CLINICAL STUDY PROTOCOL
CLYM116-NHV-101

Study Title:	A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Single-Ascending-Dose (SAD) and Multiple-Ascending-Dose (MAD) Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Subcutaneous Injection(s) of CLYM116 in Normal Healthy Volunteers
Study No.:	CLYM116-NHV-101
Study Phase:	1
Product Name:	CLYM116
Sponsor:	Climb Bio, Inc. 20 William Street, Suite 145 Wellesley Hills, MA 02481, USA
Version:	Amendment 1
Date of Protocol:	28 October 2025

SIGNATURE PAGE - SPONSOR

I have read and understand the contents of the protocol for Clinical Study CLYM116-NHV-101 Amendment 1 (dated 28 October 2025), and agree to meet all obligations of Climb Bio, Inc., as detailed in all applicable regulations and guidelines. In addition, I will ensure that the lead investigators are informed of all relevant information that becomes available during the conduct of the study.

Edgar Charles, MD, MSc.,
Chief Medical Officer
Climb Bio, Inc.

Date: October 28, 2025

INVESTIGATOR'S AGREEMENT

I agree to the terms of this study protocol. I will conduct the study according to the procedures specified herein, and according to principles of the Declaration of Helsinki, International Council for Harmonisation of Technical Requirements of Pharmaceuticals for Human Use (ICH) for Good Clinical Practice (GCP), and all applicable national and local regulations and requirements. No changes will be made to the study protocol without prior written approval of the Sponsor and the Institutional Review Board/Independent Ethics Committee.

_____

Institution/Clinic

_____

Principal Investigator Name

_____

Signature

_____

Date

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
ADA	antidrug antibody
ADCC	antibody-dependent cellular toxicity
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
APRIL	A PRoliferation-Inducing Ligand
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
β-hCG	beta human chorionic gonadotropin
BAFF	B cell activating factor
BCMA	B cell maturation antigen
BMI	body mass index
BUN	blood urea nitrogen
CDC	complement-dependent cytotoxicity
CL	clearance
C_{max}	maximum concentration
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus disease 2019
CRF	case report form
CRU	clinical research unit
CTCAE	Common Terminology Criteria for Adverse Events
ECG	electrocardiogram
eCRF	electronic case report form
EOS	end of study
ET	early termination
FDA	Food and Drug Administration

Abbreviation or Specialist Term	Explanation
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
Gd-IgA1	galactose-deficient immunoglobulin A1
GLP	Good Laboratory Practice
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	independent ethics committee
Ig	immunoglobulin
IgAN	immunoglobulin A nephropathy
INR	international normalized ratio
IRB	institutional review board
ISR	injection site reaction
IUD	intrauterine device
IV	intravenous
mAb	monoclonal antibody
MAD	multiple ascending dose
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
NHV	normal healthy volunteer
NK	natural killer
NOAEL	no-observed-adverse-effect level
PCP	phencyclidine
PCR	polymerase chain reaction

Abbreviation or Specialist Term	Explanation
PD	pharmacodynamic(s)
PCI	Potentially Clinically Important
PK	pharmacokinetic(s)
PT	prothrombin time
RBC	red blood cell
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SoA	Schedule of Activities
SRC	Safety Review Committee
$t_{½}$	terminal half-life
TACI	transmembrane activator and calcium modulator and cyclophilin ligand interactor
TBD	to be determined
TB	tuberculosis
TBNK	T, B, and natural killer cells
TEAE	treatment-emergent adverse event
TGA	Therapeutic Goods Administration
THC	tetrahydrocannabinol
T_{max}	time to maximum concentration
V_d	volume of distribution
WBC	white blood cell
WOCBP	woman of childbearing potential
WONCBP	woman of non-childbearing potential

1. PROTOCOL SUMMARY

1.1. Synopsis

1.1.1. Protocol Title

A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Single-Ascending-Dose (SAD) and Multiple-Ascending-Dose (MAD) Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Subcutaneous Injection(s) of CLYM116 in Normal Healthy Volunteers

1.1.2. Short Title

Anti-APRIL monoclonal antibody (CLYM116) SAD and MAD study in healthy volunteers

1.1.3. Number of Study Sites

The study will be conducted at one Australian clinical research unit (CRU) experienced in pharmacokinetic (PK) and pharmacodynamic (PD) studies in normal healthy volunteers (NHVs).

1.1.4. Rationale

This is a first-in-human (FIH) study to evaluate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of subcutaneously (SC) administered CLYM116, a novel anti-APRIL (A PRoliferation-Inducing Ligand) monoclonal antibody (mAb) in NHVs. The study aims to inform the planned clinical development program in patients with immunoglobulin A (IgA) nephropathy (IgAN) and other B cell mediated diseases.

The mechanism of action of CLYM116 is preventing APRIL signaling by promoting lysosomal degradation of APRIL via a pH-dependent bind-and-release process and potently blocking the binding of APRIL to its receptors. Through its unique binding profile, CLYM116 may enable rapid, deep, and durable inhibition of APRIL signaling. Clinical trials of other anti-APRIL therapeutic candidates have shown reductions in proteinuria, a key marker of disease activity, in patients with IgAN, which supports this mechanism of treatment.

In this study, a single- and multiple-ascending-dose (SAD/MAD) design will be used to establish foundational safety and pharmacology data to support the clinical development of CLYM116 in patients with IgAN.

Selection of the initial dose is based on preclinical safety, PK, and PD studies of CLYM116 in nonhuman primates, as well as modeling of comparative scientific data from other anti-APRIL mAbs in development for the treatment of IgAN.

1.1.5. Objectives and Endpoints

The study objectives and endpoints are outlined in Table 1.

Table 1: Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of single and multiple subcutaneous (SC) doses of CLYM116 in healthy volunteers	• Incidence and severity of treatment-emergent adverse events (TEAEs), including injection site reactions
Secondary	
• To characterize the pharmacokinetics (PK) of CLYM116 following single and multiple SC doses	• Serum concentrations of CLYM116 over time and PK parameters (e.g., maximum concetration [C_{max}], time to maximum concentration [T_{max}], area under the concentration-time curve [AUC], half-life [$t_{½}$])
• To assess the pharmacodynamic (PD) effects of CLYM116	• Levels of PD biomarkers (e.g., immunoglobulins, APRIL) and changes over time
• To evaluate the immunogenicity of CLYM116	• Incidence of antidrug antibodies (ADA)

1.1.6. Overall Design

This is a Phase 1, randomized, double-blind, placebo-controlled, single-center study designed to evaluate the safety, tolerability, PK, PD, and immunogenicity of CLYM116 in NHVs.

The study will be conducted at a single site. Healthy male and female adults with no chronic illnesses will be enrolled.

The study will enroll up to 64 subjects. The single ascending dose (SAD) portion will consist of up to 5 cohorts at dose levels of 25 mg, 80 mg, and 160 mg and 2 higher doses to be determined (TBD). The higher doses will not exceed 480 mg. The multiple ascending dose (MAD) portion will consist of up to 3 cohorts at the dose level of 160 mg (administered twice) and 2 higher doses TBD. The higher doses will not exceed 480 mg per dose (i.e., 960 mg in total exposure). The cohorts will be enrolled and treated sequentially. The TBD cohorts may be omitted according to decisions by the Safety Review Committee (SRC).

The dose cohorts of CLYM116 are shown in Table 2.

Table 2: CLYM116 Dosing Cohorts

Cohort	N	CLYM116 Dose	Dosing Regimen
1	8	25 mg	1 dose
2	8	80 mg	1 dose
3	8	160 mg	1 dose
4	8	Higher dose 1 TBD	1 dose
5	8	Higher dose 2 TBD	1 dose
6	8	160 mg SC	once every 2 weeks for 2 doses
7	8	Higher dose 3 TBD	once every 2 weeks for 2 doses
8	8	Higher dose 4 TBD	once every 2 weeks for 2 doses

In each cohort, 8 eligible subjects will be randomized in a 3:1 ratio to receive either CLYM116 (n=6) or placebo (n=2) in a double-blinded manner.

All SAD cohorts will use a sentinel dosing scheme: 2 sentinel subjects (1 CLYM116 and 1 placebo) will be dosed first, and the remaining non-sentinel subjects will be dosed no sooner than 48 hours later, following the safety assessments of the sentinel subjects, along with written confirmation by the investigator.

Subjects will be admitted into the inpatient CRU on Day -1 (the day before the first dose) and undergo assessments to confirm their eligibility. On Day 1, the study drug (CLYM116 or placebo) will be administered as an SC injection at the assigned dose in a double-blind manner. The subjects and investigator/site personnel will be blinded to the treatment assignment (i.e., CLYM116 or placebo) within each cohort. The pharmacy personnel responsible for preparing the study drug for administration will be unblinded. The sponsor will not be blinded.

Each subject will remain in the inpatient unit for monitoring and assessments from Day -1 through Day 4. For the SAD cohorts, subjects will return to the study site weekly through Day 29. The end-of-study (EOS) visit will occur on Day 57. For the MAD cohorts, subjects will be admitted to the CRU on Day 14, receive the second dose of the study drug on Day 15, and remain confined through Day 18. Subjects will then return to the study site weekly through Day 43. The end-of-study (EOS) visit will occur on Day 71.

If a subject's IgA, IgG, or IgM levels do not recover to 50% of baseline or lower limit of normal, the subject will be required to return to the study site monthly to assess immunoglobulin levels until recovery.

Safety will be assessed through adverse event (AE) monitoring and clinical evaluations. PK/PD will be assessed through blood sampling and biomarker analysis, including immunoglobulin levels (including IgA, IgM, IgG) and APRIL levels. Antidrug antibodies (ADA) will be measured to assess immunogenicity.

Dose escalation to the subsequent cohort(s) will be determined by the SRC (Section 1.1.11). A new cohort will not initiate study drug administration without the SRC's formal authorization.

1.1.7. Brief Summary

This study will evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of subcutaneous injections of CLYM116, an anti-CLYM116 monoclonal antibody, in healthy volunteers. Either CLYM116 or placebo will be administered on 1 day or on 2 days with a 2-week interval between doses, depending on the assigned cohort. The total duration of study participation, including screening, will be approximately 16 or 18 weeks, depending on the number of doses required.

1.1.8. Number of Subjects

Up to 64 subjects will be enrolled and randomized, including up to 48 subjects who will receive CLYM116 and up to 16 subjects who will receive placebo.

Additional alternate subjects may be screened to replace subjects who drop out. Subjects who withdraw from the study after randomization but before receiving the study drug may be automatically replaced. Subjects who withdraw from the study after dosing may be replaced at the discretion of the Sponsor and Investigator. If more than 2 subjects in a cohort withdraw after dosing, replacement subjects may be enrolled.

1.1.9. Inclusion and Exclusion Criteria

1.1.9.1. Inclusion Criteria

1. Willing and able to sign the informed consent and comply with the study protocol and visits.
2. Males or females aged 18 to 60 years (inclusive) at the time of informed consent.
3. Body mass index (BMI) between 18 and 32 kg/m^2 and body weight between 45 and 110 kg.
4. Healthy medical history with no chronic or acute illnesses at the time of screening.
5. Physical examination results are all within normal range, unless an abnormality is deemed not clinically significant by the investigator.
6. Clinical laboratory evaluations (including chemistry panel [after fasting for at least 8 hours], complete blood count, coagulation, and urinalysis) within the reference range for the test laboratory, unless an abnormality is deemed not clinically significant by the investigator. If necessary, the laboratory evaluations may be repeated once during the screening window through Day -1 to confirm eligibility.
7. Normal findings on electrocardiogram (ECG), unless an abnormality is deemed not clinically significant by the investigator.
8. Female subjects who are women with childbearing potential (WOCBP) must not be pregnant, lactating, or breastfeeding before study drug administration and not plan to become pregnant or donate eggs from Day -1 through 4 months after the study drug administration. WOCBP must agree to adhere to the specified highly effective contraceptive requirements.

9. Sexually active male subjects who have female partners of childbearing potential must agree to use a barrier contraceptive method combined with a highly effective contraceptive method used by the female partner from Day -1 through 4 months following the study drug administration.
10. Male subjects must agree to abstain from sperm donation from Day -1 through 4 months after the study treatment.
11. Either is a nonsmoker or has a history of smoking no more than 2 cigarettes per day and is willing to abstain during the inpatient stay.
12. Have completed Coronavirus disease 2019 (COVID-19) vaccination according to local guidelines (any brand recognized by Therapeutic Goods Administration [TGA]) or willing to meet the requirement prior to study drug administration.
13. Have completed influenza vaccination within 12 months prior to study drug administration.
14. Any subjects enrolled after the completion of Cohort 3 (SAD 160 mg CLYM116) must have received a pneumococcal vaccine (any brand approved by the TGA) at least 14 days prior to their initial dose of study drug.

1.1.9.2. Exclusion Criteria

1. Treatment with any investigational drug within 30 days or at least 5 times the elimination half-life of the drug (whichever is longer) prior to the study treatment, or current participation in another clinical study, or any plan of using an investigational device or drug during the study.
2. Previous medical or surgical history that may compromise the safety of the subject in the study, as assessed by the investigator.
3. Previous or current hypogammaglobulinemia (i.e., quantitative IgG, IgM, or IgA below the lower limit of normal).
4. History of an allergic reaction or significant sensitivity to constituents of the study drug (and its excipients) and/or other products in the same class.
5. Current presence of allergic reactions, such as asthma, urticaria, angioedema, and eczematous dermatitis, that are considered clinically significant by the investigator.
6. Have had any live vaccine within 21 days before study drug administration or any non-live vaccine within 14 days before study drug administration.
7. Positive urine drug screen or breath alcohol test (a single repeat is permitted in the event of a suspected false positive).
8. History of clinically significant drug (including cannabis or cannabinoids) or alcohol abuse within 1 year prior to screening, as assessed by the investigator (occasional or social drinking is allowed).

9. History of clinically significant opportunistic infection (e.g., invasive candidiasis or pneumocystis pneumonia).
10. Serious local infection (e.g., cellulitis, abscess) or systemic infection (e.g., septicemia) within 3 months prior to screening.
11. Past or current hepatitis B or C infection, syphilis, or positive QuantiFERON-TB Gold test or human immunodeficiency virus (HIV) serology.
12. Any other clinically significant disease, condition, or medical or psychiatric history that, in the investigator's opinion, would compromise subject safety, interfere with study evaluations or procedures, or make the subject unsuitable for the study.
13. In the opinion of the investigator, the subject is unlikely to complete all protocol-required study visits or procedures, including follow-up visits, or comply with the study requirements for participation.

1.1.10. Intervention Groups and Duration

1.1.10.1. Intervention Groups

- Up to 5 SAD cohorts: 25 mg, 80 mg, 160 mg CLYM116 or placebo administered on Day 1. Two additional cohorts of higher doses (not to exceed 480 mg CLYM116) may be enrolled.
- Up to 3 MAD cohorts: 160 mg CLYM116 or placebo administered for 2 doses on Day 1 and Day 15. Two additional cohorts of higher doses (not to exceed 480 mg CLYM116 per dose, i.e., 960 mg in total) may be enrolled.

1.1.10.2. Duration of Study Participation

- Screening period: up to 8 weeks
- Treatment period: 1 day (single-dose cohorts) or 14 days (multiple-dose cohorts)
- Follow-up period: approximately 8 weeks

The maximum duration of study participation is 16 weeks for subjects in the SAD part and 18 weeks for those in the MAD part, assuming timely Ig recovery. However, if a subject's IgA, IgM, or IgG level is not above 50% of baseline or not above the lower limit of normal by the scheduled EOS/early termination (ET) visit, additional follow-up visits at monthly intervals may occur until the IgA, IgM, and IgG levels recover to 50% of baseline level or the lower limit of normal, whichever occurs first.

1.1.11. Safety Review Committee (SRC)

The SRC will include, at a minimum, the investigator, medical monitor, and the sponsor's medical representative.

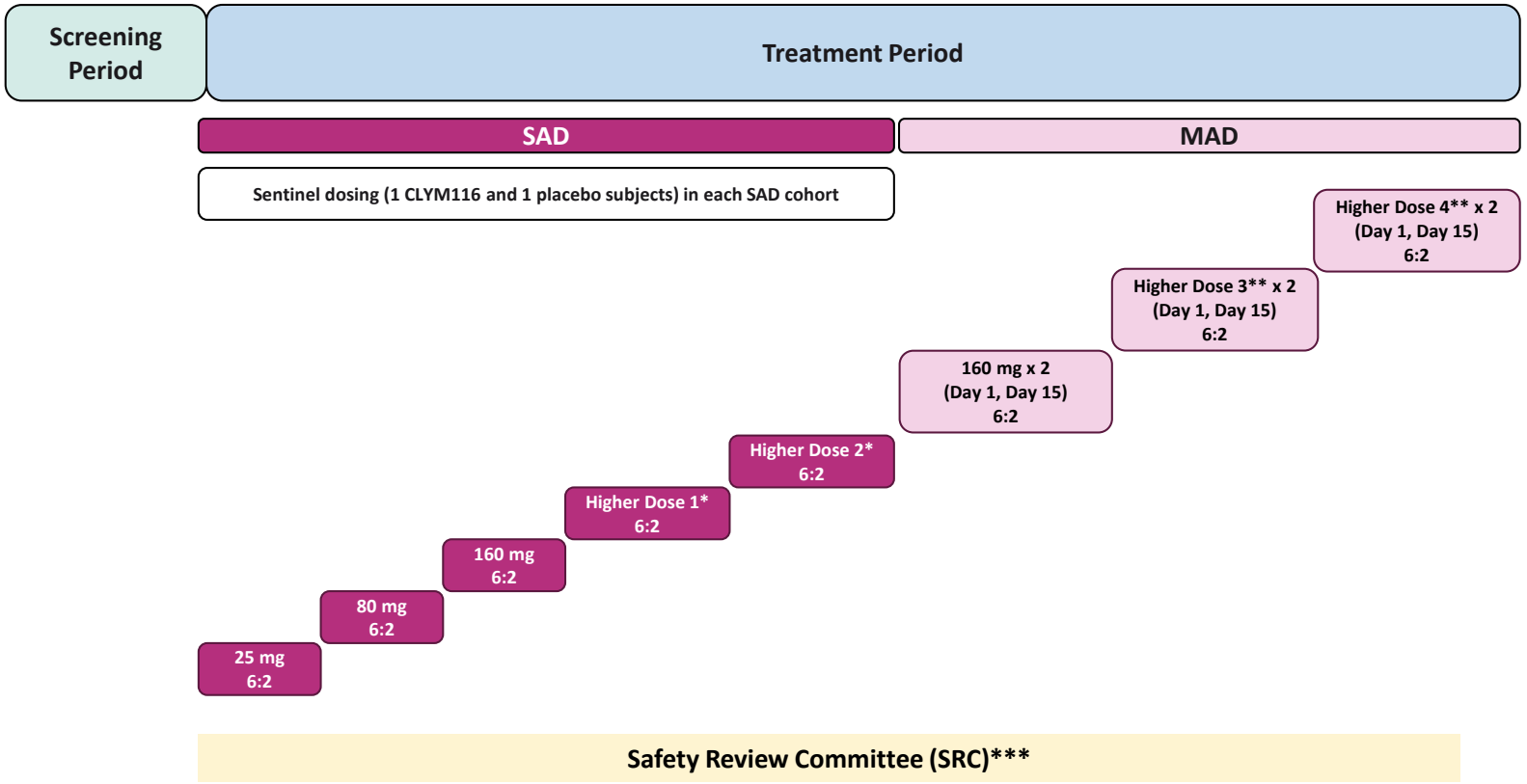
SRC meetings will be held after relevant safety and tolerability data for at least 8 days are available from at least 7 of 8 subjects in each cohort. The SRC will review all available safety,

laboratory and PK/PD data to determine whether to escalate to the next dose level, modify the next dose level, repeat a dose level, omit the next dose level, or stop dose escalation. While clinical stability through Day 8 is required to proceed, emerging data will continue to be monitored and considered in SRC decisions. A new dose cohort will not initiate study drug administration without the SRC's formal authorization.

Details will be provided in a separate SRC Charter.

1.2. Schema

Figure 1: Schematic of Study CLYM116-NHV-101



Abbreviations: MAD = multiple ascending dose; SAD = single ascending dose; SC = subcutaneous; SRC = Safety Review Committee
Footnotes:
*SAD Higher Doses 1 and 2 will be determined by SRC and will not exceed 480 mg if the cohort(s) is deemed necessary.
**MAD Higher Doses 3 and 4 will be determined by SRC and will not exceed 960 mg in total (480 mg × 2) if the cohort(s) is deemed necessary.
***SRC will review at least 8 days of data from the previous cohort and make decisions on dose escalation.

1.3. Schedule of Activities (SoA)

Table 3: Schedule of Activities for SAD Part of Study CLYM116-NHV-101

Period	**Screening**	**Inpatient**					**Follow-up**					
Visit	**Screening**	**Admitting Visit**[1]	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**EOS / ET**	**Ig Follow-up**[2]
Day (Visit Window [days])	**-56 to -2**	**-1**	**1**	**2**	**3**	**4**	**8 (±1)**	**15 (±1)**	**22 (±1)**	**29 (±1)**	**57 (±3)**	
Informed consent	X											
Demographics	X											
Eligibility criteria	X	X										
Randomization			X									
Medical history	X	X										
Infectious disease screening[3]	X											
COVID-19 test		X										
Height, weight, BMI[4]	X	X									X	
Complete physical examination[5]	X	X										
Symptom-based physical examination[6]			X	X	X	X	X	X	X	X	X	
Vital signs[7]	X	X	X	X	X	X	X	X	X	X	X	
Clinical hematology[8]	X[9]	X[9]	X	X	X	X	X	X	X	X	X	
Clinical chemistry (comprehensive)[8]	X[9]	X[9]				X	X	X	X	X	X	
Clinical chemistry (abbreviated)[8]			X	X	X							

Table 3: Schedule of Activities for SAD Part of Study CLYM116-NHV-101 (Continued)

Period	**Screening**	**Inpatient**					**Follow-up**					
Visit	**Screening**	**Admitting Visit**[1]	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**EOS / ET**	**Ig Follow -up**[2]
Day (Visit Window [days])	**-56 to -2**	**-1**	**1**	**2**	**3**	**4**	**8 (±1)**	**15 (±1)**	**22 (±1)**	**29 (±1)**	**57 (±3)**	
Coagulation[8]	X[9]	X[9]										
Urinalysis[8]	X[9]	X[9]	X				X	X	X	X	X	
Urine drug screen and alcohol breath test	X[9]	X[9]										
FSH (WONCBP only)	X											
Serum β-hCG (WOCBP only)[10]	X										X	
Urine β-hCG (WOCBP only)		X										
Inpatient confinement		X	X	X	X	X						
APRIL analysis		X	X			X	X	X		X	X	X
BAFF analysis			X				X				X	
Immunophenotyping (T, B, and NK cells)			X[11]			X	X	X	X	X	X	X
Quantitative Ig (IgA, IgE, IgG, IgM, Gd-IgA1)	X		X[11]				X	X	X	X	X	X
Serum sample for ADA			X[11]					X		X	X	X
Serum sampling for PK[12]			X	X	X	X	X	X	X	X	X	X
Antibody titers to measles, mumps, rubella, tetanus			X[11]				X				X	

Table 3: Schedule of Activities for SAD Part of Study CLYM116-NHV-101 (Continued)

Period	**Screening**	**Inpatient**					**Follow-up**					
Visit	**Screening**	**Admitting Visit**[1]	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**EOS / ET**	**Ig Follow -up**[2]
Day (Visit Window [days])	**-56 to -2**	**-1**	**1**	**2**	**3**	**4**	**8 (±1)**	**15 (±1)**	**22 (±1)**	**29 (±1)**	**57 (±3)**	
12-lead ECG[13]		X				X						
Study drug administration			X									
Injection reaction assessment[14]			X	X	X	X						
AE assessment	X	X	X	X	X	X	X	X	X	X	X	X
Prior/concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: ADA = antidrug antibody; AE = adverse event; β-hCG = beta human chorionic gonadotropin; BAFF = B cell activating factor; BMI = body mass index; COVID-19 = Coronavirus Disease 2019; CRF = case report form; CRU = clinical research unit; ECG = electrocardiogram; EOS = End of Study; ET = early termination; FSH = follicle-stimulating hormone; Gd-IgA1 = galactose-deficient IgA1; HIV = human immunodeficiency virus; Ig = immunoglobulin; ISR = injection site reaction; IV = intravenous; NK = natural killer; PK = pharmacokinetic(s); SC = subcutaneous; WOCBP = women of childbearing potential; WONCBP = women of non-childbearing potential

Footnotes:

[1] The qualifying visit will occur after a subject is admitted to the CRU on Day -1. Clinical and laboratory assessments will be conducted to confirm eligibility. Study drug administration occurs on Day 1, which is the day after Day -1 (there is no Day 0).

[2] Additional safety follow-up visits will be conducted approximately monthly for subjects whose IgA, IgM, and IgG levels have not recovered to above 50% baseline or not above the lower limit of normal at the Week 8/EOS visit.

[3] Infectious disease screening will include HIV serology, total hepatitis B core antibody (HBcAb), hepatitis B surface antibody (HBsAb), hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibody, tuberculosis (QuantiFERON-TB Gold), and syphilis serology. Prior hepatitis B vaccination will be documented in the CRF.

[4] Height is recorded at the screening visit only.

[5] Complete physical examinations will include the following body systems: general appearance, skin, head, ears, eyes, nose, throat, neck, lungs, heart, abdomen, musculoskeletal, extremities, and neurological systems. Any clinically significant findings will be recorded in the AE CRF.

[6] Symptom-based physical examination will be conducted, if clinically indicated. Any clinically significant findings will be recorded in the AE CRF.

[7] Vital signs include diastolic and systolic blood pressure, pulse rate, respiratory rate, and body temperature. On Day 1, vital signs will be collected 1 hour (±5 minutes) before, 5 and 30 minutes after, and 1, 2, 4, 8 hours (±15 minutes) after the SC injection. Refer to Section 8.2.2.

[8] Refer to Section 8.2.4 for details of required safety laboratory tests.

[9] A test may be repeated once within the screening window, at the investigator's discretion, through Day -1 to confirm eligibility. For screening, clinical laboratory tests are to be done after fasting for 8 hours.

[10] If the urine pregnancy test is positive, a serum β-hCG test will be conducted for confirmation.

[11]The blood samples should be drawn prior to study drug administration

[12]PK samples are to be drawn at the timepoints listed in Table 6

[13]ECG should be obtained in supine position after 5 minutes of rest.

[14]Injection site reactions should be assessed according to guidance in Section 8.3.9.The severity of ISRs should be assessed according to Table 13 and recorded in the ISR form (not as AEs).

Table 4: Schedule of Activities for MAD Part of the Study CLYM116-NHV-101

Period	**Screening**	**Inpatient**						**Inpatient**					**Follow-up**					
Visit	**Screening**	**Admit-ting Visit**[1]	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**EOS /ET**	**Ig Follow-up**[2]
Day (Visit Window [days])	**-56 to -2**	**-1**	**1**	**2**	**3**	**4**	**8 (±1)**	**14 (±1)**	**15 (±1)**	**16 (±1)**	**17 (±1)**	**18 (±1)**	**22 (±1)**	**29 (±1)**	**36 (±1)**	**43 (±1)**	**71 (±3)**	
Informed consent	X																	
Demographics	X																	
Eligibility criteria	X	X																
Randomization			X															
Medical history	X	X																
Infectious disease screening[3]	X																	
COVID-19 test		X																
Height, weight, BMI[4]	X	X															X	
Complete physical examination[5]	X	X						X										
Symptom-based physical examination[6]			X	X	X	X	X		X	X	X	X	X	X	X	X	X	
Vital signs[7]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Clinical hematology[8]	X[9]	X[9]	X	X	X	X	X	X	X	X	X	X	X	X		X	X	

Table 4: Schedule of Activities for MAD Part of the Study CLYM116-NHV-101 (Continued)

Period	**Screening**	**Inpatient**						**Inpatient**					**Follow-up**					
Visit	**Screening**	**Admit-ting Visit**[1]	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**EOS /ET**	**Ig Follow-up**[2]
Day (Visit Window [days])	**-56 to -2**	**-1**	**1**	**2**	**3**	**4**	**8 (±1)**	**14 (±1)**	**15 (±1)**	**16 (±1)**	**17 (±1)**	**18 (±1)**	**22 (±1)**	**29 (±1)**	**36 (±1)**	**43 (±1)**	**71 (±3)**	
Clinical chemistry (comprehensive)[8]	X[9]	X[9]				X	X	X					X	X		X	X	
Clinical chemistry (abbreviated)[8]			X	X	X				X	X	X	X						
Coagulation[8]	X[9]	X[9]						X										
Urinalysis[8]	X[9]	X[9]	X				X	X	X								X	
Urine drug screen and alcohol breath test	X[9]	X[9]																
FSH (WONCBP only)	X																	
Serum β-hCG (WOCBP only)	X																X	
Urine β-hCG (WOCBP only)[10]		X						X										
Inpatient confinement		X	X	X	X	X		X	X	X	X	X						
APRIL analysis		X	X			X	X	X	X		X	X	X					X
BAFF analysis			X				X		X								X	

Table 4: Schedule of Activities for MAD Part of the Study CLYM116-NHV-101 (Continued)

Period	**Screening**	**Inpatient**						**Inpatient**					**Follow-up**					
Visit	**Screening**	**Admit-ting Visit**[1]	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**EOS /ET**	**Ig Follow-up**[2]
Day (Visit Window [days])	**-56 to -2**	**-1**	**1**	**2**	**3**	**4**	**8 (±1)**	**14 (±1)**	**15 (±1)**	**16 (±1)**	**17 (±1)**	**18 (±1)**	**22 (±1)**	**29 (±1)**	**36 (±1)**	**43 (±1)**	**71 (±3)**	
Immunophenotyping (T, B, and NK cells)			X[11]			X	X		X			X					X	X
Quantitative Ig (IgA, IgE, IgG, IgM, Gd-IgA1)	X		X[11]				X		X				X	X	X	X	X	X
Serum sample for ADA			X[11]						X					X		X	X	X
Serum sampling for PK[12]			X	X	X	X	X		X	X	X	X	X	X	X	X	X	X
Antibody titers to measles, mumps, rubella, tetanus			X[11]				X		X[11]								X	
12-lead ECG[13]		X						X									X	
Study drug administration			X						X									
Injection reaction assessment[14]			X	X	X	X			X	X	X	X						
AE assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior/concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: ADA = antidrug antibody; AE = adverse event; β-hCG = beta human chorionic gonadotropin; BAFF = B cell activating factor; BMI = body mass index; COVID-19 = Coronavirus Disease 2019; CRF = case report form; CRU = clinical research unit; ECG = electrocardiogram; EOS = End of Study; ET = early termination; FSH = follicle-stimulating hormone; Gd-IgA1 = galactose-deficient IgA1; HIV = human immunodeficiency virus; Ig = immunoglobulin; ISR

= injection site reaction; IV = intravenous; NK = natural killer; PK = pharmacokinetic(s); SC = subcutaneous; WOCBP = women of childbearing potential; WONCBP = women of non-childbearing potential

Footnotes:

[1] The qualifying visit will occur after a subject is admitted to the CRU on Day -1. Clinical and laboratory assessments will be conducted to confirm eligibility. Study drug administration occurs on Day 1, which is the day after Day -1 (there is no Day 0).

[2] Additional safety follow-up visits will be conducted approximately monthly for subjects whose IgA, IgM, and IgG levels have not recovered to above 50% baseline or not above the lower limit of normal at the Week 8/EOS visit.

[3] Infectious disease screening will include HIV serology, total hepatitis B core antibody (HBcAb), hepatitis B surface antibody (HBsAb), hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibody, tuberculosis (QuantiFERON-TB Gold), and syphilis serology. Prior hepatitis B vaccination will be documented in the CRF.

[4] Height is recorded at the screening visit only.

[5] Complete physical examinations will include the following body systems: general appearance, skin, head, ears, eyes, nose, throat, neck, lungs, heart, abdomen, musculoskeletal, extremities, and neurological systems

[6] Symptom-based physical examination will be conducted, if clinically indicated.

[7] Vital signs include diastolic and systolic blood pressure, pulse rate, respiratory rate, and body temperature. On Day 1, vital signs will be collected 1 hour (±5 minutes) before, 5 and 30 minutes after, and 1, 2, 4, 8 hours (±15 minutes) after the SC injection. Refer to Section 8.2.2.

[8] Refer to Section 8.2.4 for details of required laboratory tests.

[9] A test may be repeated once, at the investigator's discretion, within the screening window through Day -1 to confirm eligibility. For screening, clinical laboratory tests are to be done after fasting for 8 hours.

[10] If the urine pregnancy test is positive, a serum β-hCG test will be conducted for confirmation.

[11] The blood samples should be drawn prior to study drug administration.

[12] PK samples are to be drawn at the timepoints listed in Table 6

[13] ECG should be obtained in supine position after 5 minutes of rest

[14] Injection site reactions should be assessed according to guidance in Section 8.3.9. The severity of ISRs should be assessed according to Table 13 and recorded in the ISR form (not as AEs).

Table 5: Serum Pharmacokinetic Sampling Timepoints: SAD Part

Study Day	Sampling Time Point
Day 1 (Dosing Day)	Pre-dose 8 hours (±30 minutes) after end of SC injection
Day 2	24 (±1) hours after dose
Day 3	48 (±1) hours after dose
Day 4	72 (±1) hours after dose
Day 8	7 (±1) days after dose
Day 15	14 (±1) days after dose
Day 22	21 (±1) days after dose
Day 29	28 (±1) days after dose
Day 57/EOS	56 (±3) days after dose
Ig Recovery Follow-up	1 sample at each visit until below the limit of quantitation

Abbreviation: EOS = end of study

Table 6: Serum Pharmacokinetic Sampling Timepoints: MAD Part

Study Day	Sampling Time Point
Day 1 (Dosing Day)	Pre-dose 8 hours (±30 minutes) after end of SC injection
Day 2	24 (±1) hours after dose
Day 3	48 (±1) hours after dose
Day 4	72 (±1) hours after dose
Day 8	7 (±1) days after dose
Day 15 (Dosing Day)	Pre-dose 8 hours (±30 minutes) after end of SC injection
Day 16	24 (±1) hours after dose
Day 17	48 (±1) hours after dose
Day 18	72 (±1) hours after dose
Day 22	7 (±1) days after dose
Day 29	14 (±1) days after dose

Table 6: Serum Pharmacokinetic Sampling Timepoints: MAD Part (Continued)

Study Day	Sampling Time Point
Day 36	21 (±1) days after dose
Day 43	28 (±1) days after dose
Day 71/EOS	56 (±3) days after dose
Ig Recovery Follow-up	1 sample at each visit until below the limit of quantitation

Abbreviation: EOS = end of study

2. INTRODUCTION

2.1. Study Rationale

This is a first-in-human (FIH) study to evaluate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of subcutaneously (SC) administered CLYM116, a novel anti-APRIL (A PRoliferation-Inducing Ligand) monoclonal antibody (mAb) in normal healthy volunteers (NHVs). The study aims to inform the planned clinical development program in patients with IgA nephropathy (IgAN) and other B cell-mediated diseases.

The mechanism of action of CLYM116 is preventing APRIL signaling by promoting lysosomal degradation of APRIL via a pH-dependent bind-and-release process and potently blocking the binding of APRIL to its receptors. Through its unique binding profile, CLYM116 may enable rapid, deep, and durable inhibition of APRIL signaling. Clinical trials of other anti-APRIL therapeutic candidates have shown reductions in proteinuria, a key marker of disease activity, in patients with IgAN, which supports this mechanism of treatment.

In this study, a single- and multiple-ascending-dose (SAD/MAD) design will be used to establish foundational safety and pharmacology data to support the clinical development of CLYM116 in patients with IgAN and other B cell-mediated diseases.

2.2. Background on CLYM116

CLYM116 is a novel monoclonal antibody (mAb) targeting APRIL, a cytokine involved in B cell survival and IgA class switching. APRIL is implicated in the pathogenesis of IgAN, where elevated levels of galactose-deficient IgA1 (Gd-IgA1) and APRIL correlate with disease severity. CLYM116 is designed to inhibit APRIL signaling by promoting lysosomal degradation via a pH-dependent bind-and-release mechanism and blocking receptor interactions, potentially enabling rapid and sustained suppression of APRIL activity.

To date, CLYM116 has not been evaluated in human subjects. The current study will be a first-in-human (FIH) study of CLYM116 to provide safety, PK, PD, and immunogenicity data on this mAb.

The unique pH-dependent binding profile of CLYM116 may enable rapid, deep, and sustained suppression of APRIL activity. CLYM116 is engineered in its Fc region to increase the binding affinity to FcRn at acidic pH, (which improves the endosomal recycling efficiency of CLYM116 and thereby prolonging its half-life), as well as to reduce binding to Fc receptors (thereby decreasing antibody-dependent cell-mediated cytotoxicity (ADCC) activity, antibody-dependent cellular phagocytosis (ADCP) activity, and antibody-dependent complement-dependent cytotoxicity (CDC) activity).

In nonclinical pharmacology studies, CLYM116 binds to human APRIL with high affinity, enhances APRIL degradation, and inhibits its interaction with the receptors, B cell maturation antigen (BCMA) and transmembrane activator and calcium modulator and ligand interactor (TACI).

No single-dose toxicity studies were performed with CLYM116. However, in a single-dose PK/PD study in cynomolgus monkeys, no adverse findings were noted at doses of 0.5, 2, 6, or 30 mg/kg following SC administration or 6 mg/kg following intravenous (IV) administration.

In a 4-week, dose range-finding toxicity study in cynomolgus monkeys with a 4-week recovery period, 3 groups of monkeys received SC administration of CLYM116 once weekly at 10 mg/kg or 100 mg/kg per dose. Overall, SC administration of CLYM116 every week for 1 month to cynomolgus monkeys (5 doses total) was well tolerated at doses up to 100 mg/kg. There were no deaths and no CLYM116-related clinical signs or effects on body weight, food consumption, body temperature, hematology, coagulation, clinical chemistry, urinalysis, immunophenotyping, or serum cytokine concentrations at either 10 mg/kg/dose or 100 mg/kg/dose. There were no treatment-related macroscopic findings at necropsy. Pharmacologically mediated decreases in immunoglobulin levels were seen at both dose levels with the magnitude of the effect being similar between doses. During the recovery observation period, immunoglobulin levels returned to baseline levels in the 10 mg/kg treated recovery male and trended toward baseline in the 10 mg/kg treated recovery female. The 100 mg/kg dose resulted in mean maximum concentration (C_{max}) and area under the concentration-time curve from 2 to 168 hours post-dose ($AUC_{2\text{-}168h}$) values on Day 22 of 2320 µg/mL and 304,000 µg×h/mL, respectively.

In a GLP 4-week toxicity study in cynomolgus monkeys, 4 groups of monkeys received SC administration of either a negative control (sodium chloride injection) or CLYM116 at 1, 10, or 100 mg/kg per dose on Days 1, 15, and 29. Overall, SC administration of CLYM116 once every 2 weeks for 1 month in cynomolgus monkeys (3 doses total) was well tolerated at doses up to 100 mg/kg. Microscopic findings were limited to minimal hemorrhage and inflammation at the injection site that were similar between CLYM116 and negative control. These were related to the injection procedure and were not observed at the end of the 8-week recovery period, indicating complete reversibility of these findings. Pharmacologically mediated decreases in immunoglobulin levels were seen at all dose levels with animals dosed with 1 mg/kg showing full reversal of these findings during the 8-week recovery period and animals dosed with 10 mg/kg showing partial reversal. Based on these results, the no-observed-adverse-effect-level (NOAEL) was 100 mg/kg, which correlates to mean C_{max} and $AUC_{0\text{-}336h}$ values on Day 15 of 2440 µg/mL and 543000 µg×h/mL for males, and 2340 µg/mL and 552000 µg×h/mL for females, respectively.

Further details on CLYM116 nonclinical studies can be found in the Investigator's Brochure (IB).

2.3. Benefit/Risk Assessment

To date, CLYM116 has not been evaluated in human subjects. As the subjects in this study are NHV, no direct therapeutic benefit is expected. The primary objective is to assess the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of CLYM116.

The study has been designed to minimize risk to research subjects. Subjects will be closely monitored for adverse events (AEs) throughout the study and followed until resolution of any AEs. Sentinel dosing will be implemented in all cohorts in the SAD portion of the study, and blinded safety data will be reviewed after each dose level to determine whether it is safe to

escalate to the next planned dose. Safety Review Committee (SRC) meetings will be held following each cohort and as needed to support dose escalation decisions and provide ongoing oversight.

Although CLYM116 has not yet been studied clinically, its mechanism of action is supported by preclinical data and by clinical experience with other anti-APRIL monoclonal antibodies. These agents have demonstrated acceptable safety profiles and pharmacodynamic activity consistent with APRIL inhibition in early-phase clinical trials (Kooienga et al. 2025;Mathur et al. 2022;Mathur et al. 2024). Observed effects have included reductions in circulating immunoglobulins and immune complexes, as well as favorable safety outcomes across multiple studies. These findings support the relevance of APRIL as a therapeutic target and provide a rationale for the clinical development of CLYM116.

The protocol incorporates rigorous safety measures and aligns with ethical and regulatory expectations for FIH trials. By targeting a central immunological pathway, CLYM116 may offer a novel therapeutic approach in diseases characterized by dysregulated B cell activity. Overall, the benefit-risk assessment for CLYM116 supports the initiation of this Phase 1 study in NHVs.

3. OBJECTIVES AND ENDPOINTS

The study objectives and endpoints are outlined in Table 7.

Table 7: Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of single and multiple subcutaneous (SC) doses of CLYM116 in healthy volunteers	• Incidence and severity of treatment-emergent adverse events (TEAEs), including injection site reactions
Secondary	
• To characterize the pharmacokinetics (PK) of CLYM116 following single and multiple SC doses	• Serum concentrations of CLYM116 over time and PK parameters (e.g., maximum concetration [C_{max}], time to maximum concentration [T_{max}], area under the concentration-time curve [AUC], half-life [$t_{½}$])
• To assess the pharmacodynamic (PD) effects of CLYM116	• Levels of PD biomarkers (e.g., immunoglobulins, APRIL) and changes over time
• To evaluate the immunogenicity of CLYM116	• Incidence of antidrug antibodies (ADA)

4. STUDY DESIGN

4.1. Overall Design

4.1.1. Number of Study Sites

One Australian clinical research unit (CRU) experienced in pharmacokinetic (PK) and pharmacodynamic (PD) studies in normal healthy volunteers (NHVs).

4.1.2. Study Overview

This is a Phase 1, randomized, double-blind, placebo-controlled, single-center study designed to evaluate the safety, tolerability, PK, PD, and immunogenicity of CLYM116 in NHVs.

The study will be conducted at a single site. Healthy male and female adults with no chronic illnesses will be enrolled.

The study will enroll up to 64 subjects. The SAD portion will consist of up to 5 cohorts at dose levels of 25 mg, 80 mg, and 160 mg and 2 higher dose levels to be determined (TBD). The higher doses will not exceed 480 mg. The MAD portion will consist of up to 3 cohorts at the dose level of 160 mg (administered twice) and 2 higher dose levels TBD. The higher dose cohorts will not exceed 480 mg per dose (i.e., 960 mg in total exposure). The cohorts will be enrolled and treated sequentially. The TBD cohorts may be omitted according to decisions by the Safety Review Committee (SRC).

The dose cohorts of CLYM116 are shown in Table 8.

Table 8: CLYM116 Dose Cohorts

Cohort	N	CLYM116 Dose	Dosing Regimen
1	8	25 mg	1 dose
2	8	80 mg	1 dose
3	8	160 mg	1 dose
4	8	Higher dose 1 TBD	1 dose
5	8	Higher dose 2 TBD	1 dose
6	8	160 mg SC	once every 2 weeks for 2 doses
7	8	Higher dose 3 TBD	once every 2 weeks for 2 doses
8	8	Higher dose 4 TBD	once every 2 weeks for 2 doses

In each of the subsequent cohort, 8 eligible subjects will be randomized in a 3:1 ratio to receive either CLYM116 (n=6) or placebo (n=2) in a double-blinded manner.

All SAD cohorts will use a sentinel dosing scheme: 2 sentinel subjects (1 CLYM116 and 1 placebo) will be dosed first, and the remaining non-sentinel subjects will be dosed no sooner than 48 hours later, following the safety assessments of the sentinel subjects, along with written confirmation by the investigator.

Subjects will be admitted into the inpatient CRU on Day -1 (the day before the first dose) and undergo assessments to confirm their eligibility. On Day 1, the study drug (CLYM116 or placebo) will be administered as an SC injection at the assigned dose in a double-blind manner. The subjects and investigator/site personnel will be blinded to the treatment assignment (i.e., CLYM116 or placebo) within each cohort. The pharmacy personnel responsible for preparing the study drug for administration will be unblinded. The sponsor will not be blinded.

Each subject will remain in the inpatient unit for monitoring and assessments from Day -1 through Day 4. For the SAD cohorts, subjects will return to the study site weekly through Day 29. The end-of-study (EOS) visit will occur on Day 57. For the MAD cohorts, subjects will be admitted to the CRU on Day 14, receive the second dose of the study drug on Day 15, and remain confined through Day 18. Subjects will then return to the study site weekly through Day 43. The end-of-study (EOS) visit will occur on Day 71.

If a subject's IgA, IgM, or IgG levels do not recover to 50% of baseline or lower limit of normal, the subject will be required to return to the study site monthly to assess immunoglobulin levels until recovery.

Safety will be assessed through adverse event (AE) monitoring and clinical evaluations. PK/PD will be assessed through blood sampling and biomarker analysis, including immunoglobulin levels (including IgA, IgM, IgG) and APRIL levels. Antidrug antibodies (ADA) will be measured to assess immunogenicity.

Dose escalation to the subsequent cohort(s) will be determined by a Safety Review Committee (SRC) (Section 4.1.6). A new cohort will not initiate study drug administration without the SRC's formal authorization.

4.1.3. Number of Subjects

Up to 64 subjects will be enrolled and randomized, including up to 48 subjects who will receive CLYM116 and up to 16 subjects who will receive placebo.

Additional alternate subjects may be screened to replace subjects who drop out. Subjects who withdraw from the study after randomization but before receiving the study drug may be automatically replaced. Subjects who withdraw from the study after dosing may be replaced at the discretion of the Sponsor and Investigator. If more than 2 subjects in a cohort withdraw after dosing, replacement subjects may be enrolled. If more than 2 subjects in a cohort withdraw after dosing, replacement subjects may be enrolled.

4.1.4. Intervention Groups

The following cohorts will be enrolled:

- Up to 5 SAD cohorts: 25 mg, 80 mg, 160 mg CLYM116 or placebo administered on Day 1. Two additional cohorts of higher doses (not to exceed 480 mg CLYM116) may be enrolled.

- Up to 3 MAD cohorts: 160 mg CLYM116 or placebo administered for 2 doses on Day 1 and Day 15. Two additional cohorts of higher doses (not to exceed 480 mg CLYM116 per dose, i.e., 960 mg in total) may be enrolled.

4.1.5. Duration of Study Participation

The duration of study participation includes the following periods:

- Screening period: up to 8 weeks
- Treatment period: 1 day (single-dose cohorts) or 14 days (multiple-dose cohorts)
- Follow-up period: approximately 8 weeks

The maximum duration of study participation is 16 weeks for subjects in the SAD part and 18 weeks for those in the MAD part, assuming timely Ig recovery. However, if a subject's IgA, IgM, or IgG level is not above 50% of baseline or not above the lower limit of normal by the scheduled EOS/ET visit, additional follow-up visits at monthly intervals may occur until the IgA, IgM, and IgG levels recover to 50% of baseline level or the lower limit of normal, whichever occurs first.

4.1.6. Safety Review Committee (SRC)

The SRC will include, at a minimum, the investigator, medical monitor, and the sponsor's medical representative.

SRC meetings will be held after relevant safety and tolerability data for at least 8 days are available from at least 7 of 8 subjects in each cohort. The SRC will review all available safety laboratory and PK/PD data to determine whether to escalate to the next dose level, modify the next dose level, repeat a dose level, omit the next dose level, or stop dose escalation. While clinical stability through Day 8 is required to proceed, emerging data will continue to be monitored and considered in SRC decisions. A new dose cohort will not initiate study drug administration without the SRC's formal authorization.

Details will be provided in a separate SRC Charter.

4.2. Scientific Rationale for Study Design

The primary objective of this study is to evaluate the safety and tolerability of CLYM116 in humans.

To ensure subject safety, a sentinel dosing scheme will be applied. In the SAD cohorts, the first 2 subjects in a cohort will each receive CLYM116 or placebo and will be monitored for safety and tolerability for at least 48 hours. The rest of the subjects in the same cohort will not proceed to receive the study drug until the written confirmation of no safety concerns by the investigator.

Subjects in each cohort will be randomly assigned to receive either the placebo or CLYM116 in a double-blind manner. This design will minimize bias in the assessment of safety endpoints.

4.3. Justification for Dose

The starting dose and planned dose levels of CLYM116 to be evaluated in the current study are determined based on the preclinical pharmacology, PK, and toxicology data.

In a 1-month GLP toxicity study in cynomolgus monkeys, treatment with CLYM116 had no adverse effects on body weight, food consumption, body temperature, electrocardiography, blood pressure, respiratory parameters, hematology, coagulation, clinical chemistry, urinalysis, immunophenotyping, serum cytokine concentrations, serum complement levels, gross pathology, or organ weights. No CLYM116-related microscopic findings were observed. The no-observed-adverse-effect level (NOAEL) in the 1-month study in cynomolgus monkeys was 100 mg/kg following a total of 3 doses of bi-weekly administrations. The human equivalent dose (HED), calculated using a body surface area correction, is 2,260 mg. The proposed dosing cohorts in this study—including a maximum total dose of 960 mg in the MAD portion—are well below the HED of the NOAEL, providing a conservative safety factor for first-in-human evaluation.

CLYM116 binds to APRIL and inhibits its activity. No evidence of immunostimulation has been seen in in vitro studies using human peripheral blood mononuclear cells (PBMCs) or following repeated administrations of CLYM116 to non-human primates. The proposed SC starting dose in Study CLYM116-NHV-101 is 25 mg, which is approximately 90-fold lower than the HED of the NOAEL, based on a conservative body surface area correction approach (Table 9). The next planned dose cohort (80 mg) is an approximately 3-fold escalation from the initial dose (25 mg).

A 25 mg SC dose in humans is expected to result in C_{max} and $AUC_{0\text{-}336h}$ exposures that are 333-fold and 322-fold lower, respectively, than those observed at the NOAEL in cynomolgus monkeys (Table 10).

In a PK/PD study in cynomolgus monkeys, a 0.5 mg/kg SC dose produced similar C_{max} and $AUC_{0\text{-}336h}$ values to those projected for the 25 mg human dose. At this dose level, free APRIL concentrations in serum declined rapidly following the administration of CLYM116 but remained above the limit of quantitation and returned to baseline by Day 29, indicating transient target engagement without sustained suppression.

Table 9: Human Equivalent Doses for the NOAEL in Cynomolgus Monkeys

Species	Route of Administration	NOAEL Dose (mg/kg)	Human Equivalent Dose (mg)[1]	Proposed Clinical Dose	Safety Factor
Cynomolgus monkey	SC	100	2260	25	90
				8o[2]	28
				160[3]	14

Abbreviations: NOAEL = no-observed-adverse-effect level; SC = subcutaneous

[1] The doses in mg/kg are converted to human equivalent doses on a mg/m^2 basis using conversion factors specified in the Food and Drug Administration's Guidance for Industry: Estimating the Maximum Safety Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers (2005) and assume a 70 kg human.

[2] These dose levels will be evaluated only after demonstration of safety at the lower dose level(s).

Table 10: Projected Exposure Multiples for the NOAEL in Cynomolgus Monkeys

Species	Route of Administration	NOAEL (mg/kg)	C_{max} (µg/mL)	AUC_{0-336h} (µg*h/mL)	Proposed Clinical Dose (mg)	Safety Factor[1]	
						C_{max}	AUC_{0-336h}
Cynomolgus monkey	SC	100	2390	548,000	25	333	322
					80[2]	103	94
					160[2]	51	46

Abbreviations: AUC_{0-336h} = area under the concentration-time curve from time 0 to 336 hours; C_{max} = maximum concentration; NOAEL = no-observed-adverse-effect level; SC = subcutaneous

[1] In humans, the C_{max} and AUC_{0-336h} (14 days) are projected to be 7.18 µg/mL and 1700 µg×hr/mL, respectively, following a 25 mg SC dose; 23.1 µg/mL and 5820 µg×hr/mL, respectively, following an 80 mg SC dose; and 46.9 µg/mL and 12,000 µg*hr/mL, respectively, following a 160 mg SC dose. Mean C_{max} and AUC_{0-336h} values for cynomolgus monkeys represent the average of the values in males and females.

[2] These dose levels will be evaluated only after demonstration of safety at the lower dose level(s).

4.4. End of Study Definition

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

A subject is considered to have completed the study if he/she has completed all periods of the study including the EOS visit.

5. STUDY POPULATION

Prospective approval of protocol waivers or exemptions to recruitment and enrollment criteria is not permitted.

5.1. Inclusion Criteria

Subjects must meet all of the following Inclusion Criteria to be enrolled in the study:

1. Willing and able to sign the informed consent and comply with the study protocol and visits
2. Males or females aged 18 to 60 years (inclusive) at the time of informed consent
3. Body mass index (BMI) between 18 and 32 kg/m^2 and body weight between 45 and 110 kg.
4. Healthy medical history with no chronic or acute illnesses at the time of screening
5. Physical examination results are all within normal range, unless an abnormality is deemed not clinically significant by the investigator
6. Clinical laboratory evaluations (including chemistry panel [after fasting for at least 8 hours], complete blood count, coagulation, and urinalysis) within the reference range for the test laboratory, unless an abnormality is deemed not clinically significant by the investigator. If necessary, the laboratory evaluations may be repeated once during the screening window through Day -1 to confirm eligibility.
7. Normal findings on electrocardiogram (ECG), unless an abnormality is deemed not clinically significant by the investigator
8. Female subjects who are women with childbearing potential (WOCBP) must not be pregnant, lactating, or breastfeeding before study drug administration and not plan to become pregnant or donate eggs from Day -1 through 4 months after the study drug administration. WOCBP must agree to adhere to the specified highly effective contraceptive requirements.
9. Sexually active male subjects who have female partners of childbearing potential must agree to use a barrier contraceptive method combined with a highly effective contraceptive method used by the female partner from Day -1 and through 4 months following the study drug administration.
10. Male subjects must agree to abstain from sperm donation from Day -1 through 4 months after the study treatment.
11. Either is a nonsmoker or has a history of smoking no more than 2 cigarettes per day and is willing to abstain during the inpatient stay.
12. Have completed Coronavirus disease 2019 (COVID-19) vaccination according to local guidelines (any brand recognized by Therapeutic Goods Administration [TGA]) or willing to meet the requirement prior to study drug administration.

13. Have completed influenza vaccination within 12 months prior to study drug administration.
14. Subjects enrolled into the study after the completion of Cohort 3 (SAD 160 mg CLYM116) must have received a pneumococcal vaccine (any brand approved by the Therapeutic Goods Administration [TGA]) at least 14 days prior to their initial dose of study drug.

5.2. Exclusion Criteria

Subjects must not meet any of the following Exclusion Criteria:

1. Treatment with any investigational drug within 30 days or at least 5 times the elimination half-life of the drug (whichever is longer) prior to the study treatment, or current participation in another clinical study, or any plan of using an investigational device or drug during the study
2. Previous medical or surgical history that may compromise the safety of the subject in the study, as assessed by the investigator
3. Previous or current hypogammaglobulinemia (i.e., quantitative IgG, IgM, or IgA below the lower limit of normal).
4. History of an allergic reaction or significant sensitivity to constituents of the study drug (and its excipients) and/or other products in the same class
5. Current presence of allergic reactions, such as asthma, urticaria, angioedema, and eczematous dermatitis, that are considered clinically significant by the investigator
6. Have had any live vaccine within 21 days before study drug administration or any non-live vaccine within 14 days before study drug administration
7. Positive urine drug screen or breath alcohol test (a single repeat is permitted in the event of a suspected false positive)
8. History of clinically significant drug (including cannabis or cannabinoids) or alcohol abuse within 1 year prior to screening, as assessed by the investigator (occasional or social drinking is allowed)
9. History of clinically significant opportunistic infection (e.g., invasive candidiasis or pneumocystis pneumonia)
10. Serious local infection (e.g., cellulitis, abscess) or systemic infection (e.g., septicemia) within 3 months prior to screening
11. Past or current hepatitis B or C infection, syphilis, or positive QuantiFERON-TB Gold test or human immunodeficiency virus (HIV) serology
12. Any other clinically significant disease, condition, or medical or psychiatric history that, in the investigator's opinion, would compromise subject safety, interfere with study evaluations or procedures, or make the subject unsuitable for the study.

13. In the opinion of the investigator, the subject is unlikely to complete all protocol-required study visits or procedures, including follow-up visits, or comply with the study requirements for participation.

5.3. Lifestyle Considerations

Subjects in the SAD cohorts will be confined at the CRU for 5 days, from Day -1 through Day 4 (Table 3). Subjects in the MAD cohorts will have the initial confinement period and an additional confinement period from Day 15 to 18 for the second dose (Table 4). During an inpatient period, subjects will receive meals provided by the CRU. Subjects will have the following lifestyle restrictions:

- Activities: no rigorous physical exertion from 72 hours before through the end of the inpatient confinement period
- No smoking or alcohol during inpatient stay

5.4. Screen Failures

A screen failure occurs when a subject consents to participate in the clinical study but does not meet inclusion/exclusion criteria to enter the study. A minimal set of screen failure information (demographics and reason for screen failure) is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once at the discretion of the investigator.

6. STUDY INTERVENTIONS AND CONCOMITANT THERAPY

Study intervention is defined as any investigational drug or placebo intended to be administered to a study subject according to the protocol.

6.1. Study Interventions

The study interventions in this study are CLYM116 drug product and placebo.

Inactive ingredients in the CLYM116 drug product are listed in the IB. See Pharmacy Manual for details of study drug preparation and administration. An overview of the study interventions is provided in Table 11.

Table 11: Study Interventions Administered

Intervention Label	**CLYM116**	**Placebo**
Description	CLYM116 injection solution	0.9% sodium chloride injection solution
Type	Biologic drug	Inactive solution
Dose Formulation	Sterile liquid	Sterile liquid
Unit Dose Strength	160 mg/mL	Not applicable
Dosage Levels	25, 80, and 160 mg (higher doses TBD)	Not applicable
Route of Administration	SC injection	SC injection
Use	Experimental	Placebo

6.1.1. Premedication

Premedication is not required in this study. The Investigator may choose to administer an antipyretic (e.g., acetaminophen) and/or an antihistamine before the study drug injection based on clinical judgment or the subject's reaction after the first dose.

Any premedications are considered auxiliary medicinal products. Only authorized auxiliary medicinal products will be used for premedication, and their use must be in accordance with the terms of their marketing authorizations. If premedication equivalents need to be used based on local sourcing availability, they will be selected from medicinal products that have current marketing authorization.

6.2. Preparation, Handling, Storage, and Accountability

Study drug will be prepared and dispensed by an unblinded pharmacy personnel at the study site, according to the Pharmacy Manual provided by the sponsor. The prepared SC injection solutions will have the same appearance as the matching placebo and will be administered by qualified study staff.

Study drug preparation, including dilution instructions, will be detailed in the pharmacy manual.

Study drug vials should be stored upright and refrigerated (between 2 to 8 °C) at the study site. All study drug packages must be stored in a secure, temperature-controlled refrigerator, protected from direct light, with access limited to site staff involved in the study.

6.3. Measures to Minimize Bias: Randomization and Blinding

In each dose cohort, subjects will be randomized to either CLYM116 or placebo injection. The subjects and investigator/site personnel will be blinded to the treatment assignment, except the unblinded pharmacy personnel responsible for preparing the study drug for administration. The sponsor is not blinded. To maintain blinding, the investigator will not have access to a subject's TBNK (T, B, and natural killer cells) and APRIL results for at least 28 days post dose.

The investigator may request unblinding for any SAE or dose-limiting toxicity/emergency by contacting the pharmacy or the sponsor. Only in the event of a true emergency where treatment assignment is required should a subject be unblinded.

Refer to the Pharmacy Manual for randomization process.

6.4. Stopping Rules for Dose Escalation

Dose escalation to the next higher dose level may be modified or stopped by the SRC. Dose escalation will be stopped, pending SRC review, if the following events occur:

- Two or more subjects in a dose cohort report the same SAE or severe hypersensitivity reaction that is considered related to the study drug
- Two or more subjects with Grade 3 injection site reaction (ISR) or Common Terminology Criteria for Adverse Events (CTCAE) Grade ≥3 TEAEs in same body system considered to be related to the study drug

6.5. Concomitant Therapy

Live vaccines should not be administered within 21 days before the study drug administration through the EOS visit. Non-live vaccines should not be administered within 14 days before the study drug administration through the EOS visit.

Subjects must abstain from taking prescription or nonprescription drugs (including vitamins, recreational drugs, and dietary or herbal supplements) within 7 days before the start of study drug administration through the EOS visit, unless, in the opinion of the investigator and sponsor, the medication will not interfere with the study.

Paracetamol/acetaminophen, at doses of ≤2 grams/day, is permitted for use at any time during the study. Antihistamines and ondansetron may be administered during the study if clinically indicated. Antacids and ranitidine may also be used for indigestion or heartburn. Oral contraceptives are allowed. Other concomitant medications may be considered on a case-by-case basis by the investigator in consultation with the medical monitor if required.

Contraceptives, including depot injections, are permitted for WOCBP as outlined in Section 8.3.8.2.

7. DISCONTINUATION OF STUDY INTERVENTION AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a subject to temporarily interrupt or permanently discontinue the study drug administration. For example, allergic reaction may preclude the administration of the second dose, or an occurrence of any medical condition or circumstance may expose the subject to substantial risk and/or prevent the subject from adhering to the requirements of the protocol.

If study drug administration is permanently discontinued, the subject will remain in the study to be evaluated for safety. Study staff should make every effort to complete the assessments scheduled for all follow-up visits through the EOS visit (Table 3 and Table 4). The reason for subject withdrawal must be documented in the electronic case report form (eCRF).

7.2. Subject Withdrawal from the Study

A subject may withdraw consent from the study at any time at his/her own request.

At the time of withdrawal from the study, if possible, an early discontinuation visit should be conducted, and the assessments for the EOS visit, as outlined in Table 3 and Table 4, should be completed.

If the subject withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

7.3. Lost to Follow Up

A subject will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible, counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow up, the investigator or designee must make and document every effort to regain contact with the subject (where possible, 3 telephone calls, and if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the Schedule of Activities (SoA) (Table 3 and Table 4). Protocol waivers or exemptions will not be granted.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the subject should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA (Table 3 and Table 4), is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

8.1. Screening

Informed consent and screening assessment should be completed within the screening period. On Day -1, i.e., the day before the study of drug administration, the subject will be admitted to the CRU for the qualifying assessments to confirm eligibility (Table 3 and Table 4).

8.2. Safety Assessments

8.2.1. Physical Examinations

Complete physical examinations will include the following body systems: general appearance, skin, head, ears, eyes, nose, throat, neck, lungs, heart, abdomen, musculoskeletal, extremities, and neurological systems.

Symptom-based physical examinations will be conducted, if clinically indicated.

8.2.2. Vital Signs

Body temperature, pulse rate, respiratory rate, and blood pressure will be assessed in supine position. On Day 1, vital signs will be collected 1 hour (±5 minutes) before, 5 and 30 minutes (±15 minutes) after, and 1, 2, 4, 8 hours (±15 minutes) after the SC injection of the study drug.

Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the subject in a quiet setting without distractions (e.g., television, cell phones).

If blood pressure is elevated on the first measurement, it can be repeated after an additional 5 minutes of rest. Blood pressure is to be obtained from the same arm at each assessment when possible. When unable to use the same arm, revert to the original arm as soon as is practicable.

8.2.3. Electrocardiograms

Single 12-lead ECG(s) will be obtained in a supine position at time points outlined in the SoA (Table 3 and Table 4) using an ECG machine that automatically calculates the heart rate and measures PR, RR, QRS, QT, and QTc intervals. ECG should be conducted after 5 minutes of rest.

8.2.4. Clinical Safety Laboratory Tests

Clinical laboratory tests required in the study are listed in Table 12. See the SoA (Table 3 and Table 4) for the timing and frequency of the tests.

Urine drug screening test may be repeated once within the screening window to rule out false positive. Safety laboratory tests may be repeated at the investigator's discretion to confirm the initial result and assess trends.

The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents.

All laboratory tests with values considered abnormal and clinically significant during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator. To note, if a subject's IgA or IgG level is not above 50% of baseline or the lower limit of normal by the scheduled EOS/ET visit, additional follow-up visits may be conducted monthly to measure IgA or IgG levels and assess safety.

Table 12: Protocol-Required Safety Laboratory Tests

Clinical Test	**Parameter**	
Hematology	Hematocrit Hemoglobin Platelet count RBC count (including MCV, MCH, and MCHC) WBC count (with differential in percentages and absolute counts)	
Serum Chemistry	*Complete chemistry panel*	*Abbreviated chemistry panel*
	Alanine aminotransferase (ALT) Aspartate aminotransferase (AST) Albumin Alkaline phosphatase Calcium Chloride Total bilirubin Direct bilirubin Glucose Inorganic phosphorus Potassium Sodium Bicarbonate Chloride Total protein Urea (blood urea nitrogen [BUN]) Creatinine Uric acid	ALT AST Total bilirubin Direct bilirubin Sodium Potassium Bicarbonate Chloride Urea (BUN) Creatinine

Table 12: Protocol-Required Safety Laboratory Tests (Continued)

Clinical Test	Parameter
Coagulation	PT/INR aPTT
Pregnancy-related	FSH (for WONCBP, screening; not required for women with a history of hysterectomy) Serum β-hCG (for WOCBP, screening and EOS) Urine β-hCG (for WOCBP, confirm with serum test if positive)
Urine Analyses	Bilirubin Blood Glucose Ketones Leukocytes Nitrite pH Protein Specific gravity Urobilinogen (If any clinically significant abnormalities were found, the urine sample will undergo microscopic examination.) Urine drug screen[1]
Pharmacodynamic Markers	APRIL BAFF TBNK Immunoglobulins (IgA, IgE, IgG, IgM, Gd-IgA1)
Infectious Disease Screening/ Antibody Titers	Hepatitis B surface antigen (HBsAg) and antibody (HBsAb) Total hepatitis B core antibody (HBcAb) Hepatitis C antibody HIV: anti-HIV-1 and HIV-2 antibodies QuantiFERON-TB Gold Syphilis serology[2] Measles, Mumps and Rubella antibodies Tetanus antibodies

Abbreviations: aPTT = activated partial thromboplastin time; β-hCG = beta human chorionic gonadotropin; BAFF = B cell activating factor; EOS = end of study; FSH = follicle-stimulating hormone; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; INR = international normalized ratio; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; PCR = polymerase chain reaction; PT = prothrombin time; TBNK = T, B, and natural killer cells

[1] Urine drug screen includes amphetamines, methamphetamines, methadone, barbiturates, benzodiazepines, cocaine, opiates, methylenedioxymethamphetamine, phencyclidine (PCP), tetrahydrocannabinol (THC), tricyclic antidepressants.

[2] If the initial syphilis test is positive, a confirmatory test should be performed

If laboratory values from non-protocol specified laboratory tests performed at the institution's local laboratory require a change in subject management or are considered clinically significant by the investigator (e.g., serious adverse event [SAE] or AE or dose modification), then the results must be recorded.

8.3. Adverse Events (AEs), Serious Adverse Events (SAEs) and Other Safety Reporting

8.3.1. Overview of Safety Reporting

It is the responsibility of the Principal Investigator to oversee the safety of all subjects at his/her study site and to report all AEs, including SAEs, that are observed or reported during the study, regardless of the relationship to study drug (as assessed by the investigator) or clinical significance of these events.

The Medical Monitor has medical authority to evaluate the safety aspects of this clinical study. AEs will be characterized by expectedness, intensity (severity), causality, and seriousness, based on the regulatory definitions.

Regardless of severity and causality, the Investigator will consult with the Medical Monitor regarding any AE that, in their opinion, may represent a clinically significant safety risk to the subject, to assess the safety of continued dosing in that subject.

8.3.2. Adverse Event Definitions

An AE is any untoward medical occurrence in any person partaking in a clinical investigation, regardless of the suspected cause. An AE can therefore be any unfavorable and unintended sign, symptom, disease, concurrent illness, or clinically significant abnormal laboratory finding that emerges or worsens (i.e., aggravated in severity or frequency from the Baseline condition) during the study.

An AE also includes abnormal results of diagnostic procedures if they lead to:

- Discontinuation of the study drug or from the study,
- Treatment or any other therapeutic intervention, or
- Clinical signs or symptoms judged by the Investigator to have a clinically significant impact.

8.3.2.1. Treatment-Emergent Adverse Events

All noxious and unintended responses to a medicinal product related to any dose should be considered an adverse drug reaction. "Responses" to a medicinal product means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

8.3.3. Serious Adverse Events

An SAE is any untoward medical occurrence that meets any of the following criteria:

- Results in death.
- Is immediately life-threatening (refers to an event in which the subject is at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe).
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Is a congenital anomaly/birth defect.
- Based on appropriate medical judgment, represents an important medical event that may jeopardize the subject or may require intervention to prevent 1 of the other outcomes described above.

8.3.3.1. Clarification of Serious Adverse Event Definition

- Death is an outcome of an SAE and not an SAE in itself. When death is an outcome, the event(s) resulting in death should be reported (e.g., "pulmonary embolism" with a fatal outcome). The appropriate diagnosis or term should be recorded and assigned severity Grade 5.
- In instances of death due ultimately to the underlying disease, the cause of death should be indicated as the specific event or condition resulting in death to the extent possible. If no appropriate term with a Grade 5 severity in the CTCAE can be identified, then a term should be selected from the CTCAE category "death."
- "Life-threatening" means that the subject was at immediate risk of death from the event as it occurred. This does not include an event that might have led to death if it had occurred with greater severity. Grade 4 events (e.g., thrombocytopenia) are not always serious unless they have life-threatening consequences or result in hospitalization.
- Preplanned or elective hospitalizations, including social and/or convenience situations (e.g., respite care), are excluded from SAE reporting. In addition, "admissions" under 23-hour Observation or Emergency Room visits are excluded from SAE reporting; however, such events should still be reported on the appropriate eCRF page.
- Overdose of either CLYM116 or concomitant medication without any overdose signs or symptoms unless the event meets SAE criteria (e.g., hospitalization) are excluded from SAE reporting; however, such events should still be reported on the appropriate eCRF page.

8.3.4. Adverse Event Evaluation and Classification

8.3.4.1. Assessment of Severity

The severity rating of an AE refers to its intensity. The severity of all TEAEs will be categorized using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0. For any term that is not specifically listed in the CTCAE scale, intensity should be assigned a grade of 1 through 5 using the following CTCAE guidelines:

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated

Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living

Grade 4: Life-threatening consequences; urgent intervention indicated

Grade 5: Death related to AE

8.3.4.2. Assessment of Causality

Medical judgment should be used to determine the cause of the AE, considering all relevant factors such as (but not limited to) the underlying study indication, coexisting disease, concomitant medication, relevant history, pattern of the AE, temporal relationship to the study drug, and de-challenge or rechallenge.

Related: there is a reasonable possibility that the study drug caused the event; 1 or more of the following criteria apply:

- The event follows a reasonable temporal sequence from administration of the study drug.
- The event could not be reasonably attributed to the known characteristics of the subject's clinical state, environmental or toxic factors or other modes of therapy administered to the subject.
- The event follows a known pattern of response to the study drug.
- The event disappears or decreases on cessation or reduction in dose. (It should be noted that in some situations an AE will not disappear or decrease in intensity upon discontinuation of study dosing despite other clear indications of relatedness.)

Unrelated: there is no reasonable possibility that the study drug caused the event; 1 or more of the following criteria apply:

- The event does not follow a reasonable temporal sequence from administration of the study drug.

- The event could be reasonably attributed to the known characteristics of the subject's clinical state, concurrent illness, environmental or toxic factors, or other modes of therapy administered to the subject.
- The event does not follow a known pattern of response to the study drug.
- The event does not disappear or decrease on cessation or reduction in dose, and it does not reappear or worsen when dosing is resumed.

8.3.4.3. Expectedness

An AE is judged to be "expected" if its description agrees in nature, severity, or frequency with the description of AEs previously noted with the study drug, as detailed in the Reference Safety Information within the current CLYM116 IB. An "unexpected" AE is one whose specificity, severity, or frequency is not consistent with the description in the Reference Safety Information within the current IB. The sponsor is responsible for assessing the expectedness of all AEs.

8.3.5. Documenting and Reporting Adverse Events

Reporting of AEs will begin upon the study drug administration and continue up to the last follow-up visit. Any untoward medical occurrence reported after subjects sign the Participant Informed Consent Form and prior to dosing will be recorded as medical history.

The occurrence of AEs may be volunteered spontaneously by the subject; discovered as a result of general, nonleading verbal questioning by the study staff; or determined by physical examination or other safety assessments. All AEs will be monitored and recorded in the eCRF throughout the entire study.

For all AEs, the Investigator must pursue and obtain adequate information (a description of the event, severity, time of occurrence [including whether the AE onset was before, during, or after the study medication administration if the AE started on a dosing day], duration, and any action, e.g., treatment/follow-up tests). The outcome of the event should be provided along with the Investigator's assessment of the relationship to the study medication. The Investigator must also assess whether the event meets the criteria for classification as an SAE.

It is the Investigator's responsibility to review all documentation (e.g., hospital notes, laboratory reports, and diagnostic reports) related to an AE. Wherever possible, the Investigator's diagnosis, not the individual signs and symptoms, will be documented as the AE.

Investigators are not obligated to actively seek AEs or SAEs after the subject's conclusion of study participation. However, if the Investigator learns of any SAE, including death, at any time after a subject has been discharged from the study, and he/she considers the event to be reasonably related to the study medication or study participation, the Investigator must promptly notify the sponsor.

The investigator shall report SAE to the sponsor/designee without undue delay but not later than within 24 hours of obtaining knowledge of the events. The SAE must be reported on the applicable form. All SAEs or adverse events of special interest (AESIs), regardless of

relationship to the study drug, will be followed by the Investigator until satisfactory resolution or the Investigator deems the SAE/AESI to be chronic or stable.

The sponsor shall keep detailed records of all AEs reported by the Investigator.

8.3.5.1. Special Situations Reporting

Special situation reports include reports of overdose, misuse, abuse, or medication error.

All special situation reports must be reported on the Special Situations Report Form and forwarded to the sponsor or designee within 24 hours.

All AEs associated with these special situation reports should be reported as AEs or SAEs at the same time using the AE eCRF and/or the SAE/AESI report form. Details of the symptoms and signs, clinical management and outcome will be reported when available.

8.3.6. Serious, Unexpected, Suspected Adverse Reactions

In accordance with Article 41 and 42 of Regulation (EU) No. 536/2014 and other regulatory requirements, the sponsor or designee will immediately notify regulatory authorities and the investigators, who will in turn notify their Institutional Review Board (IRB)/Independent Ethics Committee (IEC) as necessary, of any AE associated with the study drug administration or study procedures that is a serious, unexpected, suspected adverse reaction or any finding from tests in laboratory animals that suggests a significant risk for human subjects, including reports of mutagenicity, teratogenicity, or carcinogenicity. An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the IB or is not listed at the specificity or severity that has been previously observed.

8.3.7. Adverse Events of Special Interest

AESI are events of scientific or medical concern specific to a study drug that warrant ongoing monitoring and timely communication by the Investigator to the sponsor. The AESI for CLYM116 includes the following:

- Injection site reactions
- Severe infections (i.e., NCI CTCAE ≥ Grade 3)

8.3.8. Pregnancy

8.3.8.1. Definitions

Women of non-childbearing potential (WONCBP) are defined as:

- Surgically sterile: hysterectomy, bilateral salpingectomy, and/or bilateral oophorectomy at least 26 weeks before the screening visit; or
- Postmenopausal: spontaneous amenorrhea for at least 12 months, with follicle-stimulating hormone (FSH) level >40 mIU/mL

Women of childbearing potential (WOCBP) are defined as any female who:

- has experienced menarche, and
- has not undergone surgical sterilization, and
- is not postmenopausal

8.3.8.2. Contraceptive Guidelines

WOCBP may be enrolled in this study if they have a negative pregnancy test at screening and on Day -1. In addition, they must agree to use a highly effective contraceptive and refrain from egg donation throughout the study and for a minimum of 4 months after the study drug administration. Hormonal contraceptives should begin at least 1 month before screening to ensure that it is in full effect.

Male subjects who are sexually active with female partners who may become pregnant must use a condom for a minimum of 4 months after the study drug administration. Their female partners must use a highly effective contraceptive. Male subjects must also agree to abstain from sperm donation through 6 months after the study drug administration.

Subjects who are WONCBP or continuously not heterosexually active are exempted from the contraceptive requirements. (Note: Women who have undergone bilateral tubal ligation are required to use condoms when they are sexually active with a partner of the opposite sex.)

Highly effective methods of contraception, defined as methods with a failure rate of <1% when used consistently and correctly, for WOCBP include:

- Hormonal contraceptives, including oral contraceptives containing combined estrogen and progesterone, a vaginal ring, injectable and implantable hormonal contraceptives, intrauterine hormone-releasing system, and progestogen-only hormonal contraception associated with inhibition of ovulation
- Nonhormonal intrauterine device (IUD)
- Bilateral tubal occlusion
- Vasectomized subject/partner with documented azoospermia, 90 days after procedure (if the partner is the sole sexual partner)

The investigator will counsel WOCBP and male subjects who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy. The investigator will advise on the use of adequate methods of contraception, defined as the use of condom by the male partner combined with the use of a highly effective method of contraception by the female partner. Male subjects must inform their female partners who are WOCBP of the contraceptive requirements of the protocol and are expected to adhere to these requirements.

8.3.8.3. Reporting of Pregnancy

Any pregnancy in a study subject or female partner of a male subject must be reported to the sponsor/designee and the IRB/EC. The applicable eCRF should be completed within 24 hours of awareness by clinical site staff and sent to the sponsor. Close follow-up monitoring of the

pregnancy, fetus, and child should be performed. If the subject chooses to continue the pregnancy, then she should be followed for the duration of her pregnancy to determine the outcome (including spontaneous miscarriage, elective termination, normal birth, or congenital abnormality), so that any important safety information can be obtained. The investigator will ask the subject to provide informed consent to record information on the health of the baby. Generally, follow-up will be required for no longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Male subjects should inform the Investigator if their partner becomes pregnant during the study. The investigator should record and report the pregnancy as described above.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE. Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital abnormalities, ectopic pregnancy) will be considered SAEs.

8.3.9. Assessment of Injection-site Reactions (ISRs)

The severity of ISRs will be evaluated on the day(s) of study drug injection and for 3 additional days through their resolution, according to Table 13, and recorded in the ISR form (not on the AE form). ISRs can be managed by the Investigator based on clinical judgment.

Table 13: Grading Scale for Injection Site Reactions

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

Table 13: Grading Scale for Injection Site Reactions (Continued)

Local Reaction to Injectable Product	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Pruritus/ Itching	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Minimal, local, or noninvasive intervention indicated, limiting age-appropriate instrumental activities of daily living	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living	Life-threatening consequences: urgent intervention indicated
Bruising/ Ecchymosis	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Minimal, local or noninvasive intervention indicated, limiting age-appropriate instrumental activities of daily living	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living	Life-threatening consequences: urgent intervention indicated
Burning/ Warmth	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Minimal, local or noninvasive intervention indicated, limiting age-appropriate instrumental activities of daily living	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living	Life-threatening consequences: urgent intervention indicated

[1] In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.
[2] Induration/swelling should be evaluated and graded using the functional scale as well as the actual measurement
Note: Adapted from FDA guidance "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" (https://www.fda.gov/media/73679/download).

8.4. Pharmacokinetics

Serum samples will be collected at the time points listed in Table 5 (SAD) and Table 6 (MAD) for PK analyses. To maintain blinding, the serum concentration results will not be disclosed to the blinded study personnel.

Samples for PK, PD, and ADA analysis will be collected, processed, and shipped to the central laboratory in accordance with the Laboratory Manual.

8.5. Pharmacodynamics

Blood samples will be obtained for analyses of APRIL, B cell activating factor (BAFF) levels, TBNK, and quantitative Ig (IgA, IgE, IgG, IgM, and Gd-IgA1) at the timepoints specified in Table 3 and Table 4.

8.6. Immunogenicity Assessments

The presence of ADAs will be evaluated in serum samples collected from all subjects according to the SoA (Table 3 and Table 4). If ADA is present in a sample, the antibody titer will be determined, and neutralizing antibodies will be analyzed. All ADA serum samples will be analyzed by the central laboratory.

9. STATISTICAL CONSIDERATIONS

The statistical analysis plan (SAP) will be finalized prior to database lock; it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the major endpoints. The SAP will be the final plan for all statistical considerations.

9.1. Statistical Hypotheses

No statistical hypotheses will be tested in this study.

9.2. Analysis Sets

For the purposes of analysis, the following analysis sets are defined in Table 14.

Table 14: Analysis Sets Definition

Data Analysis Set	Description
Full analysis set	All randomized subjects
Safety analysis set	All randomized subjects who are exposed to any dose of study drug
PK analysis set	All randomized subjects who provide at least 1 PK sample of measurable CLYM116 concentration
PD analysis set	All randomized subjects who provide at least 1 blood sample of valid APRIL level
Immunogenicity set	All randomized subjects who provide at least 1 blood sample of ADA analysis

9.3. Statistical Analyses

9.3.1. General Considerations

All statistical summaries will be descriptive in nature (e.g., mean, standard deviation, median, minimum, and maximum for continuous variables; count and percentage for categorical variables). In addition, log-normally distributed data (e.g., PK concentrations and parameters) will be presented using the geometric mean, the geometric SD, and the geometric coefficient of variation expressed as a percentage.

Summary tables will present results by cohort for each dose cohort and placebo, with data from all subjects who receive placebo combined across dose cohorts.

Demographic and baseline characteristic data will be summarized with descriptive statistics by dose cohort and placebo, based on the full analysis set.

9.3.2. Safety (Primary) Analysis

For safety analysis, the incidence and severity of TEAEs, TEAEs leading to drug discontinuation, SAEs, and AESIs will be summarized descriptively in tables by dose cohort and detailed in subject listings. The incidences of ISRs will also be summarized by cohort.

All safety laboratory tests will be reported by visit with mean, median, and minimum and maximum. Laboratory tests meeting Potentially Clinically Important (PCI) criteria will be summarized by visit. Listings summarized by laboratory test and then by visit will be provided. Only laboratory tests of interest, such as TBNK, will be summarized by changes of baseline over time. Vital signs will be reported by visit using descriptive statistics, including mean, median and minimum and maximum. Abnormal and clinically significant findings will be flagged.

9.3.3. Pharmacokinetic (Secondary) Analysis

The serum concentrations of CLYM116 will be analyzed to determine the PK parameters, including maximum observed concentration (C_{max}), area under the concentration-time curve (AUC), time to maximum observed concentration (T_{max}), terminal half-life ($t_{½}$), apparent clearance (CL), and volume of distribution (V_d).

Details of the PK analysis will be described in a separate PK Analysis Plan.

9.3.4. Exploratory Analysis

9.3.4.1. Immunogenicity

The incidence and titer of ADA and neutralizing antibodies will be summarized. The effect of ADA on PK and selected safety parameters will be explored.

The ADAs of subjects with ISR or other hypersensitivity reactions will be compared to those without these reactions.

9.3.4.2. Pharmacodynamics

The following PD endpoints will be summarized descriptively by cohort and by visit:

- Change from baseline in APRIL levels
- Change from baseline in BAFF levels
- Changes from baseline in serum IgA, IgE, IgG, IgM, and Gd-IgA levels
- Changes from baseline in TBNK

9.4. Interim Analysis

There is no planned interim analysis in this study.

9.5. Sample Size Determination

There is no hypothesis testing in this study. The sample size of 8 subjects per dose cohort, including 6 who will receive the active drug and 2 who will receive placebo, is widely used for

first-in-human dose-escalation studies to identify the appropriate dose(s) for further clinical development.

10. REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1. Good Clinical Practice

The study will be performed in accordance with the protocol, guidelines for Good Clinical Practice (GCP) established by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), Regulation (EU) No. 536/2014 and applicable local regulatory requirements and laws with all clinical study files maintained in accordance with ICH/GCP guidelines.

10.2. Institutional Review Board/Ethics Committee Approval

The investigator must inform and obtain approval from the IRB/EC for the conduct of the study at named sites, for the protocol, informed consent form (ICF), IB, and any other written information that will be provided to the subjects and for any advertisements that will be used. Written approval must be obtained prior to recruitment of subjects into the study.

Proposed amendments to the protocol and aforementioned documents must be submitted to the sponsor for review and approval, then to the IRB/EC. Amendments may be implemented only after a copy of the approval letter from the IRB/EC has been transmitted to the sponsor.

In accordance with GCP guidelines, the investigator will be responsible for ensuring that annual updates are provided to the IRB/EC (or more frequently in accordance with the requirements, policies, and procedures as established by the IRB/EC) until the study is completed (i.e., finalization of the clinical study report) to facilitate continuing review of the study and that the IRB/EC is informed about the end of the study. Copies of the update, subsequent approvals, and final letter must be sent to the sponsor.

10.3. Regulatory Authority Approval

The study will be performed in accordance with the requirements of the local health authority (e.g., Australian TGA, US FDA) and will also meet all requirements of ICH GCP guidance. Amendments to the protocol will be submitted to health authorities prior to implementation, in accordance with applicable regulations.

10.4. Other Required Approvals

In addition to IRB/EC and regulatory authority approval, the investigator is responsible for ensuring that all other required approvals (e.g., approval from the local research and development board or scientific committee) are obtained prior to recruitment of subjects into the study.

10.5. Informed Consent

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s) and should adhere to GCP and to the ethical principles that

have their origin in the Declaration of Helsinki. Prior to the beginning of the study, the investigator should have the IRB/ EC's written approval/favorable opinion of the written ICF and any other written information to be provided to subjects.

Informed consent is a process that is initiated prior to the subjects agreeing to participate in the study and continues throughout the subjects' study participation. It is the investigator's responsibility (or designee) to obtain written informed consent from each subject after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any study procedures are initiated.

The investigator or his/her designee will explain the nature of the study to the subject or his/her legally acceptable representative and answer all questions regarding the study. The investigator is responsible for ensuring that the subject fully understands the nature and purpose of the study. Information should be given in both oral and written form whenever possible. No subject should be obliged to participate in the study. The subject must be informed that participation is voluntary, that they may withdraw at any time, and that choosing not to participate will not affect the care the subject will receive.

Each subject should be given a copy of the ICF and associated materials. The original copy of the signed and dated ICF must be retained at the site and is subject to inspection by representatives of the sponsor, regulatory authorities, or IRB/EC.

If the ICF is revised, the revised ICF must have received the IRB/IEC's approval/favorable opinion in advance of its use. Subjects must be informed of the changes to the ICF and must re-consent to the most current version during their participation in the study. The subject or the subject's legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the study. The communication of this information should be documented.

The subject will be informed that the summary of the results of the clinical study and a summary presented in terms understandable to a layperson may be made available to the public on websites such as ClinicalTrials.gov and EU Clinical Trials Registry (CTR), irrespective of the outcome of the clinical study, and, to the extent possible, when the summaries become available.

10.6. Subject Confidentiality

The investigator must ensure that the subject's privacy is maintained and that all necessary and appropriate measures consistent with applicable law will be employed to safeguard their personal, health, and medical information. On eCRFs and other documents submitted to the sponsor, subjects will be identified by their assigned subject number. Documents that are not submitted to the sponsor (e.g., signed ICFs) should be kept in a confidential file by the investigator.

All personal data gathered in this study will be treated in the strictest confidence by investigators, monitors, and all associated personnel. No data will be disclosed to any third party without the express permission of the subject concerned, except that the investigator shall permit authorized representatives of the sponsor, regulatory authorities, and the IRB/EC to review the portion of

the subject's medical record that is directly related to the study. As part of the required content of the ICF, the subject must be informed that his/her records will be reviewed in this manner.

For studies being conducted under Regulation EU No. 536/2014, as per Annex I, D (17am), the contract between the sponsor and vendors or study sites will specify the responsibilities of the parties related to data protection, including the handling of data security breaches and respective communication and cooperation of the parties.

10.7. Study Confidentiality and Disclosure of Information

Information concerning the study, the progress of the study, protocol, processes, assessments, budoprutug, scientific data, or other non-public information related to the study, or the sponsor and its representatives is confidential and remains the property of the sponsor. The lead investigator and his or her designees may use this information for the purposes of the study only.

It is understood by the lead investigator that the sponsor will use information obtained in this clinical study in connection with the clinical development program, and therefore may disclose it as it sees fit, including to other clinical investigators and to regulatory authorities. In order to allow the use of the information derived from this clinical study, the lead investigator understands that he/she has an obligation to provide complete test results, and all data obtained during this study to the sponsor.

Verbal or written discussion of the progress of the study, or the study results, prior to study completion and full reporting, should only be undertaken with written consent from the sponsor.

10.8. Publication of Study Data

The sponsor encourages the scientific publication of data from clinical research studies in a relevant peer-reviewed journal. However, investigators may not present or publish partial or complete study results individually without participation of the sponsor. The lead investigator and sponsor may propose appropriate scientific manuscripts or abstracts from the study data. All proposed publications must be reviewed and commented on by the sponsor before submission for publication. The detailed procedures for the review of publications are set out in the clinical trial agreement entered into with the sponsor in connection with this study. These procedures are in place to ensure (a) coordination of study data publication, (b) adequate review of data for publication against the validated study database for accuracy, and (c) that confidentiality of sponsor business information or subject personal information is maintained.

Qualification of authorship will follow the requirements of the International Committee of Medical Editors (www.icmje.org). The names of investigators and sponsor representatives responsible for designing the study and analyzing the results will be included in the publication(s). This custom can be adjusted upon mutual agreement of the authors and Climb Bio, Inc.

In addition, this clinical study will be registered with ClinicalTrials.gov by the sponsor or its representative and will be registered in any applicable international database or website as required by law or regulation. All data and results generated from this study belong to Climb Bio, Inc.

10.9. Ethical Standards

Climb Bio, Inc. is committed to designing, implementing, conducting, analyzing, and reporting clinical studies in compliance with the highest ethical and scientific standards. Protection of the safety subject is the overriding concern in the design of clinical studies. In all cases, Climb Bio, Inc. Clinical studies will be conducted in compliance with local and/or national regulations and in accordance with the consensus ethical principles that have their origin in the Declaration of Helsinki.

11. REFERENCES

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