PROTOCOL TITLE:	A Phase 1, Randomized, Double-blind, Placebo-controlled, Safety, Tolerability, and Pharmacokinetic Study of Single Ascending Doses and Multiple Doses of WVE-006 in Healthy Participants
PROTOCOL NUMBER	WVE-006-001
IRAS ID NUMBER	1008635
AMEDENDMENT NUMBER	Initial
DATE	29 August 2023
COMPOUND	WVE-006
BRIEF TITLE	A Phase 1, Randomized, Double-Blind, Placebo-Controlled Study in Healthy Participants
STUDY PHASE	Phase 1
SPONSOR NAME/	Wave Life Sciences UK Limited
LEGAL REGISTERED ADDRESS:	1 Chamberlain Square CS Birmingham, B3 3AX United Kingdom

CONFIDENTIAL INFORMATION

CLINICAL PROTOCOL APPROVAL FORM

SPONSOR: WAVE LIFE SCIENCES

I have read and understand the contents of this clinical protocol for Protocol No. WVE-006-001 dated 29 August 2023 and agree to meet all obligations of the Sponsor as detailed in all applicable regulations and guidelines. In addition, I will inform the Principal Investigator and all other Investigators of all relevant information that becomes available during the conduct of this Study.

Approved By:

PPD

August 2023 | 06:32 PDT

Date

Wave Life Sciences

PRINCIPAL INVESTIGATOR'S AGREEMENT

I have read and understand the contents of this clinical protocol for Protocol No. WVE-006-001 dated 29 August 2023 and will adhere to the study requirements as presented, including all statements regarding confidentiality. In addition, I will conduct the Study in accordance with current International Conference on Harmonization guidelines governing Good Clinical Practices, applicable US Food and Drug Administration (USFDA) regulations, and other local regulatory requirements:

Name of Principal Investigator:

Title: _____

Institution: _____

Address: _____

_____

Phone: _____

Fax: _____

_____ _____

Signature **Date**

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LIST OF ABBREVIATIONS

Abbreviation or Acronym	Definition
AAT	alpha-1 antitrypsin
AATD	alpha-1 antitrypsin deficiency
Ae	a measure of amount of drug excreted in the urine
Ae%	the percentage of the administered dose that is excreted in urine
AE	adverse event
AIMer	A-to-I editing oligonucleotide
ALT	alanine transaminase
aPTT	activated partial thromboplastin time
AST	aspartate transaminase
AUC; $AUC_{0\text{-}24hr}$; $AUC_{0\text{-}48hr}$; AUC_{last}; AUC_{inf}, AUC_{ext}; AUC_{tau}	area under the curve; AUC from time 0 to 24 hours; AUC from time 0 to 48 hours; AUC from time 0 to last measurable concentration; AUC from time 0 to infinity, AUC extrapolated to infinity; AUC over a dosing interval
BMI	body mass index
bpm	beats per minute
BUN	blood urea nitrogen
BSA	body surface area
CBC	complete blood count
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CL	clearance
C_{max}	maximum (peak) concentration of drug
COPD	chronic obstructive pulmonary disease
CRO	contract research organization
CRP	C-reactive protein
CRU	clinical research unit
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
cum Ae%	cumulative Ae%
CV%	percent coefficient of variation
DEC	Dose Escalation Committee
DMC	Data Monitoring Committee
EC	ethics committee

Abbreviation or Acronym	Definition
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EMEA	European Medicines Evaluation Agency
ET	early termination
FIH	first-in-human
FSH	follicle stimulating hormone
GalNAc	N-acetylgalactosamine
GCP	Good Clinical Practice
GLDH	glutamate dehydrogenase
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HED	human equivalent dose
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
HV	healthy volunteer
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
INR	international normalized ratio
IRB	institutional review board
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
M-AAT	M allele (wild type) version of AAT protein
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	messenger ribonucleic acid
MTD	maximum tolerated dose level
NCI	National Cancer Institute
CC	[redacted]

Abbreviation or Acronym	Definition
NOAEL	no observed adverse effect level
PD	pharmacodynamic
PK	pharmacokinetic
PT	preferred term
Q2W	every other week
QTcF	QT interval corrected using Fridericia's formula
RBC	red blood cell
RNA	ribonucleic acid
SAD	single ascending dose
SAE	serious adverse event
SAR	serious adverse reaction
SC	subcutaneous
SD	standard deviation
SERPINA1	Serpin Family A Member 1
SoA	schedule of assessments
SOC	system organ class
SpO_2	percentage oxygen saturation in the blood
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	terminal elimination half-life
TEAE	treatment emergent adverse event
t_{max}	time to C_{max}
ULN	upper limit of normal
USFDA	United States Food and Drug Administration
Vd	volume of distribution
WBC	white blood cell
WOCBP	women of childbearing potential
Z-AAT	Z allele (mutant) version of AAT protein

1 PROTOCOL SUMMARY

1.1 Protocol Synopsis

<table>
<tr><td>Sponsor:
Wave Life Sciences UK Limited</td><td>Investigational Product:
WVE-006</td><td>Developmental Phase:
Phase 1</td><td>IRAS ID Number:
1008635</td></tr>
<tr><td colspan="4">Protocol Title: A Phase 1, Randomized, Double-blind, Placebo-controlled, Safety, Tolerability, and Pharmacokinetic Study of Single Ascending Doses and Multiple Doses of WVE-006 in Healthy Participants</td></tr>
<tr><td colspan="4">Protocol Number: WVE-006-001</td></tr>
<tr><td colspan="4">Brief Title: A Phase 1, Randomized, Double-blind, Placebo-controlled, Single Ascending Dose and Multiple-Dose Study of WVE-006 in Healthy Participants</td></tr>
<tr><td colspan="4">Pediatric Investigation Plan Number: Not applicable</td></tr>
<tr><td colspan="4">Rationale:
Alpha-1 antitrypsin (AAT) is an acute phase protein predominantly produced by hepatocytes. Serum AAT protects the lung against proteolytic enzymes such as neutrophil elastase. Alpha-1 antitrypsin deficiency (AATD) is caused by mutations in the Serpin Family A Member 1 (SERPINA1) gene which follow an autosomal, codominant recessive inheritance pattern with a codominant genetic trait for AAT production. 95% of severe AATD cases are due to homozygous substitution of a single amino acid, Glu342Lys (protein inhibitor [PI]*ZZ). This produces a mutant (Z) misfolded and poorly secreted AAT protein (Z-AAT). The retention of misfolded Z-AAT protein in the liver causes proteotoxic stress leading to progressive gain of function liver disease from fibrosis to cirrhosis to risk of hepatocellular carcinoma. In contrast, the deficiency of AAT in serum leads to loss of function pulmonary disease which is manifested as chronic obstructive pulmonary disease (COPD), mostly emphysema and bronchiectasis.

WVE-006 is an oligonucleotide that was designed to specifically edit the SERPINA1-Z messenger ribonucleic acid (mRNA) back to wildtype (M). Editing of the SERPINA1-Z mRNA back to wild type is expected to increase the concentration of M-AAT protein in the serum and decrease the accumulation of Z-AAT in the liver, thus addressing both the lung and liver disease manifestations associated with AATD.

WVE-006 is not expected to have pharmacological activity in healthy volunteers (HV) as they do not have the mutation.</td></tr>
<tr><td colspan="4">Study Center(s): Up to 4 clinical research units</td></tr>
<tr><td colspan="4">Objectives and Endpoints:</td></tr>
<tr><td colspan="2">Objectives</td><td colspan="2">Endpoints</td></tr>
<tr><td colspan="4">Primary</td></tr>
<tr><td colspan="2">• To evaluate the safety and tolerability of WVE-006</td><td colspan="2">• Incidence of treatment emergent adverse events (TEAEs), related TEAE, severe TEAE, serious TEAE

• Changes in safety assessment parameters (e.g., physical exam, vital signs, clinical laboratory results, electrocardiograms (ECGs) [including any changes to QTcF])</td></tr>
</table>

Sponsor: Wave Life Sciences UK Limited	**Investigational Product:** WVE-006	**Developmental Phase:** Phase 1	**IRAS ID Number:** 1008635
		• Tolerability based on incidence of discontinuation due to TEAEs	
Secondary			
• To evaluate the pharmacokinetics (PK) of WVE-006 after a single dose in healthy participants • To evaluate the PK of WVE-006 after multiple doses in healthy participants		• PK parameters of WVE-006 in plasma, including AUC_{inf}, AUC_{0-24h}, AUC_{0-48h}, AUC_{last}, C_{max}, t_{max} • PK parameters of WVE-006 in plasma following first and last doses, including AUC_{tau}, AUC_{0-24h}, AUC_{0-48h}, AUC_{last}, C_{max}, t_{max}	
Exploratory			
• To evaluate urine excretion of WVE-006		• Amount excreted (Ae), Ae% and cumulative Ae% (cum Ae%) for parent drug, as well as potential metabolites in urine	

Overall Design:

The purpose of this first-in human (FIH), double-blind, randomized, placebo-controlled, single ascending dose (SAD) and multiple-dose Phase 1 study is to assess the safety, tolerability, and PK of WVE-006 compared to placebo in healthy participants following a single dose (Period 1) and multidose (Period 2) of WVE-006.

Following screening of up to 28 days, eligible participants will be enrolled into Period 1 SAD. Following evaluation of the highest single dose cohort, 8 new participants will be enrolled into Period 2 for administration of 3 doses every other week (Q2W) at the selected dose level from Period 1. In both Periods 1 and 2, participants will be evaluated for safety and tolerability through Day 85 following their last dose of WVE-006 or placebo, as well as for various PK parameters.

Period 1

Period 1 will evaluate single ascending doses of WVE-006 in up to five cohorts of up to 8 healthy participants each. An additional cohort (Cohort 6) may be included to evaluate concentration-QTc. Each cohort will include up to 6 WVE-006-treated and up to 2 placebo-treated participants (3:1 active:placebo). Participants will receive a single subcutaneous (SC) dose of WVE-006 or placebo on Day 1.

The starting dose and dose escalation are designed based on the following considerations:

CCI

The Dose Escalation Committee (DEC) and the Data Monitoring Committee (DMC) will review available safety and PK data through Day 8 for each dose cohort in combination with all available, previously accumulated safety data, as well as available PK data from participants enrolled in the study to date, to recommend subsequent dose escalation.

A sentinel strategy will be employed for the first 2 participants (1 active:1 placebo) of every new dose level during the SAD portion of the study. The sentinel participants will be dosed and monitored in the clinic for a minimum of 48 hours to identify any potential acute safety events. If neither of these sentinel participants experiences stopping criteria and if there are no other safety concerns during this 48-hour period, the remaining 6 participants will be randomized in a blinded fashion to active study drug (n=5) or placebo (n=1) and may be dosed on the same day. These participants will be observed in clinic for 48 hours after administration of study drug. Participants will attend weekly clinic visits on Weeks 0 through 12 to be followed for safety, tolerability, and PK assessments through Day 85 per schedule of assessments (SoA).

Period 2

In Period 2, a single cohort of up to 8 healthy participants including up to 6 WVE-006 and up to 2 placebo treated participants (3:1 active:placebo) will participate in a multidose cohort of WVE-006. The DEC and DMC will review available safety and PK data from Period 1 to select the maximum tolerated dose level (MTD) with an acceptable PK profile. The MTD is defined as the dose below a dose level where any of the dose escalation stopping rules were met. If the MTD is not achieved in Period 1 (i.e., no dose escalation stopping rules were met and all doses were well tolerated), then the highest dose reached in Period 1 will likely be selected for Period 2. The DEC and DMC may select a lower dose based on all available information. At least 4 weeks of safety data for the proposed dose and all available data from the study must be available from Period 1 in order to inform the DEC and DMC Period 2 dose selection. A sentinel strategy will be employed for the first 2 participants

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(1 active:1 placebo) during the multiple dose portion of the study. The sentinel participants will be dosed and monitored in the clinic for a minimum of 48 hours to identify any potential acute safety events. If neither of these sentinel participants experiences stopping criteria and if there are no other safety concerns during this 48-hour period, the remaining 6 participants will be randomized in a blinded fashion to active study drug (n=5) or placebo (n=1) and may be dosed on the same day.WVE-006 or placebo will be administered every other week (Q2W) over 4 weeks (total of 3 doses; Weeks 0, 2, and 4). Following the first dose (Week 0) and last dose (Week 4), all participants will stay in the clinic for two nights for PK assessments. Following the second dose (Week 2), all participants will be observed for safety evaluation in the clinic for at least 4 hours post-study drug administration or per local SOP (whichever is longer). All participants will attend weekly follow-up clinic visits for safety, tolerability, and PK assessments through Week 12 followed by visits every 4 weeks through week 16 or early termination visit.

Dose Escalation Stopping Criteria (Period 1):

Dose escalation will be paused until further evaluation by the DMC if any of the following criteria are met. If it is confirmed that a stopping criterion was met, no further dosing will take place until after submission and approval of a substantial amendment if the DMC recommends the trial can continue.

- One or more participants experiencing at least possibly related Common Terminology Criteria for Adverse Events (CTCAE) Grade ≥3 TEAE or CTCAE grade ≥3 laboratory abnormality in a single cohort.
    - All grade 3 toxicities for vital signs must be confirmed with a repeat measurement obtained within 1 hour.
    - All grade 3 toxicities for laboratory parameters must be confirmed with a repeat measurement obtained within 24 hours.
- Two or more participants experiencing at least possibly related CTCAE grade ≥2 TEAEs or CTCAE Grade ≥2 laboratory abnormalities in a single cohort.
    - All grade 2 toxicities for vital signs must be confirmed with a repeat measurement obtained within 1 hour.
    - All grade 2 toxicities for laboratory parameters must be confirmed with a repeat measurement obtained within 24 hours.
- One or more participants experiencing any at least possibly related SAE in a single cohort.

Period 2 Individual Stopping Criteria:

Dosing will be paused or discontinued (per Investigator judgment) for an individual participant at any time in the study if:

- Participant experiences any severe or serious adverse event considered at least possibly related to study drug.
- Participant experiences, in the Investigator's opinion, clinically significant hypersensitivity to WVE-006 (or placebo) administration.
- Participant has any medical condition that is judged by the Investigator to jeopardize the participant's safety if he or she continues to receive the study drug.

On discontinuation of treatment, participants will be encouraged to continue follow-up for safety per protocol. Per Investigator judgment with consultation with the Sponsor, the participant may be allowed to resume participation in the study if/when the event has resolved.

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Number of Participants (Planned): Up to 48 participants are planned to be enrolled; up to 40 participants in Period 1 (8 per each of the up to five planned SAD cohorts) and up to 8 new participants in the multidose Period 2.

Should the DEC and DMC recommend to include an optional SAD cohort, an additional 8 participants will be enrolled for a total of up to 56 participants. Fewer than 48 participants may be enrolled if the DEC and DMC decide fewer cohorts are needed.

Study Arms and Duration:

Study arms in both Period 1 and Period 2 are up to 6 WVE-006 and up to 2 placebo treated participants **(**3:1 active:placebo) in each of the planned cohorts.

Period 1 SAD: duration for each participant is expected to be up to 16 weeks: Screening of up to 28 days, followed by a single dose administration on Day 1, followed by safety, tolerability, and PK assessment through Day 85.

Period 2 Multidose: duration for each participant is expected to be up to 20 weeks: Screening of up to 28 days, followed by 3 dose administrations on Weeks 0, 2, and 4, followed by safety, tolerability, and PK assessment through Day 113 Visit (i.e., Day 85 following last dose administration).

Eligibility Criteria:

Participants must meet all inclusion criteria and none of the exclusion criteria. For eligibility purposes, abnormal laboratory or vital signs or ECG results may be repeated once during the Screening period or Day -1 (as applicable) for confirmation if an abnormal result is observed at the initial assessment.

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/m^2 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:
    a) Non-pregnant as determined by a negative serum pregnancy test at Screening and negative highly sensitive urine pregnancy test on Day -1.
    b) Non lactating.

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c) Agree to use a highly-effective method of contraception (as defined in Section 10.4) from CCI prior to Day 1 and for at least CCI following last study drug administration. Exception: Women exclusively engaging in same-sex sexual activities are not required to meet this criterion.
d) Must be willing to forgo ova (egg) donation for at least CCI following the last study drug administration.

9. Women of non-childbearing potential are defined as meeting at least 1 of the following criteria:
   a) At least 12 months post-menopausal and has an FSH >40 mIU/mL.
   b) 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 CCI following the last dose of study drug. In addition, participant must be willing to forgo sperm donation for at least CCI following the last dose of study drug. Men exclusively engaging in same-sex sexual activities are not required to meet this criterion.

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, if applicable per site SOP, at Screening and 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/1.73mm^2 (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 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 (45 mL) 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 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.

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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.

Blinding: The roles indicated below will not be made aware of the treatment group assignment during the study:

- Participants

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- Trial staff members (excluding pharmacy staff)
- Investigator
- DEC
- Sponsor, with certain documented exceptions as per DEC Charter

Data Monitoring/Other Committee: Because the Investigator is part of DEC and must remain blinded for long term safety evaluation, an independent unblinded DMC will review available data on PK and safety prior to dose escalation at each cohort.

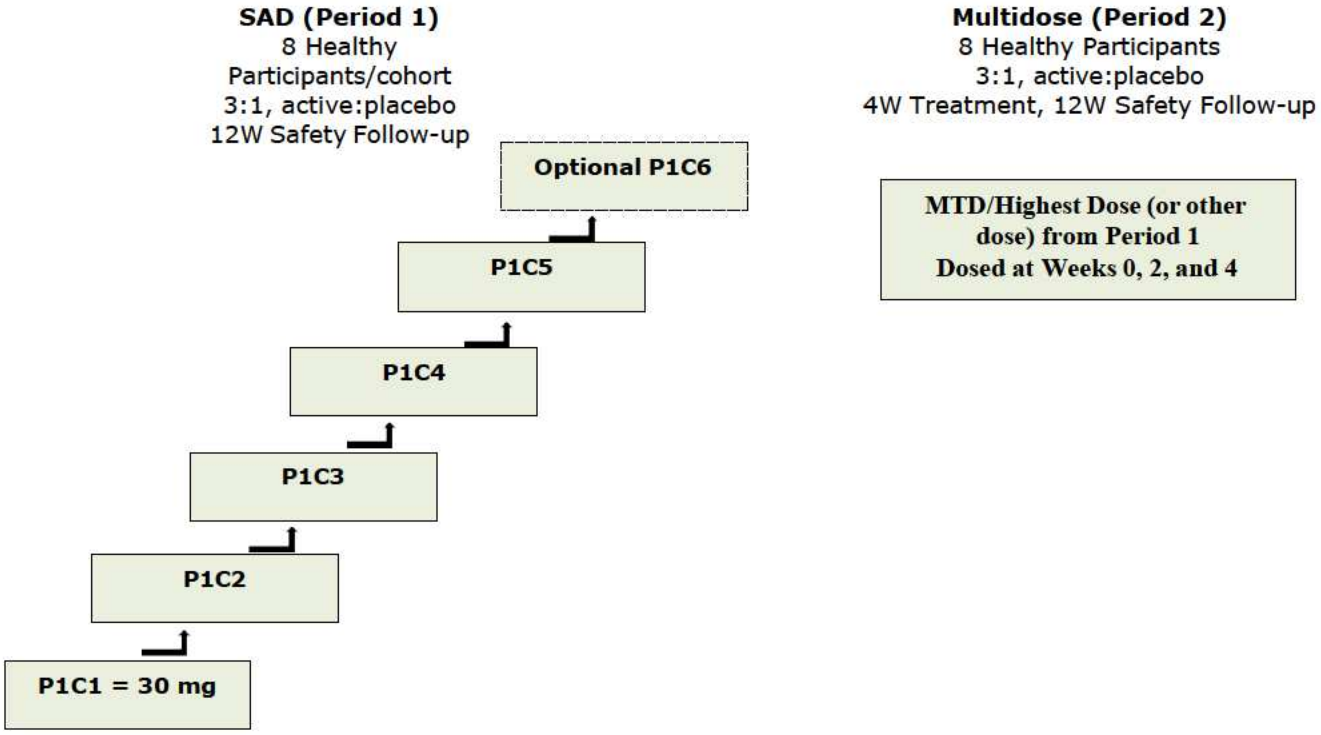
Statistical Methods:

The sample size was not calculated on the basis of statistical hypothesis testing; however, the number of participants is considered sufficient for a Phase 1 assessment of safety, tolerability, and PK.

Treatment-emergent AEs overall and assessed as related to study drug or to study procedures, and treatment emergent SAEs, will be summarized for each dose group based on MedDRA coding of verbatim terms reported by Investigators. These summaries will be presented separately for Period 1 and Period 2.

Pharmacokinetic parameters for WVE-006 will be calculated using non-compartmental methods. PK parameters will be summarized by treatment using descriptive statistics: n, arithmetic mean, median, standard deviation (SD), minimum, maximum, and percent coefficient of variation (CV%); in addition, the geometric mean and geometric CV% will be reported for C_{max} and AUCs.

1.2 Protocol Schema



P1 = Period 1; C = Cohort

1.3 Schedule of Assessments

Table 1 Overall Schedule of Assessments (Period 1)

	Screening Period[a]	**Dosing- CRU Stay**				**Follow-up**				**ET**
Visit	**1**	**2**				**3, 4, 5, 7, 8, 9, 11, 12, 13**	**6**	**10**	**14**	
Study Week	**Week -4 to Week 0**	**Week 0**				**Week 1, 2, 3, 5, 6, 7, 9, 10, 11**	**Week 4**	**Week 8**	**Week 12**	
Study Day Event/Assessment	**Day -28 to Day -2**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 8, 15, 22, 36, 43, 50, 64, 71, 78 (±3 days)**	**Day 29 (±3 days)**	**Day 57 (±3 days)**	**Day 85 (±5 days)**	
Informed Consent	X									
Demographics	X									
Medical History	X									
Prior/concomitant medications	X	X	X	X	X	X	X	X	X	X
Admission to CRU		X								
Discharge from CRU					X					
Eligibility Criteria/Recheck	X	X								
AAT Genetic Testing	X									
Serum Pregnancy Test[b]	X								X	X
Urine Pregnancy Test[b]		X			X	X	X	X		
FSH[c]	X									
Viral Serology	X									
COVID-19 Testing[d]	X	X								

	Screening Period[a]	**Dosing- CRU Stay**				**Follow-up**				**ET**
Visit	**1**	**2**				**3, 4, 5, 7, 8, 9, 11, 12, 13**	**6**	**10**	**14**	
Study Week	**Week -4 to Week 0**	**Week 0**				**Week 1, 2, 3, 5, 6, 7, 9, 10, 11**	**Week 4**	**Week 8**	**Week 12**	
Study Day Event/Assessment	**Day -28 to Day -2**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 8, 15, 22, 36, 43, 50, 64, 71, 78 (±3 days)**	**Day 29 (±3 days)**	**Day 57 (±3 days)**	**Day 85 (±5 days)**	
Safety Laboratory[e]	X	X		X	X	X	X	X	X	X
Plasma PK and Select Labs [f]			X	X	X	X	X	X	X	X
Urine PK sample[f]			X	X	X	X	X	X	X	X
Serum Sample for Immunogenicity		X					X	X	X	X
Full Physical Exam[g]	X	X			X		X	X	X	X
Symptom-directed Physical Exam[g]			X	X		X				
Body Weight/BMI[h]	X	X		X	X	X	X	X	X	X
Height	X									
Vital Signs[i]	X	X	X	X	X	X	X	X	X	X
Digital Continuous and Triplicate 12-lead ECG[j]	X	X		X	X				X	X
Urine Drug Screen[k]; Cotinine; Alcohol Breath or Urine Test	X	X				X	X	X	X	X
Study Drug Administration SC Injection			X							

	Screening Period[a]	Dosing- CRU Stay				Follow-up				ET
Visit	**1**	**2**				**3, 4, 5, 7, 8, 9, 11, 12, 13**	**6**	**10**	**14**	
Study Week	**Week -4 to Week 0**	**Week 0**				**Week 1, 2, 3, 5, 6, 7, 9, 10, 11**	**Week 4**	**Week 8**	**Week 12**	
Study Day Event/Assessment	**Day -28 to Day -2**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 8, 15, 22, 36, 43, 50, 64, 71, 78 (±3 days)**	**Day 29 (±3 days)**	**Day 57 (±3 days)**	**Day 85 (±5 days)**	
Adverse Event Monitoring	X	X	X	X	X	X	X	X	X	X

Abbreviations: AAT = alpha-1 antitrypsin; BMI = body mass index; CRU = clinical research unit; ECG = electrocardiogram; ET = early termination; FSH = follicle stimulating hormone; PK = pharmacokinetic; SC = subcutaneous.

[a] Screening assessments can occur on multiple days, provided they are within the Day -28 up to Day -2 Screening period.

[b] Negative serum pregnancy test at Screening for women of childbearing potential (WOCBP). Negative highly sensitive urine pregnancy test documented for WOCBP on Day -1.

[c] FSH only to confirm non-childbearing potential.

[d] COVID-19 testing if required per site SOPs.

[e] Safety laboratory tests include hematology, clinical chemistry, coagulation and urinalysis as noted in Table 11. Note that for urinalysis, abnormal results on dipstick or urinalysis should lead to laboratory urinalysis testing and/or urine microscopy. Any specific safety labs indicated in Table 2 will be collected according to the schedule in that table. When applicable and feasible, blood sampling should follow evaluations of vital signs and ECGs to reduce any impact on these measurements.

[f] Specific time points for PK and select laboratory assessments provided in Table 2 and Table 3. Participants should stay in the clinic for 48 hours after dose to complete assessments.

[g] Full physical examination includes (at a minimum): alertness and orientation, general appearance, skin, head, eyes, ears, nose, throat, lungs, cardiovascular, gastrointestinal, musculoskeletal, and neurologic systems. Symptom-directed physical exams to be performed by visit as necessary.

[h] Height at Screening will be used for BMI calculations at all visits.

[i] Vital signs will be taken with the participant in the supine position after ≥5 minutes of rest. Temperature, respiratory rate, and percent oxygen saturation in the blood (SpO_2) are measured once per time point. Blood pressure (systolic and diastolic) and pulse: measured ≤30 minutes pre-dose and 1 hr (±10 min), 2 hr (±10 min), 4 hr (±20 min), 12 hr (±1 hr) post dose on Day 1 and once at all other noted visits.

[j] Continuous digital ECG monitoring for at least 48 hours from Day -1 through Day 2; leads may be disconnected for ~20 minutes at 24 hours after dosing to allow for participant cleansing. Additional triplicate 12-lead ECGs are specified in Table 4. Participant must rest quietly for ≥5 minutes prior to triplicate ECGs.

[k] For drug screen panel, see Table 11 other screening tests.

Table 2 Plasma PK and Selected Laboratory Time Points (Period 1)

Visit	2											3	4	5 through 14
Study Day/ Specific Time/ Window	Day 1								Day 2		Day 3	Day 8	Day 15	Weeks 3 through 12
	Pre-dose	Post dose												
	≤30 min prior to dose[b]	30 min (±5 min)	1 hr (±5 min)	2 hr (±5 min)	4 hr (±10 min)	6 hr (±10 min)	8 hr (±10 min)	12 hr (±10 min)	24 hr (±30 min)	36 hr (±4 hr)	48 hr (±4 hr)	(±3 days)	(±3 days)	(± 3 days)
Plasma PK[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	Every week
CBC, CRP, fibrinogen, coagulation, albumin	X					X			X		X	X	X	Every week
Complement	X			X	X	X			X		X	X	X	Week 4 only
Cytokines[c]	X			X	X	X			X		X	X	X	Week 4 only

Abbreviations: CBC = complete blood count; CRP = C-reactive protein; PK = pharmacokinetic.

[a] Sufficient plasma PK sample volume to cover both WVE-006 and potential metabolites. When applicable and feasible, PK blood sampling should follow evaluations of vital signs and ECGs to reduce any impact on these measurements.

[b] Pre-dose laboratory results are NOT required prior to dosing.

[c] Cytokine samples will be collected and may be analyzed for the following cytokines: IL-1β, IL-6, IL-10, IL-12/23 (P40), IFN-γ, TNF-α, MCP-1, and MIP-1β

Table 3 Urine PK Cumulative Collection Periods (Period 1)

Study Day/ Time Frame	Day 1					Day 2	Day 3
	0-4 hr	4-8 hr	8-12 hr	12-18 hr	18-24 hr	24-36 hr	36-48 hr
Urine PK[a]	X	X	X	X	X	X	X

Abbreviation: PK = pharmacokinetic.

[a] Urine for PK assessments will be collected continuously through 48 hours per the stated time periods. For each of these time periods, total volume will be captured in the electronic case report form (eCRF).

Table 4 Triplicate ECG Assessment Time Points (Period 1)

Study Day/ Specific Time	**Day 1**										**Day 2**	**Day 3**
	Pre-dose			**Post dose**								
	-45 min ±5 min	**-30 min** ±5 min	**-15 min** ±5 min	**30 min** ±5 min	**1 hr** ±5 min	**2 hr** ±5 min	**4hr** ±10 min	**6hr** ±10 min	**8hr** ±10 min	**12hr** ±10 min	**24hr** ±30 min	**48hr** ±4 hr
ECG[a]	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: ECG = electrocardiogram

[a] Digital ECG monitoring for at least 48 hours from Day -1 through Day 2. Additional triplicate ECG measurements at the time points listed here.

Table 5 Overall Schedule of Assessments (Period 2)

	Screening Period[a]	**Treatment Period**								**Follow-up Visit**				**ET**
Visit	**1**	**2**				**4**	**6**			**3, 5, 7,8, 9, 11, 12, 13, 14, 15, 16**	**10**	**14**	**15**	
Study Week	**Week -4 to Week 0**	**Week 0 CRU Stay**				**Week 2**	**Week 4 CRU Stay**			**Week 1,3, 5, 6, 7, 9, 10, 11**	**Week 8**	**Week 12**	**Week 16**	
Study Day/ Event/ Assessment	**Day -28 to Day -2**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 15 (±3 days)**	**Day 29 (±3 days)**	**Day 30 (±3 days)**	**Day 31 (±3 days)**	**Day 8, 21, 36, 43, 50, 64, 71, 78 (±3 days)**	**Day 57 (±3 days)**	**Day 85 (±3 days)**	**Day 113 (±5 days)**	
Informed Consent	X													
Demographics	X													
Medical History	X													
Prior/concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Admission to CRU		X				X[b]	X[b]							
Discharge from CRU					X	X			X					

	Screening Period[a]	**Treatment Period**								**Follow-up Visit**				**ET**
Visit	**1**	**2**				**4**	**6**			**3, 5, 7,8, 9, 11, 12, 13, 14, 15, 16**	**10**	**14**	**15**	
Study Week	**Week -4 to Week 0**	**Week 0 CRU Stay**				**Week 2**	**Week 4 CRU Stay**			**Week 1,3, 5, 6, 7, 9, 10, 11**	**Week 8**	**Week 12**	**Week 16**	
Study Day/ Event/ Assessment	**Day -28 to Day -2**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 15 (±3 days)**	**Day 29 (±3 days)**	**Day 30 (±3 days)**	**Day 31 (±3 days)**	**Day 8, 21, 36, 43, 50, 64, 71, 78 (±3 days)**	**Day 57 (±3 days)**	**Day 85 (±3 days)**	**Day 113 (±5 days)**	
Eligibility criteria/Recheck	X	X												
AAT genetic testing	X													
Serum Pregnancy Test[c]	X												X	X
Urine Pregnancy Test[c]		X			X	X	X		X	X	X	X		
FSH[d]	X													
Viral Serology	X													
COVID-19 testing[e]	X	X												
Safety Laboratory[f]	X	X		X	X	X	X	X	X	X	X	X	X	X
Plasma PK and Select Labs[g]			X	X	X	X	X	X	X	X	X	X	X	X
Serum sample for immunogenicity		X					X				X	X	X	X
Full Physical Exam[h]	X	X			X	X	X		X		X	X	X	X
Symptom directed Physical Exam[h]			X	X				X		X				
Body Weight/BMI[i]	X	X		X	X	X	X	X	X	X	X	X	X	X
Height	X													

	Screening Period[a]	**Treatment Period**								**Follow-up Visit**				**ET**
Visit	**1**	**2**				**4**	**6**			**3, 5, 7,8, 9, 11, 12, 13, 14, 15, 16**	**10**	**14**	**15**	
Study Week	**Week -4 to Week 0**	**Week 0 CRU Stay**				**Week 2**	**Week 4 CRU Stay**			**Week 1,3, 5, 6, 7, 9, 10, 11**	**Week 8**	**Week 12**	**Week 16**	
Study Day/ Event/ Assessment	**Day -28 to Day -2**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 15 (±3 days)**	**Day 29 (±3 days)**	**Day 30 (±3 days)**	**Day 31 (±3 days)**	**Day 8, 21, 36, 43, 50, 64, 71, 78 (±3 days)**	**Day 57 (±3 days)**	**Day 85 (±3 days)**	**Day 113 (±5 days)**	
Vital Signs[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Digital Continuous and Triplicate 12-lead ECG[k]	X	X		X	X	X	X				X	X	X	X
Urine Drug Screen[l]; Cotinine; Alcohol Breath or Urine Test	X	X				X	X			X	X	X	X	X
Study Drug Administration SC Injection			X			X[m]	X							
Adverse Event Monitoring	X	X	X	X	X	X[m]	X	X	X	X	X	X	X	X

Abbreviations: AAT = alpha-1 antitrypsin; BMI = body mass index; ECG = electrocardiogram; ET = early termination; FSH = follicle stimulating hormone; PK = pharmacokinetic; SC = subcutaneous.

[a] Screening assessments can occur on multiple days, provided they are within the Day -28 up to Day -2 Screening period.

[b] If required per site SOP, admission on Day 14, and/or 28 is acceptable.

[c] Negative serum pregnancy test at Screening for WOCBP. Negative highly sensitive urine pregnancy test documented for WOCBP on Day -1 and prior to every dose.

[d] FSH only to confirm non-childbearing potential.

[e] COVID-19 testing if required per site SOPs.

[f] Safety laboratory tests include hematology, clinical chemistry, coagulation and urinalysis as noted in Table 11. Note that for urinalysis, abnormal results on dipstick or urinalysis should lead to laboratory urinalysis testing and/or urine microscopy. Any specific safety labs indicated in Table 6 will be collected according to the schedule in that table. When applicable and feasible, blood sampling should follow evaluations of vital signs and ECGs to reduce any impact on these measurements.

[g] Predose plasma PK at every dosing visit. Specific time points for PK and select laboratory Weeks 0 and 4 provided in Table 6. Participants should stay in the clinic for 48 hours after the first and last doses to complete assessments.

[h] Full physical examination includes (at a minimum): alertness and orientation, general appearance, skin, head, eyes, ears, nose, throat, lungs, cardiovascular, gastrointestinal, musculoskeletal, and neurologic systems. Symptom-directed physical examinations to be performed as necessary.

[i] Height at Screening will be used for BMI calculations at all visits.

[j] Vital signs will be taken with the participant in the supine position after ≥5 minutes of rest. Temperature, respiratory rate, and SpO^2 are measured once per time point. Blood pressure (systolic and diastolic) and pulse: measured ≤30 minutes pre-dose and 1 hr (±10 min), 2 hr (±10 min), 4 hr (±20 min), 12 hr (±1 hr) post dose on Day 1 and once at all other noted visits. Should additional post dose vital signs be collected per Site SOP, these should be captured in eCRF.

[k] Continuous digital ECG monitoring for at least 48 hours from Day -1 through Day 2 and at least 24 hours through first day of last dose (Day 29); leads may be disconnected for ~20 minutes following 24 hours after the first dose to allow for participant cleansing. Additional triplicate 12-lead ECGs are specified in Table 7. Note: only predose triplicate ECGs are required at Day 15. Participant must rest quietly for ≥5 minutes prior to triplicate ECGs.

[l] For drug screen panel, see Table 11 other screening tests.

[m] Following the second dose (Week 2) all participants will be observed for safety evaluation in the clinic for at least 4 hours post study drug administration or per local SOP (whichever is longer).

Table 6 Plasma PK and Selected Laboratory Time Points (Period 2)

Study Day/Specific Time	**Days 1, 15,29**	**Days 1 and 29**							**Days 2 and 30**		**Days 3 and 31**	**Weeks 1 through 16**
	Pre-dose	**Post dose**										
	≤30 min prior to dose[b]	**30 min (±5 min)**	**1 hr (±5 min)**	**2 hr (±5 min)**	**4 hr (±10 min)**	**6 hr (±10 min)**	**8 hr (±10 min)**	**12 hr ±10 min)**	**24 hr (±30 min)**	**36 hr (±4 hr)**	**48 hr (±4 hr)**	**Visits 3 through 15**
Plasma PK[a]	X	X	X	X	X	X	X	X	X	X	X	Every visit
CBC, CRP, fibrinogen, coagulation, albumin	X					X			X Day 2 only		X Day 3 only	Every visit
Complement	X			X	X	X			X Day 2 only		X Day 3 only	Weeks 1, 5, 6, and 8 only
Cytokines[c]	X			X	X	X			X Day 2 only		X Day 3 only	Weeks 1, 5, 6, and 8 only

Abbreviations: CBC = complete blood count; CRP = C-reactive protein; PK = pharmacokinetic.

[a] Sufficient plasma PK sample to cover both WVE-006 and potential metabolites. When applicable and feasible, PK blood sampling should follow evaluations of vital

signs and ECGs to reduce any impact on these measurements.
[b] Pre-dose laboratory results are NOT required prior to dosing
[c] Cytokines samples will be collected and analyzed for: IL-1β, IL-6, IL-10, IL-12/23 (P40), IFN-γ, TNF-α, MCP-1, and MIP-1β

Table 7 Triplicate ECG Assessment Time Points (Period 2)

Study Day/ Specific Time	**Day 1**			**Days 1 and 29**							**Days 2 and 30**	**Day 3**
	Pre-first dose			**Post first and last doses**								
	-45 min ±5 min	**-30 min** ±5 min	**-15 min** ±5 min	**30 min** ±5 min	**1 hr** ±5 min	**2 hr** ±5 min	**4hr** ±10 min	**6hr** ±10 min	**8hr** ±10 min	**12hr** ±10 min	**24hr** ±30 min	**48hr** ±4 hr
ECG[a]	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: ECG = electrocardiogram
[a] Digital ECG monitoring for at least 48 hours from Day -1 through Day 2 and at least 24 hours through first day of last dose (Day 29). Additional triplicate ECG measurements at the time points listed here.

2 INTRODUCTION

2.1 Study Rationale

WVE-006 is an oligonucleotide that was designed to specifically edit the Serpin Family A Member 1 (*SERPINA1*) mutant (Z) messenger ribonucleic acid (mRNA) back to wildtype (M). Editing of the *SERPINA1*-Z mRNA back to wildtype is expected to increase the concentration of M alpha-1 antitrypsin (M-AAT) protein in the serum and decrease the accumulation of Z-AAT in the liver, thus addressing both the lung and liver disease manifestations associated with Alpha-1 antitrypsin deficiency (AATD).

WVE-006 is not expected to have pharmacological activity in healthy volunteers (HV) since they do not have the Serpin Family A Member 1 (*SERPINA1*) mutation.

2.2 Background

AATD is a rare and clinically underrecognized condition that can affect the lung, liver, and rarely the skin. This disease can cause chronic obstructive pulmonary disease (COPD), a progressive, life-threatening lung disease, which results in severe shortness of breath, wheezing, chronic cough, and sputum production. In addition, these patients may present with asthma, chronic lung disease, emphysema, recurring chest infections, bronchitis, and bronchiectasis. AATD can also cause life-threatening liver disease, skin problems (panniculitis), and inflammation of the blood vessels (vasculitis). There are currently very limited treatment options for AATD, most of which are based on symptom management.

AATD is caused by pathogenic variants in the *SERPINA1* gene and is inherited in an autosomal and codominant manner, indicating that the two alleles are active and contribute to the genetic trait (Greene et al., 2016). The M allele is the most common allele of the alpha-1 gene and produces normal levels of M-AAT. The Z allele is the most common variant of the gene and results in 95% of severe cases of AATD (Strnad et al., 2020). The Z mutation of the *SERPINA1* gene results from a G-to-A missense mutation corresponding to a glutamic acid to lysine amino acid change at position 342 in the protein. The Z-AAT protein is misfolded and prone to aggregation in hepatocytes in a gain of function toxicity in the liver (which may lead to fibrosis, cirrhosis, or increased risk of hepatocellular carcinoma) and decreases the secretion of functional AAT into serum, resulting in a loss of functional AAT in the lung (Strnad et al., 2020).

WVE-006 is an investigational A-to-I editing oligonucleotide (AIMer) that was designed to specifically edit the *SERPINA1*-Z RNA back to wildtype.

2.3 Benefit/Risk Assessment

The information generated by this study will provide a better understanding of the study drug's safety profile and how it is distributed through and works in the human body. No significant toxicity is expected in treated participants since WVE-006 is targeted to mutant *SERPINA1-Z* RNA which will not be present in the study population. Only participants with wild type PI*MM

are included; this genotype contains 2 normal M alleles indicating that the participant does not have AATD. There may be unforeseen risks or toxicities since this will be the first time WVE-006 is administered to humans.

The WVE-006 Investigator's Brochure (IB) will be provided to the Investigator.

2.3.1 Risk Assessment

Nonclinical studies conducted in mice and monkeys yielded no toxicologically meaningful findings that would prevent initiation of clinical studies in HV or AATD patients.

CCI

[redacted]

CCI

[redacted]

2.3.2 Benefit Assessment

Since all participants will be HV without the *SERPINA1-Z* mutation, no direct benefits are expected for study participants. The knowledge gained from this testing may help to further develop WVE-006 as an effective treatment for patients with AATD.

2.3.3 Overall Benefit-Risk Conclusions

Risks to participants in this study have been minimized by the comprehensive safety assessments and the systematic review of safety data by the Data Monitoring Committee (DMC), and as such the risks are justified by the anticipated benefits that may be eventually afforded to patients with AATD.

3 OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Table 8 Study Objectives and Endpoints for WVE-006-001

Primary Objective:	**Primary Endpoint:**
• To evaluate the safety and tolerability of WVE-006	• Incidence of treatment emergent adverse events (TEAEs), related TEAE, severe TEAE, serious TEAE • Changes in safety assessment parameters (i.e., physical exam, vital signs, clinical laboratory results, ECGs (including any changes to QTcF) • Tolerability based on incidence of discontinuation due to TEAEs
Secondary Objective:	**Secondary Endpoints:**
• To evaluate the PK of WVE-006 after a single dose in healthy participants • To evaluate the PK of WVE-006 after multiple doses in healthy participants	• PK parameters of WVE-006 in plasma, including AUC_{inf}, $AUC_{0\text{-}24h}$, $AUC_{0\text{-}48h}$, AUC_{last}, C_{max}, t_{max} • PK parameters of WVE-006 in plasma following the first and last doses, including AUC_{tau}, $AUC_{0\text{-}24h}$, $AUC_{0\text{-}48h}$, AUC_{last}, C_{max}, t_{max}
Exploratory Objectives:	**Exploratory Endpoints:**
• To evaluate urine excretion of WVE-006	• Ae, Ae%, and cumulative Ae% (cum Ae%) for parent drug, as well as potential metabolites in urine

Abbreviations: Ae=amount excreted; AUC=area under the curve; C=concentration; ECG=electrocardiogram; PK=pharmacokinetic; *t*=time; TEAE=treatment-emergent adverse event

4 STUDY DESIGN

4.1 Overall Study Design

This is a double-blind, placebo-controlled, single ascending dose (SAD) and multidose Phase 1 study to assess the safety, tolerability, and PK of WVE-006 in healthy participants. Participants will be randomized to WVE-006 or placebo.

Period 1 will evaluate single ascending doses of WVE-006 in up to five cohorts of up to 8 healthy participants each (3:1 active:placebo). An additional cohort (Cohort 6) may be included to evaluate concentration-QTc. Participants may be on-study for up to 12 weeks. A sentinel strategy will be employed for the first 2 participants (1 active:1 placebo) of every new dose level during the SAD portion (Period 1) and in the multiple dose portion (Period 2) of the study, with a 48-hour observation period to assess for acute safety events. The Dose Escalation Committee (DEC) and the DMC will review available data through Day 8 that will include key PK parameters and safety for each dose cohort, as well as previously accumulated safety data and available PK data, to recommend subsequent dose escalation. Additional details are provided in Section 4.1.2.

Dose Escalation Stopping Criteria (Period 1):

Dose escalation will be paused until further evaluation by the DMC if any of the following criteria are met. If it is confirmed that a stopping criterion was met, no further dosing will take place until after submission and approval of a substantial amendment if the DMC recommends the trial can continue.

- One or more at least possibly related Common Terminology Criteria for Adverse Events (CTCAE) Grade ≥3 TEAE or CTCAE grade ≥3 laboratory abnormality in a single cohort.
    - All grade 3 toxicities for vital signs must be confirmed with a repeat measurement obtained within 1 hour.
    - All grade 3 toxicities for laboratory parameters must be confirmed with a repeat measurement obtained within 24 hours.
- Two or more at least possibly related CTCAE grade ≥2 TEAEs or CTCAE Grade ≥2 laboratory abnormalities in a single cohort.
    - All grade 2 toxicities for vital signs must be confirmed with a repeat measurement obtained within 1 hour.
    - All grade 2 toxicities for laboratory parameters must be confirmed with a repeat measurement obtained within 24 hours.
- Any at least possibly related SAE in a single cohort.

In Period 2, a single cohort of up to 8 healthy participants including up to 6 WVE-006 and 2 placebo treated participants (3:1 active:placebo) will receive multiple doses of WVE-006. Participants may be on-study for up to 16 weeks. The DEC and DMC will review available

safety and PK data from Period 1 to select the maximum tolerated dose level (MTD) or other selected dose achieved if MTD was not reached. Additional information about treatment is provided in Section 4.1.2. Individual treatment stopping criteria for participants in Period 2 are in Section 7.1.1.

4.1.1 Screening

Screening will determine participant eligibility for the study and begins when the participant signs the study informed consent form (ICF). Potential participants will initiate screening up to 4 weeks prior to dosing. The required screening evaluations for participants in the study are outlined in the Schedule of Assessments (SOA; Section 1.3).

Screening assessments can occur on multiple days, provided they are within the Screening period (Day -28 up to Day -2). The Investigator will determine whether participants meet eligibility criteria (see Section 5.1 and Section 5.2).

For management of screen failures, refer to Section 5.3.

4.1.2 Treatment

Period 1: Single Ascending Dose

Period 1 will evaluate single ascending doses of WVE-006 in up to five cohorts of up to 8 healthy participants each. Each cohort will include up to 6 WVE-006-treated and 2 placebo-treated participants (3:1 active:placebo). Participants will receive a single SC dose of WVE-006 or placebo on Day 1.

A sentinel strategy will be employed for the first 2 participants (1 active, 1 placebo) of every new dose level during the SAD portion of the study. The sentinel participants will be dosed and monitored in the clinic for 48 hours to identify any potential acute safety events. If neither of these sentinel participants experiences stopping criteria and if there are no other safety concerns during this 48-hour period, the remaining 6 participants will be randomized in a blinded fashion to active study drug (n=5) or placebo (n=1) and may be dosed on the same day. These participants will be observed in clinic for 48 hours after administration of study drug. Participants will attend weekly clinic visits on Weeks 0 through 12 to be followed for safety, tolerability, and PK assessments through Day 85 per the SoA.

If Period 1 Dose Escalation Stopping Criteria (see Section 4.1) are met at any point, dosing will be paused until further review and confirmation by the DMC. No further dosing will take place until after submission and approval of a substantial amendment if the DMC recommends the trial can continue.

Period 2: Multiple Doses

In Period 2, a single cohort of up to 8 healthy participants, including up to 6 WVE-006 and up to 2 placebo treated participants (3:1 active:placebo), will participate in a multidose assessment of WVE-006. A sentinel strategy will be employed for the first 2 participants (1 active:1 placebo), with a 48-hour observation period to assess for acute safety events. The DEC and DMC will review available safety and PK data from Period 1 to select the MTD with an acceptable PK profile. The MTD is defined as the dose below a dose level where any of the dose escalation stopping rules were met. If MTD is not achieved in Period 1 (i.e., no dose escalation stopping rules were met and all doses were well tolerated), then the highest dose reached in Period 1 will likely be selected for Period 2, though the DEC and DMC may select a lower dose based on all available information. At least 4 weeks of safety data for the proposed dose and all available data from the study must be available from Period 1 in order to inform the DEC and DMC Period 2 dose selection. WVE-006 or placebo will be administered every other week (Q2W) over 4 weeks (total of 3 doses; Weeks 0, 2, and 4). Following the first dose (Week 0) and last dose (Week 4), participants will stay in the clinic for at least two nights for PK assessments. Following the second dose (Week 2) all participants will be observed for safety evaluation in the clinic for at least 4 hours post-study drug administration or per local SOP (whichever is longer).

In Period 2, dosing will be paused or discontinued (per Investigator judgment) for an individual participant; see Section 7.1.1 for additional details.

4.1.3 Follow-up

Following completion of study treatment, participants will continue to have follow-up visits for up to 12 weeks. Safety assessments will be completed and safety laboratory samples, and PK samples will be drawn during these visits. Refer to Table 1 for Period 1 and Table 5 for Period 2 details.

4.1.4 Early Termination

If a participant withdraws from the study early, the participant should complete an early termination (ET) visit. Assessments to be performed at the ET visit are detailed in Table 1 for Period 1 and Table 5 for Period 2. Refer to Section 7 for information on early withdrawal from study drug or from the study.

4.2 Scientific Rationale for Study Design

A double-blind, placebo-controlled study will ensure unbiased assessment of safety and tolerability of WVE-006 SC injection. The single ascending doses in Period 1 will provide the best opportunity to determine a safe and potentially efficacious dose to bring forward into Period 2 and additional clinical studies.

4.3 Justification for Dose

Initial Dose

As described in the International Council for Harmonization (ICH) M3(R2) guideline, the selection of the first-in-human (FIH) dose and dose escalation plan will not be higher than that supported by NOAELs from the 5-week interim data of the GLP 13-week repeat dose toxicity studies in mice and cynomolgus monkeys. Selected doses were based on the totality of the data for both mouse and cynomolgus monkey, including the NOAEL provided by the GLP toxicity studies, projected pharmacologically active dose and assessment for potential QTc prolongation risks. The initial dose was selected using the most relevant approaches described in:

- US Food and Drug Administration (USFDA) guidance for industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers (2005).
- European Medicines Evaluation Agency (EMEA) Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products (2017)

CCI [redacted] Two interspecies scaling approaches were used for HED and safety margin projection, a conservative approach based on body surface area (BSA) scaling (FDA, 2005), as well as an empirical approach based on body weight supported by literature, which showed a 1:1 body-weight-based conversion factor from monkey to human and an approximately 1:7 body-weight-based conversion factor from mouse to human for plasma exposure (Nanavati et al., 2021; Wang et al., 2019).

The pharmacological activities of WVE-006 are not expected in HV CCI [redacted]

Dose Escalation

CCI

The planned initial dose for Period 1 is 30 mg (Period 1, Cohort 1). Subsequent dose levels will be determined by the DEC and DMC based on previous Period 1 cohort data and will not exceed a CCI increase of the prior dose. The maximum dose will not exceed the limit specified in Section 4.1.2. Dosing decisions will be communicated directly to the site.

CCI

If adequate safety and tolerability is observed in the initial dose cohorts (Cohorts 1 to 5) and no cohort stopping criterion was met, an optional cohort (Cohort 6) may be conducted in order to characterize the safety, tolerability, PK and the relationship between drug concentration and QTc prolongation at an appropriate dose.

The MTD level from Period 1 will be selected to be explored in Period 2. If the MTD is not achieved in Period 1 and the top dose is well tolerated, then the top dose will likely be selected for Period 2. The projected PK/PD profiles support every other week dosing regimen, but this recommendation is subject to change once clinical data become available. The DEC and DMC may select a lower dose based on all available information.

The exposures of the selected doses during Period 1 and Period 2 of the study will not exceed the observed exposures at the NOAEL.

4.4 End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study.

A participant is considered to have completed the study if the participant has completed all study visits including Week 12 for Period 1, Week 16 for Period 2, or the ET visit.

5 STUDY POPULATION

Participants must meet all inclusion criteria and none of the exclusion criteria during screening. For eligibility purposes, abnormal laboratory or vital signs or ECG results may be repeated once during the Screening period or Day -1 (as applicable) for confirmation if an abnormal result is observed at the initial assessment.

Participants who do not meet all inclusion/exclusion criteria will be considered screen failures. Participants who fail screening may be rescreened; for handling of screen failures and rescreening, refer to Section 5.3.

Deviations to recruitment and enrollment criteria, also known as eligibility waivers or exemptions, are not permitted.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

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/m^2 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:
    a. Non-pregnant as determined by a negative serum pregnancy test at Screening and negative highly sensitive urine pregnancy test on Day -1.
    b. Non lactating.

c. Agree to use a highly-effective method of contraception (as defined in Section 10.4) from CCI prior to Day 1 and for at least CCI following last study drug administration. Exception: Women exclusively engaging in same-sex sexual activities are not required to meet this criterion.
d. Must be willing to forgo ova (egg) donation for at least CCI following the last study drug administration.

9. Women of non-childbearing potential are defined as meeting at least 1 of the following criteria:
   a. At least 12 months post-menopausal and has an FSH >40 mIU/mL.
   b. 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 CCI following the last dose of study drug. In addition, participant must be willing to forgo sperm donation for at least CCI following the last dose of study drug. Men exclusively engaging in same-sex sexual activities are not required to meet this criterion.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

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/1.73mm^2 (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 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.

5.3 Screen Failures

A screen failure occurs when a participant who has consented to participate in the clinical study is not subsequently randomized to study drug. A minimal set of screen failure information will be collected in the electronic data capture (EDC) system and will include date of informed consent, demography (as allowed by local law), failed eligibility criteria, and SAEs.

Individuals who fail screening may be rescreened after discussion with Sponsor's Medical Monitor. Participants should be assigned a new participant number for every screening/rescreening event.

6 STUDY DRUGS AND CONCOMITANT THERAPY

Study drugs are all pre-specified, investigational products intended to be administered to the study participants during the study conduct.

6.1 Study Drugs Administered

Study drugs include WVE-006 and placebo. Details on study drugs are provided in Table 9.

Table 9 Study Drugs Administered

Study Drug Label	WVE-006	Placebo
Study Drug Name	WVE-006	Placebo
Study Drug Description	**Period 1:** SC injection, one dose per participant at varying dose levels. **Period 2:** SC injection, Q2W at a dose level identified in Period 1.	**Period 1:** SC injection, once per participant. **Period 2:** SC injection, Q2W.
Type	Drug	Drug
Dose Formulation	Lyophilized powder for reconstitution	0.9% normal saline, sterile solution for injection
Unit Dose Strengths	CCI per vial	N/A
Dosage Levels	**Period 1:** single dose Starting Dose: 30 mg Highest dose: see Section 4.1.2 **Period 2:** Q2W dosing for a total of 3 doses at the dose level selected from Period 1	N/A (same volume as corresponding WVE-006 dose)
Route of Administration	SC injection	SC injection
Use	Experimental	Placebo
Sourcing	Provided centrally by the Sponsor	Provided locally by the site
Packaging and Labeling	Study drug will be provided in 10 mL single use vial. Each vial will be labeled as required per country requirement.	N/A

Abbreviations: SC = subcutaneous; Q2W = every other week

Table 10 Study Periods

Period Title	Period 1	Period 2
Period Type	Single ascending dose	Multiple dose
Period Description	Participants will receive WVE-006 or placebo once SC starting at 30 mg and escalating as per the study schema.	Participants will receive a total of 3 doses of WVE-006 or placebo Q2W SC at the MTD, highest dose, or other selected dose

	Participants will be followed for 12 weeks.	from Period 1. Participants will be followed for 12 weeks following last study drug administration.
Associated Study Drug Labels	WVE-006, Placebo	WVE-006, Placebo

6.2 Preparation, Handling, Storage, and Accountability

1. The Investigator or designee (e.g., pharmacy staff) must confirm appropriate conditions (e.g., temperature) have been maintained during transit for all study drug received, and any discrepancies are to be reported and resolved before use of the study drug.

2. Only participants enrolled in the study may receive study drug, and only authorized site staff may supply, prepare, or administer study drug.

3. WVE-006 must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the authorized pharmacy staff.

4. The designated staff is responsible for study drug accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

5. The Investigator, pharmacy, and site staff must ensure that study blind is maintained; see Section 6.5 for more information.

6. Returned study drug should not be re-dispensed to participants.

7. Further guidance and instructions for the preparation, handling, storage, accountability, and disposition of study drug is provided in the Pharmacy Manual.

6.3 Study Drug Administration

Study drug will be dispensed at the study visits as summarized in the SoA.

Participants are dosed at the site and will receive study drug directly from the Investigator or designee, under medical supervision. Anatomical SC injection sites will be determined by the Investigator for each participant; if the abdomen is selected as an injection site, it is recommended that the participant be supine when the injection is administered. Rotation of injection sites for multiple dose period is allowed per the Investigator's judgment. The date, time, and anatomic location of each dose administered in the clinic will be recorded in the source documents and eCRF. The dose of study drug and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study drug. Please refer to the Study Manual for additional details regarding administration of study drug.

6.4 Assignment to Study Drug

All participants will be assigned to randomized study drug per assigned randomization schedule. Details will be provided in the randomization plan and executed per site standard.

6.5 Blinding

In order to maintain the blinding of the study drug (WVE-006 or placebo), all study personnel will be blinded to participant treatment assignment. Physicians, nurses, participants, contract research organization (CRO) staff, and any study personnel performing participant assessments must NOT be informed of the participant's treatment assignment (see Study Manual) except if unblinding is required or as required by regulatory authorities (Section 6.5.1).

The pharmacy personnel will be unblinded to prepare doses of study drug to ensure that the clinical site staff responsible for administering study drug and conducting assessments per the protocol, and the participant remain blinded to study treatment. In addition, a clinical research associate will be unblinded to perform drug accountability.

6.5.1 Breaking the Blind

6.5.1.1 Unblinding In Case Knowledge of Treatment May Impact Medical Management

To maintain the overall quality of data collected during the study, breaks in blinding during the conduct of the study should occur only in exceptional circumstances when knowledge of the actual treatment is essential for further management of the participant. Unblinding of the study drug for an individual can be done during the study period in the case of:

- Any AE where knowledge of the treatment assignment is deemed necessary to treat the participant
- Pregnancy of a participant or participant's partner in the study

Procedures for unblinding will be described in a Study Manual supplied to the site. The investigator should make every effort to contact the Sponsor's Medical Monitor before unblinding a participant's treatment assignment unless this could delay emergency treatment of the participant. In all circumstances other than a medical emergency, unblinding will be done only after discussion with the Sponsor's Medical Monitor. Emergency treatment unblinding must be reported to the Sponsor's Medical Monitor immediately. When it is necessary to break the blind, the investigator must notify the Ethics Committee (EC)/Institutional Review Board (IRB) as applicable. If a participant is unblinded, the participant will discontinue further treatment with study drug (i.e., MD) and will have either a routine scheduled visit if due or an unscheduled visit as soon as possible to evaluate the safety concern that prompted the unblinding.

If unblinding is deemed necessary, the Investigator should not disclose the treatment assignment to other study personnel until after database lock.

6.5.1.2 Recording the Unblinding

If an unblinding occurs, the following information should be captured at a minimum:

- Participant information
- Reason for unblinding
- Date and time of unblinding
- Name of the person requesting/responsible for unblinding.

How unblinding should be reported to the Sponsor will be detailed in a Study Manual.

6.6 Study Drug Compliance

The date, time, and anatomic location of each dose administered in the clinic will be recorded in the source documents. Errors in administration (e.g., incorrect dose, injection to incorrect anatomic area) or unexpected issues with injection should be documented and reported to the Sponsor's Medical Monitor.

6.7 Dose Modification

Dose modifications are not applicable in Period 1 since only a single dose will be administered per participant.

Participants in Period 2 will receive the DMC-approved dose at the time of their enrollment. If the DMC determines that a dose reduction is needed AFTER treatment in Period 2 has started, participants who have started study treatment in Period 2 will receive their remaining doses at the reduced dose level.

For dose modifications due to TEAEs, refer to Section 7.1.2.

6.8 Continued Access to Study Drug after the End of the Study

Continued access to WVE-006 is not planned following the end of study.

6.9 Treatment of Overdose

The study drugs are planned to be administered by trained study staff. Administration will be performed in accordance with this protocol and instructions in a Study Manual. Any incidence of overdose should be recorded as a deviation.

No data are available regarding overdose with WVE-006. As with any agent, if overdose occurs, general supportive measures and close observation should be instituted. Misuse of the study drug is not expected in this study as participants have no direct access to the study drug.

6.10 Prior and Concomitant Therapy

Medications with a start date before the first dose of investigational drug will be classified as prior medications. Any medication that the participant began taking after the first dose of investigational drug will be classified as concomitant. Any medication that a participant started before the first dose of investigational drug and continued to take during the study will be classified as both prior and concomitant. Any medication that was stopped on the same day as the first dose of investigational drug will be considered a prior medication. If the stop date of a given medication is missing, then the medication will be classified as concomitant.

It is required that the drug name, dose, indication, and the dates of administration are to be recorded. This will include all prescription drugs, herbal products, vitamins, minerals, and over-the-counter medications. Any changes in concomitant medications will also be recorded in the participant's electronic case report form (eCRF).

Any concomitant medication deemed necessary for the welfare of the participant during the study may be given at the discretion of the Investigator. However, prophylactic medications for injection site reactions are NOT permitted unless first discussed between the Investigator and Medical Monitor.

Prescription or non-prescription drugs, including vitamins, herbal and dietary supplements should not be taken throughout the duration of the study unless required to treat an AE, with the exception of paracetamol and ibuprofen.

Participants should not receive a vaccination, including COVID-19 vaccine injection, within 14 days prior to first dose until completion of the post-study follow up visit.

If intake of any prior or concomitant medication is necessary during the study, the daily dosage, duration and reasons for administration will be recorded on the participant's eCRF.

7 DISCONTINUATION OF STUDY DRUG AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Participants are free to withdraw from the study or discontinue study treatment at any time upon request without prejudice to their future medical care by the Investigator or at the study site. Participation in the study may also be stopped at any time at the discretion of the Investigator or at the request of the Sponsor. Participants who withdraw or discontinue from study treatment will no longer receive investigational drug.

7.1 Discontinuation of Study Treatment in Period 2

A participant must permanently discontinue study treatment for any of the following:

- The participant is withdrawn from the study (Section 7.1.2).
- The participant experiences an AE that in the Investigator's opinion requires treatment discontinuation.
- A change in the participant's medical condition not consistent with the protocol requirements or that justifies discontinuation of study drug.
- Pregnancy (refer to Section 10.3.6).

If a participant discontinues treatment, they will be encouraged to complete the ET visit, unless consent is withdrawn.

The reason for discontinuation of study treatment must be recorded in the eCRF and source documentation.

7.1.1 Period 2 Individual Stopping Criteria:

Dosing will be paused or discontinued (per Investigator judgment) for an individual participant at any time in the study if:

- Participant experiences any severe event or SAE considered at least possibly related to study drug.
- Participant experiences clinically significant hypersensitivity to WVE-006 (or placebo) administration.
- Participant has any medical condition that is judged by the Investigator to jeopardize the participant's safety if he or she continues to receive the study drug.

7.1.2 Withdrawal of Participants from the Study

Participants must be withdrawn from the study for any of the following:

- The participant withdraws consent
- At the discretion of the Investigator for medical reasons

- At the discretion of the Investigator or Sponsor for noncompliance
- Major protocol deviation that may impact interpretation of data (after discussion with Sponsor) (see Section 10.5.2)
- Termination of the study by the Sponsor (see Section 10.1.9)
- At the discretion of the Sponsor for any reason

Any participant for whom consent to participate in the study is withdrawn will be removed from further treatment and study observation immediately upon the date of request. If possible, the early termination study procedures (Section 4.1.4) and observations should be completed before the participant withdraws consent. All information, including the reason for withdrawal from the study (if known), must be recorded in the eCRF and source documentation. Any information collected prior to withdrawal of consent will be used for study purposes.

7.2 Dose Interruption

In Period 2, if a participant is unable to be dosed at a visit, all other assessments planned for that visit per the SoA (Section 1.2) should still be conducted as planned with the exception of PK samples which do not need to be collected. If participant is unable to come to clinic for a visit, that entire visit will be skipped.

If a TEAE caused the second dose to be skipped for a participant in Period 2, it should have resolved or returned to baseline before the participant is restarted on study treatment after consultation with the Sponsor's Medical Monitor.

7.3 Lost to Follow-up

Participants who fail to return for assessments will be contacted by the site in an attempt to have them comply with the protocol. A minimum of 3 documented contact efforts should be made on different days over the course of 2 weeks. If site requirements to consider a participant lost to follow-up are more stringent, the site requirements must be fulfilled. Contact efforts can include phone call, text message, email, or contacting the participant's partner (if applicable). If the participant is unreachable, a registered letter will be sent to the participant requesting him or her to contact the study center. If contact with the participant is not established after all above attempts, this participant will be considered as lost to follow-up.

7.4 Replacements

In Period 1 or 2, additional participants may be enrolled as replacements for discontinued or withdrawn participants (refer to Section 7) in consultation with the Sponsor.

Any participants enrolled but withdrawn prior to the first dose will be replaced. Any participants withdrawn or discontinued after receiving at least one dose may be replaced at the discretion of the Sponsor.

Enrollment/randomization numbers will not be reused. A new, unique enrollment/randomization number will be given to the new participant.

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in Section 1.2. Additional details of each assessment are given below. Screening assessments must meet eligibility criteria as listed in Section 5. Deviations from protocol procedures are not allowed unless required to protect the immediate safety of the participant. In such instances, the Investigator should make every attempt to discuss the need with the Sponsor's Medical Monitor in advance, but no later than within 24 hours after the deviation was implemented. The safety reason(s) for the deviation should be documented.

Results of assessments will be recorded in the eCRF and source documents. In general, any assessment or result the Investigator considers clinically significant should be recorded as an AE.

8.1 General Baseline and Administrative Assessments

8.1.1 Medical History and Demographics

A general medical history will be obtained at the Screening Visit. Investigator assessment of past medical history at Screening will include information regarding any significant medical, surgical, and psychiatric conditions and treatments.

Demographic data will be collected.

8.1.2 Height and Weight

The participant's height and weight will be measured at the time points described in the SoA. To the extent possible, the same scale should be used through the study. BMI will be automatically calculated based on the entered height and weight and will not need to be manually entered.

8.1.3 Eligibility Criteria Review

The Investigator will review the participant's social history, Screening laboratory, and other assessments to confirm that the participant meets all eligibility criteria.

8.1.4 Drug, Alcohol, and Cotinine Screening

A commercially available urine drug screen, alcohol breath or urine test, and cotinine screen will be conducted at the time points described in the SoA. Screening results must meet eligibility criteria. Positive results while the participant is on study must be recorded in the participant's medical record and discussed with the Medical Monitor.

Participants will be instructed to not eat food containing poppy and/or sesame seeds for 3 days before each visit to the Clinical Unit, as consumption of poppy and/or sesame seeds can lead to a positive opiate result in the drugs of abuse test.

8.1.5 Follicle Stimulating Hormone

FSH testing will be done at Screening only as needed to confirm a female participant is not of child-bearing potential.

8.1.6 Viral Serology

Viral serology for hepatitis B, hepatitis C and HIV 1/2 (where testing for HIV is permitted per local regulations) will be conducted at Screening to confirm the participant meets eligibility criteria.

8.1.7 COVID-19 Testing

If applicable, COVID-19 testing will be performed per site SOP at Screening and/or on Day -1 to ensure the participant meets eligibility criteria. Additional COVID-19 testing may be performed if required during the conduct of the study, per site SOPs, at other visits.

8.2 Efficacy Assessments

There are no efficacy assessments as this HV study is focused on safety and PK.

8.3 Safety Assessments

The safety assessments will include the following:

- AEs
- Concomitant medications
- Full and symptom-directed physical examinations
- Vital signs
- Weight / BMI
- Digital continuous and triplicate 12-lead ECGs
- Clinical laboratory evaluations (as per Table 11)
- Pregnancy testing (if applicable)

Strenuous exercise must be completely avoided from 3 days before the first dose of study drug until the final study visit.

See Section 10.3 to determine if abnormal laboratory test results or other safety assessments qualify as AEs.

8.3.1 Prior and Concomitant Medications

It is the responsibility of the Investigator to ensure that details regarding the medication(s) are recorded in full in the eCRF. Refer to Section 6.10 for more details regarding prior and concomitant medications.

8.3.2 Physical Examination

At Screening, a full physical examination will include (but is not limited to) an examination of skin, head, eyes, ears, nose, throat, respiratory, cardiovascular, gastrointestinal, endocrine, metabolic, blood, lymphatic, musculoskeletal, psychiatric, and neurologic (including mental status, cranial nerves, motor system, reflexes, coordination and gait, and sensory system) systems. A full physical examination is required at other visits, as noted in the SoA.

At some time points, a symptom-directed physical examination will include systems to be evaluated as appropriate for the participant's condition and symptoms.

8.3.3 Vital Signs

Vital sign measurements will be taken with the participant in a supine position after the participant has been resting quietly for a period of at least 5 minutes. Blood pressure (systolic and diastolic), temperature, pulse, respiratory rate, and SpO_2 will be measured by qualified personnel at the time points described in the SoA. If the initial reading is high, the measurements will be repeated once to confirm the results.

8.3.4 Digital Continuous and Triplicate 12-Lead ECG

Digital continuous ECG monitoring (e.g., Holter monitor) will be used at the time points specified in Table 4 and Table 7.

For all other time points where an ECG is required, computerized, good quality, 12-lead ECGs will be collected in triplicate and recorded. Recordings will be obtained in the supine position after the participant has rested comfortably for ≥5 minutes. If the initial reading is abnormal, the measurements will be repeated once to confirm the results.

The ECG tracing will be read locally. In the case of clinically significant findings, an ECG may be further reviewed by a board-certified cardiologist for a second opinion. Information should be recorded as to whether the ECG is normal or abnormal and, if deemed abnormal, what the abnormality is, and whether it is clinically significant or not clinically significant.

8.3.5 Clinical Laboratory Evaluations

Clinical laboratory safety testing, as detailed in Section 10.2 will be collected at the time points described in the SoA. Safety laboratory assessments will be conducted by a certified laboratory. If the initial reading is abnormal, the measurements will be repeated once to confirm the results.

When applicable and feasible, blood sampling should follow evaluation of vital signs and ECGs to reduce any impact on these measurements.

8.3.6 Pregnancy Testing

For WOCBP, a serum pregnancy test will be done at Screening and at the final study visit or ET visit. Urine pregnancy tests will be done on Day -1 and at the visits noted in the SoA while on study. A positive urine pregnancy test will be confirmed, as soon as possible, with a serum pregnancy test. If a participant becomes pregnant while on study, refer to Section 10.3.6 for instructions on how this should be reported.

8.4 Adverse Events

The definitions of AEs and SAEs and how they should be recorded, assessed, and reported can be found in Section 10.3.

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE, and remain responsible for following all ongoing AEs to the final study visit or ET visit, at a minimum, or until the Investigator and the Sponsor agree that further follow-up is not required. This includes events reported by the participant or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative.

8.5 Pharmacokinetic Assessments

- Blood samples will be collected for measurement of plasma concentrations of WVE-006 and for potential analysis of metabolites as specified in the SoA (Table 2 and Table 6). The actual date and time (24-hour clock time) of each sample will be recorded. Instructions for the collection and handling of biological samples will be provided by the Sponsor in a Laboratory Manual.

- Plasma and urine samples for analysis of exposure to WVE-006 will be collected at the time points specified in Table 2, Table 3, and Table 6. Samples will be collected at the following time points:

    - Period 1 Plasma PK: Samples will be collected predose within 30 min prior to dose, and postdose at 30 min (±5 min), 1 hr (±5 min), 2 hr (±5 min), 4 hr (±10 min), 6 hr (±10 min), 8 hr (±10 min), 12 hr (±10 min), 24 hr (±30 min), 36 hr (±4 hr), and 48 hr (±4 hr). A sample will be collected at each of the following visits: Days 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, 78 (±3 days), and Day 85 (±5 days)/ET.

    - Period 1 Urine PK: Samples will be collected over 0-4 hr, 4-8 hr, 8-12 hr, 12-18 hr, 18-24 hr, 24-36 hr, and 36-48 hr.

    - Period 2 Plasma PK: Day 1 and Day 29 samples will be collected predose within 30 min prior to dose, and postdose at 30 min (±5 min), 1 hr (±5 min), 2 hr

(±5 min), 4 hr (±10 min), 6 hr (±10 min), 8 hr (±10 min), 12 hr (±10 min), 24 hr (±30 min), 36 hr (±4 hr), and 48 hr (±4 hr). A Day 15 predose sample will be collected at 30 min prior to dose. A sample will be collected at each of the following visits: Days 8, 21, 36, 43, 50, 57, 64, 71, 78, 85 (±3 days) and Day 113 (±5 days) / ET.

- Urine samples will be collected for measurement of concentration of WVE-006 and potential metabolites as specified in the SoA (Table 3). The following parameters will be estimated for the parent drug:
  - Ae: amount excreted in urine
  - Ae%: the percentage of the administered dose that is excreted in urine
  - Cum Ae%: cumulative Ae%
- The timing of sampling may be altered, and PK samples may be obtained at additional time points during the course of the study based on newly available data (e.g., to obtain data nearer the time of peak plasma concentration) to ensure appropriate monitoring of the PK profile.
- Blood samples will be used to evaluate the PK profile of WVE-006 assessed by the following PK parameters, if applicable:
  - AUC_{inf}: area under the curve from time 0 to infinity
  - $AUC_{0\text{-}24h}$: area under the curve from time 0 to 24 hours
  - $AUC_{0\text{-}48h}$: area under the curve from time 0 to 48 hours
  - AUC_{last}: area under the curve from time 0 to the last measurable concentration
  - AUC_{ext}: area under the curve extrapolated to infinity
  - AUC_{tau}: area under the curve over a dosing interval
  - C_{max}: maximum observed concentration
  - t_{max}: time to occurrence of C_{max}
  - $t_{½}$: terminal half-life
  - V_d: volume of distribution
  - CL: clearance
- Samples collected for analyses of WVE-006 plasma concentration may also be used to evaluate safety aspects arising during or after the study.
- PK information that would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

8.6 Pharmacodynamic Assessments

No PD assessments are included in this study.

8.7 Genetics

A blood sample for *SERPINA1* AAT genetic testing will be collected from all participants at Screening. Participants who do not wish to participate in the AAT genetic research will not be able to participate in the study.

Details on processes for collection, shipment, and destruction of these samples can be found in the Laboratory Manual.

8.8 Biomarkers

Biomarkers are not evaluated in this study.

8.9 Immunogenicity Assessments

Samples for antibodies to WVE-006 will be collected and may be analyzed in the future.

8.10 Health Economics

Health economics parameters are not evaluated in this study.

9 STATISTICAL CONSIDERATIONS

The final analyses will be conducted on data collected from participants after the study database is locked at the end of the study.

The statistical analysis plan will be created and finalized prior to the study database lock, and it will include more details of the planned statistical analysis for data that have been collected in this study. This section is a summary of the planned statistical analyses for the most important endpoints.

9.1 Sample Size Determination

The sample size for this Phase 1 study on HV was not calculated on the basis of statistical hypothesis testing. However, the number of participants (up to 40 in the SAD period and 8 in the multiple-dose period) is considered sufficient for this study to assess safety and tolerability for WVE-006 and to establish PK profile of WVE-006.

9.2 Analysis Populations

The following analysis sets will be defined for SAD and multiple-dose portions of the data analyses.

- Safety population will include randomized participants who have received at least 1 dose of study medication. The safety population will be the analysis set used for summaries of safety data collected in the respective period.
- PK population will consist of participants in the safety population with at least 1 post dose plasma concentration measurement.

9.3 Statistical Analyses

9.3.1 General Considerations

Data collected in the SAD and multiple-dose periods will be summarized and reported separately by dose groups (e.g., a given dose cohort will be a dose group). For the SAD period, data from participants who received placebo will be pooled across cohorts and summarized and presented as the “Placebo” dose group, which will be handled as one of the dose groups throughout this section.

Baseline for a SAD participant is defined as the last non-missing measurement collected prior to the administration of the single dose. Baseline for a multiple-dose participant is defined as the last non-missing measurement collected prior to the administration of study drug at Week 0 of multiple-dose period. Unless otherwise specified, the analyses described in the following sections apply to data collected in both SAD and multiple-dose periods.

Descriptive statistics (n, mean, standard deviation [SD], median, minimum and maximum values for continuous variables, and number and percentage of participants in each category for categorical variables) will be used for data summary by treatment group for each cohort.

9.3.2 Disposition of Participants

Screened participants are defined as any participant who signed the ICF, and the number of screened participants will be summarized by dose group.

Randomized participants consist of participants who signed the ICF and were subsequently randomly assigned. For each cohort, the number of randomized participants receiving placebo or WVE-006 will be tabulated.

The number and percentage of participants who discontinued from the study along with the reasons of discontinuation will be summarized by dose group for the safety population.

9.3.3 Participants' Demographics and Baseline Characteristics

Participants' demographics (age, gender, and race) and other baseline characteristics will be summarized by dose group for the safety population.

9.3.4 Study Drug Exposure and Compliance

The number of participants who received study drug will be summarized by dose group, and compliance (for Period 2) will also be summarized for the safety population.

9.3.5 Analysis of Safety Data

Safety analyses will be performed on the safety population.

9.3.5.1 Adverse Events

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study drug, whether or not considered related to the study drug.
- A treatment-emergent AE (TEAE) is defined as an AE not present before exposure to study treatment or any event already present that worsens in severity or frequency from the date of receiving first dose of study treatment to study completion or discontinuation.

General rules of analysis and reporting of AEs:

- AEs reported by Investigators will be coded to system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA).
- For an event with multiple occurrences during the study, the event is only counted once in occurrence summary, the maximum severity is used when reporting the severity, the highest level of association will be used to characterize relatedness to study drug in reporting.

The number and percentage of participants who have at least a TEAE, a grade 3 or 4 TEAE, a study drug-related TEAE as judged by the Investigator will be summarized by dose group. In addition, the number and percentage of participants who have a TEAE that leads to study drug discontinuation or who died due to occurrence of a TEAE will also be summarized by dose group. The percentage for the aforementioned summaries will be calculated based on the number of participants in each dose group.

For each dose group, TEAEs will be presented by PT with the descending frequency of occurrence based on the pooled WVE-006 dose groups. In addition, TEAEs will also be summarized by SOC, PT, and the severity for each dose group.

The number and percentage of participants who had at least one SAE will be summarized by SOC and PT for each dose group. In addition, SAEs will be tabulated by dose group.

9.3.5.2 Analysis of Clinical Laboratory Evaluations, Vital Signs, and ECG Parameters

For laboratory parameters, change from baseline to maximum or minimum value during the study will be summarized by dose group for each parameter and reported by laboratory group, respectively. In addition, changes from baseline to each post-baseline visit will also be summarized by dose group.

Clinically significant changes will be summarized by dose group for vital signs.

A shift table presenting the shift from baseline to each post-baseline assessment in terms of Normal or Abnormal by dose group will be used to report ECG findings during the study.

9.3.6 Pharmacokinetic Analysis

PK data will be summarized descriptively and presented in both graphical and/or tabular formats.

PK parameters for WVE-006 and potential metabolites will be calculated using non-compartmental methods. PK parameters will be summarized for each WVE-006 dose group on the PK population using descriptive statistics: n, arithmetic mean, median, SD, minimum, maximum, and percent coefficient of variation (CV%); in addition, the geometric mean and geometric CV% will be reported for C_{max} and AUCs.

The PK parameters described in Section 8.5 will be calculated for participants who receive at least one dose of WVE-006 during the study. Additional PK parameters may be evaluated if deemed necessary.

When appropriate, the correlation between QTcF and WVE-006 will be evaluated, and the results may be reported separately from the Clinical Study Report.

When appropriate, the identification and quantification of WVE-006 and its metabolites in urine will be performed and the results may be reported in a separate report.

9.3.7 Interim Analyses

No interim analyses are planned.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines
  - Applicable ICH Good Clinical Practice (GCP) guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/EC by the Investigator and reviewed and approved by the IRB/EC before the study is initiated.
- Any substantial amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will be responsible for the following, as applicable:
  - Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
  - Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/EC, European regulation 536/2014 for clinical studies, European Medical Device Regulation 2017/745 for clinical device research, and all other applicable local regulations

10.1.2 Financial Disclosure

Investigators and sub-investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are

responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3 Informed Consent Process

- ICF templates will be provided to investigative sites. If any institution-specific modifications to study-related procedures are proposed or made by the site, the ICF(s) must be reviewed by the Sponsor or its designee or both before IRB/EC submission. Once reviewed, the ICF(s) will be submitted by the Investigator to his or her IRB/EC for review and approval before the start of the study. If the ICF(s) is revised during the course of the study, active participants must sign the revised form.

- Before Screening, each prospective participant will be given a full explanation of the study and be allowed to read the approved ICF, as well as consult with others, as appropriate.

- The Investigator or the Investigator's qualified representative will explain the nature of the study, including the risks and benefits, to the potential participant and answer all questions regarding the study.
- Once the Investigator is assured that the participant understands the implications of participating in the study, the participant will be asked to give consent to participate in the study by signing the appropriate ICF.
- Potential participants must be informed that their participation is voluntary and that they will be required to sign a statement of informed consent.
- The Investigator will use the approved ICF, which is intended to meet the requirements of 21 CFR 50, the Declaration of Helsinki, local regulations, ICH and GCP guidelines, privacy and data protection laws and regulations, as applicable, and the IRB/EC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- The ICF must be signed prior to conduct of any study-related activities for the participant.
- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.
- The Investigator will retain the signed original ICF(s).
- A copy of the ICF(s) must be provided to the participant.

10.1.4 Privacy and Data Protection

10.1.4.1 Privacy

The Sponsor and Investigator(s) will ensure that this study is conducted in accordance with the most recent version of the applicable privacy laws, including local privacy laws. Additional information on how the Sponsor handles privacy can be found at https://wavelifesciences.com/privacy/.

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that their personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the ICF.
- The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities, as applicable.
- The contract between the Sponsor and study sites specifies responsibilities of the parties related to data protection, including handling of data security breaches and respective communication and cooperation of the parties.
- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data.

10.1.5 Committees Structure

10.1.5.1 Data Monitoring Committee

An independent DMC composed of relevant medical experts and a statistician will be established to oversee study safety and recommend dose selection and escalation. DMC members will be unblinded. The DMC will oversee the overall safety of the study and will also provide input on dose escalation decisions along with the DEC (see Section 10.1.5.2). Details of the DMC such as composition, content (e.g., safety assessments to be summarized or listed) and frequency of data reports, and meeting frequency will be recorded in the DMC charter.

10.1.5.2 Dose Escalation Committee

A DEC will be established to oversee dose selection and escalation decisions in Periods 1 and 2. The DEC will consist of the Investigator and blinded Sponsor representative. Details of the DEC such as composition and blinded data the DEC will require for each dose escalation decision will be recorded in the DEC charter.

10.1.6 Dissemination of Clinical Study Data

Whether the study is completed or terminated prematurely, the Sponsor will ensure that a final report is prepared and provided to the regulatory agency(ies), as applicable. The Sponsor will also ensure that the clinical study reports (CSRs) in marketing applications meet the standards of the ICH Guideline E3: Structure and Content of Clinical Study Reports.

In accordance with local regulatory requirements, an Investigator will be identified for the approval and signoff of the clinical study report. The Investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results.

10.1.7 Data Quality Assurance

- All participant data relating to the study will be recorded on the eCRFs unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- Guidance on completion of eCRFs will be provided in eCRF Completion Guidelines.
- The Investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source documents.
- Monitoring details describing strategy, including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan and/or contracts.
- The Sponsor or designee is responsible for the data management of this study, including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (e.g., CROs).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the study drug unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.7.1 Electronic Case Report Forms and Data Management

Data will be entered directly from the source documents to the eCRFs within the Sponsor-provided EDC system following the eCRF Completion Guidelines. Source documents should be clear, complete, and accurate and should include all the details of study assessments performed per the protocol. The Investigator is responsible for ensuring the data entered on the eCRFs are accurate and complete and all data are entered in a timely manner.

The final eCRF data and audit trails will be archived in an electronic media and placed in the Investigator's study file.

10.1.7.2 Inspection of Records

Investigators and institutions involved in the study will permit study-related monitoring, audits, IRB/EC review, and regulatory inspections by providing direct access to all study records, or as appropriate per local regulations. In the event of an audit, the Investigator agrees to allow the Sponsor, representatives of the Sponsor, or regulatory authorities access to all study records.

The Investigator should notify the Sponsor promptly of any audits scheduled by any regulatory authorities and will promptly forward copies of any audit reports to the Sponsor.

10.1.8 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. Current medical records must be available.
- Definition of what constitutes source data and its origin can be found in the monitoring plan.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Sponsor or designee will perform monitoring to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.9 Study and Site Start and Closure

First Act of Recruitment

The first act of recruitment is the signing of the first ICF and will be the study start date.

Study/Site Termination

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure by the Sponsor or Investigator may include but are not limited to:

- For study termination:
  - Discontinuation of further study drug development
- For site termination:
  - Failure of the Investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the Sponsor's procedures, or GCP guidelines
  - Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the Investigator

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IRBs/ECs, the regulatory authorities, and CROs used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Upon completion or termination of the study, the study monitor will conduct site closure activities with the Investigator or site staff (as appropriate), in accordance with applicable regulations, ICH GCP, and SOPs.

10.1.10 Publication Policy

All information regarding WVE-006 supplied by the Sponsor to the Investigator or generated as a result of any clinical studies is privileged and confidential information belonging to the Sponsor. The Investigator agrees to use Sponsor's confidential information solely to accomplish the study and will not use or publish such information for any other purposes without the prior written consent of the Sponsor. The Investigator is obligated to provide the Sponsor with complete and accurate data obtained during the study. The information obtained from the clinical study will be used toward the development of WVE-006 and may be disclosed by the Sponsor to regulatory authority(ies), other Investigators, corporate partners, and consultants as required.

It is anticipated that the results of this study may be presented at scientific meetings and/or published in a peer-reviewed scientific or medical journal. The Investigator may publish results from the study in compliance with their agreements with the Sponsor. A pre-publication

manuscript is to be provided to the Sponsor at least 45 days prior to the submission of the manuscript to a publisher.

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 11 will be performed per the Sponsor provided Laboratory Manual.
- Laboratory tests will be done at the time points per the SoA in Section 1.3. Urine dipstick and urine pregnancy test results will be recorded in the participant's medical record and corresponding eCRFs.
- Protocol-specific laboratory value requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.
- Investigators must document their review of each laboratory safety report. Any laboratory result considered by the Investigator as clinically significant must be documented as AE and graded per CTCAE criteria. (see Section 10.3).

Table 11 Detailed Clinical Laboratory Tests

Laboratory Tests	Parameters	
Hematology[1]	• Platelet count	
	• Red blood cell (RBC) count	
	– RBC indices	– Mean corpuscular volume (MCV) – Mean corpuscular hemoglobin (MCH) – Mean corpuscular hemoglobin concentration (MCHC) – %Reticulocytes
	• White blood cell (WBC) count with differential:	– Neutrophils – Lymphocytes – Monocytes – Eosinophils – Basophils
	• Hemoglobin	
	• Hematocrit	
	• Markers of Inflammation	– C-reactive protein – Complement (C3, Bb, C3a, and sC5b9)
Clinical chemistry[2]	• Blood urea nitrogen (BUN) • Potassium • Creatinine • Sodium • Gamma glutamyl transferase • Chloride • Bicarbonate • Blood glucose	• Aspartate transaminase (AST) • Alanine transaminase (ALT) • Alkaline phosphatase • Total Bilirubin (direct bilirubin if Total Bilirubin is elevated) • Creatine phosphokinase • Total protein • Albumin[1] • Glutamate dehydrogenase (GLDH)

Coagulation[1]	• Prothrombin time or international normalized ratio (INR) (per site's laboratory standards) • Activated partial thromboplastin time (aPTT) • Fibrinogen
Routine urinalysis	• Specific gravity, pH, glucose, protein, blood, ketones, bilirubin, urobilinogen – If abnormal findings (excluding trace) by dipstick or urinalysis are noted, urine microscopy is required
Pregnancy testing	• FSH testing will be conducted at baseline if needed to confirm WOCBP status. • Highly sensitive serum or urine human chorionic gonadotropin (hCG) pregnancy test (as needed, for women of childbearing potential)
Other screening tests	• *SERPINA1* genotyping • Alcohol breath or urine test • Cotinine • Drug screen, which will include: – Amphetamines – Methamphetamines – Methadone – Barbiturates – Benzodiazepines – Cocaine – Opiates – Methylenedioxymethamphetamine – Phencyclidine – Tetrahydrocannabinol • Serology (HIV antibody, C-19 [if applicable], hepatitis B surface antigen [HBsAg], hepatitis C virus antibody,). If hepatitis B or C serology is positive, the following reflex testing should be done: – Hepatitis B: total anti-HBc, IgM anti-HBc, and anti-HBs – Hepatitis C: HCV-RNA

NOTES:

1. Refer to Table 2 and Table 6 for specific time points at which these laboratory assessments are required.

10.3 Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

An AE is defined as any untoward medical occurrence in a participant enrolled into this study regardless of its causal relationship to study treatment. Participants will be instructed to contact the Investigator at any time after enrolling if any symptoms develop.

The Investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to study treatment or their clinical significance.

AE information will be collected beginning at enrollment (time of signed ICF) and up to the end of the study. All ongoing AEs at the end of the study will be followed to resolution, stabilization, or until the Investigator and the Sponsor agree that further follow-up is not required.

A TEAE is defined as any new AE that begins following study drug treatment that was not present before exposure to study drug treatment or any condition already present that worsens in either intensity or frequency after exposure to study drug treatment.

10.3.1 Eliciting and Documenting Adverse Events

All AEs reported or observed during the study will be recorded on the AE page in the eCRF and in the site source notes. The eCRFs used to document AEs are designed to help ensure this information is collected in a standard way. Information to be collected includes AE term, date and time of onset, date and time of resolution, Investigator-specified assessment of severity and relationship to study treatment, action taken with respect to study treatment, seriousness, any required treatment or evaluations, and outcome. For AEs of injection site reactions, additional information will be collected in the eCRF and source document. The sites will be provided with completion guidelines for the eCRF, which will further guide them on how to record the data, including AEs. MedDRA will be used to code all AEs.

In addition to observations of the participant, AEs identified from any study data (e.g., laboratory values, physical examination findings, ECG changes) or identified from review of other documents that are considered clinically significant will be documented on the AE page in the eCRF.

AEs will be assessed at each visit by direct questioning from site staff, as well as elicited from physical examination by site staff (when applicable). In addition, all sites in the study must ensure participants have a 24-hour telephone number to contact medical site staff for the duration of the study in case of emergent AEs or SAEs.

If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

10.3.2 Time Period and Frequency for Collecting AE and SAE Information

AEs and SAEs will be collected beginning with the signing of the ICF until the last study visit or ET visit.

Medical occurrences that begin before the start of study drug but continue after obtaining informed consent will be recorded as medical history/current medical conditions, not as AEs unless the condition has worsened in terms of severity or frequency.

Investigators are not obligated to actively seek information on AEs after conclusion of study participation. SAEs that occur after the final follow-up visit need not be reported unless the Investigator considers them at least possibly related to study drug. However, if the Investigator learns of any pregnancy within a month after a participant completed or was discharged from the study, the Investigator must promptly notify the Sponsor (see Section 10.3.6).

10.3.3 Follow-up of AEs and SAEs

After the initial AE, the Investigator is required to follow each participant at subsequent visits/contacts. AEs will be followed until resolution, stabilization, the event is otherwise explained, the final study visit, or the participant is lost to follow-up (as defined in Section 7.3).

10.3.4 Definitions of Adverse Event Severity and Relationship to Study Drug

10.3.4.1 Severity

The severity or intensity of an AE refers to the extent to which an AE affects the participant's daily activities. AE severity (except for injection site reactions, covered in Section 10.6) will be evaluated using the criteria outlined in National Cancer Institute (NCI)-CTCAE Version 5.0 to determine its severity. The full reference can be found at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf.

Table 12 NCI-CTCAE General Grading Criteria

Grade	AE Severity	Definition
1	**Mild**	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	**Moderate**	Moderate; minimal, local or noninvasive intervention indicated.
3	**Severe**	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care.
4	**Life-threatening**	Life-threatening consequences; urgent intervention indicated.
5	**Death**	Death related to AE.

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; NCI = National Cancer Institute.
Note: the most applicable grading criteria should be used based on the nature of the AE, and this table should be used if none of the specific criteria match the AE.

Changes in the severity of an AE should be documented in the eCRF to allow an assessment to be performed related to the duration of the event at each level of intensity.

10.3.4.2 Relationship to Study Drug

The Investigator's assessment of an AE's relationship to study treatment is part of the documentation process. All AEs, regardless of relationship, will be recorded in the eCRF. In addition, SAEs will be reported to regulatory authorities as required by local regulation (Section 10.3.5.4).

The relationship or association of the study drug in causing or contributing to the AE will be characterized using the following classification and criteria presented in Table 13.

Table 13 Guidelines for Determining the Relationship (if any) Between Adverse Event and the Study Drug

AE Relationship	Definition
Definite	This relationship suggests that a definite causal relationship exists between treatment administration and the AE, and that other conditions (concurrent illness, progression/expression of disease state, or concurrent medication reaction) do not appear to explain the event. The event reappears or worsens if the study treatment is re-administered.
Probable	This relationship suggests that a reasonable temporal sequence of the event with treatment administration exists, and, based upon the known pharmacological action of the treatment, known or previously reported adverse reactions to the treatment or class of treatment, or judgment based on the Investigator's clinical experience, the association of the event with the study treatment seems likely. The event disappears or decreases on cessation of study treatment.
Possible	This relationship suggests that the study treatment caused or contributed to the AE, i.e., the event follows a reasonable temporal sequence from the time of treatment administration or follows a known response pattern to the study treatment but could also have been caused by alternative factors.
Unlikely Related	This relationship suggests an improbable (but not impossible) association between the study medication and the reported event.
Not Related	This relationship suggests no association between the study treatment and the reported event.

Abbreviations: AE=adverse event.

10.3.5 Serious Adverse Events

10.3.5.1 Serious Adverse Events Criteria

An SAE is defined as any event that results in:

- Death
- Is immediately life-threatening. A life-threatening event does not include an AE that if it had occurred in a more severe form, might have caused death.
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity

- Is a congenital anomaly
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when they, based upon appropriate medical judgment, may jeopardize the participant or may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Any hospital admission with at least one overnight stay will be considered an inpatient hospitalization. However, emergency department visits that do not result in overnight hospitalization would only be considered an SAE if they meet other SAE criteria (e.g., important medical event). Admission to the hospital for social or situational reasons (e.g., no place to stay, long distance for hospital visits, etc.) will not be considered as meeting hospitalization criteria for defining an SAE.

Hospitalization for an elective or outpatient procedure for a pre-existing condition will not be considered as an SAE and should be captured under procedures in the eCRF. However, unexpected complications and/or prolongation of hospitalization during elective surgery/procedure should be reported as an SAE.

Serious AEs must be reported within 24 hours; any updated SAE data will also be reported within 24 hours of it being available. SAEs that occur after the final follow-up visit need not be reported unless the Investigator considers them at least possibly related to study drug.

10.3.5.2 Suspected Unexpected Serious Adverse Reaction

A suspected unexpected serious adverse reaction (SUSAR) is an SAE for which there is a reasonable possibility that the study drug caused the event, and this SAE has not been previously identified as an expected/listed AE. A list of expected AEs (if applicable) is provided in the current version of the IB and is considered the Reference Safety Information (RSI) for the study. Generally, the indication for which a product is intended would not be on the list of expected serious adverse reactions (SAR), but if it did occur, would not be considered "unexpected" for SUSAR reporting. As an example, a flare-up of symptoms consistent with the underlying disease under treatment that required hospitalization would constitute a SAR; however, the event would not be considered unexpected. An exception would be if the reporter believed that study drug worsened the underlying condition.

10.3.5.3 Serious Adverse Event Follow-up

Appropriate remedial measures should be taken by the Investigator using his/her best medical judgment to treat the SAE. These measures and the participant's response to these measures should be recorded. All SAEs, regardless of relationship to study drug, will be followed by the Investigator until resolution or stabilization. Clinical, laboratory, and diagnostic measures should be employed by the Investigator as needed to adequately determine the etiology of the event.

10.3.5.4 Serious Adverse Event Reporting

10.3.5.4.1 Reporting Requirements

Any AE that meets SAE criteria must be reported to the Sponsor and/or designee immediately (i.e., within 24 hours) after the time site personnel first learn about the event using the SAE Report Form provided for the study. Regardless of causality, all SAEs must be reported and will be collected and recorded from the time the participant/legal guardian signs the ICF until completion of the final follow-up visit. All SAEs must also be recorded in the participant's source documentation and on the AE page of the participant's eCRF.

The initial report should include at least the following information:

- Study number
- Participant's identification number
- Description of the event
- Date and time of onset of the event
- Seriousness criteria
- Causality assessment to study drug

If follow-up is obtained or requested by the Sponsor and/or designee, the additional information should be emailed on an SAE Report Form to the Sponsor in a timely manner according to the procedures and timelines outlined above. Copies of discharge summaries, consultant reports, autopsy reports, and any other relevant documents may also be requested.

The Investigator will be responsible for reporting all SAEs to the IRB or EC. The Sponsor will be responsible for reporting to the regulatory authorities and Central Ethics Committees, as per local requirements.

An Investigator who receives an Investigator Safety Report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and file it along with the IB and will notify the IRB/EC, if appropriate according to local requirements.

10.3.5.4.2 SAE Contact Information

Current SAE contact information can be found in the Study Manual.

10.3.6 Pregnancies

If a participant becomes pregnant during the study, she must be discontinued from study drug and monitoring of the participant and fetus should be conducted until the pregnancy outcome is known. The Investigator should notify the Medical Monitor, and a Pregnancy Notification Form should be completed. At the completion of the pregnancy, the Investigator will document the outcome of the pregnancy.

If a male participant's partner becomes pregnant during the study, the same reporting and monitoring requirements will apply, but the partner must first consent to being followed.

If the Investigator becomes aware of a pregnancy up to a month after participant's completion of the study, the pregnancy will be reported to the Sponsor's Medical Monitor and followed up as described above.

Pregnancy in and of itself is not an SAE. Complications of the pregnancy that meet seriousness criteria (e.g., hospitalization) should be reported to the Sponsor within 24 hours of knowledge by the Investigator (i.e., if the mother is hospitalized for dehydration) and an SAE form must be completed. In addition, if the pregnancy ends for any reason before the anticipated date, the Investigator should notify the Sponsor. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting an SAE.

10.4 Appendix 4: Contraceptive and Barrier Guidance

Participants who are sexually mature and sexually active must be willing to use contraception as noted in Section 10.4.2 from CCI prior to Day 1 through CCI after the last dose of study drug for females and from Day 1 through CCI after the last dose of study drug for males. If site requirements for contraception are more stringent, the site requirement will be followed.

Of note, men or women exclusively engaging in same-sex sexual activities are not required to use contraception.

10.4.1 Definitions

10.4.1.1 Non-Childbearing Potential

A woman of non-childbearing potential is defined in criterion 9 of Section 5.1.

If a female participant's child-bearing potential is uncertain in the Investigator's opinion, FSH testing will be conducted at Screening (see Table 1 and Table 5).

10.4.2 Highly Effective Methods of Contraception

Contraception methods that can achieve a failure rate of <1% per year when used consistently and correctly are considered highly effective. Such methods include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Injectable
  - Implantable
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal ligation
- Vasectomized sole partner (for a participant who is a WOCBP)

For male participants only:

- Condom, with or without spermicide, or
- At least 3 months following successful vasectomy

10.5 Appendix 5: Management of Protocol Amendments and Deviations

10.5.1 Modification of the Protocol

Changes in this research activity, except those necessary to remove an apparent, immediate hazard to the participant, must be reviewed and approved by the Sponsor or designee. Amendments to the protocol must be submitted in writing to the Investigator's IRB/EC and regulatory authorities for approval before participants can be enrolled into an amended protocol.

10.5.2 Protocol Deviations

A deviation from the protocol is any change, divergence, or departure from the study design or procedures defined in the protocol and associated manuals, ICF, recruitment process, or study materials approved by the Sponsor, Investigator, and the IRB/EC.

Important protocol deviations are a subset of protocol deviations that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a participant's rights, safety, or well-being. For example, important protocol deviations might include enrolling participants in violation of key eligibility criteria designed to ensure a specific study population or failing to collect data necessary to interpret primary endpoints, as this may compromise the scientific value of the study.

All processes and procedures defined in this protocol must be adhered to. Emergency departures from the protocol that eliminate an apparent immediate hazard to a particular participant and that are deemed by the Investigator as crucial for the safety and well-being of that participant may be instituted for that participant only and documented as deviations. The Investigator will contact the Medical Monitor as soon as possible regarding such a deviation. These departures do not require preapproval by the IRB/EC; however, the IRB/EC and Medical Monitor must be notified in writing as soon as possible in accordance with the IRB/EC policies after the departure has been made.

Protocol deviations will be documented by the clinical monitor in the clinical study management system and on monitoring reports throughout the course of monitoring visits. Investigators will be notified in writing by the monitor of deviations. As required by local regulatory authorities, the Investigator will notify the IRB/EC of any applicable protocol deviations in a timely manner.

No protocol deviations to eligibility, also known as waivers, will be permitted.

10.6 Appendix 6: Grading of Injection Site Reactions

Individual signs or symptoms (e.g., erythema, swelling, etc.) at the injection site reported by a participant following study drug administration will be recorded as an injection site reaction and as an AE if grade 1 or more.

Grading of Injection Site Reactions (FDA, 2007)

Local Reaction to Injectable Product	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room (ER) visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/Redness	2.5 – 5 cm	5.1 – 10 cm	>10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling*	2.5 – 5 cm and does not interfere with activity	5.1 – 10 cm or interferes with activity	>10 cm or prevents daily activity	Necrosis

* Induration/Swelling should be evaluated and graded using the functional scale, as well as the actual measurement.

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