AQUALUNG THERAPEUTICS

TARGETING RUNAWAY INFLAMMATION

PUERTA

(Pioneering the Utility of eNAMPT-Reducing Therapies in Acute Respiratory Distress Syndrome [ARDS]/ ventilator-induced lung injury [VILI])

A Phase 2a, multi-center, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of ALT-100 in patients with moderate to severe acute respiratory distress syndrome (ARDS)

Investigational Product(s)	ALT-100
Active Ingredient(s)	Humanized monoclonal antibody (mAb)
Protocol Number	ALT-100-002
Phase	2a
Version Number	3.0
Version Date	30 May 2023
Amendment	2
IND Number	153308
Sponsor	Aqualung Therapeutics Corporation. 6080 N. Pinchot Road Tucson, AZ, 85750, USA

Confidentiality Statement

STATEMENT OF COMPLIANCE

The study will be conducted in compliance with this clinical study protocol, Good Clinical Practices (GCP) as outlined by International Council for Harmonization (ICH) E6(R2), and all applicable local and national regulatory requirements. Enrollment at any clinical research unit may not begin prior to that site receiving approval from the ethics committee of record for the protocol and all materials provided to potential participants.

Any amendments to the protocol or changes to the consent document will be approved before implementation of that amendment. Reconsent of previously enrolled participants may be necessary depending on the nature of the amendment.

The Principal Investigator will ensure that changes to the study plan as defined by this protocol will not be made without prior agreement from the Sponsor and documented approval from the ethics committee of record, unless such a change is necessary to eliminate an immediate hazard to the study participants.

All personnel involved in the conduct of this study have completed Human Participants Protection and GCP Training as outlined by their governing institution.

SPONSOR'S APPROVAL

Title	PUERTA (Pioneering the Utility of eNAMPT-Reducing Therapies in Acute Respiratory Distress Syndrome [ARDS]/ ventilator-induced lung injury [VILI]) A Phase 2a, multi-center, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of ALT-100 in patients with moderate to severe ARDS
Protocol Number	ALT-100-002
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Amendment	2

The design of this study as outlined by this protocol has been reviewed and approved by the Sponsor's responsible personnel as indicated in the signature table below.

Sponsor Representative		
Name:	**Title:**	**Signature and Date:**
Joe GN Garcia, MD	CEO and Founder, Aqualung Therapeutics Corporation	Joe GN Garcia MD Joe GN Garcia MD (May 30, 2023 18:09 PDT)

INVESTIGATOR'S AGREEMENT

I have read the protocol, appendixes, and accessory materials related to ALT-100-002 and agree to the following:

- To conduct this study as described by the protocol and any accessory materials
- To protect the rights, safety, and welfare of the participants under my care
- To provide oversight to all personnel to whom study activities have been delegated
- To control all investigational products provided by the Sponsor and maintain records of the disposition of those products
- To conduct the study in accordance with all applicable local and national regulations, the requirements of the ethics committee of record for my site, and GCP as outlined by ICH E6(R2)
- To obtain approval for all written materials provided to participants and protocol prior to initiating the study at my site
- To obtain informed consent – and updated consent in the event of new information or amendments – from all participants at my site prior to initiating any study-specific procedures or administering investigational products to those participants
- To maintain records of each participant's participation and all data required by the protocol

Name	**Title**	**Institution**
Signature		**Date**

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADA	Anti-drug antibodies
AE	Adverse event
ANOVA	Analysis of variance
AR	Adverse reaction
ARDS	Acute respiratory distress syndrome
ATC	Anatomical Therapeutic Chemical
BAL	Bronchoalveolar lavage
BLQ	Below the limit of quantification
BMI	Body mass index
cGMP	Current good manufacturing practice
CI	Confidence interval
COVID-19	Corona Virus Disease 2019 caused by SARS-CoV-2
CRO	Clinical research organization
CSR	Clinical study report
CT	Computed tomography
CTMS	Clinical Trial Management System
CV	Coefficient of variation
DAMP	Damage-associated molecular pattern
DMARDS	Disease modifying anti-rheumatic drugs
DoD	Day of discharge
DSMC	Data Safety Monitoring Committee
ECG	Electrocardiogram
ECMO	Extracorporeal membrane oxygenation
eCRF	Electronic case report form
eNAMPT	Extracellular nicotinamide phosphoribosyltransferase
EoS	End of study
ET	Early termination
FIH	First-in-human
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practices
GLP	Good Laboratory Practice
H&E	Hematoxylin and eosin
HCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HFD	Hospital-free days
HFNO	High flow nasal oxygen
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Council for Harmonization
ICU	Intensive care unit

Abbreviation	Definition
IEC	Independent ethics committee
IGRA	Interferon gamma release assay
IND	Investigational new drug
INR	International normalized ratio
IP	Investigational product
IRB	Institutional review board
ITT	Intention-to-treat
IUD	Intrauterine device
JAK	Janus kinase
LAR	Legally authorized representative
LIS	Lung injury score
LPS	Lipopolysaccharide
MDRD	Modification of diet in renal disease
MedDRA	Medical Dictionary for Regulatory Activities
MM	Medical monitor
MV	Mechanical ventilation
MVFD	Mechanical ventilation-free days
NAMPT	Nicotinamide phosphoribosyltransferase
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NIPPV	Non-invasive positive pressure ventilation
NIV	Non-invasive ventilation
NOAEL	No observable adverse effect level
OCP	Oral contraceptive pills
PCR	Polymerase chain reaction
PD	Pharmacodynamic
PEEP	Positive end-expiratory pressure
PI	Principal investigator
PICF	Participant informed consent form
PK	Pharmacokinetics
PM	Project manager
PMNs	Polymorphonuclear neutrophils
PN	Preferred name
PP	Per protocol
PPD	Purified protein derivative
PT	Preferred term
PV	Pharmacovigilance
RNA	Ribonucleic acid
RT-PCR	Reverse transcription polymerase chain reaction
SAD	Single ascending dose
SAE	Serious adverse event
SAP	Statistical analysis plan

Abbreviation	Definition
SAR	Suspected adverse reaction
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus-2
SD	Standard deviation
SMC	Safety monitoring committee
SNP	Single nucleotide polymorphism
SoA	Schedule of assessments
SoC	Standard of care
SOC	System organ class
SOFA	Sequential organ failure assessment
SUSAR	Suspected unexpected serious adverse reaction
TB	Tuberculosis
TBD	To be determined
TEAE	Treatment-emergent adverse event
TK	Toxicokinetic
ULN	Upper limit of normal
US	United States
VILI	Ventilator-induced lung injury
WHO	World Health Organization
WOCBP	Women of child-bearing potential

Laboratory analysis related acronyms are defined in Table 6.

Pharmacokinetic related acronyms are defined in Table 7.

1 SYNOPSIS

Title	PUERTA *(Pioneering the Utility of eNAMPT-Reducing Therapies in Acute Respiratory Distress Syndrome [ARDS]/ ventilator-induced lung injury [VILI]):* A Phase 2a, multi-center, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of ALT-100 in patients with moderate to severe ARDS
Protocol Number	ALT-100-002
Phase of Development	Phase 2a
Study Sites	Approximately 2 sites in Australia and 8 sites in the United States (US)

Objectives and Endpoints

Primary	**Objectives**	**Endpoints**
	Safety	
	Safety and tolerability of a single intravenously (IV) infused dose of ALT-100 in subjects with moderate to severe ARDS.	• Incidence and severity of all treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) until end of study (EoS).
Secondary	***Efficacy***	
	To evaluate the impact of a single IV infusion of ALT-100 on respiratory support.	• Number of mechanical ventilation (MV)-free days (MVFD) over 28 days following study treatment (ie, MVFDs by Day 29).
	To assess the effect of ALT-100 on duration of hospitalization.	• Time to hospital discharge based on days since admission to discharge. • Hospital-free days (HFD) to Day 29.
	To assess the effect of ALT-100 as measured by the Sequential Organ Failure Assessment (SOFA) score.	• Total and component SOFA score assessed daily while in the intensive care unit (ICU).
	To assess the effect of ALT-100 on oxygen-related parameters.	• Changes as measured by change from baseline in plethysmographic pulse oximetry derived oxygen saturation / fraction of inspired oxygen (SpO_2/FiO_2) and ROX Index (SpO_2/FiO_2 divided by respiratory rate [RR]), assessed daily while hospitalized. • If the participant is receiving MV, the P/F ratio will be used (ie, partial pressure of oxygen [PaO_2]/FiO_2).
	To assess the effect of ALT-100 on oxygenation requirements.	• Incidence and duration of oxygen use (via conventional oxygen therapy, or non-invasive respiratory support, positive

		pressure by face mask or high flow nasal oxygen) during the study
	To assess the effect of ALT-100 on requirement for vasoactive support	• Number of days of vasoactive agent usage • Vasopressor free days
	Pharmacodynamics	
	To investigate the effects of ALT-100 on immune function biomarkers and cellular response.	• Changes from baseline in plasma levels of extracellular nicotinamide phosphoribosyltransferase (eNAMPT) and other biomarkers of interest including but not limited to TNF-α, IL-1β, IL-1RA, IL-6, Angiopoietin-2. • Changes from baseline in cellular response with ALT-100 compared to placebo, as assessed by neutrophil, monocyte, and lymphocyte counts in whole blood.
	Pharmacokinetic	
	To characterize the plasma PK profile of single IV infused doses of ALT-100.	• Determination of plasma concentrations of ALT-100. • Estimation of PK parameters.
	Safety	
	To further evaluate the safety and tolerability of a single intravenously (IV) infused dose of ALT-100.	Secondary safety and tolerability outcomes while hospitalized or if discharged, on Days 8, 15, 22, 29, and 60 will include: • Laboratory safety data (chemistry, hematology, coagulation, and urinalysis parameters) • Vital signs (blood pressure, heart rate, respiration rate, body temperature) • Physical examination • Concomitant medication use • Oxygenation (FiO_2 and PaO_2 or SpO_2) • Ventilation support: type of ventilation (heated and humidified high flow nasal O_2 [HFNO], non-rebreathing mask, bilevel positive airway pressure [BiPAP]/ continuous positive airway pressure [CPAP], or MV), FiO_2, SpO_2, PaO_2 (if available), ventilation rate based on respiratory rate, heart rate, ventilator settings (tidal volume, positive end-expiratory pressure [PEEP], and airway pressure [peak and plateau]).
	To investigate the presence of anti-ALT-100 antibodies.	• Presence and characterization of anti-drug antibodies (ADA) over the study period

		(from baseline [Day 1 pre-dose], and post treatment on Days 8, 15, 29, and 60).
Exploratory	Exploratory detection of *NAMPT* genetic variants in blood.	• Determination of ARDS-associated *NAMPT* promoter SNP expression in baseline blood samples from all participants using a *NAMPT* genotyping platform. • Assessment of predictive capacity of *NAMPT* SNPs and plasma eNAMPT levels to identify participants who respond to single dose treatment with ALT-100.
	To explore the effect of ALT-100 on other measurements of lung injury that may be performed during standard care (eg, Lung Injury Score [LIS], chest radiography, PaO_2/FiO_2, need for extracorporeal membrane oxygenation [ECMO])	• Change from baseline in LIS (to be performed daily) while hospitalized. • Change from baseline in chest radiographic assessment (if performed). • Change from baseline in P/F ratio (if performed) daily while hospitalized. • Utilization of ECMO.
	To assess the effect of ALT-100 on respiratory support requirements over time	• MVFDs by Days 8, 15, 22, and 60. • Proportion of participants not on MV support on Days 8, 15, 22, 29, and 60. • Number of participants progressing from non-invasive to invasive MV by Days 8, 15, 22, 29, and 60. • Time of progression from non-invasive to invasive MV to Day 60. • Proportion of participants weaned from MV within 28-days from treatment (by Day 29).
	To explore the effect of ALT-100 on mortality	• Mortality in all participants by Days 8, 15, 22, 29, and 60. • Time to death by Day 60.

Note: Where data permit, various exploratory sensitivity and subgroup analyses may be performed. These may include analyses of progression to MV in ALT-100 versus placebo-treated ARDS patients on heated and humidified HFNO or non-invasive positive pressure ventilation (NIPPV; ie, BiPAP/CPAP), and assessment of the effect of ALT-100 on overall duration of hospitalization based on participant ventilator requirements at the time of enrollment.
Exploratory analyses may be reported separately to the final study report.

Methodology and Study Design

PUERTA is a Phase 2a, randomized, double-blind, placebo-controlled study in adults with moderate to severe ARDS consequent to sepsis, septic shock, trauma, and/or bacterial or viral pneumonia, who have been hospitalized. The safety and tolerability, PK, preliminary efficacy, and PD of a single IV infusion of ALT-100 will be assessed.

Patients with respiratory distress admitted to participating institutions/hospitals will be screened for study eligibility. Participants included in the study can be patients requiring immediate intubation/MV (ie, within 4 hours of their moderate or severe ARDS diagnosis), as well as patients

receiving heated and humidified HFNO: ≥ 30 L/min and 100% FiO_2 or NIPPV (ie, BiPAP/ CPAP) or 12 continuous hours with high flow nasal oxygen (HFNO) using gas flow of ≥ 40 L/min or treated with non-invasive ventilation (NIV). All participants will receive study drug within 12 hours of their ARDS diagnosis and within 4 hours of initiation of MV (in the case where participants require immediate MV).

It is planned that 90 eligible participants will be randomized at a 2:1 ratio to receive a single dose of either ALT-100 or placebo via IV infusion. An additional 9 participants may be randomized if an optional cohort of low or intermediate ALT-100 dose is enrolled.

The study will be conducted in 2 parts:

- Part A: a dose escalation phase

  followed by

- Part B: dose expansion phase

Dose Escalation (Part A)

Part A will assess 2 doses of ALT-100 in sequentially enrolled cohorts of up to 9 participants in each cohort. The planned doses of ALT-100 are 0.4 mg/kg (Cohort 1a) and 1.0 mg/kg (Cohort 1b).

An optional dose cohort (Cohort 3a) of up to 9 participants may be enrolled based on the recommendations of the independent Data Safety Monitoring Committee (DSMC – see **Safety Oversight**). The dose for the optional Cohort 3a may be a lower or intermediate dose relative to Cohorts 1a and 2a and will be selected by the DSMC based on available safety, PK, and early efficacy and PD data up to and including Day 29 from all participants in Cohort 1a and Cohort 2a. The dose for Cohort 3a will not exceed 1.0 mg/kg.

Dose Expansion (Part B)

Following DSMC review of all data up to and including Day 29 from the 9 participants in each cohort in Part A, additional participants (up to 36 per dose cohort) may be enrolled into 2 dose expansion cohorts, the dose of which will also be determined by the DSMC. Part B of the study will further explore the safety, preliminary efficacy, PK, immune cell, and systemic biomarker profile of ALT-100 in this patient population.

Participants enrolled in Part A may not be re-enrolled in Part B.

Planned Dose Cohorts

Cohort	ALT-100		Placebo
	Dose (mg/kg)	Participants (N)	Participants (N)
Part A: Dose Escalation			
Cohort 1a	0.4	6	3
Cohort 2a	1	6	3
Cohort 3a (optional*)	X	6	3
Part B: Dose Expansion			
Cohort 1b	TBD[#]	24	12
Cohort 2b	TBD[#]	24	12

Abbreviation: N = number of participants; TBD = to be determined.
*An optional, additional dose level cohort may be enrolled based on DSMC recommendations following the review of data from Cohorts 1a and 2a.
[#]Dose to be determined (TBD) by DSMC based on all safety, available PK data, and any early efficacy and PD data from all Part A cohort participants completing up to and including Day 29.
The highest dose of ALT-100 will not exceed 1.0 mg/kg.

The Screening, Treatment, and Safety Follow-up schedules are the same for Part A (dose escalation) and Part B (dose expansion) cohorts.

Screening Period (Day -3 to Day 1)

Screening will occur within 3 days prior to enrollment of participants into the study and may occur on the day of treatment (Day 1). Written informed consent (from the patient or their legally authorized representative [LAR]) must be documented before any study-specific procedures, including for screening, are performed. Screening may occur from time of recognition of at-risk conditions for ARDS (presenting with sepsis, septic shock, and/or bacterial or viral pneumonia). At-risk patients will be monitored closely for development of moderate-severe ARDS. Those at-risk patients who do not meet any exclusion criteria will be enrolled with the understanding that once moderate-severe ARDS criteria are met, they will be randomized to treatment.

Individuals who fail to meet eligibility requirements may be rescreened (once), on a case-by-case basis, as determined by the MM.

Consenting, hospitalized patients who meet all the eligibility criteria at screening will be enrolled into the study after confirmation of eligibility.

Participants will be randomized on Day 1 to receive a single dose of either ALT-100 or placebo via IV infusion. All study participants will receive supportive care according to the local standard of care (SoC).

Baseline assessments will be conducted prior to administration of study treatment on Day 1. Screening and baseline assessments are outlined in the Schedule of Assessments (SoA).

Study Treatment Period (Day 1)

All randomized participants will be administered a single IV infusion of study treatment according to their randomization on Day 1.

Participants requiring immediate MV support (ie, requiring ventilation via endotracheal tube or tracheostomy tube within 4 hours of diagnosis of moderate or severe ARDS on Day 1) must receive study treatment within 4 hours of the initiation of MV. All participants will receive study drug within 12 hours of their ARDS diagnosis and within 4 hours of initiation of MV (in the case where participants require immediate MV).

Follow-up Period (Day 2 to Day 60)

Participants will be assessed daily while hospitalized. Follow-up assessments are planned through to Day 60. If the participant is discharged from the hospital at an earlier timepoint, follow-up onsite visits will occur on Days 2 to 8, 15, 22, 29, and 60, within the allowable window specified in the SoA. All participants will undergo a series of safety, plasma PK, efficacy, PD, and exploratory assessments as detailed in the SoA.

All participants who are discharged from the hospital during the study will undertake day of discharge (DoD) assessments prior to discharge.

Any participant who discontinues from the study early will complete an Early Termination (ET) Visit, wherever possible. All subjects who discontinue the study early will be followed for safety until Day 60, wherever possible.

Safety Oversight

The safety of the study will be overseen by an independent DSMC. The independent DSMC will actively monitor the emerging data to review the ongoing safety of study participants and can make recommendations about early study closure or changes to the protocol and conduct of the study. The Sponsor may decide to stop or make adaptations to the study based upon DSMC recommendations. The independent DSMC members will include 2 to 4 physicians with relevant medical specialty training and 1 statistician. The operation of the independent DSMC will be governed by a charter describing further details such as frequency of meeting, procedures (including but not limited to periodic safety monitoring) and requirements for the reporting of

observations to the Sponsor. The DSMC Charter will be finalized prior to the enrollment of participants into the study.

At a minimum, the DSMC will convene to determine if dose escalation (Part A) may proceed based on review of all safety, available PK data, and any early efficacy and PD data from the 9 participants from each sequential dose level cohort completing up to and including Day 29. This will include consideration of an optional additional Part A dose cohort (Cohort 3a) of up to 9 participants based on available safety, PK, and early efficacy and PD data up to and including Day 29 from all participants in Cohort 1a and Cohort 2a. The DSMC will also meet at the conclusion of Part A to determine if the cohort expansion phase (Part B) may proceed. The decision to initiate Part B will be based on review of all safety, available PK data, and any early efficacy and PD data from all Part A cohort participants completing Day 29.

Data from participants receiving placebo and ALT-100 will be considered.

Dose escalation decisions will be based upon the nature, severity, and frequency of any safety and/or tolerability observations, including any AEs or SAEs, changes in vital signs and/or safety laboratory parameters, and physical findings. The DSMC will also consider the available efficacy and PD data when making their decision. Plasma PK samples will be analyzed by cohort, and available results will be provided to the DSMC prior to meetings. The exposure and the predicted exposure for the subsequent dose group in Part A will be provided based on the information available. In the case of premature withdrawal of a participant from the study prior to Day 29, all available safety, PK, efficacy, and PD data up to the time of withdrawal will be reviewed by the DSMC.

DSMC evaluation of study data may occur more frequently, if warranted by the treatment emergent data, and in cases where the protocol defined stopping criteria are met.

Stopping Rules

Participants will be carefully monitored throughout the study for the occurrence of AEs and SAEs. The following stopping rules will trigger a DSMC unscheduled review of the cumulative study data:

Serious Adverse Events

For treatment emergent SAEs, further dosing of study participants at the dose level associated with the treatment emergent SAE will be paused for DSMC review in the following cases:

- Any treatment emergent SAE(s) suspected to be treatment-related (as assessed by the investigator).
- Treatment emergent SAEs (i.e., in the same system organ class [SOC]), regardless of assigned causality occurring in ≥2 participants in Part A and ≥3 participants in Part B.

Non-serious Adverse Events

For non-serious TEAEs, further dosing of study participants at the dose level associated with the TEAE will be paused pending DSMC review in the following cases:

- Severe TEAEs (Grade 3 according to the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE] v5.0) suspected to be treatment-related, independent of whether the AE is in the same SOC, that occur in ≥2 participants in Part A and in ≥3 participants in Part B if showing signs of reversibility, or in ≥1 participants in Part A and ≥2 participants in Part B if not resolving.
- Treatment emergent AEs of moderate severity (Grade 2 according to NCI-CTCAE v5.0), that occur in ≥3 participants (if in the same SOC), or in ≥4 participants (independent of whether the AE is in the same SOC), if showing signs of reversibility (for both Part A and Part B). Grade 2 TEAEs that do not resolve in ≥2 participants (for Part A) and in ≥3 participants (for Part B) will trigger a dosing pause and DSMC review.

Based on the data review, the DSMC will determine whether to proceed with dosing or may recommend temporary or permanent stopping of dosing. This may include suspension of dosing of all ongoing and planned dosing cohorts including those at lower exposures, and of further enrolment of study participants. After a temporary halt, further measures for safety may be introduced. Continuation of the study may require a substantial amendment to the study design and assessments to ensure participant safety. All amendments to the protocol will first be subject to review and approval by the relevant independent ethics committee (IEC)/ institutional review board (IRB).

Guidelines on the management of acute infusion-related reactions and associated stopping rules in individual participants are provided in Section 6.2 (Table 5) of the clinical study protocol.

Early study discontinuation criteria for individual participants and conditions under which study termination will occur are detailed in Section 7.2 and Section 7.3, respectively, of the clinical protocol.

Number of Participants (Planned)

It is planned that 90 eligible participants will be randomized at a 2:1 ratio to receive a single dose of either ALT-100 or placebo via IV infusion. An additional 9 participants may be randomized if an optional cohort of low or intermediate ALT-100 dose is enrolled in Part A which will be determined by the DSMC.

Eligibility Criteria

Inclusion criteria

To be eligible for this study, a participant must meet all of the following criteria:

1. Hospitalized (or documentation of a plan to admit to the hospital if the patient is in an emergency department) male or non-pregnant female ≥ 18 years of age at time of enrollment.
2. Participant (or LAR) is able and willing to provide written informed consent, which includes compliance with study requirements and restrictions listed in the consent form.
3. Participant has a diagnosis of moderate or severe ARDS:

   A participant with a diagnosis of moderate or severe ARDS according to the Berlin definition of ARDS:
   a. Acute onset of respiratory failure within 1 week of a known clinical insult or new or worsening respiratory symptoms.
   b. Respiratory failure associated with known ARDS risk factors and not fully explained by either cardiac failure or fluid overload (an objective assessment of cardiac failure or fluid overload is needed if no risk factors for ARDS are present).
   c. Radiological abnormalities on chest x-ray or computed tomography (CT) scan, ie, bilateral opacities that are not fully explained by effusions, nodules, masses, or lobar/lung collapse.
   d. Hypoxemia:

      i. Moderate ARDS: PaO_2/FiO_2 > 100 mmHg (> 13.3 kPa) to ≤ 200 mmHg (≤ 26.6 kPa) with PEEP ≥ 5 cmH_2O, or imputed SpO_2/FiO_2 equivalent.

      ii. Severe ARDS: PaO_2/FiO_2 ≤ 100 mmHg (≤ 13.3 kPa) with PEEP ≥ 5 cmH_2O.

   Note: Acceptable imaging tests (chest x-ray, CT scans) done within 3 days of Day 1 can be used to determine eligibility, however, the radiological and hypoxemia criteria (3 [c] and [d]) must occur within the same 24-hour period. The time of onset of ARDS is defined as the time when the last of these 2 ARDS criteria is met.

   OR

Participant presents with acute respiratory failure phenotypically similar to ARDS in a setting demonstrating clinical risk for ARDS, whether or not they meet the Berlin criteria, and requiring heated and humidified HFNC ≥ 30 L/min and 100% FiO_2, or NIPPV (ie, BiPAP/CPAP) for hypoxemia.

OR

Participant presents with acute respiratory failure phenotypically similar to ARDS in a setting demonstrating clinical risk for ARDS, does not meet the Berlin criteria, and is initially treated with ≥ 12 continuous hours with HFNO using gas flow of ≥ 40 L/min or treated with non-invasive ventilation (NIV), and has a PEEP of ≥ 5 cm H_2O and PaO_2/FIO_2 < 200 mm Hg.

4. Administration of study treatment must be planned to occur within 12 hours of the participant's moderate or severe ARDS diagnosis and within 4 hours of initiation of MV (in the case of individuals requiring immediate MV).
5. Females must be non-pregnant and non-lactating, and either surgically sterile (eg, tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy), or use highly effective contraceptive method (oral contraceptive pills [OCPs], long-acting implantable hormones, injectable hormones, a vaginal ring or an intrauterine device [IUD]) from screening until study completion, or be post-menopausal for ≥ 12 months. Post-menopausal status will be confirmed through testing of follicle-stimulating hormone (FSH) levels at screening for amenorrheic female participants but the result is not required prior to enrollment. Female participants whose only partner has had a vasectomy, and female participants who are abstinent from heterosexual intercourse as part of their usual lifestyle will also be eligible for participation.
6. Women of child-bearing potential (WOCBP) must have a negative pregnancy test at screening and admission and be willing to have additional pregnancy tests as required throughout the study.
7. Males must be surgically sterile (> 30 days since vasectomy with no viable sperm), abstinent, or if engaged in sexual relations with a WOCBP his partner must be surgically sterile (eg, tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy) or using an acceptable, highly effective contraceptive method from screening until study completion, including the Follow-up Period. Acceptable methods of contraception include the use of condoms and the use of an effective contraceptive for the female partner (WOCBP) that includes: OCPs, long-acting implantable hormones, injectable hormones, a vaginal ring, or an IUD. Male participants whose female partner is post-menopausal, and participants who are abstinent from heterosexual intercourse as part of their usual lifestyle will also be eligible.
8. Male participants must agree to refrain from donating sperm from screening until study completion, including the Follow-up Period, for at least 60 days after the last dose of study treatment.
9. Participant is willing and able to undergo all study procedures and attend the scheduled follow-up visit/s per protocol.

Exclusion criteria

A participant who meets any of the following criteria must be excluded from the study:

1. Participants with ARDS consequent to COVID-19 infection.
2. Participants requiring immediate MV who have been intubated and on MV for > 4 hours prior to the planned administration of study treatment on Day 1.
3. Moribund participant not expected to survive > 24 hours, in the opinion of the Investigator.
4. Use of extracorporeal life support (eg, ECMO) or, in the opinion of the Investigator, there is a high likelihood that extracorporeal life support will be initiated within 48 hours after randomization.

5. Participant has an underlying clinical condition where, in the opinion of the Investigator, it would be unlikely that the participant would be able to come off ventilation, eg, chronic progressive neuromuscular or respiratory disease.
6. Severe chronic respiratory disease (eg, known chronic obstructive pulmonary disease [COPD], pulmonary arterial hypertension [PAH], idiopathic pulmonary fibrosis [IPF], interstitial lung disease [ILD]) requiring supplemental oxygen therapy or MV pre-hospitalization [eg, prior to ARDS diagnosis]).
7. Evidence of life-threatening dysrhythmia (eg, ventricular tachycardia, ventricular fibrillation) or cardiac arrest on presentation.
8. Evidence of new or preexisting decompensated heart failure.
9. Absolute neutrophil count < 1000 per mm^3.
10. Platelet count < 50000 per mm^3.
11. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 5 × upper limit of normal (ULN).
12. Estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73m^2 (based on Modification of Diet in Renal Disease [MDRD] equation) or requiring hemofiltration or dialysis.
13. Known or suspected active and untreated tuberculosis (TB), human immunodeficiency virus (HIV), hepatitis B or C infection.

    Note: Results of TB, hepatitis B and C, and HIV tests are not required prior to enrollment if there is no suspicion of active infection.

14. Known history of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric, human, or humanized antibodies, fusion proteins, ALT-100 excipients, or a history of drug or other allergy including severe allergic reaction that in the opinion of the Investigator, contraindicates participant participation.
15. Use of any immunomodulatory biologic (eg, anti-IL-1, anti-IL-6R, anti-TNF, inhibitors of complement signaling), cell therapies (eg, mesenchymal stem cells), or small molecule Janus kinase (JAK) inhibitors within the past 7 days or within 5 half-lives (whichever is longer), or planned use of any of these agents from screening until Day 60 of the study, unless approved by the medical monitor (MM). The following will be allowed/disallowed as indicated:
    a. Immunomodulatory biologics for treatment of COVID-19 are excluded and should not be used until Day 60 unless discussed with the MM. Other non-biologic immunomodulators (non-JAK inhibitors), eg, medicines for previous transplantation, or disease modifying anti-rheumatic drugs (DMARDS), if on a stable dose for ≥ 8 weeks are permitted.
    b. Ongoing chronic (≥ 4 weeks) use of corticosteroids > 10 mg/day of prednisone or equivalent at the time of randomization is prohibited. A chronic corticosteroid dose that has been tapered to 10 mg or less/day within 14 days of screening is also prohibited.
    c. Acute corticosteroid use during the study, if clinically indicated as determined by the treating physician, is permitted.
16. Participants using vasopressors are eligible for study participation, with the following exceptions as noted:
    a. Participants who present at screening with ARDS and septic shock may be enrolled if the participant is on one vasopressor or, if on 2 vasopressors, if the Levofed (norepinephrine) dose is ≤ 1 μg/kg/min.
    b. Participants with ARDS and septic shock who are on ≥ 3 vasopressors ie, Vasopressin, Levofed (norepinephrine), Neosynephrine (phenelephreine), at screening are excluded from study participation.
    c. Participants with ARDS and septic shock who are on 2 vasopressors where the Levofed dose is > 1 μg/kg/min are excluded from study participation.

    Note: Participants who require vasopressors for sedation-related hypotension may be eligible for inclusion, per approval from the MM.

17. Participation in a clinical research study evaluating another investigational product (IP) or therapy within 3 months and less than 5 half-lives of the IP prior to screening.
18. Any physical examination findings, and/or history of any other illness, concomitant medications, or recent live vaccines that, in the opinion of the Investigator, might confound the results of the study or pose an additional risk to the participant by their participation in the study.
19. Administered a live vaccine within 14 days prior to screening and throughout the duration of the study.

Note: As indicated previously (see **Methodology and Study Design – Screening Period**), patients at-risk for ARDS (presenting with sepsis, septic shock, and/or bacterial or viral pneumonia), who do not meet any exclusion criteria, will be enrolled with the understanding that once moderate-severe ARDS criteria are met, they will be randomized to treatment.

Length of Participation

Treatment: A single IV infusion on Day 1 with ALT-100 or placebo per assigned treatment and dose level cohort.

Study participation: Participation in the study is comprised of a Screening Period of up to 3 days, Treatment on Day 1, and a Follow-up Period to Day 60 with onsite visits on Days 2 to 8, 15, 22, 29, and 60, if the participant has been discharged from the hospital. The Day 60 EoS Follow-up Visit constitutes the end of study participation.

Investigational Product, Dosage, and Mode of Administration

ALT-100

ALT-100 is a humanized murine mAb that specifically binds to eNAMPT, consisting of 2 kappa light chains and 2 gamma heavy chains of the IgG4 isotype.

The Sponsor will be responsible for the supply of ALT-100 to the sites. ALT-100 will be manufactured by WuXi Biologics (Suzhou) Co. Ltd (China) according to cGMP and will be suitable for human use. All IP will be labeled in accordance with cGMP and local regulations.

The IP is formulated as a sterile liquid, pH 5.5, and is provided in 10 mL glass vials containing 10 mg/mL of ALT-100. Each vial is filled with 10.5 mL to ensure an extractable volume of at least 10.0 mL (ie, at least 100 mg of ALT-100 per vial).

ALT-100 is to be stored at 2 to 8°C and protected from light during storage. Current and ongoing stability studies support the labeled expiry date of ALT-100.

ALT-100 should be inspected visually for particulate matter and discoloration prior to administration. ALT-100 should be a clear, colorless liquid, and should not be used if particulates or discoloration are present in the vial.

For administration in this study, ALT-100 will be diluted in normal sterile saline to the appropriate volume required to deliver a dose of 0.4 mg/kg up to 1.0 mg/kg ALT-100 and will be given as a single IV infusion via pump in a total volume of ~ 50 mL with a constant infusion rate. ALT-100 should be administered within 4 hours of dilution. A filter should be used during infusion (≤ 0.3 micron; preferably 0.2 micron). ALT-100 is to be infused at a rate to complete in 20 minutes (~2.5 mL/min). The rate of infusion may be reduced in the event of an infusion-related reaction, to conclude in 60 minutes, at the discretion of the Investigator. Guidelines on the management of acute infusion reactions are provided in the protocol.

Reference Therapy, Dosage, and Mode of Administration

Placebo

The placebo for this study will be commercially available normal saline, supplied by each site and administered as an IV infusion at a constant infusion rate in a total volume and appearance matched to the ALT-100 for the relevant dosing cohort.

Statistical Methods

Statistical methods will be further outlined in a Statistical Analysis Plan (SAP).

Sample size calculation

Power calculation and determination of sample size per scenario assumes 2 active dose levels and a placebo group are investigated and is based on the primary efficacy endpoint of MVFDs over the 28 days following treatment (ie, by Day 29).

Equal treatment effect for both active treatment groups; standard deviation of 9 days; n = 30 per group

A sample size of n = 30 participants per group (2 active treatment groups and 1 placebo group) allows greater than 80% power (exact power =87.4%) to demonstrate statistical significance ($P < 0.05$; analysis with analysis of variance [ANOVA]) with a mean difference in MVFDs from placebo of 7 days for both active treatment groups and a standard deviation of 9 days.

Different/ spaced treatment effect for each active treatment groups; standard deviation of 9 days; n = 30 per group

A sample size of n = 30 participants per group (2 active treatment groups and 1 placebo group) allows greater than 80% power (exact power = 86.7%) to demonstrate statistical significance ($P < 0.05$; with ANOVA) with a mean difference in MVFDs from placebo of 4 and 8 days for active treatment groups 1 and 2, respectively, and a standard deviation of 9 days.

Combined Active Dose Groups into single treatment group; standard deviation of 9 days; N=60 (30+30) 'active' treatment and n = 30 placebo group

A sample size of n = 30 participants per group (2 active treatment groups and 1 placebo group) with both active treatment groups combined into a single treatment group (ie, n = 60) allows greater than 80% power (exact power = 83.9%) to demonstrate statistical significance ($P < 0.05$; analysis with un-paired t-test) with a mean difference in MVFDs from placebo of 6 days for the combined active treatment group, respectively and a standard deviation of 9 days.

Randomization will occur centrally using an interactive voice or web response system.

The following analysis populations are defined for the study:

Intent-to-Treat (ITT): includes all randomized participants. The ITT participants will be analyzed according to randomized treatment, irrespective of whether or not they have prematurely discontinued. Participants who withdraw from treatment and/or the study early will be followed until Day 60 for safety. All baseline characteristic analyses will be performed using the ITT Population.

Modified Intent-to-Treat (mITT): includes all randomized participants who receive any amount of study drug. The ITT participants will be analyzed according to randomized treatment, irrespective of whether or not they have prematurely discontinued. Participants who withdraw from treatment and/or the study early will be followed until Day 60 for safety. All efficacy analyses will be performed using the mITT Population.

Safety: includes all randomized participants who receive any amount of study drug. The Safety Population will be analyzed according to the treatment received. This population will be used for the safety analyses.

Per Protocol (PP): includes all participants in the ITT Population who complete the Day 29 Visit with no major protocol violations. The PP Population will be used for supportive analyses of clinical efficacy measurements.

PK: includes all randomized participants who were administered ALT-100 and who have sufficient plasma concentration-time data to determine at least C_{max} and AUC_{0-t}. The PK Population will be used to summarize PK parameter data.

PD: includes all randomized participants who receive any amount of study drug (ALT-100 or placebo), who have results from baseline and from ≥ 1 post-baseline PD assessment and will be based on the actual treatment/dose level received, if this differs from what the participant is randomized to. The PD Population will be used to summarize PD data.

Participant inclusion into each population will be determined after database lock and prior to unblinding for the final analysis.

For the summary of data by treatment group, placebo participants from each cohort will be pooled into a single treatment group.

Efficacy Analyses

Individual results for MV, hospitalization duration, SOFA Score, oxygenation parameters, and vasoactive support will be listed.

Efficacy data will be analyzed as follows for the sub-groups MV versus non-MV:

- Duration of event (eg, MV-free days; hospitalization duration) will be summarized as median days with quartiles. Treatment differences will be assessed using an ANOVA model with treatment and MV status (MV vs non-MV) as fixed effects. The least square means and the estimated treatment differences, as well as the corresponding 95% confidence intervals (Cis) and p-values will be presented. A non-parametric method (Kruskal-Wallis test) may also be performed if the distributional assumptions are violated.
- Incidence data will be summarized as a percentage with 95% Clopper-Pearson CIs. Treatment comparison may be performed using the Cochran-Mantel-Haenszel test with MV status (MV vs non-MV) and treatment as stratification factors.
- The continuous variables, including the changes from baseline, will be summarized by the treatment with the mean, SD, median, and the range. Where appropriate, treatment comparisons will be performed using the same ANOVA model and non-parametric methods as described above.
- The time-to-event endpoints will be summarized with Kaplan Meier estimates and 95% confidence bounds by the treatment. The results will also be presented graphically. Treatment comparisons will be performed using a Cox proportional hazards model. The hazard ratio of ALT-100 versus placebo will be presented with 95% CI and p-values.

Full details will be provided in the SAP.

Safety and Tolerability:

AEs will be coded using the most current Medical Dictionary for Regulatory Activities (MedDRA®) available at the time of study commencement. A by participant AE data listing, including verbatim term, preferred term (PT), system organ class (SOC), treatment, severity, and relationship to study drug, will be provided. The number of participants experiencing TEAEs and number of individual TEAEs will be summarized by SOC and PT for each treatment group and overall (ie, all participants combined). TEAEs will also be summarized by severity and relationship to study drug for each treatment group and overall.

Laboratory evaluations and vital signs assessments will be listed for each participant and summarized by treatment group and protocol specified collection timepoint. A summary of change from baseline results at each protocol specified timepoint will also be presented.

Changes in physical examinations will be listed for each participant.

Immunogenicity data (ADA) will be listed for each participant and summarized by treatment group and protocol specified collection timepoint.

Concomitant medications will be listed by participant and coded using the most current WHO drug dictionary available at the commencement of the study.

Medical history will be listed by participant.

Pharmacokinetics:

Individual plasma ALT-100 concentration data will be listed and summarized by treatment group and protocol specified collection timepoints, with descriptive statistics (sample size [N], arithmetic mean, standard deviation [SD], coefficient of variation [CV%], median, minimum, maximum and geometric mean). Individual and mean ALT-100 concentration-time profiles will also be presented graphically by treatment group.

Where data are sufficient for parameter determination the following plasma ALT-100 non-compartmental PK parameters will be estimated, as appropriate:

- Area under concentration-time curve from time 0 (pre-dose) to the last quantifiable data point (AUC_{0-t})
- Area under concentration-time curve from time 0 (pre-dose) extrapolated to infinity ($AUC_{0-\infty}$)
- Other AUC intervals may be determined as data permits eg, AUC_{0-24} and AUC_{0-48}
- Maximum concentration (C_{max})
- Dose normalized C_{max} (determined by C_{max}/dose [D]) and dose normalized AUC (determined by AUC/D)
- The percent of the $AUC_{0-\infty}$ extrapolated to infinity ($\%AUC_{extrap}$; normally should be no more than 20%)
- Time to reach maximum concentration (t_{max})
- Terminal elimination rate constant (k_{el})
- Elimination half-life ($t½$)
- Total body clearance (CL)
- Volume of distribution at the terminal phase (Vz)

Other PK parameters used to characterize the terminal elimination phase will be listed and described in further detail in the SAP but may include: R_2-adjusted, k_{el} upper, k_{el} lower, number of data points used in the regression of the terminal phase.

Pharmacokinetic parameters will be listed for each individual and summarized by treatment group using descriptive statistics (N, arithmetic mean, SD, CV%, median, minimum, maximum, geometric mean and geometric CV%).

If > 2 dose levels are investigated dose proportionality will be tested using a power regression model for $AUC_{0-\infty}$, AUC_{0-t}, and $C_{max.}$

Pharmacodynamics:

Individual cell and biomarker results will be listed and summarized by treatment group, with presentation of descriptive statistics (N, arithmetic mean, SD, CV%, median, minimum, and maximum). A summary of change from baseline results for each treatment group at each protocol specified timepoint may also be presented if appropriate. Figures of cell and biomarker results over time may also be presented, where appropriate.

Table 1 Schedule of Assessments

Study Day (± window)	**Screening**[a]	**Treatment Period**			**Follow-up Period** (Visits will be in-hospital, or will require an onsite visit if the participant has been discharged)					
	Day -3 to Day 1	**Day 1**			**Day 2 to Day 8**	**Day 15** (±1 day)	**Day 22** (±2 days)	**Day 29** (±3 days)	**DoD/ET**[t] (-)	**Day 60/ EoS** (±5 days)
		Baseline/ Pre-dose	**Dosing**	**Post dose**						
Procedure:										
Informed consent[b]	X									
Eligibility criteria review	X	X								
Demographics[c]	X									
Medical history	X	X								
Prior medications	X	X								
Local QuantiFERON test[d]	X									
Virology screen (HBsAg, HCV RNA/Ag, HIV)[d]	X									
Serum β-HCG (for WOCBP only) and FSH (women only)[e]	X									
Urine pregnancy test (for WOCBP only)[e]									X	X
12-lead ECG[v]		X								
Physical exam[f]		X		X	Daily while hospitalized and at DoD/ET. If discharged, at each scheduled visit through Day 60					
Body weight and height[g]	X									
Vital signs[h]	X	X		X	Daily while hospitalized and at DoD/ET. If discharged, at each scheduled visit through Day 60					
Chest x-ray or chest CT scan[i]	X									

Table 1 Schedule of Assessments

Study Day (± window)	**Screening**[a]	**Treatment Period**			**Follow-up Period** (Visits will be in-hospital, or will require an onsite visit if the participant has been discharged)					
	Day -3 to Day 1	**Day 1**			**Day 2 to Day 8**	**Day 15** (±1 day)	**Day 22** (±2 days)	**Day 29** (±3 days)	**DoD/ET**[t] (-)	**Day 60/ EoS** (±5 days)
		Baseline/ Pre-dose	**Dosing**	**Post dose**						
Hematology/ coagulation/ chemistry[k]	X			X[j]	Day 4 and Day 8 only	X	X	X	X	X
Urinalysis[l]	X			X[j]	Day 4 and Day 8 only	X	X	X	X	X
Randomization		X								
IV infusion of study treatment[m]			X							
Blood sample for *NAMPT*-Gene genotyping assessment		X								
PK blood sampling[n]		X		X	X	X		X	X[u]	
Immunogenicity/ADA blood sample[o]		X			Day 8 only	X		X	X	X
Blood sampling for plasma biomarkers[p]		X		X	Day 2, Day 3, Day 4, Day 8 only	X		X	X[u]	
Whole blood for PD cellular parameters[p]		X		X	Day 2, Day 3, Day 4, Day 8 only	X	X	X	X	X
SOFA score		X		X[q] Only if in ICU	Daily; only if in ICU, including the last day in the ICU if the participant leaves the ICU before Day 29					
SpO_2/FiO_2, and if performed, PaO_2/FiO_2 (can be imputed)	X	X		X[q]	Daily; only while hospitalized through to DoD/ET or Day 60					

Table 1 Schedule of Assessments

Study Day (± window)	**Screening**[a]	**Treatment Period**			**Follow-up Period** (Visits will be in-hospital, or will require an onsite visit if the participant has been discharged)					
	Day -3 to Day 1	**Day 1**			**Day 2 to Day 8**	**Day 15** (±1 day)	**Day 22** (±2 days)	**Day 29** (±3 days)	**DoD/ET**[t] (-)	**Day 60/ EoS** (±5 days)
		Baseline/ Pre-dose	**Dosing**	**Post dose**						
Oxygenation requirements	X	X		X[q]	Daily while hospitalized and at DoD/ET. If discharged, at each visit through Day 60					
Lung Injury Score (LIS)	X	X		X[q]	Daily while hospitalized and at DoD/ET. If discharged, at each visit through Day 60					
Ventilation requirements[r]	X	X		X[q]	Daily; only while hospitalized through to DoD/ET or Day 60					
ECMO utilization		X		X[q]	Daily; only while hospitalized through to DoD/ET or Day 60					
AE review[s]	X	X	X	X	Daily while hospitalized and at DoD/ET. If discharged, at each visit through Day 60					
Concomitant medication review[s]	X	X	X	X	Daily while hospitalized and at DoD/ET. If discharged, at each visit through Day 60					

Abbreviations: ADA = anti-drug antibody; AE = adverse event; Ag = antigen; β-HCG = beta human chorionic gonadotropin; CT = computerized tomography; DoD = Day of discharge; ECG = electrocardiogram; ECMO = extracorporeal membrane oxygenation; EoS = end of study; ET = early termination; FSH = follicle-stimulating hormone; HbsAg = hepatitis B antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; ICU = intensive care unit; IV = intravenous; LIS = lung injury score; *NAMPT* = nicotinamide phosphoribosyltransferase; PaO_2 = partial pressure of oxygen; PD = pharmacodynamics; PK = pharmacokinetic; RNA = ribonucleic acid; SOFA = Sequential Organ Failure Assessment; SpO_2/FiO_2 = peripheral capillary oxygen saturation/fraction of inspired oxygen; TB = tuberculosis; WHO = World Health Organization; WOCBP = women of child-bearing potential.

Note: Whenever vital signs, and PK/ PD blood draws are scheduled for the same nominal time, the assessments should occur in the following order: vital signs, PK/ PD blood draws; so that the timing of the assessments allow the blood draw to occur at the exact nominal time. No more than 500 mL of blood will be collected over the duration of the study, including any extra assessments that may be required.

[a] Screening will occur within 3 days prior to enrollment of participants into the study and may occur on the day of treatment (Day 1). Screening may occur from time of recognition of at-risk conditions for ARDS (presenting with sepsis, septic shock, and/or bacterial or viral pneumonia). At-risk patients will be monitored closely for development of moderate-severe ARDS. Those at-risk patients who do not meet any exclusion criteria will be enrolled with the understanding that once moderate-severe ARDS criteria are met, they will be randomized to treatment. Individuals who marginally fail to meet eligibility requirements may be rescreened (once), on a case-by-case basis, as determined by the MM.

[b] Written informed consent (from the participant or their LAR) must be documented before any study-specific procedure, including for screening, is performed.

[c] Year of birth, age (calculated), sex, ethnicity, and race will be recorded as part of the screening procedures.

[d] Sample will be collected, but enrollment can continue without receiving results first. Hepatitis C virus (HCV) testing can be ribonucleic acid (RNA) or antigen (Ag)-based, only to confirm suspected infection. If a participant is diagnosed with latent tuberculosis (TB; by positive QuantiFERON Gold or purified protein derivative [PPD] test), hepatitis B or C, or HIV during the study, the Investigator must discuss this with the MM. In the event the QuantiFERON Gold assay is not available, and the site performs a different interferon gamma release assay (IGRA), then the alternative IGRA will be acceptable for patient screening and enrollment. Enrollment should not be delayed to obtain the QuantiFERON Gold assay in lieu of the IGRA available at the site. If no IGRA test is available, a PPD test can be used. If TB testing and viral serology is missed during screening it must be completed and results received prior to participant discharge from hospital. If not completed or unable to obtain results, further discussion with the MM is required.

[e] All WOCBP will have a serum pregnancy test at screening. Urine pregnancy tests will be performed for WOCBP at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. Post-menopausal status will be confirmed through testing of FSH levels at screening for amenorrheic female participants but the result is not required prior to enrollment.

[f] An abbreviated, targeted physical examination will be performed based on the participant's clinical status and what the treating physician feels is appropriate. If a physical examination is performed as SoC by appropriate personnel the same day that consent is signed or the same day of any scheduled study visit, results from that examination may be used if site staff consider additional examinations are unwarranted due to already having been performed as SoC.

[g] Body mass index (BMI) will be calculated at screening by dividing the participant's body weight in kilograms by the participant's height in meters squared (BMI = kg/m^2). Estimated height and weight are acceptable if the participant's clinical condition precludes assessment of body weight and height.

[h] Includes respiratory rate, heart rate, and systolic and diastolic blood pressure. Where possible the participant will be at rest in a supine position (after ≥ 5 minutes resting supine) or if required lying in the prone position (after ≥ 5 minutes resting in the prone position) for vital sign measurements. Body temperature will also be recorded. On the day of dosing, vital signs will be assessed ≤ 15 minutes before the start of infusion and ≤ 15 minutes from the end of infusion, and at 2 (±5 mins), 4 (±10 mins), 8 (±15 mins), and 12 hours (±15 mins) after the end of infusion. If vital signs measurements are performed as SoC by appropriate personnel the same day that consent is signed or the same day of any scheduled study visit, results from that assessment may be used if site staff consider additional measurements are unwarranted due to already having been performed as SoC. Assessment of vital signs may occur at additional time points, at the Investigator's discretion.

[i] Imaging (chest x-ray, CT scans) done within 3 days of Day 1 can be used for determining study eligibility.

[j] On the day of dosing (Day 1), hematology/coagulation/chemistry/urinalysis samples will be taken at 4 hours from the end of infusion.

[k] Hematology, coagulation and chemistry parameters measured are listed in Table 6. Blood samples will be taken at screening, 4 hours after the end of infusion on Day 1, and on Days 4, 8, 15, 22, 29, and 60. Participants will not be required to fast prior to collection of blood samples for safety laboratory testing.

[l] Includes dipstick (pH, specific gravity, glucose, protein, ketones, blood), as well as microscopic analysis (sediment [per local practice], RBCs, WBCs, casts, crystals, epithelial cells, bacteria) on the basis of dipstick results.

[m] All participants will receive study drug within 12 hours of their ARDS diagnosis and within 4 hours of initiation of MV (in the case where participants require immediate MV).

[n] Plasma samples for PK analysis of ALT-100 will be collected within 1 hour before the start of infusion on Day 1, then at 1 hour (±5 minutes), and 24, 48, 72, 96, 120, (±4 hours end time of infusion) 144, and 168 hours (±8 hours) from the end time of infusion, 15 days from date of infusion (±1 day), and 29 days from date of infusion (±3 days). The actual date and time of each blood sample collection will be recorded. The timing of PK samples may be altered and/or PK samples may be obtained at additional time points to ensure thorough PK monitoring.

[o] Additional immunogenicity/ADA samples may be collected in participants with signs and symptoms of infusion-related reactions, at the discretion of the Investigator. A corresponding additional PK sample will be obtained at the same time point as required.

[p] Blood samples for analysis of eNAMPT and other exploratory biomarkers of interest and for assessment of peripheral circulating neutrophil, monocyte and lymphocyte counts in whole blood will be assessed at baseline and at 8, 24 (Day 2), 48 (Day 3), 72 (Day 4), and 168 (Day 8) hours (±2 hours) after the end of infusion, Day 15 (±1 day), and Day 29 (±3 days)..

[q] To be assessed within 4 to 8 hours from the end of infusion.

[r] If the participant is receiving ventilation support, the following parameters will be recorded: type of ventilation (high flow nasal O_2 [HFNO], non-rebreathing mask, bilevel positive airway pressure [BiPAP]/ continuous positive airway pressure [CPAP], or MV), FiO_2, SpO_2, PaO_2 (if available), ventilation rate based on respiratory rate, heart rate, ventilator settings (tidal volume, PEEP, and airway pressure [peak and plateau]).

[s] Documentation of all AEs and use of concomitant medication will occur at each interaction with the participant from the time of informed consent. Participants will be monitored during hospitalization for AEs to the study treatment and/or procedures. Upon discharge, participants will be questioned at each return visit regarding AEs and concomitant medication use and will also be instructed to inform the Investigator or clinic staff of any AEs or inter-current illnesses experienced at any time during the trial.

[t] Day of discharge (DoD) assessments can be performed one day prior to discharge if the participant has been labeled as 'ready for discharge'. All participants who are discharged from the hospital will undergo all DoD Visit assessments; daily in-hospital assessments will only need to be performed once on DoD. All participants who discontinue from the study prematurely will undergo all ET Visit assessments, whenever possible. All participants who discontinue the study early will be followed for safety until Day 60, wherever possible.

[u] Samples collect at early termination (ET) visit only if participant discontinues prior to Day 29 and does not wish to be followed up until Day 60.

[v] A12-lead ECG will be performed at baseline (before dosing) on Day 1 and as part of the participants SoC. Where possible the participant will be at rest in a supine position (after ≥ 5 minutes resting supine) or if required lying in the prone position (after ≥ 5 minutes resting in the prone position) for ECGs. ECGs should occur prior to PK/PD blood draws; so that the timing of the assessments allow the blood draw to occur at the scheduled time.

2 INTRODUCTION

2.1 Background

2.1.1 Target Indication and Population

Acute respiratory distress syndrome (ARDS) is a life-threatening condition which is characterized by poor oxygenation, pulmonary infiltrates, and acute onset in patients that are seriously ill (Umbrello 2016; Matthay 2019; Diamond 2021). The condition almost always necessitates mechanical ventilation (MV) support and the mortality rate in patients with ARDS is 30 to 40%. Acute respiratory distress syndrome is also a serious complication of severe acute respiratory syndrome corona virus 2 (SARS-CoV-2), the coronavirus which causes coronavirus disease 2019 (COVID-19). Patients with COVID-19 who develop ARDS have worse outcomes compared to patients with ARDS from other causes, and increased mortality (ranging between ~66% to ~94%) (Wu 2020).

ARDS develops after an insult provokes a dysregulated host inflammatory response in the lungs, usually within the first 12 to 48 hours of exposure to the trigger (Aronson and Rajwani 2017). The syndrome progresses through different phases, starting with a proliferative phase of alveolar-capillary damage and a final fibrotic phase signaling the end of the acute disease process (Diamond 2021). The histological hallmark of ARDS is diffuse alveolar damage (Aronson and Rajwani 2017). This causes the release of proinflammatory cytokines such as tumor necrosis factor [TNF], interleukin [IL]-1, IL-6, and IL-8, leading to pulmonary neutrophil recruitment, and the activation and release of toxic levels of reactive oxygen species and inflammatory mediators that damage the capillary endothelium and alveolar epithelium in the lung resulting in profound alveolar edema. The clinical manifestation of this dysregulated host inflammatory response is compromised gas exchange, severe hypoxemia, reduced pulmonary compliance, and respiratory failure (Rawal 2018). The pattern of injury seen in ARDS is not uniform and increases in circulating levels of inflammatory cytokines can also produce edema outside the lung in multiple critical organs such as the kidneys, heart, brain, liver, and gastrointestinal tract, which may lead to multiorgan dysfunction and death (Diamond 2021).

The primary treatment strategy in patients with ARDS is supportive care:

1. reducing shunt fraction
2. increasing oxygen delivery
3. decreasing oxygen consumption
4. avoiding further lung and other vital organ injury

Patients are typically mechanically ventilated, closely monitored for fluid overload, and provided with nutritional support (Diamond 2021).

Recently, dexamethasone has shown efficacy in severe COVID-associated ARDS (RECOVERY Collaborative Group 2021) but there is currently no Food and Drug Administration (FDA)-approved ARDS therapies in the US, and this remains a serious unmet need in the current global pandemic (Bime 2020; Bime 2021).

A common sequalae of exposure to MV is the development of ventilator-induced lung injury (VILI). VILI is acute lung injury which occurs due to increased mechanical stress inflicted or aggravated by MV during treatment. Importantly, VILI can be an important contributor to both the development and worsening of ARDS by directly inducing the inflammatory

response and contributes to the mortality of ARDS (Hong 2008; Sweeney 2016; Acute Respiratory Distress Syndrome Network 2000).

2.1.2 Extracellular Nicotinamide Phosphoribosyltransferase (eNAMPT)

Extracellular nicotinamide phosphoribosyltransferase (eNAMPT) has been identified as a novel ARDS biomarker and potential therapeutic target (Ye 2005; Bime 2020; Bime 2021; Hong 2008; Bermudez 2022; Sammani 2022). A cytozyme (cytokine/enzyme) whose expression is induced by ARDS-relevant stimuli (hypoxia, trauma, infection, ventilator-induced mechanical stress), eNAMPT functions as a tissue damage-associated molecular pattern (DAMP) and binds Toll-like receptor 4 (TLR4) to elicit profound Nuclear Factor kappa-light-chain-enhancer of activated B cells (NFκB)-driven inflammation (Ye 2005; Sun 2014; Camp 2015; Sun 2020). Elevated eNAMPT plasma levels and *NAMPT* single nucleotide polymorphisms (SNPs) have been linked to sepsis/trauma-induced ARDS severity and mortality (Ye 2005; Bajwa 2007; Bime 2020; Bime 2021).

2.1.3 Description of Product

Aqualung Therapeutics Corporation has developed ALT-100, a humanized murine monoclonal antibody (mAb) that specifically targets and neutralizes eNAMPT and prevents TLR4 binding and activation of the NFκB proinflammatory signaling cascade. It is proposed that the activity of ALT-100 will block induction of the cytokine storm that characterizes ARDS pathobiology and multiorgan dysfunction, leading to improved clinical outcomes in ARDS patients.

2.1.4 Supportive Non-Clinical Data

2.1.4.1 Non-clinical Pharmacology

Results from the non-clinical pharmacology studies using animal ARDS lung injury models (ie, mice and rats exposed to intratracheal lipopolysaccharide [LPS] administration; and mice, rats, minipigs exposed to intratracheal LPS administration followed by MV [VILI]) support the targeting of the eNAMPT inflammatory pathway as a potential strategy to reduce inflammatory lung injury and mortality in ARDS.

The effective pharmacological dose of ALT-100 was initially evaluated in a series of pilot studies in mice using LPS and LPS/VILI ARDS models. In both models, ALT-100 administered IV at doses from 0.4 mg/kg to 2 mg/kg were effective in reducing lung injury.

Treatment with the ALT-100 mAb in these ARDS/VILI models (mice, rats, and minipigs) demonstrate that a single dose of 0.4 mg/kg ALT-100 given IV at the time of ARDS/VILI induction significantly reduces lung injury. When 1.0 mg/kg ALT-100 was administered after LPS exposure, the maximum protection occurred at 4 hours after exposure but continued to significantly reduce lung injury in rats when provided up to 12 hours after exposure, and before ventilation exposure.

Similarly, in a septic shock (LPS IV infusion over 2 hours)/VILI porcine model, when ALT-100 at a dose of 0.4 mg/kg was administered either 2 or 6 hours after onset of LPS/VILI, there was dramatic and significant protection from inflammatory lung injury. ALT-100 at a single dose of 0.4 mg/kg was also able to preserve lung fluid balance and minimize multiorgan dysfunction when delivered to LPS/VILI-exposed minipigs with established inflammatory lung injury.

The multiple indices of lung injury significantly reduced by ALT-100 in preclinical ARDS/VILI models include:

- Histological damage - assessed by Haematoxylin and Eosin (H&E) staining (mice, rats, and pigs).
- Bronchoalveolar lavage (BAL) protein levels (mice, rats, and minipigs).
- BAL numbers of cells and polymorphonuclear neutrophils (PMNs) (mice, rats, and minipigs).
- Reduction of plasma inflammatory biomarkers such as eNAMPT (mice, rats, minipigs), IL-6 (mice, rats, minipigs), tumor necrosis factor alpha (TNF-α) (rats), Interleukin 1Receptor antagonist (IL-1RA) (pigs; but not statistically significant), and plasma angiopoetin-2 (ANG-2) (minipigs).
- Serum lactate levels (a marker of septic shock) (minipigs).
- 8-oxo-2-deoxyguanosine (8-oxo-DG) (a marker of reactive oxygen species [ROS]) levels (minipigs).
- Static and dynamic lung compliance (minipigs).
- Lung tissue albumin levels (mice and minipigs).
- Ultrasound-based measurements of lung edema (minipigs).

2.1.4.2 Non-clinical Pharmacokinetics

The in vivo PK of a single IV injection of ALT-100 was determined in Sprague Dawley rats. A single dose of ALT-100 at 0.1, 0.4, or 4.0 mg/kg administered IV demonstrated a short distribution phase in plasma and a longer elimination phase. Elimination half-life ($t_{½}$) was inconsistent with increasing dose and was calculated to be 10.8, 6.5, and 7.8 days in the 0.1, 0.4, or 4.0 mg/kg groups, respectively.

Toxicokinetic (TK) data from a 14-day study in the rat, indicated a single IV dose of 5, 15, or 50 mg/kg ALT-100 demonstrated dose proportional C_{max} to a greater than dose proportional exposure shown by AUC_{0-t} in male rats and a less than dose proportional exposure (C_{max} and AUC_{0-t}) in female rats over the dose range explored. Following a second ALT-100 IV dose administered 1 week later, exposure (C_{max} and AUC_{0-t}) increased proportionally to ALT-100 dose between 5 and 15 mg/kg in male and female rats, greater than dose proportional in males between 15 and 50 mg/kg, and less than dose proportional in female rats between 15 and 50 mg/kg. There was a higher (< 2-fold increase) exposure in male rats compared to female rats after the second dose of 15 mg/kg and after the first and second dose of 50 mg/kg, but no sex difference was seen at 5 mg/kg. The elimination rate did not vary by dose or sex and was similar to that reported in other single dose PK studies, with the $t_{½}$ ranging between 8.55 to 12.2 days in males and 7.64 to 8.82 days in females after 2 doses administered 1 week apart. Accumulation (based on AUC_{0-t}) was observed after the second dose in both sexes.

The TK data for a minipig 14-day study indicated variable t_{max} following IV infusion over 5 minutes, ranging from 17 minutes to 2 hours after the first dose and 14 minutes to 20 hours after the second dose. ALT-100 showed a greater than dose proportional increase in C_{max} and AUC_{0-168h} between doses of 5 and 15 mg/kg after 1 or 2 doses, with the exception of a slightly less than dose proportional increase in C_{max} for females after the second dose. ALT-100 exposure increased approximately dose proportional between 15 and 50 mg/kg on Day 1, with the exception of female C_{max} which was slightly less than dose proportional. After the second dose, ALT-100 exposure increased in a less than dose proportional manner between 15 and 50 mg/kg. There were no clear sex differences in exposure. Exposure was increased

after the second dose which was < 2-fold. The $t_{½}$ in minipigs could only be calculated based on the recovery animals dosed at 50 mg/kg and was approximately 30 days.

2.1.4.3 Non-clinical Safety

The toxicity of ALT-100 was evaluated in 14-day Good Laboratory Practice (GLP) toxicity studies in Sprague Dawley rats and Göttingen minipigs. Two IV doses (Days 1 and 7) of vehicle, 5, 15, or 50 mg/kg were given as a bolus injection in the rat, and doses of 0, 5, 15, or 50 mg/kg were given as a slow injection (over 5 minutes) in the minipig. There were no mortalities, or any effects related to ALT-100 on in-life parameters or histopathology in any organ following 2 IV doses up to 50 mg/kg in the rat or minipig.

The no observable adverse effect level (NOAEL) for ALT-100 in both the rat and minipig following 2 IV doses administered 1 week apart was considered to be 50 mg/kg.

A GLP tissue cross reactivity study investigated the binding of ALT-100 (1 and 5 µg/mL) to a wide range of normal human (n = 3) tissues and indicated membranous staining of labeled ALT-100 to lymphocytes found in numerous tissues (spleen, thymus, tonsils, lymph nodes, and colon in decreasing incidence). This is considered an on-target binding as it is consistent with the distribution of NAMPT.

Further details regarding non-clinical studies for ALT-100 are provided in the Investigator's Brochure.

2.1.5 Supportive Clinical Data

Study ALT-100-001 (Clinicaltrials.gov identifier: NCT05426746), a Phase 1 FIH study of ALT-100, is a randomized, double-blind, placebo-controlled study which aims to investigate the safety, tolerability, and PK profile of single ascending doses of ALT-100 administered via IV infusion to healthy participants. The PD effects and immunogenicity of ALT-100 are also being explored. The study is ongoing at the time of writing this protocol and being conducted at a single center in Australia.

The data presented here is blinded and includes available data up until the interim data cut which occurred on the 27 January 2023 as follows:

- Demographic, safety, and tolerability data for Cohorts 1, 2, 3, and 4
- PK data for Cohorts 1, 2, and 3
- PD data for Cohorts 1, 2, and 3 up to Day 29

Thirty-two evaluable participants were planned and have been sequentially enrolled and randomized in a 3:1 ratio (ALT-100:placebo) to 1 of 4 planned single ascending dose (SAD) cohorts as described in Table 2. A sentinel dosing strategy was utilized for the first 2 participants (n=1 active; n=1 placebo) in each dosing cohort.

Table 2 Single Ascending Dose Cohorts

Cohort	ALT-100		Placebo (normal saline)
	Dose (mg/kg)	No. of Participants	No. of Participants
1	0.1	6	2
2	0.4	6	2
3	1.0	6	2
4	4.0	6	2

At the time of a blinded interim analysis, with a data cut off date of 27 January 2023, a total of 32 healthy participants have been enrolled to Study ALT-100-001 and treated. At the time of this interim data cut, 13 (40.6%) of 32 participants have completed the study (all participants in cohort 1, and 5 [62.5%] of 8 participants in cohort 2). The participation of 18 (56.3%) of 32 participants is ongoing (2 [25.0%] participants in cohort 2 and 8 participants in each of cohorts 3 and 4) and 1 participant in cohort 2 has discontinued from the study (consent withdrawn). All 32 participants are included in safety analysis set for the blinded interim analysis.

Demographic characteristics for the enrolled study population are broadly consistent across all treatment cohorts.

Safety and Tolerability

Overall, a single IV administration by infusion of ALT-100 up to 4.0 mg/kg appears to be safe and well tolerated. At the time of the interim data cut, there were no serious or severe adverse events (AEs) and no evidence of increasing incidence of treatment-related AEs associated with increasing ALT-100 dose. A total of 52 treatment emergent adverse events (TEAEs) have been reported in 22/32 (68.8%) participants, of which 14 events in 9 (28.1%) participants were considered possibly related to study treatment by the investigator. The TEAE of highest incidence was headache (in 7 [21.9%] participants overall and reported in all cohorts), followed by vessel puncture site bruise (associated with the infusion; in 5 [15.6%] participants overall and reported in all cohorts). All other TEAEs occurred in no more than 1 participant per cohort. The most common TEAEs considered possibly related to study drug were those of headache (in 4 [12.5%] participants overall and reported in all cohorts except the highest dose level cohort [4 mg/kg/placebo]). All other TEAEs considered possibly related to the study drug (catheter site pain, fatigue, feeling hot, tonsilitis, ECG PR prolongation, somnolence, anxiety, dyspnea, and flushing) were single events which occurred in no more than 1 participant.

The majority of all TEAEs were mild (47 events in 22/32 [68.8%] participants). Moderate severity TEAEs occurred in 5/32 (15.6%) participants overall and were reported in no more than 2 participants per dose cohort. Moderate severity TEAEs included 1 event of headache and 1 event of hay fever in 1 participant each in cohort 2 (0.4 mg/kg/placebo); 1 event of dyspnea and 1 event of tonsillitis in 1 participant each in cohort 3 (1 mg/kg/placebo); and 1 event of anxiety leading to interruption of study drug in 1 participant in cohort 4 (4 mg/kg or placebo). All TEAEs of moderate severity were deemed by the investigator to be possibly related to the study drug, with the exception of the TEAE of hay fever, which was considered to be unrelated. Regardless of causality assigned, all TEAEs of moderate severity resolved.

Changes from baseline in hematologic, coagulation and biochemistry parameters did occur but these shifts were not considered to be clinically significant and none met the criteria for an AE. To date there are no trends of clinical concern with respect to vital signs (body temperature, respiratory rate, heart rate, systolic and diastolic blood pressure) or ECG findings following single IV infusion of ALT-100 in healthy volunteers. One participant in cohort 2 (0.4 mg/kg/placebo) with no cardiac history had an abnormal ECG PR prolongation after the administration of study drug on Day 1 and resolved by Day 15 without treatment. The TEAE of ECG PR prolongation was mild and asymptomatic, and was considered by the investigator to be possibly related to the study drug.

Anti-drug antibody (ADA) formation is being monitored for in the ongoing study, however insufficient data is available to report at the time of data-cut.

Pharmacokinetics

Interim PK analysis was conducted on 3 cohorts administered 0.1, 0.4 or 1 mg/kg ALT-100 by IV infusion over 20 minutes. ALT-100 was quantifiable at all doses evaluated, although the number of quantifiable samples was limited at 0.1 mg/kg. Maximal plasma concentration of ALT-100 occurred at or slightly later than the end of infusion. C_{max} appears dose proportional in the range of 0.1 to 1 mg/kg and within the constraints of the interim analysis, AUC_{last}, appears to be dose proportional within the range 0.4 to 1 mg/kg.

The t½ for ALT-100 was determined to be 330 to 460 h (or 14 to 19 days) where sufficient range of quantifiable concentrations was available for cohorts 2 and 3. The elimination phase was biphasic with fast elimination within the first 24 to 48 hours followed by a slower phase.

Terminal volume of distribution (V_z) was reliably quantifiable for one participant at 24 mL/kg in the range of systemic blood circulation but at the lower end, typically observed for large biologic molecules. Clearance for this subject was 0.038 mL/kg/h and in agreement with a long t½.

Pharmacodynamics

Preliminary exploratory cytokine data (available at the time of data cut only for cohorts 1, 2 and 3 up to Day 29), showed large inter-participant variability, with no clear dose effects. Summary data demonstrated elevations in IL-6 at the end of infusion relative to baseline, that did not correspond with ALT-100 dose, in all evaluated cohorts. IL-6 levels returned to or were approaching baseline levels thereafter. There were no notable shifts from baseline in the early data available for IL-8, TNF or IL-1RA. At the time of reporting, data for eNAMPT levels in plasma is not available.

The Phase 1 ALT-100-001 is further described in the Investigator's Brochure.

2.1.6 Dosing Rationale and Exposure Limits

Pharmacological efficacy (reduction of eNAMPT and the associated inflammatory cascade) has been demonstrated in both rats and minipigs. In 14-day toxicity studies 2 doses of ALT-100 were administered by IV injection, given 1 week apart. In these studies, ALT-100 has been well tolerated and support the NOAEL as the high dose in the rat and minipig. As ALT-100 is a large protein being administered IV, regulatory guidance (FDA 2005) supports normalizing the dose between species on a mg/kg body weight basis. No adverse toxicity has been observed in either species after the administration of 2 IV doses of ALT-100, therefore based on a mg/kg comparison of the animal NOAELs compared to the proposed human starting dose of 0.1 mg/kg, there is an approximate 500-fold safety margin. Comparing the total delivered dose (in mg) administered to rats (14 to 18 mg) and minipigs (500 mg) relative to the starting dose in humans (6 mg for a 60 kg person) there is an estimated safety margin of 2- to 3-fold in the rat and approximately 83-fold in the minipig. The lower margin based on delivered dose to the rat is related to the small body weight of the animal (260 to 330 g) and is not considered to reflect a greater toxicological sensitivity in this species.

No adverse effects have been seen in the minipig at much larger delivered doses, supporting the safety of ALT-100.

In the FIH study in healthy adults, a single dose of ALT-100 was administered at doses of 0.1 mg/kg, 0.4 mg/kg, 1.0 mg/kg, and 4.0 mg/kg via IV infusion to healthy adults. Preliminary data suggests that ALT-100 is safe and well tolerated. Therefore, the maximum dose in this patient study (a single administration of 1.0 mg/kg) is within what has been demonstrated to be safe and well tolerated.

Dose Escalation (Part A)

Part A will assess 2 doses of ALT-100 in sequentially enrolled cohorts of up to 9 participants in each cohort. The planned doses of ALT-100 will be 0.4 mg/kg (Cohort 1a: low dose) and a high dose (Cohort 1b: 1.0 mg/kg).

An optional dose cohort (Cohort 3a) of up to 9 participants may be enrolled based on the recommendations of the DSMC. The dose for Cohort 3a can be a lower or intermediate dose relative to Cohorts 1a and 2a and will be selected based on all safety, available PK, and early efficacy and PD data up to and including Day 29 from all participants in Cohort 1a and Cohort 2a. The dose for Cohort 3a will not exceed 1.0 mg/kg.

Dose Expansion (Part B)

Following DSMC review of available data up to and including Day 29 from the 9 participants from Part A, additional participants (up to 36 per dose level cohort) may be enrolled into 2 dose expansion cohorts, the dose of which will be determined by the DSMC if the optional Cohort 3a is utilized in Part A. Part B will further explore the safety, preliminary efficacy, PK, systemic biomarker profile of ALT-100.

2.1.7 Benefit:Risk Assessment

This is the first study to evaluate ALT-100 in patients with ARDS, and the benefits and safety are unknown. However, ALT-100 has demonstrated efficacy in reducing lung injury and proinflammatory biomarkers in a range of non-clinical models of ARDS and the preliminary blinded safety data from the FIH study in healthy volunteers appears to be reassuring with no SAEs or safety signals of concern following single IV doses of 0.1 mg/mL to 4.0 mg/mL ALT-100 (refer to Section 2.1.5). The reduction in eNAMPT activity and inhibition of eNAMPT binding to TLR4, thereby blocking the eNAMPT/TLR4 signaling by ALT-100 may dampen the inflammatory cascade, thereby improving outcomes for patients with ARDS.

For this Phase 2a study, ALT-100 will be administered via IV infusion, and is expected to be generally safe and well tolerated. Monoclonal antibodies, such as ALT-100, may be associated with a potential immune response, eg, hypersensitivity or hypersensitivity-like reactions, including severe, anaphylactic reactions, or target-mediated cytokine release. These potential risks will be monitored and managed over the duration of the study.

Administration of ALT-100 and all procedures related to the study will be performed by appropriately qualified persons at an investigational site suitable for conducting human studies.

To further minimize any potential risk, monitoring of each participant will be conducted throughout the study to detect any adverse events (AEs) and/or safety signals through physical examination, vital signs (heart rate, systolic and diastolic blood pressures, respiratory rate, heart rate, and body temperature), and laboratory parameters (hematology, coagulation, chemistry, and urinalysis). Adverse event reporting, review of concomitant medication use, and development of ADAs will also occur throughout.

Known potential risks to study participants are outlined in the ALT-100 Investigator's Brochure.

2.2 Study Rationale

The administration of a single IV dose of ALT-100 has demonstrated efficacy in reducing lung injury and proinflammatory biomarkers in a range of non-clinical models of ARDS and supports the clinical investigation of ALT-100 treatment as a potential therapeutic strategy in patients with ARDS.

A FIH study of single escalating doses of ALT-100 in healthy adult volunteers assessed the safety, tolerability, PK, preliminary PD, and immunogenicity of ALT-100. The FIH study demonstrated that a single dose of ALT-100 administered via IV infusion up to a dose of 4.0 mg/kg was safe and well tolerated in healthy volunteers.

This study aims to assess the safety and tolerability of ALT-100 up to a maximum dose of 1.0 mg/kg in patients with ARDS. Furthermore, the PK, preliminary efficacy, and PD of a single infusion of ALT-100 will also be assessed in this Phase 2a, randomized, double-blind, placebo-controlled study.

3 OBJECTIVES AND ENDPOINTS

Table 3 Objectives and Endpoints

	Objectives	Endpoints
Primary	***Safety***	
	Safety and tolerability of a single intravenously (IV) infused dose of ALT-100 in subjects with moderate to severe ARDS	• Incidence and severity of all TEAEs and SAEs until EoS.
Secondary	***Efficacy***	
	To evaluate the impact of a single IV infusion of ALT-100 on respiratory support.	• Number of MV-free days (MVFD) over 28 days following study treatment (ie, MVFDs by Day 29).
	To assess the effect of ALT-100 on duration of hospitalization.	• Time to hospital discharge based on days since admission to discharge. • HFD to Day 29.
	To assess the effect of ALT-100 as measured by the SOFA score.	• Total and component SOFA score assessed daily while in the ICU.
	To assess the effect of ALT-100 on oxygen-related parameters.	• Changes as measured by change from baseline in plethysmographic pulse oximetry derived oxygen saturation / fraction of inspired oxygen (SpO_2/FiO_2) and ROX Index (SpO_2/FiO_2 divided by respiratory rate [RR]), assessed daily while hospitalized. • If the participant is receiving MV, the P/F ratio will be used (ie, partial pressure of oxygen [PaO_2]/FiO_2).
	To assess the effect of ALT-100 on oxygenation requirements	• Incidence and duration of oxygen use (via conventional oxygen therapy, or non-invasive respiratory support positive pressure by face mask or HFNO) during the study
	To assess the effect of ALT-100 on requirement for vasoactive support	• Number of days of vasoactive agent usage • Vasopressor free days
	Pharmacodynamics	
	To investigate the effects of ALT-100 on immune function	• Changes from baseline in plasma levels of extracellular nicotinamide

Table 3 Objectives and Endpoints

	Objectives	Endpoints
	biomarkers and cellular response.	phosphoribosyltransferase (eNAMPT) and other biomarkers of interest including but not limited to TNF-α, IL-1β, IL-1RA, IL-6, Angiopoietin-2. • Changes from baseline in cellular response with ALT-100 compared to placebo, as assessed by: neutrophil, monocyte, and lymphocyte counts in whole blood.
	Pharmacokinetics	
	To characterize the plasma PK profile of single IV infused doses of ALT-100.	• Determination of plasma concentrations of ALT-100. • Estimation of PK parameters.
	Safety	
	To further evaluate the safety and tolerability of a single intravenously (IV) infused dose.	Secondary safety and tolerability outcomes while hospitalized or if discharged on Days 8, 15, 22, 29, and 60 will include: • Laboratory safety data (chemistry, hematology, coagulation, and urinalysis parameters) • Vital signs (blood pressure, heart rate, respiration rate, body temperature) • Physical examination • Concomitant medication use • Oxygenation (FiO_2 and PaO_2 or SpO_2) • Ventilation support: type of ventilation (heated and humidified high flow nasal O_2 [HFNO], non-rebreathing mask, bilevel positive airway pressure [BiPAP]/ continuous positive airway pressure [CPAP], or MV), FiO_2, SpO_2, PaO_2 (if available), ventilation rate based on respiratory rate, heart rate, ventilator settings (tidal volume, PEEP, and airway pressure [peak and plateau]).
	To investigate the presence of anti-ALT-100 antibodies.	• Presence and characterization of ADA over the study period (baseline [Day 1 pre-dose], and post treatment on Days 8, 15, 29, and 60).
Exploratory	Exploratory detection of *NAMPT* genetic variants in blood.	• Determination of ARDS-associated *NAMPT* promoter SNP expression in baseline blood

Table 3 Objectives and Endpoints

	Objectives	Endpoints
		samples from all participants using a *NAMPT* genotyping platform. • Assessment of predictive capacity of *NAMPT* SNPs and plasma eNAMPT levels to identify participants who respond to single dose treatment with ALT-100.
	To explore the effect of ALT-100 on other measurements of lung injury that may be performed during standard care (eg, LIS, chest radiography, PaO_2/FiO_2, need for extracorporeal membrane oxygenation [ECMO])	• Change from baseline in LIS (to be performed daily) while hospitalized. • Change from baseline in chest radiographic assessment (if performed). • Change from baseline in P/F ratio (if performed) daily while hospitalized. • Utilization of ECMO.
	To assess the effect of ALT-100 on respiratory support requirements over time	• MVFDs by Days 8, 15, 22, and 60. • Proportion of participants not on MV support on Days 8, 15, 22, 29, and 60. • Number of participants progressing from non-invasive to invasive MV by Days 8, 15, 22, 29, and 60. • Time of progression from non-invasive to invasive MV to Day 60. • Proportion of participants weaned from MV within 28-days from treatment (by Day 29).
	To explore the effect of ALT-100 on mortality	• Mortality in all participants by Days 8, 15, 22, 29, and 60. • Time to death by Day 60.

Note: Where data permit, various exploratory sensitivity and subgroup analyses may be performed. These may include analyses of progression to MV in ALT-100 versus placebo-treated ARDS patients on heated and humidified HFNO or NIPPV (ie, BiPAP/CPAP), and assessment of the effect of ALT-100 on overall duration of hospitalization based on participant ventilator requirements at the time of enrollment.
Exploratory analyses may be reported separately to the final study report.

4 STUDY PLAN

4.1 Study Design

PUERTA is a Phase 2a, randomized, double-blind, placebo-controlled study in adults with moderate to severe ARDS consequent to sepsis, septic shock, trauma, and/or bacterial or viral pneumonia who have been hospitalized. The safety and tolerability, PK, preliminary efficacy and PD of a single infusion of ALT-100 will be assessed.

Patients with respiratory distress and hypoxemia admitted to participating institutions/ hospitals will be screened for study eligibility. Participants included in the study can be patients requiring immediate intubation/MV (ie, within 4 hours of their moderate or severe ARDS diagnosis), as well as patients receiving heated and humidified HFNO (≥ 30 L/min and 100% FiO_2) or NIPPV (ie, BiPAP/ CPAP) or 12 continuous hours with high flow nasal oxygen (HFNO) using gas flow of ≥ 40 L/min or treated with non-invasive ventilation (NIV). All participants will receive study drug within 12 hours of their ARDS diagnosis and within 4 hours of initiation of MV (in the case where participants require immediate MV).

It is planned that 90 eligible participants will be randomized at a 2:1 ratio to receive a single dose of either ALT-100 or placebo via IV infusion at the time the diagnosis of moderate to severe ARDS is made. An additional 9 participants may be randomized if an optional cohort of low or intermediate ALT-100 dose is enrolled.

The study will be conducted in 2 parts:

- Part A: a dose escalation phase

  followed by

- Part B: dose expansion phase

Dose Escalation (Part A)

Part A will assess 2 doses of ALT-100 in sequentially enrolled cohorts of up to 9 participants in each cohort. The planned doses of ALT-100 are 0.4 mg/kg (Cohort 1a) and 1.0 mg/kg (Cohort 2a).

An optional dose cohort (Cohort 3a) of up to 9 participants may be enrolled based on the recommendations of the DSMC. The dose for Cohort 3a can be a lower or intermediate dose relative to Cohorts 1a and 2a and will be selected based on available safety, PK, and early efficacy and PD data up to and including Day 29 from all participants in Cohort 1a and Cohort 2a. The dose for Cohort 3a will not exceed 1.0 mg/kg.

Dose Expansion (Part B)

Following DSMC review of all data up to and including Day 29 from the 9 participants in each cohort in Part A, additional participants (up to 36 per dose cohort) may be enrolled into 2 dose expansion cohorts, the dose of which will be determined by the DSMC. Part B will further explore the safety, preliminary efficacy, PK, and systemic biomarker profile of ALT-100.

Participants enrolled in Part A may not be re-enrolled in Part B.

Planned dosing cohorts for the study are presented in Table 4.

Table 4 Planned Dose Cohorts

Cohort	ALT-100		Placebo
	Dose (mg/kg)	Participants (N)	Participants (N)
Part A: Dose Escalation			
Cohort 1a	0.4	6	3
Cohort 2a	1.0	6	3
Cohort 3a (optional*)	X	6	3
Part B: Dose Expansion			
Cohort 1b	TBD[#]	24	12
Cohort 2b	TBD[#]	24	12

Abbreviation: N = number of participants; TBD = to be determined.
*An optional, additional dose level cohort may be enrolled based on DSMC recommendations following the review of data from Cohorts 1a and 2a.
[#] Dose to be determined (TBD) by DSMC based on all safety, available PK data, and any early efficacy and PD data from all Part A cohort participants completing up to and including Day 29. The highest dose of ALT-100 will not exceed 1.0 mg/kg.

The screening, Treatment, and Safety Follow-up schedules are the same for Part A (dose escalation) and Part B (dose expansion) cohorts.

Screening Period (Day -3 to Day 1)

Screening will occur within 3 days prior to enrollment of participants into the study and may occur on the day of treatment (Day 1). Written informed consent (from the patient or their legally authorized representative [LAR]) must be documented before any study-specific procedures, including for screening, are performed. Screening may occur from time of recognition of at-risk conditions for ARDS (patient presenting with sepsis, septic shock, and/or bacterial or viral pneumonia).

Individuals who fail to meet eligibility requirements may be rescreened (once), on a case-by-case basis, as determined by the MM.

Consenting, hospitalized patients who meet all the eligibility criteria at screening will be enrolled into the study after confirmation of eligibility.

Participants will be randomized on Day 1 to receive a single dose of either ALT-100 or placebo via IV infusion. All study participants will receive supportive care according to the local standard of care (SoC).

Patients identified to be at-risk of developing moderate-severe ARDS will be monitored closely and those who do not meet any exclusion criteria will be enrolled with the understanding that once moderate-severe ARDS criteria are met, they will be randomized to treatment.

Baseline assessments will be conducted prior to administration of study treatment on Day 1. Screening and baseline assessments are outlined in the SoA (Table 1).

Study Treatment Period (Day 1)

All randomized participants will be administered a single IV infusion of study treatment according to their randomization on Day 1.

Participants requiring immediate MV support (ie, requiring ventilation via endotracheal tube or tracheostomy tube within 4 hours of diagnosis of moderate or severe ARDS on Day 1) must receive study treatment within 4 hours of the initiation of MV. All participants will receive study drug within 12 hours of their ARDS diagnosis and within 4 hours of initiation of MV (in the case where participants require immediate MV).

Follow-up Period (Day 2 to Day 60)

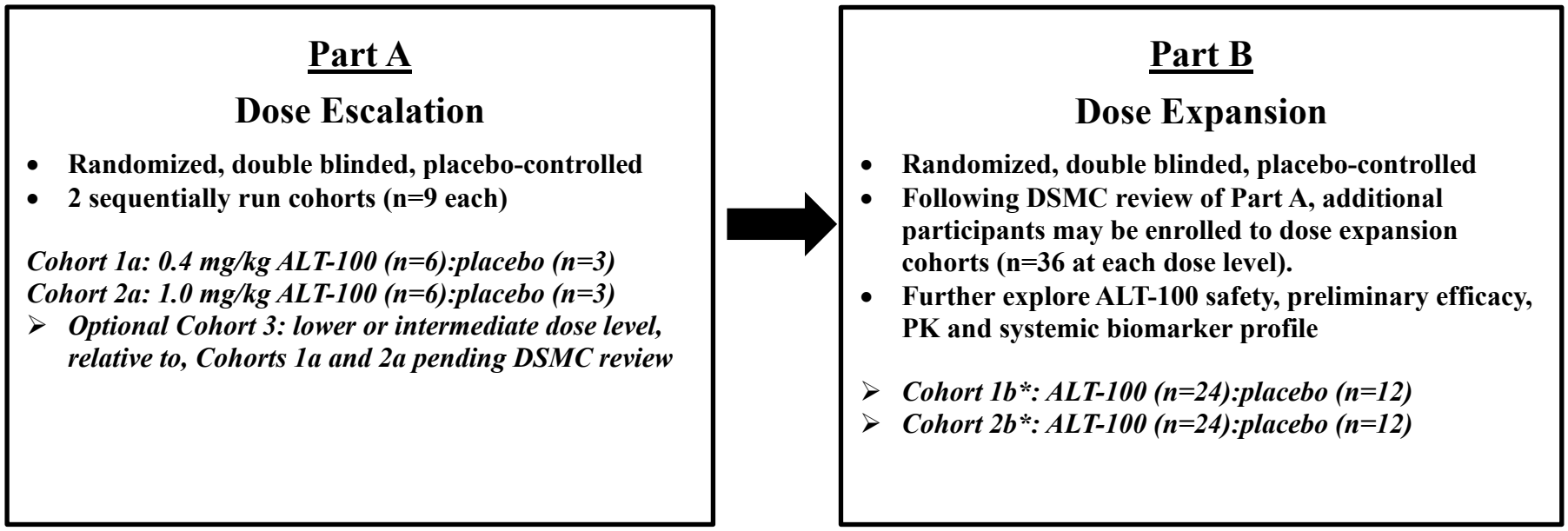
Participants will be assessed daily while hospitalized. Follow-up assessments are planned through to Day 60. If the participant is discharged from the hospital at an earlier timepoint, follow-up, onsite visits will occur on Days 2 to 8, 15, 22, 29, and 60, within the allowable window specified in the SoA. All participants will undergo a series of safety, plasma PK, efficacy, PD, and exploratory assessments as detailed in the SoA (Table 1).

All participants who are discharged from the hospital during the study will undertake DoD assessments prior to discharge.

Any participant who discontinues from the study early will complete an ET Visit, wherever possible. All participants who discontinue the study early will be followed for safety until Day 60, wherever possible.

The design of the study is summarized in Figure 1 (Part A and Part B) and Figure 2 (Study Periods).

Figure 1 Study Design: Part A (Dose Escalation) and Part B (Dose Expansion)



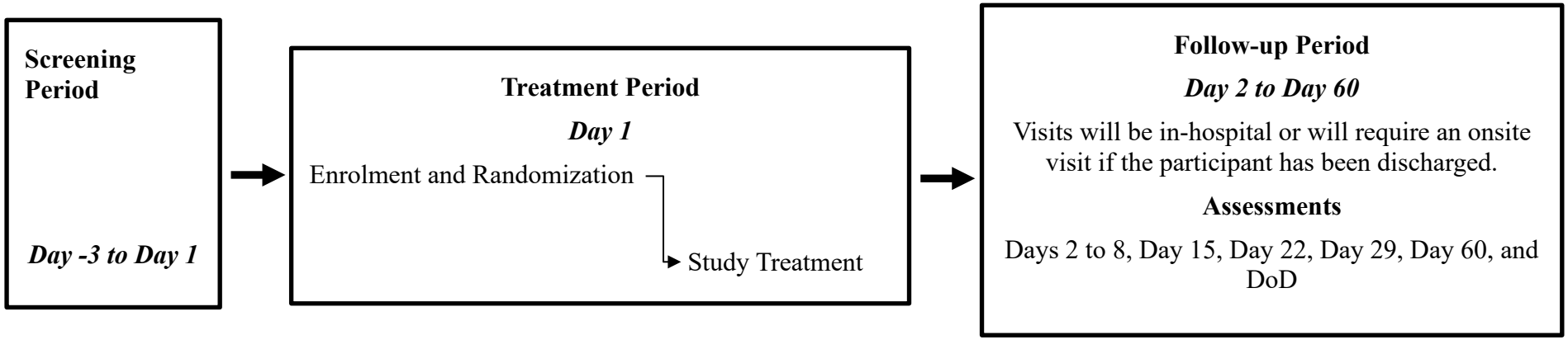
DSMC review:

Review of all safety, PK, efficacy, and PD data from 9 participants per dose level cohort who complete the study up to and including Day 29 in Part A.

**Dose levels for Part B will be determined by the DSMC based on the data from Part A.*

Abbreviations: DSMC = Data Safety Monitoring Committee; n = number of participants; PK = pharmacokinetic; TBD = to be determined.

Figure 2 Part A and Part B Study Periods



Abbreviation: DoD = day of discharge.

5 POPULATION

5.1 Definitions

A screen failure is a consented participant who has been deemed ineligible on the basis of 1 or more study eligibility criteria or who has withdrawn consent prior to treatment.

Eligible, consenting participants will be enrolled to the study. Prior to enrollment of a participant, the following must occur:

- Confirmation that the participant or their LAR has signed the participant informed consent form (PICF).
- Confirmation that the participant meets all of the inclusion, none of the exclusion criteria, and has been assessed by the Investigator as being an appropriate candidate for study participation.

5.2 Inclusion Criteria

To be eligible for this study, a participant must meet all of the following criteria:

1. Hospitalized (or documentation of a plan to admit to the hospital if the patient is in an emergency department) male or non-pregnant female ≥ 18 years of age at time of enrollment.
2. Participant (or LAR) is able and willing to provide written informed consent, which includes compliance with study requirements and restrictions listed in the consent form.
3. Participant has a diagnosis of moderate or severe ARDS:

   A participant has a diagnosis of moderate or severe ARDS according to the Berlin definition of ARDS:

   a. Acute onset of respiratory failure within 1 week of a known clinical insult or new or worsening respiratory symptoms

   b. Respiratory failure associated with known ARDS risk factors and not fully explained by either cardiac failure or fluid overload (an objective assessment of cardiac failure or fluid overload is needed if no risk factors for ARDS are present)

   c. Radiological abnormalities on chest x-ray or CT scan, ie, bilateral opacities that are not fully explained by effusions, nodules, masses, or lobar/lung collapse.

   d. Hypoxemia:

      i. Moderate ARDS: PaO_2/FiO_2 > 100 mmHg (> 13.3 kPa) to ≤ 200 mmHg (≤ 26.6 kPa) with PEEP ≥ 5 cmH_2O, or imputed SpO_2/FiO_2 equivalent

      ii. Severe ARDS: PaO_2/FiO_2 ≤ 100 mmHg (≤ 13.3 kPa) with PEEP ≥ 5 cmH_2O

   Note: Acceptable imaging tests (chest x-ray, CT scans) done within 3 days of Day 1 can be used to determine eligibility, however, the radiological and hypoxemia criteria (3 [c] and [d]) must occur within the same 24-hour period. The time of onset of ARDS is defined as the time when the last of these 2 ARDS criteria is met.

   OR

Participant presents with acute respiratory failure phenotypically similar to ARDS in a setting demonstrating clinical risk for ARDS, whether or not they meet the Berlin criteria, and requiring heated and humidified HFNC ≥ 30 L/min and 100% FiO_2, or NIPPV (ie, BiPAP/CPAP) for hypoxemia.

OR

Participant presents with acute respiratory failure phenotypically similar to ARDS in a setting demonstrating clinical risk for ARDS, does not meet the Berlin criteria, and is initially treated with ≥ 12 continuous hours with HFNO using gas flow of ≥ 40 L/min or treated with NIV, and has a PEEP of ≥ 5 cm H_2O and PaO_2/FIO_2 < 200 mm Hg.

4. Administration of study treatment must be planned to occur within 12 hours of the participant's moderate or severe ARDS diagnosis and within 4 hours of initiation of MV (in the case of individuals requiring immediate MV).
5. Females must be non-pregnant and non-lactating, and either surgically sterile (eg, tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy), or use highly effective contraceptive method (oral contraceptive pills [OCPs], long-acting implantable hormones, injectable hormones, a vaginal ring or an IUD) from screening until study completion, or be post-menopausal for ≥ 12 months. Post-menopausal status will be confirmed through testing of FSH levels at screening for amenorrheic female participants but the result is not required prior to enrollment. Female participants whose only partner has had a vasectomy, and female participants who are abstinent from heterosexual intercourse as part of their usual lifestyle will also be eligible for participation.
6. WOCBP must have a negative pregnancy test at screening and admission and be willing to have additional pregnancy tests as required throughout the study.
7. Males must be surgically sterile (> 30 days since vasectomy with no viable sperm), abstinent, or if engaged in sexual relations with a WOCBP his partner must be surgically sterile (eg, tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy) or using an acceptable, highly effective contraceptive method from screening until study completion, including the Follow-up Period. Acceptable methods of contraception include the use of condoms and the use of an effective contraceptive for the female partner (WOCBP) that includes: OCPs, long-acting implantable hormones, injectable hormones, a vaginal ring, or an IUD. Male participants whose female partner is post-menopausal, and participants who are abstinent from heterosexual intercourse as part of their usual lifestyle will also be eligible.
8. Male participants must agree to refrain from donating sperm from screening until study completion, including the Follow-up Period, for at least 60 days after the last dose of study treatment.
9. Participant is willing and able to undergo all study procedures and attend the scheduled follow-up visit/s per protocol.

5.3 Exclusion Criteria

A participant who meets any of the following criteria must be excluded from the study:

1. Participants with ARDS consequent to COVID-19 infection.
2. Participants requiring immediate MV who have been intubated and on MV for > 4 hours prior to the planned administration of study treatment on Day 1.

3. Moribund participant not expected to survive > 24 hours, in the opinion of the Investigator.
4. Use of extracorporeal life support (eg, ECMO) or, in the opinion of the Investigator, there is a high likelihood that extracorporeal life support will be initiated within 48 hours after randomization.
5. Participant has an underlying clinical condition where, in the opinion of the Investigator, it would be unlikely that the participant would be able to come off ventilation, eg, chronic progressive neuromuscular or respiratory disease.
6. Severe chronic respiratory disease (eg, known chronic obstructive pulmonary disease [COPD], pulmonary arterial hypertension [PAH], idiopathic pulmonary fibrosis [IPF], interstitial lung disease [ILD]) requiring supplemental oxygen therapy or MV pre-hospitalization (eg, prior to ARDS diagnosis).
7. Evidence of life-threatening dysrhythmia (eg, ventricular tachycardia, ventricular fibrillation) or cardiac arrest on presentation.
8. Evidence of new or preexisting decompensated heart failure.
9. Absolute neutrophil count < 1000 per mm^3.
10. Platelet count < 50000 per mm^3.
11. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 5 × ULN.
12. Estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73m^2 (based on MDRD equation) or requiring hemofiltration or dialysis.
13. Known or suspected active and untreated tuberculosis (TB), HIV, hepatitis B or C infection.

    Note: Results of TB, hepatitis B and C, and HIV tests are not required prior to enrollment if there is no suspicion of active infection.

14. Known history of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric, human, or humanized antibodies, fusion proteins, ALT-100 excipients, or a history of drug or other allergy including severe allergic reaction that in the opinion of the Investigator or MM, contraindicates participant participation.
15. Use of any immunomodulatory biologic (eg, anti-IL-1, anti-IL-6R, anti-TNF, inhibitors of complement signaling), cell therapies (eg, mesenchymal stem cells), or small molecule Janus kinase (JAK) inhibitors within the past 7 days or within 5 half-lives (whichever is longer), or planned use of any of these agents from screening until Day 60 of the study, unless approved by the MM. The following will be allowed/ disallowed as indicated:
    a. Immunomodulatory biologics for treatment of COVID-19 are excluded and should not be used until Day 60 unless discussed with the MM. Other non-biologic immunomodulators (non-JAK inhibitors), eg, medicines for previous transplantation, or DMARDS, if on a stable dose for ≥ 8 weeks are permitted.
    b. Ongoing chronic (≥ 4 weeks) use of corticosteroids > 10 mg/day of prednisone or equivalent at the time of randomization is prohibited. A corticosteroid dose that has been tapered to 10 mg or less within 14 days of randomization is also prohibited.

    c. Acute corticosteroid use during the study, if clinically indicated as determined by the treating physician, is permitted.

16. Participants using vasopressors are eligible for study participation, with the following exceptions as noted:
    a. Participants who present at screening with ARDS and septic shock may be enrolled if the participant is on one vasopressor or, if on 2 vasopressors, if the Levofed (norepinephrine) dose is ≤ 1 μg/kg/min.

b. Participants with ARDS and septic shock who are on ≥ 3 vasopressors ie, Vasopressin, Levofed (norepinephrine), Neosynephrine (phenelephreine), at screening are excluded from study participation.
c. Participants with ARDS and septic shock who are on 2 vasopressors where the Levofed dose is > 1 µg/kg/min are excluded from study participation.

Note: Participants who require vasopressors for sedation-related hypotension may be eligible for inclusion, per approval from the MM.

17. Participation in a clinical research study evaluating another IP or therapy within 3 months and less than 5 half-lives of the IP prior to the Screening Visit.
18. Any physical examination findings, and/or history of any other illness, concomitant medications, or recent live vaccines that, in the opinion of the Investigator, might confound the results of the study or pose an additional risk to the participant by their participation in the study.
19. Administered a live vaccine within 14 days prior to IP administration and throughout the duration of the study.

To assess any potential impact on participant eligibility with regards to safety, the Investigator must refer to the Investigator's Brochure for detailed information regarding warnings, precautions, contraindications, AEs, and other significant data pertaining to the IP being used in this study.

5.4 Study Restrictions

5.4.1 Contraceptive Requirements

Contraception requirements are described in Section 5.2.

5.4.2 Fasting and Dietary Restrictions

There are no fasting or dietary restrictions for this study.

5.5 Prior and Concomitant Therapies

Participants are to be administered therapies as per the local SoC and as considered necessary by the Investigator for ARDS and underlying condition/s.

Any therapy administered from informed consent until study treatment will be documented as prior therapy. Any therapy taken from the start of the study infusion until Day 60 will be documented as concomitant therapy.

5.5.1 Prior and Concomitant Therapy Restrictions

As per the study eligibility criteria presented in Section 5.3, the following restrictions for prior and concomitant medication use will apply:

- Use of any immunomodulatory biologic (eg, anti-IL-1, anti-IL-6R, anti-TNF, inhibitors of complement signaling), cell therapies (eg, mesenchymal stem cells), or small molecule Janus kinase (JAK) inhibitors within the past 7 days or within 5 half-lives (whichever is longer), or planned use of any of these agents from screening until Day 60 of the study, unless approved by the MM. The following will be allowed/ disallowed as indicated:

- Immunomodulatory biologics for treatment of COVID-19 are excluded and should not be used until Day 60 unless discussed with the MM. Other non-biologic immunomodulators (non-JAK inhibitors), eg, medicines for previous transplantation, or DMARDS, if on a stable dose for ≥ 8 weeks are permitted.
- Ongoing chronic (≥ 4 weeks) use of corticosteroids > 10 mg/day of prednisone or equivalent at the time of randomization is prohibited. A corticosteroid dose that has been tapered to 10 mg or less within 14 days of randomization is also prohibited.
- Acute corticosteroid use during the study, if clinically indicated as determined by the treating physician, is permitted.

- Participants using vasopressors are eligible for study participation, with the following exceptions as noted:
  - Participants who present at screening with ARDS and septic shock may be enrolled if the participant is on 1 vasopressor or, if on 2 vasopressors and the Levofed (norepinephrine) dose is ≤ 1 μg/kg/min.
  - Participants with ARDS and septic shock who are on ≥ 3 vasopressors ie, Vasopressin, Levofed (norepinephrine), Neosynephrine (phenelephreine), at screening are excluded from study participation.
  - Participants with ARDS and septic shock who are on 2 vasopressors where the Levofed dose is > 1 μg/kg/min are excluded from study participation.

    Note: Participants who require vasopressors for sedation-related hypotension may be eligible for inclusion, per approval from the MM.
- Participation in a clinical research study evaluating another IP or therapy within 3 months and less than 5 half-lives of the IP prior to screening
- Participants who have been administered a live vaccine within 14 days prior to screening are excluded from study participation. The administration of live vaccines throughout the duration of the study is not permitted.

6 STUDY INTERVENTIONS

6.1 Description of Products

6.1.1 ALT-100

ALT-100 is a humanized murine monoclonal antibody (mAb) that specifically binds to eNAMPT, consisting of 2 kappa light chains and 2 gamma heavy chains of the IgG4 isotype.

The Sponsor will be responsible for the supply of ALT-100 to the sites. ALT-100 will be manufactured by WuXi Biologics (Suzhou) Co. Ltd (China) according to) cGMP and will be suitable for human use. All IP will be labeled in accordance with cGMP and local regulations.

The IP is formulated as a sterile liquid, pH 5.5, and is provided in 10 mL glass vials containing 10 mg/mL of ALT-100. Each vial is filled with 10.5 mL to ensure an extractable volume of at least 10.0 mL (ie, at least 100 mg of ALT-100 per vial).

ALT-100 is to be stored at 2 to 8°C and protected from light during storage. Current and ongoing stability studies support the labeled expiry date of ALT-100.

ALT-100 should be inspected visually for particulate matter and discoloration prior to administration. ALT-100 should be a clear, colorless liquid, and should not be used if particulates or discoloration are present in the vial.

For administration in this study, ALT-100 will be diluted in normal sterile saline to the appropriate volume required to deliver a dose of 0.4 mg/kg up to 1.0 mg/kg ALT-100 and will be given as a single IV infusion via pump in a total volume of ~ 50 mL with a constant infusion rate. ALT-100 should be administered within 4 hours of dilution. A filter should be used during infusion (≤ 0.3 micron; preferably 0.2 micron). ALT-100 is to be infused at a rate to complete in 20 minutes (~2.5 mL/min). The rate of infusion may be reduced in the event of an infusion-related reaction, to conclude in 60 minutes, at the discretion of the Investigator. Guidelines on the management of acute infusion reactions are provided in Section 6.2.

Details regarding the storage, preparation, and administration of the ALT-100 are provided in the Pharmacy Manual.

6.1.2 Placebo

The placebo for this study will be commercially available normal saline, supplied by each site and administered as an IV infusion at a constant infusion rate in a total volume and appearance matched to the ALT-100 for the respective cohort.

6.2 Management of Infusion-related Reactions

Infusion-related reactions are defined as any event within 24 hours of an infusion described as an allergic or anaphylactoid reaction, or any event occurring on the day of dosing described as allergic reaction, anaphylactoid reaction, fever, chills, or dyspnea. Guidelines on the management of acute infusion-related reactions are provided in Table 5.

Table 5 Guidelines for Management of Acute Infusion-related Reactions

Severity	Treatment
Grade 1 (Mild) Mild reaction; intervention not indicated	Stop infusion and monitor symptoms. If symptoms resolve without intervention, the infusion may be restarted at 50% of the original infusion rate.
Grade 2 (Moderate) Requires infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, antipyretics, IV fluids); prophylactic medications indicated for ≤ 24 hours	Stop infusion and monitor symptoms. Additional appropriate medical therapy may include but is not limited to IV fluids, antihistamines, and antipyretics. Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the Investigator. If symptoms resolve following supportive treatment, the infusion may be restarted at 50% of the original infusion rate. Otherwise, participants will be discontinued from further trial treatment administration.
≥ Grades 3 (Severe) *Grade 3*: Prolonged (ie, not rapidly responsive to medication interruption; recurrence of symptoms following initial improvement;) *Grade 4*: Life-threatening	Stop infusion and increase monitoring of vital signs as medically indicated. Additional appropriate medical therapy may include but is not limited to IV fluids, IV steroids (eg, hydrocortisone 100 to 200 mg or corticosteroid equivalent), IV antihistamines, vasopressors, and antipyretics. Participants with signs or symptoms that may be consistent with cardiac etiology should be assessed by ECGs, cardiac enzymes (eg, creatinine-MB isoenzyme, troponins, brain natriuretic peptide) to rule out myocardial infarction, and echocardiogram should be performed unless cardiac failure is ruled out by preceding investigations. Participant is permanently discontinued from further trial treatment administration.

6.3 Treatment Assignment and Bias Minimization

6.3.1 Treatment Allocation

It is planned that 90 eligible participants will be randomized at a 2:1 ratio to receive a single dose of either ALT-100 or placebo via IV infusion in a double blinded manner. An additional 9 participants may be randomized if an optional cohort of low or intermediate ALT-100 dose is enrolled which will be determined by the DSMC.

Dose Escalation (Part A)

Part A will assess 2 doses of ALT-100 in sequentially enrolled cohorts of up to 9 participants in each cohort. The planned doses of ALT-100 will be 0.4 mg/kg (Cohort 1a) and 1.0 mg/kg (Cohort 1b).

An optional dose cohort (Cohort 3a) of up to 9 participants may be enrolled based on the recommendations of the DSMC. The dose for Cohort 3a can be a lower or intermediate dose relative to Cohorts 1a and 2a and will be selected based on available safety, available PK, and

early efficacy and PD data up to and including Day 29 from all participants in Cohort 1a and Cohort 2a. The dose for Cohort 3a will not exceed 1.0 mg/kg.

Dose Expansion (Part B)

Following DSMC review of all data up to and including Day 29 from the 9 participants from Part A, additional participants (up to 36 per dose level cohort) may be enrolled into 2 dose expansion cohorts, the dose of which will be determined by the DSMC if the optional Cohort 3a is utilized in Part A. Part B will further explore the safety, preliminary efficacy, PK, and systemic biomarker profile of ALT-100.

Participants enrolled in Part A may not be re-enrolled in Part B.

6.3.2 Randomization Strategy and Procedure

At screening each potential participant will be assigned an identification number. The participant identification number will consist of the site number followed by an automatically assigned number, so that each participant will be uniquely identified.

Once deemed eligible for study participation, the participant will be enrolled and (where applicable) assigned a sequential randomization number based on a randomization schedule generated by the study statistician. The randomization schedule will be provided to the unblinded study pharmacist. Participants will receive a randomization number prior to application of study treatment. This randomization number together with the participant's identification number assigned at screening number will ensure identification throughout the study.

Randomization will occur centrally using an interactive voice or web response system.

Participants who withdraw for any reason without completing all screening evaluations successfully will be considered screen failures. Screen failures will not receive a participant randomization number.

A participant can be randomized only once.

Details regarding the randomization procedure are documented in the study Randomization Plan.

6.3.3 Extent and Maintenance of Blinding

The Investigator, other site staff, and study participants will remain blinded throughout the conduct of the study, except in circumstances where unblinding is determined by the Investigator, Sponsor or SMC to be important for the safety of a participant, or for the purposes of meeting expedited safety reporting requirements. In addition, the site monitor, and the clinical research organization (CRO; excluding unblinded statistical and clinical monitoring teams) and the Sponsor will be blinded to the assigned treatment.

The following personnel will remain unblinded:

- unblinded site pharmacy monitor
- the study pharmacist and personnel involved in study treatment handling (receipt and storage)
- unblinded statistician
- unblinded project administrator
- unblinded trial supply manager

- personnel at the bioanalytical laboratory involved in the determination of plasma concentrations of ALT-100.

If an emergency unblinding is required, the Investigator will have immediate access to individual participant codes.

6.4 Assessment and Verification of Compliance

ALT-100 or placebo (as applicable) will be administered to all participants onsite at the site under the supervision of the Investigator or designee. Administration of study treatment will be recorded in the eCRF.

6.5 Study Treatment Accountability

A record will be maintained by the site, which will account for all dispensing and return of any used and unused IP. At the end of the study the IP will be reconciled, and a copy of the record given to the study monitor.

6.6 Study Treatment Storage and Disposal

The Investigator will be fully responsible for the inventory, security, accessibility, and storage of the IP while they are at the site. The inventory must be available for inspection by the study monitor.

ALT-100 and placebo intended for use in the study are to be stored in a secure, limited-access location in accordance with the labeled storage conditions. Limited responsibility may be delegated to a member of the trial team, and this delegation must be documented. Temperature monitoring is required at the storage location to ensure that the IP is maintained within the established temperature range, per the product label. Excursion from the established range will require site investigation as to cause and remediation.

Upon completion of the study, any surplus supplied will be either destroyed upon receipt of written approval from the Sponsor and evidence of destruction supplied to the study monitor, or will be returned to the supplier. If no supplies remain, this will be documented in the dispensing record.

7 STUDY CONDUCT

Whenever vital signs and PK/ PD blood draws are scheduled for the same nominal time, the assessments should occur in the following order: vital signs then PK/PD blood draws; so that the timing of the assessments allow the blood draw to occur at the exact nominal time.

All study procedures should be completed as close to the prescribed/scheduled times as possible. Any non-scheduled procedures required for urgent evaluation of safety concerns take precedence over all scheduled routine procedures.

7.1 Study Procedures

7.1.1 Screening Period (Day -3 to Day 1)

Informed consent must be documented before any study-specific procedure is performed.

Screening for the study will occur within 3 days prior to enrollment and may occur on the day of study treatment (Day 1). Screening may occur from time of recognition of at-risk conditions for ARDS (presenting with sepsis, septic shock, and/or bacterial or viral pneumonia). At-risk patients will be monitored closely for development of moderate-severe ARDS. Randomization will only occur if they develop moderate-severe ARDS.

Individuals who fail to meet eligibility requirements may be rescreened (once), on a case-by-case basis, as determined by the MM.

Screening assessments include:

- Determination of participant eligibility for study (ie, inclusion/exclusion criteria)
- Documentation of demographics (year of birth, age [calculated], sex, ethnicity, and race)
- Height and body weight measurement/estimation; calculation of BMI
- Documentation of medical history
- Review and documentation of use of prior medication
- Measurement of vital signs (systolic and diastolic blood pressures, respiratory rate, heart rate, and body temperature)
- Blood collection for safety laboratory investigations (hematology, coagulation, and chemistry)
- Urine collection for urinalysis testing
- Viral serology (HBsAg, HCV RNA/Ab, HIV-1 and HIV-2) (enrollment can continue before results available)
- Local QuantiFERON test (enrollment can continue before results available)
- Blood collection for serum pregnancy test for WOCBP and FSH test for post-menopausal women
- Chest x-ray or CT scan (not required if imaging data within 3 days of screening is available)
- Measurement of SpO_2/FiO_2 and imputation of PaO_2/FiO_2
- Documentation of oxygenation requirements
- Documentation of ventilation requirements (type of ventilation [high flow nasal O_2 {HFNO}], non-rebreathing mask, bilevel positive airway pressure [BiPAP]/ continuous positive airway pressure [CPAP], or MV), FiO_2, SpO_2, PaO_2 (if available), ventilation rate based on respiratory rate, heart rate, ventilator settings (tidal volume, PEEP, and airway pressure [peak and plateau])

- Lung injury score
- Review and documentation of AEs and concomitant medication

Participants will be informed of all study restrictions.

7.1.2 Treatment Period (Day 1)

7.1.2.1 Prior to Infusion with ALT-100 or Placebo /Baseline

Prior to the administration to study treatment the following procedures will be performed:

- Confirmation of participant eligibility
- Review and update documentation of prior medication medical history

After the completion of confirmation of eligibility and update of the use of prior medication and medical history, the participant will be randomized to study treatment. After randomization, the following baseline assessments will be performed:

- Abbreviated targeted physical examination (if required)
- Measurement of vital signs (≤ 15 minutes prior to the start of infusion)
- 12-lead ECG (≤ 1 hour prior to the start of infusion)
- Blood sample for *NAMPT*-Gene genotyping
- Blood sample for PK analysis (≤ 1 hour prior to the start of infusion)
- Blood sample for immunogenicity analysis
- Blood sample for plasma biomarker analysis
- Blood sample for analysis of PD cellular parameters
- Determination of SOFA Score
- Measurement of SpO_2/FiO_2 and imputation of PaO_2/FiO_2
- Documentation of oxygenation requirements
- Documentation of ventilation requirements
- Documentation of ECMO utilization
- Lung injury score
- Review and documentation of AEs and concomitant medication
- Participants will be reminded of all study restrictions.

7.1.2.2 ALT-100 or Placebo Infusion

Administration of study treatment (ALT-100 or placebo) must be planned to occur within 4 hours of the participant's moderate or severe ARDS diagnosis. Participants requiring immediate MV support (ie, those individuals requiring ventilation via endotracheal tube or tracheostomy tube within 4 hours of their moderate or severe ARDS diagnosis on Day 1) must receive treatment with their assigned study treatment within 4 hours of initiation of MV.

During the infusion of study treatment, the following will occur as necessary:

- Review and documentation of AEs and concomitant medication

7.1.2.3 After Infusion with ALT-100 or Placebo

- Abbreviated targeted physical examination (if applicable)
- Measurement of vital signs (≤ 15 minutes of the end of the infusion, and at 2 (±5 mins), 4 (±10 mins), 8 (±15 mins), and 12 hours (±15 mins) from the end of infusion)

- Blood collection for safety laboratory investigations (4 hours from the end of infusion)
- Urine collection for urinalysis testing (4 hours from the end of infusion)
- Blood samples for PK analysis (1-hour from the end of infusion)
- Blood sample for plasma biomarker analysis
    - All participants: 8-hours from the end of infusion
- Blood sample for analysis of PD cellular parameters
    - All participants: 8-hours from the end of infusion
- Determination of SOFA Score for participants in ICU only (4 hours from the end of infusion)
- Measurement of SpO_2/FiO_2 and imputation of PaO_2/FiO_2 (4 hours from the end of infusion)
- Documentation of oxygenation requirements (4 hours from the end of infusion)
- Documentation of ventilation requirements (4 hours from the end of infusion)
- Documentation of ECMO utilization (4 hours from the end of infusion)
- Lung injury score (4 hours from the end of infusion)
- Review and documentation of AEs and concomitant medication

7.1.3 Follow-up Period (Day 2 to Day 60)

During the Follow-up Period for the study, visits will be performed in-hospital for participants who are hospitalized. Participants who are not hospitalized will return to the site on the days indicated for follow-up visits.

The procedures for the Follow-up Period include:

7.1.3.1 Day 2 to Day 29

- Abbreviated targeted physical examination
    - Hospitalized participants: daily
    - Participants not hospitalized: Days 2 to 8, 15 (±1 day), 22 (±2 days), and 29 (±3 days)
- Measurement of vital signs
    - Hospitalized participants: daily
    - Participants not hospitalized: Days 2 to 8, 15 (±1 day), 22 (±2 days), and 29 (±3 days)
- Blood collection for safety laboratory investigations
    - All participants: Days 4, 8, 15 (±1 day), 22 (±2 days), and 29 (±3 days)
- Urine collection for urinalysis testing
    - All participants: Days 4, 8, 15 (±1 day), 22 (±2 days), and 29 (±3 days)
- Blood samples for PK analysis
    - All participants: Days 2 to 8 (ie, 24, 48, 72, 96, 120, 144, and 168 hours [±1 hour] from the end of infusion) Day 15 (±1 day), and Day 29 (±3 days)
- Blood samples for immunogenicity analysis
    - All participants: Days 8, 15 (±1 day), and 29 (±3 days)
- Blood sample for plasma biomarker analysis
    - All participants: 24-, 48-, 72-, and 168-hours (±2 hours) from the end of infusion, Days 15 (±1 day), and 29 (±3 days)
- Blood sample for analysis of PD cellular parameters

    - All participants: 24-, 48-, 72-, and 168-hours (±2 hours) from the end of infusion, Days 15 (±1 day), 22 (±2 days), and 29 (±3 days)
- Determination of SOFA Score
    - participants in ICU: daily including the last day in ICU if the participant leaves ICU before Day 29
- Measurement of SpO_2/FiO_2 and imputation of PaO_2/FiO_2
    - Hospitalized participants: daily
- Documentation of oxygenation requirements
    - Hospitalized participants: daily
    - Participants not hospitalized: Days 2 to 8, 15 (±1 day), 22 (±2 days), and 29 (±3 days)
- Documentation of ventilation requirements
    - Hospitalized participants: daily
- Documentation of ECMO
    - Hospitalized participants: daily
- Lung injury score:
    - Hospitalized participants: daily
    - Participants not hospitalized: Days 2 to 8, 15 (±1 day), 22 (±2 days), and 29 (±3 days)
- Review and documentation of AEs and concomitant medication
    - Hospitalized participants: daily
    - Participants not hospitalized: Days 2 to 8, 15 (±1 day), 22 (±2 days), and 29 (±3 days)

7.1.3.2 Days 30 to 59

Participants who are hospitalized will undergo the following daily procedures:

- Abbreviated targeted physical examination
- Measurement of vital signs
- Determination of SOFA Score, participants in ICU only
- Measurement of SpO_2/FiO_2 and imputation of PaO_2/FiO_2
- Documentation of oxygenation requirements
- Documentation of ventilation requirements
- Documentation of ECMO
- Lung injury score:
    - Hospitalized participants: daily
- Review and documentation of AEs and concomitant medication

7.1.3.3 Day of Discharge/Early Termination

If a participant is discharged from hospital prior to the end of the study (ie, EoS = Day 60) the participant will undergo a DoD study visit. In the case of premature discontinuation from the study, the participant (whether in hospital or not) will be asked to return to the site and complete an ET Visit.

The procedures for the DoD and ET visits include:

- Urine collection for urine pregnancy test for WOCBP
- Abbreviated targeted physical examination
- Measurement of vital signs

- Blood collection for safety laboratory investigations
- Urine collection for urinalysis testing
- Blood samples for immunogenicity analysis
- Blood sample for analysis of PD cellular parameters
- Measurement of SpO_2/FiO_2 and imputation of PaO_2/FiO_2
- Documentation of oxygenation requirements
- Documentation of ventilation requirements (type of ventilation [(high flow nasal O_2 {HFNO}], non-rebreathing mask, bilevel positive airway pressure [BiPAP]/ continuous positive airway pressure [CPAP], or MV), FiO_2, SpO_2, PaO_2 (if available), ventilation rate based on respiratory rate, heart rate, ventilator settings (tidal volume, PEEP, and airway pressure [peak and plateau])
- Documentation of ECMO
- Lung injury score
- Review and documentation of AEs and concomitant medication

All participants who discontinue the study early will be followed for safety until Day 60, wherever possible.

7.1.3.4 Day 60/End of Study

On Day 60, participants who are not hospitalized will return to the site for the EoS procedures. All participants will undergo:

- Urine collection for urine pregnancy test for WOCBP
- Abbreviated targeted physical examination
- Measurement of vital signs
- Blood collection for safety laboratory investigations
- Urine collection for urinalysis testing
- Blood samples for immunogenicity analysis
- Blood sample for analysis of PD cellular parameters
- Documentation of oxygenation requirements
- Lung injury score
- Review and documentation of AEs and concomitant medication

In addition to the above procedures, hospitalized participants will undergo:

- Determination of SOFA Score for participants in ICU only
- Measurement of SpO_2/FiO_2 and imputation of PaO_2/FiO_2
- Documentation of ventilation requirements
- Documentation of ECMO

Participants have completed the study when all procedures for the Day 60 visit are completed and at the discretion of the Investigator.

7.1.3.5 Day of Discharge/Early Termination

If a participant is discharged from hospital prior to the end of the study (ie, EoS = Day 60) the participant will undergo a DoD study visit. In the case of premature discontinuation from the study, the participant (whether in hospital or not) will be asked to return to the site and complete an ET Visit.

7.1.4 Unscheduled Visit

The Investigator may request additional, unscheduled study visits. Assessments at unscheduled visits will be performed at the discretion of the Investigator.

7.2 Discontinuation or Withdrawal

7.2.1 Individual Participants

7.2.1.1 Withdrawal from the Study

A participant has the right to withdraw from the study, at any time and for any reason, without prejudice to their future medical care.

If a participant withdraws consent, the date and reason for consent withdrawal should be documented. Participant data will be included in the analysis up to the date of the withdrawal of consent.

Apart from withdrawal of consent, reasons for ET of individual participants may include:

- Protocol deviations or participant non-compliance (must be specified on the appropriate eCRF)
- AEs
- The Investigator considers that it is in the participant's best interest to discontinue their participation in the study
- Participant is lost to follow-up
- Other (must be specified)

If a participant is withdrawn because of an AE, the Investigator should follow each AE until the event has resolved to baseline grade or better, the event is assessed as stable by the Investigator, the participant is lost to follow-up, or the participant withdraws consent. Every effort should be made to follow all SAEs considered to be related to study treatment or trial-related procedures until a final outcome can be reported.

Wherever possible, all participants who discontinue from the study early will be followed for safety until Day 60.

7.2.1.2 Replacement of Participants

Participants who are enrolled but do not receive a dose of their assigned study treatment will be replaced.

7.2.1.3 Participants Lost to Follow-up

At least 3 documented attempts will be made to contact any participant who does not attend their scheduled onsite follow-up visits, requesting that they return to the site for completion of all evaluations. Participants who do not attend the follow-up visits and cannot be contacted will be considered lost to follow-up.

7.2.1.4 Guidelines for Managing Participants During the COVID-19 Pandemic

For this study, each site should follow their national, state, and local government mandated guidelines regarding COVID-19.

Participants who test positive for the COVID-19 virus during participation in the study should not visit the site for study-specific visits while infectious to avoid potentially infecting site staff or other patients. Follow-up with the participant should be conducted remotely (via phone call).

Contingency measures implemented during this study to protect trial participants and manage study conduct during possible disruption occurring as a result of the COVID-19 pandemic will be described in the final clinical study report (CSR). The impact of COVID-19 on study withdrawal, treatment discontinuation, and protocol deviations will be captured through documentation of any COVID-19 related events in the eCRF and will also be reported in the CSR.

7.3 Study Termination

The study will be completed as planned unless:

- New information or other evaluation regarding the safety of the study treatment indicates a change in the known risk/benefit profile for the compound, such that the risk/benefit is no longer acceptable for study participants. This may be determined by the Sponsor, the Investigator, and the SMC, the IEC/IRB, or regulatory authorities.
- The study is terminated by the Sponsor for administrative reasons.

If the Sponsor, the IEC/IRB, or regulatory authority elects to terminate or suspend the study or the participation of the investigational site, a study-specific procedure for ET or suspension will be provided by the Sponsor. The procedure will be followed by the site during the course of termination or study suspension.

7.4 Study Assessments

Study assessments will be performed at the timepoints as outlined in the SoA (Table 1).

7.4.1 Baseline and Demographic Assessments

7.4.1.1 Medical/Surgical History and Prior Medications

At screening the participants prior and current medical, surgical, and medication use will be documented.

Any event or change in the participant's condition or health status prior to treatment on Day 1 will be reported in the relevant medical history/current medical conditions section of the participant's eCRF.

7.4.1.2 Demographics

Year of birth, age (calculated), sex, ethnicity, and race will be recorded at screening.

7.4.1.3 Body Weight and Height/Body Mass Index

Body mass index (BMI) will be calculated by dividing the participant's body weight in kilograms by the participant's height in meters squared (BMI = kg/m^2) at screening. An estimation of the participant's height and weight are to be made if the measurement of height and weight is not possible due to the participant's condition.

7.4.1.4 Imaging

Imaging (chest x-ray, CT scans) is to be done within 3 days of Day 1 to diagnose any radiological abnormalities (ie, bilateral opacities that are not fully explained by effusions, nodules, masses, or lobar/lung collapse) to confirm moderate or severe ARDS.

7.4.2 Safety Assessments

Additional safety assessments may be performed at unscheduled time points if deemed necessary by the Investigator.

7.4.2.1 Physical Examination

Abbreviated, targeted physical examinations will be performed based on the participant's clinical status and at the discretion of the Investigator. If a physical examination is performed as SoC the same day that consent is signed or the same day of any scheduled study visit, results from that examination may be used if site staff consider additional examinations are unwarranted.

Physical examinations may be performed at unscheduled time points if deemed necessary by the Investigator.

7.4.2.2 Vital Signs

Assessment of vital signs includes respiratory rate, heart rate, systolic and diastolic blood pressure, and body temperature (tympanic). Where possible the participant will be at rest in a supine position (after ≥ 5 minutes resting supine) or if required lying in the prone position (after ≥ 5 minutes resting in the prone position) for vital sign measurements.

Whenever vital signs, and PK/PD blood draws are scheduled for the same nominal time, vital signs should occur prior to PK/PD blood draws; so that the timing of the assessments allow the blood draw to occur at the exact scheduled time.

7.4.2.3 12-lead Electrocardiogram

A12-lead ECG will be performed at baseline (before dosing) on Day 1. Where possible the participant will be at rest in a supine position (after ≥ 5 minutes resting supine) or if required lying in the prone position (after ≥ 5 minutes resting in the prone position) for ECGs.

ECGs should occur prior to PK/PD blood draws; so that the timing of the assessments allow the blood draw to occur at the scheduled time.

7.4.2.4 Oxygenation and Ventilation

Assessment of participant oxygen levels who are not receiving ventilation support will include FiO_2 and PaO_2 or SpO_2. Additional follow-up tests may be performed at the Investigator's discretion after consultation with the MM and as clinically indicated.

If the participant is receiving ventilation support, the following parameters will be recorded:

- Type of ventilation (heated and humidified high flow nasal O_2 [HFNO], non-rebreathing mask, bilevel positive airway pressure [BiPAP]/continuous positive airway pressure [CPAP], or MV)
- FiO_2
- SpO_2

- PaO_2 (if available)
- Ventilation rate based on respiratory rate
- Heart rate
- Ventilator settings (tidal volume, PEEP)
- Airway pressure [peak and plateau]).

7.4.2.5 Laboratory Investigations

Safety laboratory tests will include hematology, coagulation, chemistry, and urinalysis.

Medically indicated laboratory tests (emergency or unscheduled tests) should be conducted at the local laboratory.

Details regarding the handling and processing of specimens are provided in the Study Laboratory Manual.

7.4.2.5.1 Hematology, Coagulation, and Chemistry

A blood sample will be collected from each participant for hematology, coagulation, and chemistry analysis. The parameters assessed are listed in Table 6.

Participants are not required to fast prior to the collection of samples for laboratory testing.

Table 6: Hematology, Coagulation, and Chemistry Assessments

Test	Parameters
Chemistry (Serum or plasma)	Sodium, Potassium, Chloride, Calcium, Glucose, Bicarbonate, Albumin and Total protein, C-reactive protein (CRP), Creatinine, Estimated GFR (eGFR), Blood urea nitrogen (BUN) or Urea, Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), gamma glutamyl transferase (GGT), Alkaline phosphatase (ALP), Phosphorus, Total bilirubin (direct and indirect), Amylase, Cholesterol (total, low density lipoprotein [LDL], high density lipoprotein [HDL]), Triglycerides, Uric acid, Creatine phosphokinase (CPK), Lactate dehydrogenase (LDH), and Magnesium.
Hematology	White blood cell (WBC) count, Red blood cell (RBC) count, Hemoglobin, Hematocrit, Platelet count, Differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).
Coagulation	International Normalized Ratio (INR), Activated Partial Thromboplastin Time (aPTT), Prothrombin Time.

7.4.2.5.2 Urinalysis

A urinalysis test (dipstick) will include pH, specific gravity, glucose, protein, ketones, and blood. Urine microscopy will be performed in the event of abnormal dipstick and will include assessment of urinary sediment (per local practice), RBCs, WBCs, casts, crystals, epithelial cells, and bacteria.

7.4.2.5.3 Virology

Virology (HBsAg, HBcAb, HCV RNA, HIV-1, and HIV-2) will be assessed using standard methods at screening.

7.4.2.5.4 QuantiFERON Test

Participants will be tested for tuberculosis (TB) by positive QuantiFERON Gold or PPD test. If a participant is found to have latent TB, the Investigator must discuss this with the MM.

In the event the QuantiFERON Gold assay is not available, and the site performs a different IGRA, then the alternative IGRA will be acceptable for patient screening and enrollment. Enrollment should not be delayed to obtain the QuantiFERON Gold assay in lieu of the IGRA available at the site.

If no IGRA test is available, a PPD test can be used.

If TB testing is missed during screening it must be completed and results obtained prior to participant discharge from hospital. If not completed or unable to obtain results, further discussion with the MM is required.

7.4.2.5.5 Human Chorionic Gonadotropin (HCG) Pregnancy Test

Serum or urine pregnancy tests will be performed on all WOCBP. For inclusion into the study and prior to receiving study treatment, all female participants undergoing testing must have a negative serum pregnancy test at screening. All WOCBP will have a urine pregnancy test at DoD/ET and/or Day 60/ES, as applicable. Any participant who has a positive pregnancy test during the study will undergo confirmatory testing by a serum pregnancy test. Reporting of pregnancies is described in Section 8.5.

7.4.2.5.6 Follicle-stimulating Hormone Test

Post-menopausal status will be confirmed and documented through confirmation of FSH levels at screening for amenorrheic female participants.

7.4.2.5.7 Coronavirus Disease 2019 (COVID-19) Testing

A nose and/or throat swab or saliva sample may be collected and analyzed for COVID-19 at screening, and at 1 or multiple timepoints during the study as per local, state, and national guidelines and requirements at the site. Samples will be analyzed by polymerase chain reaction (PCR) and/or rapid antigen testing as appropriate and in accordance with all applicable guidelines.

7.4.2.6 Adverse Events

The incidence, severity, seriousness, and expectedness of all AEs which occur during the study will be monitored, treated, and documented as outline in Section 8.

7.4.2.7 Concomitant Medication

Concomitant medication is any medication administered from then start of the infusion until the end of the study. Prior medications which are ongoing at the time of the start of infusion will be considered concomitant medications. All use of concomitant medications will be documented in the participant's eCRF.

7.4.2.8 Immunogenicity Assessments

Blood samples will be collected for serum ADA monitoring and will be analyzed for the presence of ALT-100 ADA using a validated bridging immunoassay. Additional samples for ADA assessment in serum may be collected in participants with signs and symptoms of

infusion-related reactions following treatment on Day 1, at the discretion of the Investigator. In such cases, a corresponding additional PK sample will be obtained at the same time point as the observed infusion-related reaction. The relevant IEC/ IRB will be notified of any additional PK or ADA samples collected from participants with suspected infusion reactions as part of standard safety reporting for the study.

Antibody levels in participants that seroconvert should be monitored until the antibodies return to baseline.

The maximum volume of blood that will be collected from each participant for ADA analysis will be 30 mL.

Where binding antibodies are detected, levels and specificity of the antibodies will be evaluated and compared to pre-dose levels. Further exploratory characterization of these antibodies may be performed but findings will be reported separately to the final study report.

Samples for ADA testing should be banked until the immunogenicity assays are fully validated, reviewed, and approved by the competent regulatory authority.

7.4.3 Pharmacokinetic Assessments

Blood samples for plasma PK analysis of ALT-100 will be collected ≤ 1 hour prior to the start of the infusion on Day 1, and at 1 hour (±5 minutes), 24, 48, 72, 96, and 120 hours, (±4 hours), 144 hours and 168 hours (±8 hours) from the end of infusion. On Day 15, the PK sample collection should be 15 days ±1 day from date of infusion. On Day 29, the PK sample collection should be 29 days ±3 days from the date of infusion.

The maximum volume of blood that will be collected from each participant for PK analysis will be 44 mL.

The actual date and time of each blood sample collection will be recorded. Any changes to the PK sampling times will be notified to the relevant IEC/ IRB for approval prior to sampling.

The concentration of ALT-100 in plasma will be determined by an accredited laboratory, using a suitably qualified analytical method. The bioanalytical laboratory will be unblinded to allow for analysis of the PK samples.

Details of PK blood sample collection (including volume to be collected), processing, storage and shipping procedures will be provided in the Study Laboratory Manual.

7.4.4 Pharmacodynamic Assessments

The Sponsor will provide complete written instructions for collection, handling, processing, storage, and shipping (as applicable) of PD biomarker and whole blood samples in the Study Laboratory Manual.

7.4.4.1 Blood Sampling for Biomarkers

Biomarkers for analysis will include (but are not limited to) plasma levels of eNAMPT, TNF-α, IL-1β, IL-1RA, IL-6, and angiopoietin-2.

The analysis of PD cellular parameters (peripheral circulating neutrophil, monocyte, and lymphocyte counts in whole blood) will be assessed from the samples collected for the

assessment of hematology parameters where possible. An additional whole blood sample (same volume and collection tube) on Day 2 and Day 3 will be collected.

The maximum volume of blood that will be collected from each participant for biomarker analysis will be 20 mL.

7.4.5 Efficacy Assessments

7.4.5.1 Mechanical Ventilation

The number of MVFD over 28 days following study treatment (ie, by Day 29) will be documented for each participant.

Mechanical ventilation is defined as ventilation via endotracheal tube or tracheostomy tube.

MVFDs to Day 28 are defined as the number of days from the time of initiating unassisted breathing to Day 29, assuming survival for at least 48 hours after initiating unassisted breathing and continued unassisted breathing to Day 29. If a participant returns to assisted breathing and subsequently achieves unassisted breathing to Day 29, VFDs will be counted from the end of the last period of assisted breathing to Day 29. A period of assisted breathing lasting less than 24 hours and for the purpose of a surgical procedure will not count against the MVFD calculation. If a participant was receiving assisted breathing at Day 28 or dies prior to Day 29, MVFDs will be zero.

7.4.5.2 Hospitalization Duration

The time to hospital discharge based on days since hospital admission and the number of HFD to Day 29 will be documented for each participant.

Hospital free days are defined as all days alive that are spent outside of an acute care hospital, long-term acute care hospital, or in an emergency department. This includes days spent wholly or in part under ‘observation’ status. All other days, including days spent in a long- or short-stay nursing facility, rehabilitation facility, or at home (including those with home-based medical services) are to be considered as being HFD.

7.4.5.3 Sequential Organ Failure Assessment (SOFA) Score

Total and component SOFA scores will be determined daily for each participant while they are in the ICU.

7.4.5.4 Oxygenation

7.4.5.4.1 Oxygenation Parameters

Improvements in participants oxygenation parameters will be measured as a change from baseline (ie, Day 1 prior to study treatment) in:

- Plethysmographic pulse oximetry derived oxygen saturation/fraction of inspired oxygen (SpO_2/FiO_2)
- ROX Index (SpO_2/FiO_2 divided by respiratory rate [RR]), assessed daily while hospitalized.

If the participant is receiving MV, the P/F ratio will be used (ie, partial pressure of oxygen [PaO_2]/FiO_2).

The assessments should be prioritized as follows:

1. PaO_2/FiO_2 if arterial line available
2. Imputed SpO_2/FiO_2 equivalent for non-ventilated participants on conventional oxygen therapy
3. ROX index for participants on non-invasive respiratory support

7.4.5.4.2 Requirement of Oxygenation Support

Incidence and duration of oxygen use (via conventional oxygen therapy, or non-invasive respiratory support positive pressure by face mask or HFNO) be documented for each participant for the duration of the study, as applicable.

7.4.5.5 Requirement for Vasoactive Support

Incidence and duration of vasoactive support (ie, type of ventilation (heated and humidified high flow nasal O_2 [HFNO], non-rebreathing mask, bilevel positive airway pressure [BiPAP]/ continuous positive airway pressure [CPAP], or MV), FiO_2, SpO_2, PaO_2 (if available), ventilation rate based on respiratory rate, heart rate, ventilator settings (tidal volume, positive end-expiratory pressure (PEEP), and airway pressure [peak and plateau]) will be documented for each participant for the duration of the study, as applicable.

7.4.6 Exploratory Assessments

7.4.6.1 Genotyping

A baseline blood sample for *NAMPT*-Gene genotyping assessment will be collected baseline (ie, Day 1 prior to study treatment) and stored for later analysis. The Sponsor will provide details regarding the collection, handling, processing, storage, and shipping (as applicable) of blood samples for genotyping assessment in the Study Laboratory Manual.

7.4.6.2 Lung Injury

Other measurements of lung injury that may be performed during standard care (eg, LIS, chest radiography, PaO_2/FiO_2, need for ECMO) will be documented for each participant.

7.4.6.3 Respiratory Support

Participant requirements for respiratory support will be documented.

7.4.6.4 Mortality

Mortality will be assessed as time until death up to the end of the study (Day 60).

8 SAFETY MONITORING

8.1 Adverse and Serious Adverse Events

In this study, AEs will be reported in all participants from the time the participant signs the PICF until the completion of the EoS visit on Day 60 ±5 days. Adverse events reported from the time of consent until the start of the infusion on Day 1 will be recorded as pre-treatment AEs. Study procedure-related AEs will be evaluated specifically from the time of consent until the start of the infusion on Day 1. TEAEs will be evaluated from the time of the start of the infusion on Day 1 until the final follow-up visit on Day 60 ±5 days.

All spontaneously volunteered and enquired for, as well as observed AEs, will be recorded in the participant's medical records as well as the eCRF.

8.1.1 Definitions

- **Adverse event (AE)** – An AE is any untoward medical occurrence associated with the use of an intervention in humans whether or not it is considered intervention-related.
- **Serious adverse event (SAE)** – An event is considered "serious" if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:
  - Death
  - A life-threatening AE (an event is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the patient or participant at immediate risk of death. It does not include an AE or suspected adverse reaction (AR) that, had it occurred in a more severe form, might have caused death.)
  - Inpatient hospitalization or prolongation of existing hospitalization
  - A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
  - A congenital anomaly/birth defect
  - Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or participant and 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.
- **Adverse reaction (AR)** – An adverse reaction is any AE caused by a study treatment.
- **Suspected adverse reaction (SAR)** – An SAR is any AE for which there is a reasonable possibility that the study treatment caused the AE. For the purposes of Investigational New Drug (IND) safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the study treatment and the AE. SAR implies a lesser degree of certainty about causality than AR.
- **Unexpected** – An event is considered unexpected if it is not listed in the Investigator's Brochure, is not listed at the specificity or severity that has been observed. Unexpected also refers to events that are mentioned in the Investigator's Brochure as occurring with a class of treatment or as anticipated from the pharmacological

properties of the treatment but are not specifically mentioned as occurring with the particular treatment under investigation.

8.1.2 Severity of an Adverse Event

The investigator will assess severity for each AE and SAE reported during the study. AEs and SAEs should be assessed and graded based upon the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0.

Adverse events that are not specified in the NCI-CTCAE v5.0 will be defined as follows:

Grade 1 = Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

Grade 2 = Moderate: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.

Grade 3 = Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

Any AE that is graded as severe should not be confused with an SAE. Severity refers to the intensity of an event and both AEs and SAEs can be severe. An event is defined as 'serious' when it meets one of the predefined outcomes as described in Section 8.1.1.

Grade 4 = Life-threatening: A type of AE that is not treated will result in death.

Grade 5 = Death: A type of AE that results in death.

8.1.3 Causal Relationship of an Adverse Event

The Investigator will assess the relationship between the study treatment and the occurrence of each AE. The Investigator's assessment of the relationship of each AE to the study treatment will be recorded in the source documents and the eCRF. Alternative causes, such as medical history, concomitant therapy, other risk factors, and the temporal relationship of the event to the IP should be considered and investigated, if appropriate.

- **Not related:** The event is clearly related to other factors such as the participant's environment or clinical state, therapeutic interventions or concomitant drugs administered to the participant. This is especially so when an event occurs prior to the commencement of treatment with the IP.
- **Unlikely Related:** The event is probably related to other factors such as the participant's environment or clinical state, therapeutic interventions or concomitant drugs administered to the participant.
- **Possible:** The event follows a reasonable temporal sequence from the time of IP administration or follows a known response to the IP but could have been produced by other factors such as the participant's clinical state, other therapeutic interventions, or concomitant drugs administered to the participant.
- **Probable:** The event follows a reasonable temporal sequence from the time of IP administration and follows a known response to the IP and cannot be reasonably explained by other factors such as the participant's clinical state, other therapeutic interventions, or concomitant drugs administered to the participant.

- **Related:** The event follows a reasonable temporal sequence from the time of IP administration and follows a known response to the IP and cannot be explained by other factors such as the participant's clinical state, other therapeutic interventions, or concomitant drugs administered to the participant.

8.1.4 Action Taken with Investigational Products

Should the Investigator need to alter the administration of the IP from the procedure described in the protocol in order to protect the well-being and safety of the participant then the action taken will be recorded on the AE eCRF page, as one of the following options:

- Dose and/or infusion rate reduced
- Dose interrupted
- Dose withdrawn
- Not applicable
- Unknown (or participant lost to follow-up)

8.1.5 Outcome of Adverse Event

Outcome of an AE will be recorded on the AE eCRF as follows:

- Recovered/Resolved
- Recovering/Resolving
- Recovered/Resolved with sequelae
- Not recovered/Not resolved
- Fatal
- Unknown

8.2 Documenting Adverse Events

Any AE occurrence during the study must be documented in the participant’s medical records and on the AE page of the eCRF. Serious adverse events that occur during the study must be documented in the participant’s medical record, in the AE eCRF, and on the SAE form.

The Investigator should attempt to establish a diagnosis of the events based on the signs, symptoms and/or other clinical information. In such cases, the diagnosis should be documented as the AE (and SAE if serious) and not the individual signs/symptoms.

If a clinically significant abnormal laboratory finding or other abnormal assessment meet the definition of an AE, then the AE eCRF page must be completed as appropriate. In addition, if the abnormal assessment meets the criteria for being serious, the SAE form must also be completed. A diagnosis, if known, or clinical signs and symptoms if the diagnosis is unknown, rather than the clinically significant laboratory finding or abdominal assessment, should be used to complete the AE/SAE page. If no diagnosis is known and clinical signs and symptoms are not present, then the abnormal finding should be recorded. If an SAE report is completed, pertinent laboratory data should be recorded on the SAE form, preferably with baseline values and copies of laboratory reports.

The SAE page should be completed as thoroughly as possible and signed by the Investigator before transmittal to the study Sponsor and CRO. It is very important that the Investigator provides an assessment of causal relationship between the event and the study treatment at the time of the initial report, as this will be useful for submission to regulatory authorities.

8.3 Reporting Adverse Events

The reporting of any SAEs to applicable regulatory agencies will be the responsibility of the Sponsor in compliance with applicable country regulations.

All SAEs must be reported to the IEC/IRB (as applicable) by the Investigator, in accordance with their regulations.

8.3.1 Notification of Serious Adverse Events and Suspected Unexpected Serious Adverse Reactions

An SAE may qualify for reporting to regulatory authorities if the SAE is considered to have a possible causal relationship to the study product, and is unexpected (suspected unexpected serious adverse reaction [SUSAR]). In order to meet the requirements for reporting of SAEs that meet the specific requirements for expedited notification to the applicable regulatory authorities and IECs/IRBs, all SAEs must be reported to the Sponsor and CRO within 24 hours from the time the site investigational team first becomes aware of the event. The procedures for reporting all SAEs and SUSARs, regardless of causal relationship, are outlined in the Safety Management Plan.

For this study, the platform for reporting the SAEs is: Veeva Safety.

All SAEs, as defined in (Section 8.1.1), require reporting within 24 hours, regardless of the relationship of the event to the study treatment regimen.

The SAE form should be completed and signed by the PI as thoroughly as possible with all available details of the event, including a determination of causality (even if preliminary).

The process and procedures to be followed for the collection, distribution and reporting of SAEs will be detailed in a separate Safety Management Plan.

The Investigator (with support from site staff) will complete an initial SAE form with information available and notify Novotech Pharmacovigilance Department (PV), Novotech MM and the Novotech Project Manager (PM) by both updating the eCRF and sending the completed SAE form to:

safety@novotech-cro.com

Both routes must be used for immediate notification of the event. Novotech PV will notify the Sponsor within 24 hours of the initial SAE report.

The Investigator should contact Novotech PV if there are questions regarding the reporting of an SAE or if any information needs to be transmitted that cannot be recorded on the SAE forms (eg, medical records, discharge summaries, laboratory reports).

For SUSARs, reports will be disseminated and provided to Investigators at each site. When required and according to local law and regulations, SUSARs or other SAEs will be reported to the IRB/IEC and regulatory authorities.

If not all information regarding an SAE is initially available, the Investigator should not wait to receive additional information before completing the AE eCRF and SAE forms. For initial SAE reports, the Investigator should record all case details that can be garnered on the SAE form and the AE eCRF page. Relevant follow-up information is to be submitted on updated SAE forms as soon as it becomes available. As further information regarding the SAE becomes available, such follow-up information should be documented on a new SAE report

form, marked as a follow-up report, scanned, and emailed to the address at the bottom of the form.

Withdrawal from the study in the event of an SAE and therapeutic measures taken shall occur at the discretion of the Investigator. A full explanation for the discontinuation from the study should be made in the participant's medical records and in the eCRF.

The Investigator must take all clinical and therapeutic measures necessary for resolution of the SAE.

SAEs which have causality assessed as possible, probable, or related to ALT-100 and which do not appear as expected AEs within the Investigator's Brochure, will be reported as SUSARs to the appropriate regulatory authorities, IEC/ IRB, and Investigators.

8.4 Clinical Laboratory Findings

Abnormal laboratory findings (eg, chemistry) or other abnormal assessments (eg, vital signs) per se are not reported as AEs. However, those abnormal findings that are deemed clinically significant by the Investigator or are associated with signs and/or symptoms must be recorded as AEs if they meet the definition of an AE (or recorded as an SAE if they meet the criteria of being serious) as described previously. Clinically significant abnormal laboratory or other abnormal findings that are detected after consent or that are present at baseline and worsen after consent are included as AEs (and SAEs if serious).

The Investigator should exercise his/her medical and scientific judgment in deciding whether an abnormal laboratory finding, or other abnormal assessment is clinically significant. Usually, the abnormality should be associated with a clinically evident sign or symptom, or be likely to result in an evident sign or symptom in the near term, to be considered clinically significant.

8.5 Pregnancy

Should a pregnancy occur, it must be reported and recorded in the Sponsor Pregnancy form. Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP may have interfered with the effectiveness of a contraceptive medication.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) must be followed up and documented even if the participant was discontinued from the study.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs.

8.6 Overdose or Misuse

Overdose for this study is defined as any participant receiving > 1.0 mg/kg ALT-100. The controlled use of ALT-100 in the clinical trial should prevent overdose occurring. Participants should be managed with appropriate supportive care if overdose occurs.

9 ANALYSIS

Statistical methods will be outlined in a SAP, which will be finalized before database lock.

In general, descriptive statistics (mean, SD, median, minimum, and maximum) will be calculated for summaries of continuous data, and frequency counts and percentages (where appropriate) will be calculated for summaries of discrete/ categorical data.

Baseline will be defined as the last measurement obtained prior to administration of ALT-100 or placebo (as applicable) on Day 1.

9.1 Population

9.1.1 Sample Size Rationale

Power calculation and determination of sample size per scenario assumes 2 active dose levels and a placebo group are investigated and is based on the primary efficacy endpoint of MVFDs over the 28-days following treatment (ie, by Day 29).

Equal treatment effect for both active treatment groups; SD of 9 days; n = 30 per group

A sample size of n = 30 participants per group (2 active treatment groups and 1 placebo group) allows greater than 80% power (exact power = 87.4%) to demonstrate statistical significance ($P < 0.05$; analysis with analysis of variance [ANOVA]) with a mean difference in MVFDs from placebo of 7 days for both active treatment groups and a SD of 9 days.

Different/spaced treatment effect for each active treatment groups; SD of 9 days; n = 30 per group

A sample size of n = 30 participants per group (2 active treatment groups and 1 placebo group) allows greater than 80% power (exact power = 86.7%) to demonstrate statistical significance ($P < 0.05$; with ANOVA) with a mean difference in MVFDs from placebo of 4 and 8 days for active treatment groups 1 and 2, respectively, and a SD of 9 days.

Combined Active Dose Groups into single treatment group; SD of 9 days; N = 60 (30 + 30) 'active' treatment and n=30 placebo group

A sample size of n = 30 participants combined into a single treatment group (ie, n = 60) allows greater than 80% power (exact power = 83.9%) to demonstrate statistical significance ($P < 0.05$; analysis with un-paired t-test) with a mean difference in MVFDs from placebo of 6 days for the combined active treatment group, respectively, and a SD of 9 days.

9.1.2 Analysis Sets

Participant inclusion into each data set will be determined after database lock and prior to unblinding for the final analysis.

For the summary of data by treatment group, participants administered placebo from each cohort will be pooled into a single treatment group.

The following analysis sets are defined for the study:

Intent-to-Treat (ITT): includes all randomized participants. The ITT participants will be analyzed according to randomized treatment, irrespective of whether or not they have prematurely discontinued. Participants who withdraw from treatment and/or the study early

will be followed until Day 60 for safety. All baseline characteristic analyses will be performed using the ITT Population.

Modified Intent-to-Treat (mITT): includes all randomized participants who receive any amount of study drug. The ITT participants will be analyzed according to randomized treatment, irrespective of whether or not they have prematurely discontinued. Participants who withdraw from treatment and/or the study early will be followed until Day 60 for safety. All efficacy analyses will be performed using the mITT Population.

Safety: includes all randomized participants who receive any amount of study treatment. The Safety Set will be analyzed according to the treatment received. This population will be used for the safety analyses.

Per Protocol (PP): includes all participants with no major protocol deviations in the ITT Set who complete the Day 29 Visit. The PP Set will be used for supportive analyses of the efficacy measurements.

Pharmacokinetic (PK): includes all randomized participants who were administered ALT-100 and who have sufficient plasma concentration-time data to determine at least C_{max} and AUC_{0-t}. The PK Set will be used to summarize PK data.

Pharmacodynamic (PD): includes all randomized participants who receive any amount of study treatment (ALT-100 or placebo), who have results from baseline and from ≥ 1 post-baseline PD assessment and will be based on the actual treatment/dose level received, if this differs from what the participant is randomized to. The PD Set will be used to summarize PD data.

9.2 Statistical Analysis

9.2.1.1 Disposition

A disposition listing will present date of informed consent, date of randomization, date of administration of study treatment, treatment/study completion or study discontinuation, the reason for discontinuation, and whether included in each analysis set, for each participant.

The number of participants that completed and discontinued the study as well as reasons for discontinuation will be summarized by treatment group.

A listing of participants that did not meet all inclusion and/or met exclusion criteria (including details of the applicable criteria), will also be presented.

9.2.1.2 Demographics

All demographic data recorded at screening will be listed and summarized descriptively.

9.2.1.3 Baseline Characteristics

Medical history will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA®) available at the time of study commencement (version 23.0 Update or greater) and will be presented in a by participant data listing.

Prior and concomitant medications will be coded using the latest version of the World Health Organization Drug Dictionary (WHODrug) available at the time of study commencement. Medications will be mapped to Anatomical Therapeutic Chemical (ATC) Levels 2 and 4, and

preferred name (PN), as the primary interest for the analysis. The prior and concomitant medications are defined as follows:

- Prior medications are defined as any medication where the use was stopped prior to the date of first administration of the study treatment.
- Concomitant medications are defined as any medication (other than the study treatment) that was used at least once after the date of first administration of the study treatment.

Medications that were commenced prior to the first administration of study treatment and continued after administration of study treatment will be classified as prior and concomitant medications. Medications that were stopped on the same date as the first study treatment administration will be defined as prior and concomitant medications.

9.2.1.4 Impact of COVID-19

There is a possibility that the COVID-19 pandemic may lead to changes in the study such as revisions to the study schedule or missed visits, resulting in missing information (eg, for protocol specified procedures). The impact of COVID-19 on study discontinuation, treatment discontinuation, and protocol deviations will be captured for this study.

In addition, the Medical Dictionary for Regulatory Activities (MedDRA®) version 23.0 Update has been extended to include COVID-19 related terms, as such this or a later (more recent) version will be used. The PT related to COVID-19 will be used to identify AEs in participants infected with COVID-19.

9.2.2 Safety Analysis

Statistical methods for the safety analyses will be primarily descriptive in nature and will be performed for the Safety Set.

AEs will be coded using the most current MedDRA® available at the time of study commencement. A by participant AE data listing, including verbatim term, PT, SOC, treatment, severity, and relationship to study treatment, will be provided. The number of participants experiencing TEAEs and number of TEAEs will be summarized by SOC and PT for each treatment group and overall (ie, all participants combined). TEAEs will also be summarized by severity and relationship to study treatment for each treatment group and overall.

Laboratory evaluations and vital signs assessments will be listed for each participant and summarized by treatment group and protocol specified collection timepoint. A summary of change from baseline results at each protocol specified timepoint will also be presented.

Changes in physical examinations will be listed for each participant.

Immunogenicity data (ADA) will be listed for each participant and summarized by treatment group and protocol specified collection timepoint.

Concomitant medications will be listed by participant and coded using the most current WHO drug dictionary available at the commencement of the study.

Medical history will be listed by participant.

9.2.3 Pharmacokinetic Analysis

Individual plasma ALT-100 concentration data will be listed and summarized by treatment group and protocol specified collection timepoints, with descriptive statistics (sample size [N], arithmetic mean, SD, CV%, median, minimum, maximum, geometric mean, and geometric CV%). Individual and mean ALT-100 concentration-time profiles will also be presented graphically by treatment group.

Where data are sufficient for parameter determination the following plasma ALT-100 non-compartmental PK parameters will be estimated, as appropriate:

Table 7 Pharmacokinetic Parameters

Parameter	Definition
$AUC_{(0-t)}$	Area under concentration-time curve from time 0 (pre-dose) to the last quantifiable data point
$AUC_{(0-\infty)}$	Area under concentration-time curve from time 0 (pre-dose) extrapolated to infinity
$AUC_{(0-x)}$	Area under concentration-time curve from time 0 (pre-dose) to time *x* as data permits eg, AUC_{0-24} and AUC_{0-48}
C_{max}	Maximum concentration
C_{max}/dose(D)	Dose normalized C_{max}
AUC/D	Dose normalized AUC
$\%AUC_{extrap}$	The percent of the $AUC_{0-\infty}$ extrapolated to infinity
t_{max}	Time to reach maximum concentration
k_{el}	Terminal elimination rate constant
$t_{½}$	Elimination half-life
CL	Total body clearance
V_z	Volume of distribution at the terminal phase

Other PK parameters used to characterize the terminal elimination phase will be listed and described in further detail in the SAP but may include: R_2-adjusted, k_{el} upper, k_{el} lower, number of data points used in the regression of the terminal phase.

Pharmacokinetic parameters will be listed for each individual and summarized by treatment group using descriptive statistics (N, arithmetic mean, SD, CV%, median, minimum, maximum, geometric mean, and geometric CV%).

If > 2 dose levels are investigated dose proportionality will be tested using a power regression model for $AUC_{0-\infty}$, AUC_{0-t}, and C_{max}.

9.2.4 Pharmacodynamics and Biomarker Analysis

Individual cell and biomarker results will be listed and summarized by treatment group, with presentation of descriptive statistics (N, arithmetic mean, SD, CV%, median, minimum, and

maximum). A summary of change from baseline results for each treatment group at each protocol specified timepoint may also be presented if appropriate. Figures of cell and biomarker results over time may also be presented, where appropriate.

9.2.5 Efficacy Analysis

Individual results for MV, hospitalization duration, SOFA Score, oxygenation parameters, and vasoactive support will be listed.

Efficacy data will be analyzed as follows for the sub-groups MV versus non-MV:

- Duration of event (eg, MV-free days; hospitalization duration) will be summarized as median days with quartiles. Treatment differences will be assessed using an ANOVA model with treatment and MV status (MV vs non-MV) as fixed effects. The least square means and the estimated treatment differences, as well as the corresponding 95% confidence intervals (Cis) and p-values will be presented. A non-parametric method (Kruskal-Wallis test) may also be performed if the distributional assumptions are violated.
- Incidence data will be summarized as a percentage with 95% Clopper-Pearson CIs. Treatment comparison may be performed using the Cochran-Mantel-Haenszel test with MV status (MV vs non-MV) and treatment as stratification factors.
- The continuous variables, including the changes from baseline, will be summarized by the treatment with the mean, SD, median, and the range. Where appropriate, treatment comparisons will be performed using the same ANOVA model and non-parametric methods as described above.
- The time-to-event endpoints will be summarized with Kaplan Meier estimates and 95% confidence bounds by the treatment. The results will also be presented graphically. Treatment comparisons will be performed using a Cox proportional hazards model. The hazard ratio of ALT-100 versus placebo will be presented with 95% CI and p-values.

Full details will be provided in the SAP.

9.2.6 Exploratory Analysis

Exploratory analyses may be reported separately to the final study report.

9.2.6.1 Genotyping

Determination of *NAMPT SNP* assessment in baseline blood samples from all participants will be listed by participant and may be correlated to PK and PD measures for exploratory purposes.

9.2.6.2 Lung Injury

All measurements of lung injury that are performed during standard care will be listed.

9.2.6.3 Respiratory Support

Individual results for the requirement of respiratory support will be listed and will be assessed by:

- MVFDs by Days 8, 15, 22, and 60
- Proportion of participants not on MV support on Days 8, 15, 22, 29, and 60

- Number of participants progressing from non-invasive to invasive MV by Days 8, 15, 22, 29, and 60
- Time of progression from non-invasive to invasive MV to Day 60
- Proportion of participants weaned from MV within 28-days post treatment (ie, Day 29)

9.2.6.4 Mortality

Individual results for time until death will be listed.

9.2.6.5 Other

Where data permit, exploratory sensitivity and subgroup analyses may be performed. These may include analyses of the progression to MV in ALT-100 versus placebo-treated ARDS patients on heated and humidified HFNO or NIPPV (ie, BiPAP/CPAP), and assessment of the effect of ALT-100 on overall duration of hospitalization based on participant ventilator requirements at the time of enrollment.

9.3 Planned Interim Analysis

No formal interim analysis is planned.

10 ETHICAL CONSIDERATIONS

10.1 Good Clinical Practice

This study will be conducted in accordance with the principles of the current Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Participants). The conduct of the study will be in accordance with the Integrated Addendum to ICH E6 (R1), Guideline for GCP E6 (R2).

10.2 Ethics Review

This study will be conducted under a protocol reviewed and approved by an IEC/IRB, as applicable, and investigations will be undertaken by scientifically and medically qualified persons; where the benefits of the study are in proportion to the risks. The study will be overseen by an Investigator who, prior to study start, will have read and agreed to an understanding of the protocol requirements and will agree to conduct the study in accordance with the above guidelines.

Prior to the commencement of the study, written approval will be required by the relevant IEC/IRB responsible for the investigational site. The Investigator must also inform the IEC/ IRB of any protocol changes or amendments, updates to the Investigator's Brochure, expedited reports of SAEs, and other significant safety concerns according to the applicable regulations.

10.3 Informed Consent

The Investigator will ensure that the participant, or their LAR if applicable, is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Participants/LAR must also be notified that they are free to discontinue from the study at any time without prejudice. The participant/LAR should be given the opportunity to ask questions and allowed time to consider the information provided before voluntarily signing the written informed consent form.

The participant’s (or their LAR if applicable) signed and dated informed consent must be obtained before conducting any study procedures. The participants/LARs will be informed of their rights to privacy but will be made aware that the study data will be submitted to the Sponsor and possibly to drug regulatory authorities for review and evaluation. They will also be informed that the study monitor may inspect their medical records to verify the accuracy and completeness of the study records and results.

The acquisition of informed consent should be documented in the participant’s medical records, as required by the Integrated Addendum to ICH E6 (R1), GCP E6 (R2). The informed consent form (ICF) will be signed and personally dated by the participant and by the person who conducted the informed consent discussion (not necessarily an Investigator).

The Investigator must maintain the original, signed ICF. A copy of the signed ICF must be given to the participant or legal representative. The date that informed consent was signed will be recorded on the eCRF.

10.4 Data Privacy

Participants will be informed that data will be held on file by the Sponsor and that these data may be viewed by staff including the study monitor and by external auditors on behalf of the Sponsor and appropriate regulatory authorities. Participants will also be informed that a study

report will be prepared and may be submitted to regulatory authorities and for publication. However, participants will be identified in such reports only by study identification number, sex, and age. All participant data will be held in strict confidence.

10.5 Disclosure

By signing this protocol, the Investigator agrees to keep all information provided by the Sponsor in strict confidence and to request similar confidentiality from his/her staff and the local IEC/IRB. Study documents provided by the Sponsor (protocols, Investigator's Brochure, eCRFs, etc.) will be stored appropriately to ensure their confidentiality. The information provided by the Sponsor to the PI may not be disclosed to others without direct written authorization from the Sponsor, except to the extent necessary to obtain informed consent from participants who wish to participate in the study.

The Investigator must ensure that the participant’s anonymity is also maintained. Participants should only be identified by their initials and a participant study number on the eCRFs and other source documents. Other study-related documents (eg, signed informed consent forms) should be kept in strict confidence by the Investigator.

10.6 Biological Specimens and Data

Biological samples will be retained for the time required for completion of study assessments and may then be discarded. Safety, immunogenicity, and PK/PD samples may be held for up to 5 years with the permission of the participants for any retrospective assessments.

11 SAFETY OVERSIGHT

11.1 Independent Monitoring

11.1.1 Data Safety Monitoring Committee

The safety of the study will be overseen by an independent DSMC. The independent DSMC will actively monitor the emerging data to review the ongoing safety of study participants and can make recommendations about early study closure or changes to the protocol and conduct of the study. The Sponsor may decide to stop or make adaptations to the study based upon DSMC recommendations. The independent DSMC members will include 2 to 4 physicians with relevant medical specialty training and 1 statistician. The operation of the independent DSMC will be governed by a charter describing further details such as frequency of meeting, procedures (including but not limited to periodic safety monitoring) and requirements for the reporting of observations to the Sponsor. The DSMC Charter will be finalized prior to the enrollment of participants into the study.

At a minimum, the DSMC will convene to determine if dose escalation (Part A) may proceed based on review of all safety, available PK data, and any early efficacy and PD data from the 9 participants from each sequential dose level cohort completing up to and including Day 29. This will include consideration of an optional additional Part A dose cohort (Cohort 3a) of up to 9 participants based on available safety, PK, and early efficacy and PD data up to and including Day 29 from all participants in Cohort 1a and Cohort 2a. The DSMC will also meet at the conclusion of Part A to determine if the cohort expansion phase (Part B) may proceed. The decision to initiate Part B will be based on review of all safety, available PK data, and any early efficacy and PD data from all Part A cohort participants completing up to and including Day 29.

Data from participants receiving placebo and ALT-100 will be considered.

Dose escalation decisions will be based upon the nature, severity, and frequency of any safety and/or tolerability observations, including any AEs or SAEs, changes in vital signs and/or safety laboratory parameters, and physical findings. The DSMC will also consider the available efficacy and PD data when making their decision. Plasma PK samples will be analyzed by cohort, and available results will be provided to the DSMC prior to meetings. The exposure and the predicted exposure for the subsequent dose group in Part A will be provided based on the information available. In the case of premature withdrawal of a participant from the study prior to Day 29, all available safety, PK, efficacy, and PD data up to the time of withdrawal will be reviewed by the DSMC.

DSMC evaluation of study data may occur more frequently, if warranted by the treatment emergent data, and in cases where the protocol defined stopping criteria are met.

11.1.1.1 Stopping Rules

Participants will be carefully monitored throughout the study for the occurrence of AEs and SAEs. The following stopping rules will trigger a DSMC unscheduled review of the cumulative study data:

Serious Adverse Events

For treatment emergent SAEs, further dosing of study participants at the dose level associated with the treatment emergent SAE will be paused for DSMC review in the following cases:

- Any treatment emergent SAE(s) suspected to be treatment-related (as assessed by the investigator).
- Treatment emergent SAEs (i.e., in the same system organ class [SOC]), regardless of assigned causality occurring in ≥2 participants in Part A and ≥3 participants in Part B.

Non-serious Adverse Events

For non-serious TEAEs, further dosing of study participants at the dose level associated with the TEAE will be paused pending DSMC review in the following cases:

- Severe TEAEs (Grade 3 according to the NCI-CTCAE v5.0) suspected to be treatment-related, independent of whether the AE is in the same SOC, that occur in ≥2 participants in Part A and in ≥3 participants in Part B if showing signs of reversibility, or in ≥1 participants in Part A and ≥2 participants in Part B if not resolving.
- Treatment emergent AEs of moderate severity (Grade 2 according to NCI-CTCAE v5.0), that occur in ≥3 participants (if in the same SOC), or in ≥4 participants (independent of whether the AE is in the same SOC), if showing signs of reversibility (for both Part A and Part B). Grade 2 TEAEs that do not resolve in ≥2 participants (Part A) and in ≥3 participants (Part B) will trigger a dosing pause and DSMC review.

Based on the data review, the DSMC will determine whether to proceed with dosing or may recommend temporary or permanent stopping of dosing. This may include suspension of dosing of all ongoing and planned dosing cohorts including those at lower exposures and further enrolment of study participants. After a temporary halt, further measures for safety may be introduced. Continuation of the study may require a substantial amendment to the study design and assessments to ensure participant safety. All amendments to the protocol will first be subject to review and approval by the relevant independent ethics committee (IEC)/ institutional review board (IRB).

Guidelines on the management of acute infusion-related reactions and associated stopping rules in individual participants are provided in Section 6.2 (Table 5).

Early study discontinuation criteria for individual participants and conditions under which study termination will occur are detailed in Section 7.2 and Section 7.3, respectively.

11.2 Quality Control and Assurance

11.2.1 Monitoring

Before an investigational site can enter a participant into the study, a representative of the Sponsor will visit the site to:

- Determine the adequacy of the facilities
- Discuss with the Investigator(s) and other personnel their responsibilities with regards to protocol adherence, and the responsibilities of the Sponsor and/or its

representatives. This will be documented in a Clinical Study Agreement between the Sponsor and the Investigator.

The Sponsor has appointed a CRO to manage and monitor the study to ensure the adequate conduct of the study and to act as the contact with the investigational site. A study monitor will be identified and will be responsible for liaison with, and support of, the investigational site.

The study monitor and regulatory authority inspectors are responsible for contacting and visiting the site for the purpose of inspecting the facilities and, upon request, inspecting the various records of the study (eg, eCRFs, essential documentation, and other pertinent data), provided that participant confidentiality is respected.

During the study, the monitor will maintain regular contact with the investigational site to ensure the following:

- Provide information and support to the Investigators
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the case report forms, and that IP accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the eCRFs with the participant's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each participant (eg, clinic charts)
- Record and report any protocol deviations not previously sent to the Sponsor
- Confirm AEs and SAEs have been properly documented on eCRFs, confirm any SAEs have been forwarded to the Sponsor, and that those SAEs that met criteria for reporting have been forwarded to the IEC/IRB, as applicable

The monitor will be available between visits if the Investigators or other staff needs information or advice.

11.2.2 Audits and Inspections

In accordance with ICH GCP, this study may be selected for audit and/or inspection. Inspection or audit of site facilities (eg, pharmacy, medication storage areas, laboratories) and review of study-related records may occur by the Sponsor, the Sponsor's representative, or regulatory authority to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

The Investigator should contact the Sponsor immediately if contacted by a regulatory agency about an inspection.

11.2.3 Protocol Amendments

Neither the Investigator nor the Sponsor will modify or alter this protocol without the agreement of the other. All agreed protocol amendments will be clearly documented and will be signed and dated by the original protocol approving signatories. All protocol amendments will be submitted to the relevant institutional IEC/IRB for approval before implementation, as required by local regulations. The only exception will be when the amendment is necessary to eliminate an immediate hazard to a trial participants. In this case, the necessary action will be taken first, with the relevant protocol amendment following shortly thereafter.

11.2.4 Protocol Deviations

Protocol deviations are to be captured in the Clinical Trial Management System (CTMS) with the following attributes:

- Date
- Protocol deviation category (major or minor)
- Inclusion/exclusion criteria not met
- Study treatment not administered as per protocol
- Non-compliance with visit schedule
- Description of the deviation
- Other

A deviation will be categorized as major if it meets any of the following criteria:

- Compromises the safety of the participant
- Creates a potentially unsafe condition for other participants in the cohort, or full study
- Compromises the validity of primary results for a cohort, or the full study
- Impairs the conduct of the study
- Violates regulatory constraints or guidance
- Compromises the privacy of a participant

Should a major protocol deviation occur, it must be reported to the study monitor and Sponsor within 24 hours of awareness. The deviation and the reason for its occurrence must be documented and reported to the relevant IEC/IRB (if required), and included in the final study report.

11.2.5 Records

11.2.5.1 Data Capture and Management

All data will be recorded in individual source documents. An eCRF will be created by the data management group for recording of the required data in the study database. All eCRF information is to be entered by trained site staff. If an item is not available or is not applicable, this fact should be indicated. Blank spaces should not be present unless otherwise directed.

The study monitor will perform source data verification of data entered into the eCRF, and raise queries for correction by the site. The data entered into the eCRF will be participant to data validation checks for consistency and completeness by the data management group. Data queries will then be generated and sent to the investigational site(s) for response before the database is locked and released for statistical analysis.

11.2.5.2 Source Documentation and Records Retention

All source data, clinical records, and laboratory data relating to the study will be archived as per local requirements.

All data will be available for retrospective review or audit.

Source documents are original documents and are records from which the participant's eCRF data are obtained. These include, but are not limited to: hospital records, clinical and office charts, laboratory and pharmacy records, radiographs, angiograms, IP accountability logs, and correspondence. eCRF entries may be considered source data if the eCRF is the site of

the original recording (ie, there is no other written or electronic record of data). In this case, a note to the file should indicate which eCRFs are considered source documents.

The Investigator and study staff are responsible for maintaining a comprehensive filing system of all study-related (essential) documentation. These include, but are not limited to IEC/IRB correspondence, IP accountability logs, and curricula vitae of all personnel participating in the study. These files must be suitable for inspection at any time by the Sponsor, monitor, and/or applicable regulatory authorities.

No study document should be destroyed without prior written agreement between the Sponsor and the Investigator. If the Investigator wishes to assign the study records to another party or move them to another location, they must notify the Sponsor in writing of the new responsible person and/or the new location.

11.3 Study Termination or Clinical Research Unit Closure

The Sponsor, Investigator, and the IEC/IRB reserve the right to terminate or suspend the study at any time; however, this should be discussed between the relevant parties beforehand and the reason for such decision recorded. Should this occur, all data available will also be recorded in the eCRFs. The Investigator should notify the relevant IEC/IRB in writing of the study's completion or early discontinuation.

Clinical Research Units will be closed upon study completion. A site is considered closed when all required documents and study supplies have been collected and a site closure visit has been performed.

The Investigator may initiate 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 of a site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of participants by the Investigator.
- Discontinuation of further study treatment development.

12 CLINICAL STUDY REPORT

A CSR will be prepared in accordance with ICH Guidance E3.

Consideration will be given to any comments on a draft report. The report will incorporate the analytical and statistical results and methods produced by the Sponsor or their agents. A final report will be prepared to contain all those sections in the draft and a statement of compliance covering all the areas of the study conducted at the investigational site and the report, with GCP. The report will be issued under the Sponsor's responsibility.

Where required by the applicable regulatory requirements, an Investigator signatory will be identified for the approval of the CSR. The Investigator will be provided reasonable access to statistical tables, figures and relevant reports and will have the opportunity to review complete study results. The Sponsor will also provide the Investigator with the full summary of study results.

The full CSR, or where required the CSR synopsis, will be submitted to the competent authorities within 12 months from the end date of the study.

13 PUBLICATION POLICY

All manuscripts, abstracts or other modes of presentation arising from the results of the trial must be reviewed and approved in writing by Aqualung Therapeutics in advance of submission. The review is aimed at protecting Aqualung Therapeutics' proprietary information existing either at the date of the commencement of the study or generated during the trial.

Communication and/or publication of documents or data relating to this trial is not permitted without the written approval of Aqualung Therapeutics.

Acknowledgment will be given to collaborating institutions and hospitals and other individuals and organizations providing finance or facilities. Participant confidentiality will be maintained by referring to individual participants by their identifying code used in the trial. Data will not be released publicly until the manuscript is accepted for publication. In the case of no publication, information will only be released to the public and media in accordance with approval granted by Aqualung Therapeutics.

Study data that have not been published, presented or otherwise disclosed in accordance with the clinical trial agreement shall remain confidential information of Aqualung Therapeutics; the Investigator may not disclose or permit the disclosure of such unpublished data to any third party, nor may they disclose or permit the disclosure of any study data to any third party in greater detail than the same have been disclosed in any permitted publication, presentation or other disclosure.

The results summary will be posted to an appropriate Clinical Trials Registry as required by legal agreement, local law, or regulation.

14 FINANCING AND INSURANCE

The Sponsor will ensure sufficient insurance is available to enable them to indemnify and hold the PI(s) and relevant staff as well as any hospital, Institution, ethics committee or the like, harmless from any claims for damages for unexpected injuries, including death, that may be caused by the investigational therapy but only to the extent that the claim is not caused by the fault or negligence of the patients or PI(s). An insurance certificate will be supplied to the involved parties, including the Investigators and CRO(s) as appropriate.

The financial arrangements for this study are addressed in a separate agreement.

The Investigator will be required to disclose any financial arrangement whereby the value of the compensation for conducting the trial could be influenced by the outcome of the trial.

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Final Audit Report 2023-05-31

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