed at the clinical unit at the time of clinical conduct).
Participants may have been required to have a negative COVID-19 test prior to admission to the clinical unit for any overnight stays as defined within the study protocol. This procedure may

cause some mild discomfort in the nose or throat when the swab is being taken but this should resolve after the procedure has been completed.
Additionally, at the clinical unit, participants were asked to wear a facemask during procedures where clinical staff could not maintain a 2 m distance. It is noted that if participants had a medical exemption from wearing a face mask, they were not required to do so. In any circumstance, to prevent risk of transmission between staff and participants, all staff wore appropriate personal protective equipment, i.e., face masks, face shields etc, during the course of the study.

Harm to the unborn child:
Female participants of childbearing potential or male participants with a female partner of childbearing potential agreed to use a highly effective form of contraception from 28 days prior to Day 1 (first dose) until at least 16 weeks following the last dose of WVE-006 for female participants of childbearing potential and from Day 1 (first dose) until at least 24 weeks following the last dose of WVE-006 for male participants.

Drug administration:
It is possible that administration of the drug may have caused some mild discomfort, irritation, redness and bruising at the site of the injection but this should resolve within a couple of days. We monitored for any specific reactions at the injection site and provided appropriate treatment and care for these reactions as deemed necessary.

Throughout the study the health of the participants was regularly monitored and appropriate treatment for any medical condition was provided if required. All doctors employed by Simbec-Orion are trained and certified in Advanced Life Support Procedures in order to deal with a medical emergency. Nurses and other clinical staff were also trained in emergency procedures. Simbec-Orion also had an agreement with Prince Charles Hospital for referral of participants if required following a medical emergency.

Where is the study run from?
The study was conducted at Simbec-Orion Clinical Pharmacology Unit, an MHRA Phase I accredited CRO based in South Wales (UK)

When is the study starting and how long is it expected to run for?
November 2023 to February 2025

Who is funding the study?
Wave Life Sciences UK Limited (UK)

Who is the main contact?
Mara Kochaba, Wave Life Sciences UK Limited

Contact information

Type(s)
Public, Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
1008635

ClinicalTrials.gov (NCT)
NCT06186492

Protocol serial number
WVE-006-001

Study information

Scientific Title
A Phase I, randomized, double-blind, placebo-controlled, safety, tolerability, and pharmacokinetic study of single ascending doses and multiple doses of WVE-006 in healthy participants

Acronym
RestorAATion-1

Study objectives

The primary objective of this study was:
1. To evaluate the safety and tolerability of WVE-006.

The secondary objectives of this study were:
1. To evaluate the pharmacokinetic (PK) of WVE-006 after a single dose in healthy participants.
2. To evaluate the PK of WVE-006 after multiple doses in healthy participants.

Ethics approval required
Ethics approval required

Ethics approval(s)
1. approved 19/10/2023, Wales Research Ethics Committee 2 (Health and Care Research Wales, Castlebridge 4, 15-19 Cowbridge Road East, Cardiff, CF11 9AB, United Kingdom; +44 (0)2922 941119; Wales.REC2@wales.nhs.uk), ref: 23/WA/0236

2. approved 06/11/2023, MHRA (10 South Colonnade, Canary Wharf, London, E14 4PU, United Kingdom; +44 (0) 20 3080 6000; info@mhra.gov.uk), ref: CTA 51170/0010/001-0001

Study design
Two-part first-in-human trial in up to 56 healthy participants

Primary study design
Interventional

Study type(s)
Safety, Other

Health condition(s) or problem(s) studied
Healthy volunteers

Interventions
This was a double-blind, placebo-controlled, single ascending dose (SAD) and multidose Phase I study to assess the safety, tolerability, and PK of WVE-006 in healthy participants. Participants were randomised to WVE-006 or placebo.

Period 1: Single Ascending Dose
Period 1 evaluated single ascending doses of WVE-006 in 4 cohorts of 8 healthy participants and 1 cohort of 7 healthy participants. Each cohort included up to 6 WVE-006-treated and 2 placebo-treated participants (3:1 active:placebo) at different dose strengths.

Screening assessments were conducted during the Screening period (Day -28 up to Day -2). Participants received a single subcutaneous (SC) dose of WVE-006 or placebo on Day 1 and were then subsequently followed up across 12 return visits (Days 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, 78 & 85 – defined as the end of study visit).

Period 2: Multiple Doses
In Period 2, a single cohort of 8 healthy participants including up to 6 WVE-006 and 2 placebo-treated participants (3:1 active:placebo) received multiple doses of WVE-006 at a dose strength selected from doses evaluated in Period 1. Screening assessments were conducted during the Screening period (Day -28 up to Day -2). Participants received single SC doses of WVE-006 or placebo every other week (Q2W) over 4 weeks (total of 3 doses; Weeks 0, 2, and 4) and were

then subsequently followed up across 11 return visits (Days 8, 21, 36, 43, 50, 57, 64, 71, 78, 85 & 113 – defined as the end of study visit).

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
WVE-006 lyophilized powder for injection

Primary outcome(s)
The primary endpoints for this study were safety endpoints and were defined as follows:
1. Incidence of treatment-emergent adverse events (TEAEs), related TEAEs, severe TEAE, serious TEAEs
2. Changes in safety assessment parameters (i.e., physical exam, vital signs, clinical laboratory results, electrocardiograms (ECGs) (including any changes to QT interval corrected using Fridericia's formula [QTcF])
3. Tolerability based on incidence of discontinuation due to TEAEs

Timepoints:
Adverse Events (AEs) & Serious Adverse Events (SAEs):
AEs & SAEs were recorded from the point of informed consent up to the final post-study follow-up visit

Laboratory Safety Testing:
Period 1: Set timepoints from Screening until Day 85 (end of study visit)
Period 2: Set timepoints from Screening until Day 113 (end of study visit)

Vital Signs:
Period 1: Set timepoints from Screening until Day 85 (end of study visit)
Period 2: Set timepoints from Screening until Day 113 (end of study visit)

12-Lead ECG:
Period 1: Set timepoints from Screening until Day 85 (end of study visit)
Period 2: Set timepoints from Screening until Day 113 (end of study visit)

Key secondary outcome(s))
The secondary endpoints for this study were pharmacokinetic (PK) parameters derived from analysis of plasma samples for concentrations of WVE-006. Endpoints were defined as follows:
1. PK parameters of WVE-006 in plasma, including AUCinf, AUC0-24h, AUC0-48h, AUClast, Cmax, tmax
2. PK parameters of WVE-006 in plasma following the first and last doses, including AUCtau, AUC0-24h, AUC0-48h, AUClast, Cmax, tmax

Timepoints:
Plasma PK Sampling:
Period 1: 23 samples taken at set timepoints from Day 1 pre-dose to Day 85 (end of study visit)
Period 2: 34 samples taken at set timepoints from Day 1 pre-dose to Day 113 (end of study visit)

Completion date
13/02/2025

Eligibility

Key inclusion criteria
1. Participant is capable of understanding and be willing to provide written informed consent prior to any study-related procedures.
2. Participant is capable of understanding and adhering to all the requirements, procedures, instructions, and restrictions required by the protocol including scheduled visits, drug administration plan, laboratory tests, and likely to complete the study as planned.
3. Healthy as determined by the Investigator, based on a medical evaluation, including medical history, concomitant medications, full physical examination, vital signs, laboratory tests, and ECGs at Screening and Day -1. Per Investigator's judgement, there should be no evidence of cardiovascular, pulmonary, endocrine, hepatic, biliary, gastrointestinal, neurological, hematological, immunological, metabolic, skeletal, renal, psychiatric disorders, or cancer within the past 5 years prior to Screening Visit (except localized or in situ cancer of the skin). Clinical abnormality or laboratory parameter(s) outside normal range must not be clinically significant or unlikely to introduce additional risk to the participant nor interfere with the study procedures nor the interpretation of any of the study assessments.
4. Male or female healthy participants 18-65 years of age at Screening Visit.
5. Participant has a body mass index (BMI) between 18 to 32 kg/m2 inclusive at Screening and Day -1 Visits.
6. Genetic testing confirming PI*MM.
7. Participant has been a non-smoker for at least 1 year prior to screening and agrees to abstain from tobacco and nicotine containing products for the duration of the study.
8. Women of childbearing potential (WOCBP) must be:
8.1. Non-pregnant as determined by a negative serum pregnancy test at Screening and negative highly sensitive urine pregnancy test on Day -1.
8.2. Non lactating.
8.3. Agree to use a highly-effective method of contraception (as defined in Section 10.4) from 28 days prior to Day 1 and for at least 16 weeks following last study drug administration. Exception: Women exclusively engaging in same-sex sexual activities are not required to meet this criterion.
8.4. Must be willing to forgo ova (egg) donation for at least 16 weeks following the last study drug administration.
9. Women of non-childbearing potential are defined as meeting at least 1 of the following criteria:
9.1. At least 12 months post-menopausal and has an FSH >40 mIU/mL.
9.2. Surgically sterile, defined as having a documented bilateral oophorectomy, or hysterectomy.
10. Male participants must be willing to follow contraceptive requirements (as defined in Section 10.4) and should not impregnate anyone while they are in the study and for at least 24 weeks following the last dose of study drug. In addition, participant must be willing to forgo sperm donation for at least 24 weeks following the last dose of study drug. Men exclusively engaging in same-sex sexual activities are not required to meet this criterion.

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
Yes

Age group
Mixed

Lower age limit
18 years

Upper age limit
65 years

Sex
All

Total final enrolment
47

Key exclusion criteria
1. Participant has a history of multiple drug allergies or of allergic reaction to an oligonucleotide or to N-acetylgalactosamine (GalNAc).
2. Participant has a history of intolerance or any medical condition that might interfere with SC injection(s).
3. History or signs or symptoms of severe (bacterial, viral, parasitic, or fungal) infection within 4 weeks prior to Screening or Day 1 Visits.
4. History or signs or symptoms of an acute illness (including COVID-19) within 10 days prior to dosing on Day 1 Visit. Exception: mild seasonal allergies.
5. Positive COVID-19 test at time of Screening (if required per site SOP) and at Day -1 Visit.
6. Participant received a COVID-19 or any other vaccine within 14 days before dosing on Day -1 Visit or is scheduled for vaccination anytime during the study.
7. Participant has total bilirubin > upper limit of normal (ULN) though participants with documented Gilbert's syndrome with normal conjugated bilirubin are eligible; aspartate transaminase (AST) and/or alanine transaminase (ALT) >ULN at Screening and Day -1.
8. Participant has estimated glomerular filtration rate (eGFR) ≤60 ml/min/1.73mm2 (calculated by the Cockcroft-Gault formula) at Screening and Day -1.
9. Participant has a positive serology for hepatitis B or hepatitis C at Screening; participants with positive hepatitis B serology may be enrolled if there is evidence that the participant received HBV immunization.
10. Participant is known to be positive for human immunodeficiency virus (HIV) and/or positive serology for HIV 1/2 where testing is permitted per local regulations.
11. Participant has a history of regular alcohol consumption exceeding 14 standard drinks/week. 1 standard drink is equivalent to 14g ethanol or 5 US fluid ounces (fl oz) (150 mL) of wine (approximately 12% alcohol by volume), 12 fl oz (360 mL) of beer (approximately 5% alcohol by volume), or 1.5 fl oz (45mL) of hard liquor (approximately 40% alcohol by volume), within 1 year prior to the Screening Visit.
12. Participant has a history of caffeine consumption exceeding 8 cups of coffee/day (1 cup = 8 fl oz [240mL]) within 14 days prior to first study dose, or consumption of any caffeine or chocolate containing products for 3 days prior to clinical research unit (CRU) admission. Caffeine-containing food and/or beverages (e.g., tea, cola) should be considered equivalent to coffee.
13. Unwilling to abstain from alcohol for 48 hours prior to dosing at each of the dosing visits.
14. Participant has a positive alcohol test at Screening and/or Day -1 Visits.
15. Any prescribed or recreational substance use (irrespective of legality) within 6 months prior to screening or unwilling to refrain from such use for the duration of the study.
16. Positive drug screen at Screening and/or Day -1 Visits.

17. Positive cotinine test at Screening and/or Day -1 Visits.
18. Use of prescription or non-prescription medications, including vitamin, dietary, and herbal supplements (including St John's Wort) within 7 days or 5 half-lives (whichever is longer) prior to the first dose of study treatment unless, in the opinion of the Investigator and Sponsor, the medication will not interfere with interpretation of study assessments. Contraception and hormone replacement therapy (HRT) are permitted. If needed, over-the-counter (OTC) medications such as paracetamol/acetaminophen may be used acutely.
19. History of major surgery in the 3 months prior to Screening Visit and/or planned surgery for the duration of the study.
20. Sustained hypertension defined as at least 2 repeated measurements at least 15 minutes apart of systolic pressure exceeding 130 mm Hg and/or diastolic pressure exceeding 80 mm Hg at Screening and/or Day -1 Visits.
21. Supine pulse rate <45 beats per minute (bpm) or >100 bpm at Screening and/or Day -1 Visits.
22. One or more of the following abnormal ECG findings at Screening and/or Day -1 Visits:
a. Second- or third-degree atrioventricular block
b. QRS >120 msec
c. QTcF >450 msec for males or >470 msec for females
d. PR interval >200 msec
e. Any rhythm other than sinus rhythm that is considered clinically significant by the Investigator.
23. History of risk factors for Torsade de Pointes including unexplained syncope, known long QT syndrome, heart failure, myocardial infarction, angina, or clinically significant abnormal laboratory assessments including hypokalemia, hypercalcemia, or hypomagnesemia.
24. Family history of long QT syndrome or Brugada syndrome.
25. Donation of blood or blood products in excess of 500 mL within 12 weeks prior to Screening Visit and/or unwilling to refrain from blood donation for the duration of the study.
26. Participant has any medical or social condition which in the opinion of the Investigator, would make the participant unsuitable for participation in the study, for study treatment, or could interfere with the assessments of safety or PK, or completion of the study.
27. Participant has received an investigational agent within 3 months or 5 half-lives (if known), or twice the duration of biological effect (if known), whichever is longer, before Screening, or who is in follow-up of another clinical study of an investigational agent at the time of the Screening Visit.
28. Exposure to more than 4 new chemical entities within 12 months prior to the Day 1 Visit.
29. Prior treatment with any oligonucleotide or small interfering RNA within 12 months prior to the Day 1 Visit.
30. Participant is directly or indirectly involved in the conduct and administration of this trial as an Investigator, sub-investigator, trial coordinator, or other trial staff member, or the participant is a first-degree family member, significant other, or relative residing with one of the above persons involved directly or indirectly in the trial.

Date of first enrolment
14/11/2023

Date of final enrolment
03/06/2024

Locations

Countries of recruitment
United Kingdom

Wales

Study participating centre
Simbec Research Limited
Simbec House Merthyr Tydfil Industrial Park
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Sponsor information

Organisation
Wave Life Sciences (United States)

ROR
https://ror.org/015x34y38

Funder(s)

Funder type
Industry

Funder Name
Wave Life Sciences UK Limited

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Basic results		27/01/2026	27/01/2026	No	No