THE UNIVERSITY OF QUEENSLAND
AUSTRALIA

SYNEOS HEALTH PROTOCOL# 7013800

Protocol number: UQ-1-SARS-CoV-2-Sclamp

A PHASE 1 RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED, DOSAGE -ESCALATION, SINGLE CENTRE STUDY TO EVALUATE THE SAFETY AND IMMUNOGENICITY OF AN ADJUVANTED SARS-CoV-2 SCLAMP PROTEIN SUBUNIT VACCINE IN HEALTHY ADULTS, AGED 18 TO 55 YEARS AND HEALTHY OLDER ADULTS, AGED 56 YEARS AND OVER

Short Title:

A SAFETY, TOLERABILITY, AND IMMUNOGENICITY STUDY OF ADJUVANTED SARS-CoV-2 SCLAMP PROTEIN SUBUNIT VACCINE IN HEALTHY ADULTS AND HEALTHY OLDER ADULTS

Sponsor: University of Queensland
School of Chemistry & Molecular Biosciences
Building 68, St Lucia QLD 4072
Australia
Tel.: +61 7 3365 4622

Contract Research Organization:

Protocol Version: v2.2

Date of Protocol: 02-Nov-2020

CONFIDENTIAL

Protocol Historical File

Version number	Brief description/summary of changes	Date
Final	Version submitted to the HREC.	22-MAY-2020
Amendment 1	Updated version submitted to the HREC	03-JUL-2020
Amendment 2	Section 1.3 Australian Redcross Lifeblood laboratory details added. Section 5.2.1 and Section 11.2 Additional clarification around immunological assays. Section 4 Clarification to Schedule of Events, footnote 13 use of subject diary, and Footnote 17 Blood sample collection. Section 9.9.1 Inclusion of samples storage and retention period. Section 9.9 Inclusion of an additional blood sample collected at Day 57 to allow adequate serum collection for IgG and virus neutralisation. Section 9.10.6.6. Revised macroscopic examination to microscopic which was previously written in error. Section 9.10.7 Added clarifying text around the use of the subject eDiary and review of the ediary at site. Revisions to minor inconsistencies in document related to the hyperlinks within the protocol, along with the Table of Contents. Section 9.15.1 Additional information included to clarify the definition of a solicited event and an unsolicited adverse event Section 9.15.2 Additional information included to clarify the definition of solicited events as Adverse Events Section 9.15.2.2 Deletion of Table 6 COVID Symptoms Prompt.	28-JUL-2020
Version 2.0	**Major Protocol amendment to include healthy older adults aged 56 years and over** Section 2 Synopsis of Protocol Study Title amended to reflect inclusion of healthy older adult population Study Design amended to reflect study to be conducted in 2 parts where Part 1 will include a young healthy adult population aged ≥ 18 - ≤ 55 years and Part 2 will include an older healthy adult population aged 56 years and over. Part 1 will be a single and multiple ascending dose, 4-arm, parallel study initiated before commencement of Part 2 so that safety can be assessed in the young adult population prior to exposure of the older adult population. Part 2 will be a	19-AUG- 2020

	multiple ascending dose, 3-arm, parallel study, with 3 new Cohorts 4, 5 & 6. A total of 216 subjects now planned to be recruited. A paper diary will be available for those subject who do not have a device to support an eDiary application. Study Vaccine and Placebo Dosage Form amended to reflect actions taken to maintain blind. Inclusion Criteria: amended to reflect criteria applicable to healthy adult and older healthy adult population so Part 1 Inclusion criteria and Part 2 Inclusion criteria. Exclusion Criteria: amended to reflect criteria applicable to healthy adult and older healthy adult population so Part 1 Exclusion criteria and Part 2 Exclusion criteria. Statistical Analysis: included an interim analysis for safety and immunogenicity up to day 57 for older healthy adult cohort to be an addendum to the CSR. Safety Review Committee: clarified that vaccination of older healthy adults (Part 2) will commence only when the safety evaluation for Part 1 Vaccination Dose 1 is completed. Section 5 Section 5.2 amended to reflect study to be conducted in 2 parts where Part 1 will include a young healthy adult population aged ≥ 18 - ≤ 55 years and Part 2 will include an older healthy adult population aged 56 years and over. Part 1 will be initiated before commencement of Part 2 so that safety can be assessed in the young adult population prior to exposure of the older adult population. Section 6 Study design amended to reflect study to be conducted in 2 parts where Part 1 will include a young healthy adult population aged ≥ 18 - ≤ 55 years and Part 2 will include an older healthy adult population aged 56 years and over. Part 1 will be a single and multiple ascending dose, 4-arm, parallel study initiated before commencement of Part 2 so that safety can be assessed in the young adult population prior to exposure of the older adult population. Part 2 will be a multiple ascending dose, 3-arm, parallel study, with 3 new Cohorts 4, 5 & 6. An additional 96 subjects will be recruited, with approximately equal subjects aged ≥ 56 - ≤ 65 years of age and ≥ 66 years of age and older. Updated Figure 1 to show revised study design. Section 6.1 Updated to clarify that vaccination for Cohorts 4,5,6 will only commence once the SRC have completed their review of the aggregated safety and tolerability data for Cohorts 1,2,3.	

	Section 7.1 Clarified the SRC responsibility for study progression from Part 1 to Part 2. Section 8.1 Updated to provide rationale for inclusion of older adults in study population. Section 8.2 Sample size updated to include numbers of subjects and their treatment assignment in the new Cohorts 4, and 6. Section 8.3 Inclusion Criteria- included new Part 2 Inclusion criteria for healthy older adult cohort. Section 8.4 Exclusion Criteria -included new Part 2 Exclusion criteria for healthy older adult cohort. Section 9.3 included blinding status up until Day 57 for Part 2 subjects. Section 9.4 included Part 2 Cohorts 4,5 & 6 for allocation of subjects to treatment and method of assignment to treatment groups . Section 9.5 updated blinding details for study vaccine and administration. Section 9.5 included cohorts 4, 5 & 6 in study medication treatment groups. Section 9.6 updated storage conditions for prepared vaccine. Section 9.8.3 inserted missing word “excluded” which was an oversight from previous versions. Section 9.9 Inserted new table for summary of samples to be collected for Part 2 subjects (fewer samples). Section 9.10.7 inserted option for Paper diary (Diary) for subject self-reporting. Section 9.10.8 Included Diary along with eDiary for injection site examination. Section 9.15.2 included paper diary card (Diary) Section 11 Included new interim analysis for Day 57 for Part 2 subjects which will be an addendum to the CSR. Section 11.4.3 updated definition for Immunogenicity population for the Day 57 analyses to include Part 1 and Part 2. Section 12 Included new interim analysis for Day 57 for Part 2 subjects which will be an addendum to the CSR .	

	General : minor editorial change - standardised document to "subjects" rather than mix of subjects and partipants throughout.	
Version 2.1	**Inclusion of exploratory endpoint to determine if an immune response to the molecular clamp of the Sclamp antigen can trigger a false positive for HIV testing** Objectives: Inclusion of objective to assess whether SARS-CoV-2 Sclamp vaccination can cause false positive in subsequent HIV testing Endpoints: Evaluation of participant blood samples by a range of HIV point of care and rapid diagnostic tests to determine if the post vaccination response results in a false positive outcome, and if so, the rate of false positive detection. Section 11.2 update to include assessment of HIV diagnostics	07-SEP-2020
Version 2.2	**Inclusion of additional visit to inform the participants of vaccine induced HIV diagnostic interference and provide written and verbal information around this result** **Amendment of exploratory endpoint to determine probability and duration of the preliminary positive results following some point of care and rapid HIV tests.** Section 4, Schedule of Events: update to include additional vist at Day 120 for subset of participants from Cohorts 1-2. Section 9.2 Clinical visits and follow up (additional visits added) Section 9.9, Sample Collection and Processing: addition of immunology samples will be collected at Day 120, 209 and 394 to further test probability and duration of the preliminary positive results following some point of care and rapid HIV tests.	02-NOV-2020

Signature Page

Sponsor

University of Queensland

School of Chemistry & Molecular Biosciences
Building 68, St Lucia QLD 4072
Australia
Tel.: +61 7 3365 4622

University of Queensland Representative:

Associate Professor Keith Chappell
Chief Investigator

6-11-2020

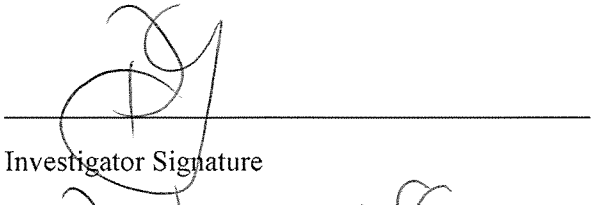
Associate Professor Keith Chappell Date

Signature Page

Clinical Site – Q-Pharm

Investigator:

I have carefully read this study protocol and agree that it contains all necessary information required to conduct this study. I agree to conduct the study according to this protocol (including any amendments) and in accordance with the clinical site's Standard Operating Procedures (SOPs), ICH Good Clinical Practice (GCP), Directive 2001/83/EC Annex I, as amended by Directive 2003/63/EC and Directive 2001/20/EC, all other applicable regulations, and the recommendations laid down in the most recent version of the Declaration of Helsinki.



Investigator Signature

Date

Investigator Printed Name

Q-Pharm

Name of the Clinical Facility

Brisbane, Australia

Location of Facility (city, country)

1. Facilities and Responsible Staff

1.1 Clinical Research Organization (CRO)

INC Research LLC, a Syneos Health company ("Syneos Health")
3201 Beechleaf Court, Suite 600
Raleigh NC 27604, USA
Tel.: +1 91 9876 9300

1.2 Clinical Research

This study will be conducted at the following facility:

Q-Pharm Pty Ltd
Level 5, Clive Berghofer Cancer Research Centre (CBCRC)
300c Herston Road
Herston QLD 4006, Australia
Tel.: +61 8 8222 2763

1.3 Biomedical Laboratory Facilities

Biomedical laboratory testing will be performed by the following laboratories:

SydPath
Level 6 Xavier Building
St. Vincent's Hospital
Victoria Street
Darlinghurst NSW 2010, Australia
Tel.: +61 2 8382 9119

University of Queensland
QBI Building 79
St. Lucia QLD 4072, Australia
Tel. +61 7 3365 1111

TetraQ
Level 7, Block 6
Royal Brisbane and Women's Hospital
Herston Road
Herston QLD 4029, Australia
Tel.: +61 7 3365 5115

The Peter Doherty Institute for Infection and Immunity
University of Melbourne
79 Elizabeth Street
Melbourne VIC 3000, Australia
Tel.: +61 3 9035 3555

Pathology Queensland
Level 3, Block 7
Royal Brisbane and Women's Hospital
Herston Road

Herston QLD 4029, Australia
Tel.: +61 7 3365 5115

Australian Red Cross Lifeblood
44 Musk Avenue, Kelvin Grove 4059, QLD, Australia

If another biomedical laboratory is used, this will be documented and annexed to the protocol.

1.4 Clinical Pharmacology and Regulatory Affairs

Syneos Health
2500, rue Einstein
Québec (Québec), Canada, G1P 0A2
Tel.: 1-418-527-4000

Stéphane Lamouche, Ph.D.
Director, Regulatory & Scientific Affairs

Protocol writing:

Matthew Bendikov, Ph.D.
Clinical Research Scientist

1.5 Medical Monitor

Dr. Jon Rankin, MB BS Grad. Dip. PH SCHP JD(Hons)
Syneos Health
159 Port Road, Hindmarsh,
Adelaide SA 5007 Australia
Mobile: +61 499 222 117

Table of Contents

1. FACILITIES AND RESPONSIBLE STAFF 9
1.1 CLINICAL RESEARCH ORGANIZATION (CRO) 9
1.2 CLINICAL RESEARCH 9
1.3 BIOMEDICAL LABORATORY FACILITIES 9
1.4 CLINICAL PHARMACOLOGY AND REGULATORY AFFAIRS 10
1.5 MEDICAL MONITOR 10

2. SYNOPSIS OF PROTOCOL 13

3. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS 29

4. SCHEDULE OF EVENTS 32

5. INTRODUCTION 36
5.1 BACKGROUND INFORMATION 36
5.2 RATIONALE FOR STUDY DESIGN 37
5.2.1 Analytes to be Measured 38
5.2.2 Choice of the Dose 38
5.3 STUDY OBJECTIVES 40
5.4 STUDY ENDPOINTS 40

6. STUDY DESIGN 42
6.1 STUDY PROGRESSION AND EVALUATIONS 45
6.2 STARTING DOSE 45
6.3 DOSE ESCALATION SCHEME 45

7. DOSE ESCALATION CRITERIA 45
7.1 DATA REVIEW BY THE SAFETY REVIEW COMMITTEE 45
7.2 DOSE HALTING RULES 46

8. STUDY POPULATION 47
8.1 RATIONALE FOR THE STUDY POPULATION 47
8.2 SAMPLE SIZE 48
8.3 INCLUSION CRITERIA 48
8.4 EXCLUSION CRITERIA 51

9. CLINICAL PROCEDURES 55
9.1 SCREENING PROCEDURES 55
9.2 CLINICAL VISITS AND FOLLOW-UP 56
IN ADDITION, SUBJECTS WILL BE ASKED TO RETURN TO THE CLINIC AT APPROXIMATELY 6 AND 12 MONTHS POST SECOND DOSE (APPROXIMATELY DAYS 209 AND 394) FOR A SAFETY FOLLOW-UP AND BLOOD DRAWS FOR ASSESSMENT OF THE DURATION OF THE IMMUNE RESPONSE TO THE VACCINE. 56
9.3 RANDOMISATION AND BLINDING 56
9.4 ALLOCATION OF SUBJECTS TO TREATMENT 57
9.5 STUDY MEDICATION 57
9.6 TREATMENT SUPPLIES AND ACCOUNTABILITY 58
9.7 STUDY TREATMENT ADMINISTRATION 59
9.8 STUDY RESTRICTIONS 59
9.8.1 Food and Fluids 59
9.8.2 Tobacco, Alcohol, and Illicit Drugs 60
9.8.3 Prior and Concomitant Medications 60
9.8.4 Posture and Physical Activity 60
9.9 SAMPLE COLLECTION AND PROCESSING 60
9.9.1 SAMPLES STORAGE 61
9.10 SUBJECT MONITORING 62
9.10.1 Vital Signs 63
9.10.2 ECG 63
9.10.3 Physical Examination 63
9.10.4 Drug and Alcohol Screen 63

9.10.5 Pregnancy Test 63
9.10.6 Laboratory Assessments 64
9.10.7 Subject Self-Reporting 65
9.10.8 Injection Site Examination 65
9.11 Study Exit Procedures 66
9.12 Data Collection and Evaluation 66
9.13 Subject Withdrawal and Replacement 66
9.14 Early Termination Visit 67
9.15 Adverse Events 67
9.15.1 Definition of Adverse Events 67
9.15.2 Recording of Adverse Events 68
9.15.3 Serious Adverse Events 72
9.15.4 Suspected Unexpected Serious Adverse Reactions 74
9.16 Pregnancy 74
9.17 Reportable Disease 75
9.18 Premature Termination of the Study 75
10. ANALYTICAL METHODOLOGY 75
11. STATISTICAL ANALYSES 76
11.1 Safety Measurements 77
11.2 Immunogenicity 79
11.3 Success Criteria 79
11.4 Analysis Populations 79
11.4.1 Intent-to-Treat (ITT) Population (Full Analysis Set, FAS) 79
11.4.2 Safety Population 80
11.4.3 Immunogenicity Population up to Day 57 80
11.4.4 Full Immunogenicity Population 80
11.5 Immunogenicity Analysis 80
12. FINAL REPORT 81
13. REGULATORY CONSIDERATIONS AND QUALITY ASSURANCE 82
13.1 Independent Ethics Committee Approval of Protocol and Other Study Documents 82
13.2 Compliance 82
13.3 Quality Assurance Program 83
13.4 Audits, Inspections and Monitoring 83
14. CONFIDENTIALITY AND RETENTION OF STUDY RECORDS 83
15. REFERENCES 84
APPENDIX I CHECKLIST FOR MEDICAL HISTORY FOLLOW-UP FOR PERSONS WHO MEET THE PROTOCOL DEFINED COVID-19 CASE DEFINITION. 85

2. Synopsis of Protocol

Project No.:	Syneos number: 7013800 Protocol number: UQ-1-SARS-CoV-2-Sclamp
Study Title:	A Phase 1, Randomised, Double-Blind, Placebo-Controlled, Dosage-Escalation, Single Centre Study to Evaluate the Safety and Immunogenicity of an Adjuvanted SARS-CoV-2 Sclamp Protein Subunit Vaccine in Healthy Adults, Aged 18 to 55 years and Healthy Older Adults, Aged 56 years and over.
Study Vaccine:	Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2) Sclamp protein subunit vaccine (with squalene based adjuvant, MF59C.1)
Study Phase and Type:	Phase 1 – First-In-Human (FIH), Interventional
Objectives:	Primary Safety Objective: • To assess the safety and tolerability of SARS-CoV-2 Sclamp vaccine compared to placebo. Primary Immunogenicity Objective: • To assess the total serum antibody and neutralising antibody (NAb) immune responses elicited by SARS-CoV-2 Sclamp vaccine compared to placebo at Day 29 (28 days after first dose) and Day 57 (28 days after second dose). Secondary Immunogenicity Objective: • To compare the total serum antibody and NAb immune responses at Day 1 (baseline), Day 15, Day 29 (28 days after the first dose), Day 43, Day 57 (28 days after the second dose), Day 209 (6 months after the second dose), and Day 394 (12 months after the second dose). Exploratory Immunogenicity Objectives: • To follow subjects for 12 months following study treatment administration to record infections with SARS-CoV-2 and evaluate the frequency and severity of all cases of laboratory confirmed COVID-19 disease. • To conduct a detailed analysis of humoral and cellular immune responses elicited to Sclamp antigen upon vaccination compared to placebo and comparisons between dosing levels and across time course post-vaccination. • Assess whether SARS-CoV-2 Sclamp vaccination can cause false positives in subsequent HIV testing
Endpoints:	Primary Safety Endpoints: • Frequency, duration, and intensity of solicited local adverse events (AEs), including pain, redness, and induration for 7 days following each study treatment (for Days 1-3, Days 4-7 and Days 1--7). • Frequency, duration, and intensity of solicited systemic adverse events (AEs), including fever, nausea, chills, diarrhoea, headache,

	fatigue, and myalgia for 7 days following each study treatment (for Days 1-3, Days 4-7 and Days 1-7). • Frequency, duration, intensity, duration, and relatedness of unsolicited AEs through to Day 57. Frequency of Serious Adverse Events (SAEs), Medically-Attended Adverse Events (MAAEs), and any AEs leading to study withdrawal (including decision by the Principal Investigator (PI) not to proceed with the second dose) at any time during study through to Day 394. Frequency and intensity of unsolicited AEs through to Days 57, 209, and 394 <u>Primary Immunogenicity Endpoints</u>: • Geometric mean titre (GMT) of the serum antibody response to the Sclamp antigen compared to placebo by antigen specific ELISA at Day 29 (28 days after first dose) and Day 57 (28 days after second dose). • GMT of the serum NAb titres to SARS-CoV-2 virus compared to placebo by microneutralisation (MN) assay at Day 29 (28 days after first dose) and Day 57 (28 days after second dose). <u>Secondary Immunogenicity Endpoints</u>: • Proportion of subjects with ≥4 fold increase in titre above baseline by ELISA at Days 15, 29, 43, 57, 209, and 394 post-vaccination compared to placebo. • Proportion of subjects with ≥4 fold increase in titre above baseline by MN assay at Days 15, 29, 43, 57, 209, and 394 post-first study treatment administration compared to placebo. • GMT of the serum antibody response to the Sclamp antigen compared to placebo by antigen specific ELISA at Days 1, 15, 29 (28 days after first dose), and Days 43, 57 (28 days after second dose) and Days 209 and 394 (6 and 12 months post-second dose respectively). • GMT of the serum NAb titres to SARS-CoV-2 virus compared to by MN assay at Days 1, 15, 29 (28 days after first dose), and Days 43, 57 (28 days after second dose) and Days 209, 394. <u>Exploratory Immunogenicity Endpoints</u>: • Proportion of subjects experiencing laboratory confirmed SARS-CoV-2 infection and/or severity graded COVID-19 disease between Days 57 and 394 compared to placebo. • Proportion of subjects with titres of ≥1:80 and ≥ 1:160 by MN assay at Days 1, 15, 29, 43, 57, 209, and 394 compared to placebo. • Proportion of subjects with ≥10 fold increase in titre above baseline by MN assay at Days 1, 15, 29, 43, 57, 209, and 394 compared to placebo. • Proportion of subjects showing an increase in antigen specific CD4+ T-cells at Days 15, 29, 36, 43, and 57 compared to pre-vaccination for vaccine antigen dose versus placebo.

	• Proportion of subjects showing an increase in antigen specific CD8+ T-cell at Days 15, 29, 36, 43, and 57 compared to pre-vaccination for vaccine antigen dose versus placebo. • Evaluation of antibody dependent cellular cytotoxicity (ADCC) at Days 1, 15, 29, 43, 57, 209, and 394 compared to placebo for vaccine antigen dose versus placebo. • Evaluation of domain specificity of the elicited humoral immune response, specifically the proportion of antibodies elicited to the Receptor Binding Domain (RBD), N-Terminal Domain (NTD), and clamp trimerization domain by a custom Luminex assay and/or ELISA for vaccine antigen dose versus placebo on Days 1, 15, 29, 43, 57, 209, and 394. • Evaluation of antigen specific humoral immune responses including isotypes IgM, IgA, IgE, and subtypes IgG1, IgG2, IgG3, and IgG4 at Days 1, 15, 29, 43, 57, 209, and 394 compared to placebo by a custom Luminex assay. • Evaluation of participant blood samples by a range of HIV point of care and rapid diagnostic tests to determine if the post vaccination response results in a false positive outcome, and if so, the rate of false positive detection and duration of the response.
Study Design:	This will be a single centre, Phase 1, FIH, randomised, double-blind, placebo controlled, single and multiple ascending dose, 4-arm, parallel study. The study will be conducted in two parts: Part 1 will include a young healthy adult population aged ≥ 18 - ≤ 55 years and Part 2 will include an older healthy adult population aged 56 years and over. Part 1 will be a single and multiple ascending dose, 4-arm, parallel study initiated before commencement of Part 2 so that safety can be assessed in the young adult population prior to exposure of the older adult population. Part 2 will be a multiple ascending dose, 3-arm, parallel study. This study will consist of 6 cohorts (2 cohort each of a lower, intermediate, and higher dose, examining both a single and two dose administration regimen). Cohorts 1,2 and 3 will include subjects aged ≥ 18 - ≤ 55 years of age and cohorts 4,5 and 6 will include subjects aged 56 years and older. Cohorts 4, 5 and 6 will include an approximately equal number of subjects aged ≥ 56 - ≤ 65 years of age, and ≥ 66 years of age and older. Cohort 1 will include 32 subjects (8 receiving placebo and 24 subjects receiving a lower dose of SARS-CoV-2 Sclamp vaccine administered in a two dose regimen 28 days apart). Cohort 2 will include 32 subjects (8 receiving placebo and 24 subjects receiving an intermediate dose of SARS-CoV-2 Sclamp vaccine administered in a two dose regimen 28 days apart). Cohort 3 will include 56 subjects (8 subjects receiving placebo, 24 subjects receiving a higher dose of SARS-CoV-2 Sclamp vaccine administered in a two dose regimen 28 days apart, and 24 subjects receiving a single dose of the high-dose of SARS-CoV-2 Sclamp vaccine dosed once followed by placebo 28 days later). Cohort 4 will include 32 subjects (8 receiving placebo and 24 subjects receiving a lower dose of SARS-CoV-2 Sclamp vaccine administered in a two dose regimen 28 days apart). Cohort 5 will include 32 subjects (8 receiving placebo and 24 subjects receiving an intermediate dose of SARS-CoV-2 Sclamp vaccine administered in a two dose regimen 28 days apart). Cohort 6 will include 32 subjects (8 subjects receiving placebo, 24 subjects receiving a higher

	dose of SARS-CoV-2 Sclamp vaccine administered in a two dose regimen 28 days apart). A total of 216 subjects are planned to be included in the study. Since this is a FIH study with a novel vaccine antigen, a conservative approach to vaccine dosing will be adopted to ensure safety of study subjects. Sentinels will be used for each of cohorts 1, 2 and 3 such that two randomly selected subjects will receive either the first dose of SARS-CoV-2 Sclamp vaccine or placebo on Day 1 (and again on Day 29 for the second dose). After at least 24 hours from the time of administration of the first dose a review of the immediate post-vaccination safety data will be conducted by the Safety Review Committee (SRC) in accordance with the study protocol. Should there be no safety concerns the remaining subjects in the cohort will be dosed. The step-wise dose escalation study design is an additional precautionary measure, where the lower dose cohort will complete their first vaccination, and the cumulative safety data from the first 7 days will be evaluated by the SRC prior to initiating vaccination with sentinels of the intermediate dose of vaccine; same repeated at next (higher) dose level. After the first vaccination dose has been administered to Cohorts 1, 2 and 3 and the aggregated safety data reviewed, vaccination will be initiated for Cohorts 4, 5 and 6. Subjects will also have access to an electronic diary to capture solicited and unsolicited AEs and a memory prompt for symptoms of COVID-19. A paper diary will be available for those subjects in Cohorts 4, 5 and 6 who do not have a device that can support the eDiary application. Subjects will be instructed to advise the clinical site if they have been diagnosed with COVID-19, shown symptoms of COVID-19, or returned from overseas in the interim period. Where an acute respiratory illness, or any other relevant signs or symptoms that are clinically suspect for COVID-19, is identified and confirmed by nasal/oropharyngeal swab and SARS-CoV-2 specific polymerase chain reaction (PCR), subjects will be advised to contact the clinical site immediately. Subjects will be given an information sheet that defines the symptoms for COVID-19 at the time of receipt of their first study vaccination.
Subjects:	Approximately 216 healthy adult males or non-pregnant females, ≥18 years of age, non-smokers and social smokers (defined as the equivalent of fewer than 10 cigarettes per week), with BMI >18.0 and <34.0 kg/m^2, will be recruited for participation in this study. Subjects will be randomly divided into6 cohorts stratified by age group. Each cohort will receive two single doses at 28 days apart (with a treatment assignment of active + active, active + placebo, or placebo + placebo).
Screening Procedures:	After an individual has consented to participate in the study and informed consent is signed, that individual will be assigned a unique screening number. Screening procedures will include, documenting demographic data, medical and medication histories (such as history of diabetes mellitus, hypertension, and asthma, excluding childhood asthma) complete physical examination, body measurements, ECG (12-lead), vital signs including tympanic temperature (TT), blood pressure and oxygen saturation (SpO_2), haematology, random blood sugar (non-fasting), biochemistry, coagulation (PT, APTT and fibrinogen), human immunodeficiency virus (HIV), hepatitis B (HBsAg) and hepatitis C (HCV) tests, SARS-CoV-2 test (nasal/oropharyngeal swab and reverse transcription polymerase chain reaction [RT-PCR], and serum antibodies by ELISA), urinalysis, serum pregnancy test, alcohol breath test, urine drug screen, and an FSH test (if required) to confirm post-menopausal status.

Safety Measurements	Safety will be assessed by measuring the frequency and intensity of local and systemic solicited AEs, unsolicited AEs, SAEs, and safety laboratory data for all subjects. Solicited AEs will be assessed by the proportion (%) of subjects with solicited local and systemic AEs up to 7 days after each vaccination by symptom and intensity for the periods: Days 1-3, Days 4-7, and Days 1--7. Unsolicited AEs will be assessed by the proportion (%) of subjects with any unsolicited AEs within 28 days after each treatment dose or until Day 57. Proportion (%) of subjects with SAEs, medically attended AEs (MAAEs), and any AEs leading to study withdrawal or decision by the Principal Investigator (PI) not to proceed with the second dose will be collected from study start until study exit. A MAAE is defined as any AE that requires an unscheduled/unplanned (at the time of visit 1) medical appointment with a primary care physician, or any other health professional. Solicited local and systemic AEs will be collected using electronic diary cards for 7 days following each vaccination dose. Subjects will be requested to take an oral temperature reading for the first 7 days after vaccination and to record other systemic and local AEs that may develop, as well as medication that they have received. Solicited local AEs include pain, redness, and induration at the injection site. Solicited systemic AEs include raised oral temperature (≥38 °C), chills, nausea, headache, fatigue, diarrhoea, and myalgia. All other AEs will be collected at specified safety follow-up visits (Days 8, 15, 36, 43, 57, 209, and 394).
Clinical Visits:	Each subject will come for a visit to the clinical facility on Days 1 and 29 to receive their assigned treatment administration. After each dose subjects will remain in the clinic for at least 2 hours under observation for monitoring of immediate hypersensitivity reactions such as anaphylaxis. Samples for immunological and safety laboratory assessments will be taken pre-dose during subject screening and on Day 1 and Day 29. Subjects will return on Days 2 and 30, and on Days 8 and 36 for a 24-hour and 7-day post-dose safety assessment. Subjects will also return on Days 8, 29, 36, and 57 where they will be assessed for safety, including clinical laboratory safety assessments and immunological response. Subjects will return on Days 15 and 43 where they will be assessed for immunological response only. A time tolerance of ±1 day for visits from Days 8 and 15, ±2 days for visits from Day 29, 30, 36, 43 and 57, and ±5 days for visits from Day 209 onwards, will be allowable.
Follow-Up Visits:	Subjects will also be asked to return at 6 and 12 months after their last dose (Days 209 and 394) for a follow-up safety and immunology assessment to evaluate the duration of the immune response to the vaccine. Subjects will be asked to return for an adhoc visit in early November where they will be informed of findings related to vaccine related HIV diagnostic interference. Subjects will receive written and verbal information on the potential for vaccination to elicit a reactive HIV results on some diagnostics and assured that this result does NOT indicate a HIV positive result.

	A subset of subjects will also be asked to return at 3 months after their last dose (Day 120) for additional immunology assessment to evaluate the duration of HIV diagnostic cross-reactivity.
Study Vaccine and Placebo Dosage Form	Drug product (DP) will be provided as separate single-use vials containing each, the SARS-CoV-2 Sclamp antigen (CSIRO Manufacturing, Clayton VIC 3168, Australia). PBS for DP dilution will be provided as separate single-use vials (Sypharma Pty Ltd, 27 Healy Rd Dandenong, VIC 3175). Squalene adjuvant material, MF59C.1, will be supplied in pre-filled syringes each containing a total volume of 0.25 mL. (Seqirus). DP and adjuvant will be mixed at the clinical site, and 0.5 mL of the vaccine suspension will be drawn into a syringe for IM injection as the final investigational medicinal product (IMP). Placebo will be provided in a single-use vial containing sterile saline for injection (Pfizer, Mulgrave VIC 3170). 0.5 mL of the placebo will be drawn into a syringe for injection. All vaccine and placebo materials will be received and handled while observing aseptic techniques. After preparation, the vaccination dose will be transported in a blinding bag placed in a box, and blinded dosers will be used to preserve the blinding, as physical masking of the syringe to preserve the blind is not possible.
Study Vaccine or Placebo Administration:	Subjects will receive two single IM doses of the following study treatments at 28 days apart as follows: IM administration (to the deltoid region of the subjects nondominant arm or deltoid area of other arm should a tattoo be present) of SARS-CoV-2 Sclamp adjuvanted vaccine, or placebo, administered on Days 1 and 29, of one of the following treatments: Treatment A (Test 1): SARS-CoV-2 Sclamp vaccine 1 x 5 mcg in 0.5 mL suspension, administered as two separate doses at least 28 days apart Treatment B (Test 2): SARS-CoV-2 Sclamp vaccine 1 x 15 mcg in 0.5 mL suspension, administered as two separate doses at least 28 days apart Treatment C (Test 3): SARS-CoV-2 Sclamp vaccine 1 x 45 mcg in 0.5 mL suspension, administered as two separate doses at least 28 days apart Treatment D (Test 4): SARS-CoV-2 Sclamp vaccine 1 x 45 mcg in 0.5 mL suspension, administered as the first dose, followed by placebo as the second dose at least 28 days apart Placebo: 0.5 mL solution (sterile saline for injection)
Inclusion Criteria:	**Part 1** Subjects must meet all of the following criteria to be included in the study: 1. Healthy male or non-pregnant female, ≥18 and ≤55 years of age, with BMI >18 and <34.0 kg/m^2 and body weight ≥50.0 kg for males and ≥45.0 kg for females. 2. Healthy as defined by: a. The absence of clinically significant illness and surgery within 28 days prior to dosing. Subjects displaying signs or symptoms of an acute and/or febrile illness within 24 hours pre-dose (with at least 3 symptom-free pre-dose days required) will be carefully evaluated for upcoming

	illness/disease. Inclusion pre-dosing is at the discretion of the Investigator, and the subject may have their scheduled dosing postponed until the condition resolves. b. The absence of clinically significant history of neurological, endocrine, cardiovascular, respiratory, haematological, immunological, psychiatric, gastrointestinal, renal, hepatic, and metabolic disease. 3. Non-smokers or social smokers (defined as the equivalent of fewer than 10 cigarettes per week). Ex-heavy smokers (heavy smoking defined as the equivalent of 25 or more cigarettes per day) may be admitted if they have quit,or reduced their cigarette intake to the defined level of social smoking, for a period of at least 12 months. 4. Women of childbearing potential (WOCBP) or men whose sexual partners are WOCBP must be able and willing to use at least 2 highly effective methods of contraception commencing at enrolment, during the study and for 3 months after last treatment administration. A female subject is considered to be a WOCBP following menarche and until she is in a post-menopausal state for 12 consecutive months (without an alternative medical cause) or otherwise permanently sterile (for which acceptable methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy). A follicle-stimulating hormone (FSH) test may be used to confirm post-menopausal state. Examples of acceptable methods of contraceptive methods (for female subjects) to be used throughout the study include: a. Simultaneous use of hormonal contraceptives, started at least 28 days prior to first study treatment administration and must agree to use the same hormonal contraceptive throughout the study, and condom for the male partner; b. Simultaneous use of intra-uterine contraceptive device, placed at least 28 days prior to first study treatment administration, and condom for the male partner; c. Simultaneous use of diaphragm or cervical cap and male condom for the male partner, started at least 28 days prior to first study treatment administration; d. Sterile male partner (vasectomized since at least 6 months prior to first study treatment administration); e. True abstinence, defined as no sexual intercourse with a male partner, (for heterosexual couples) for at least 28 days prior to first study treatment administration and for at least the duration of the study. Periodic abstinence and withdrawal are not acceptable methods. 5. WOCBP must have a negative urine pregnancy test prior to receiving each dose. 6. Male subjects (including men who have had a vasectomy) with a pregnant partner, a female partner not of childbearing potential, or a same sex partner, must agree to use a condom from the first study treatment administration until at least 90 days after the last study treatment administration.

7. Male subjects must be willing not to donate sperm until 90 days following the last study treatment administration.

8. Must be able to attend all visits for the duration of the study and to comply with all study procedures according to the study schedule.

9. Capable of, and have given, written informed consent.

Part 2

Subjects must meet all of the following criteria to be included in the study:

1. Healthy male or non-pregnant female ≥ 56 years of age, with BMI >18 and <34.0 kg/m^2 and body weight ≥50.0 kg for males and ≥45.0 kg for females.

2. Healthy as defined by:

    a. The absence of clinically significant illness and surgery within 28 days prior to dosing. Subjects displaying signs or symptoms of an acute and/or febrile illness within 24 hours pre-dose (with at least 3 symptom-free pre-dose days required) will be carefully evaluated for upcoming illness/disease. Inclusion pre-dosing is at the discretion of the Investigator, and the subject may have their scheduled dosing postponed until the condition resolves.

    b. The absence of clinically significant history of a pre-existing medical condition that is not stable (neurological, endocrine, cardiovascular, respiratory, haematological, immunological, psychiatric, gastrointestinal, renal, hepatic, and metabolic disease). A stable medical condition is defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 3 months before enrolment.

3. Non-smokers or social smokers (defined as the equivalent of fewer than 10 cigarettes per week). Ex-heavy smokers (heavy smoking defined as the equivalent of 25 or more cigarettes per day) may be admitted if they have quit,or reduced their cigarette intake to the defined level of social smoking, for a period of at least 12 months.

4. Women of childbearing potential (WOCBP) or men whose sexual partners are WOCBP must be able and willing to use at least 2 highly effective methods of contraception commencing at enrolment, during the study and for 3 months after last treatment administration. A female subject is considered to be a WOCBP following menarche and until she is in a post-menopausal state for 12 consecutive months (without an alternative medical cause) or otherwise permanently sterile (for which acceptable methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy). A follicle-stimulating hormone (FSH) test may be used to confirm post-menopausal state. Examples of acceptable methods of contraceptive methods (for female subjects) to be used throughout the study include:

	a. Simultaneous use of hormonal contraceptives, started at least 28 days prior to first study treatment administration and must agree to use the same hormonal contraceptive throughout the study, and condom for the male partner; b. Simultaneous use of intra-uterine contraceptive device, placed at least 28 days prior to first study treatment administration, and condom for the male partner; c. Simultaneous use of diaphragm or cervical cap and male condom for the male partner, started at least 28 days prior to first study treatment administration; d. Sterile male partner (vasectomized since at least 6 months prior to first study treatment administration); e. True abstinence, defined as no sexual intercourse with a male partner, (for heterosexual couples) for at least 28 days prior to first study treatment administration and for at least the duration of the study. Periodic abstinence and withdrawal are not acceptable methods. 5. WOCBP must have a negative urine pregnancy test prior to receiving each dose. 6. Male subjects (including men who have had a vasectomy) with a pregnant partner, a female partner not of childbearing potential, or a same sex partner, must agree to use a condom from the first study treatment administration until at least 90 days after the last study treatment administration. 7. Male subjects must be willing not to donate sperm until 90 days following the last study treatment administration. 8. Must be able to attend all visits for the duration of the study and to comply with all study procedures according to the study schedule. 9. Capable of, and have given, written informed consent.
Exclusion Criteria:	<u>Part 1</u>: Subjects to whom any of the following applies will be excluded from the study: 1. Any clinically significant abnormality or vital sign abnormality at physical examination (including baseline high blood pressure [140/90] after 3 repeated measurements or high random blood sugar [non-fasting]), clinically significant abnormal laboratory test results or positive test for HIV, hepatitis B, or hepatitis C found during medical screening. 2. Any acute or chronic ongoing illness which, in the judgement of the investigator, may preclude the subject's participation. 3. Any subject that has an active COVID-19 infection (positive COVID-19 test: nasal/oropharyngeal swab and/or positive serum antibody response) at screening, or Day 1, or has been in close contact with someone who has an active COVID-19 infection, or has recovered from a previous COVID-19, SARS-CoV--1, or MERS infection.

	4. Positive pregnancy, urine drug screen, or alcohol breath test at screening. 5. Known history of allergic reactions or hypersensitivity to vaccines, or to any excipient in the formulation (including the adjuvant, MF59C.1). 6. Presence of a known, or suspected, impairment of the immune system including, but not limited to, HIV, autoimmune disorders, immunosuppressant therapy, and diabetes mellitus. 7. History of a known, or suspected, respiratory system disorder including, but not limited to, cystic fibrosis, reactive airway disease, emphysema, chronic bronchitis, chronic obstructive pulmonary disease (COPD), or asthma, excluding childhood asthma. 8. History of significant alcohol abuse within 12 months year prior to screening. 9. Positive test for drugs of abuse (such as marijuana/tetrahydrocannabinol [THC] products, amphetamine, methamphetamine, methadone, barbiturates, benzodiazepines, cocaine, opiates, methylenedioxymethamphetamine [MDMA], or phencyclidine [PCP]) at screening, prior to dosing, or a history of drug abuse within 12 months prior to screening. 10. Participation in a clinical research study involving the administration of an investigational, or marketed, drug or device within 30 days prior to receiving the first treatment administration, or administration of a biological product in the context of a clinical research study within 90 days prior to the first dosing, or concomitant participation in an investigational study involving no drug, vaccine, or device administration, or intent to participate in another clinical study at any time during the conduct of the study. 11. Use of medications for the timeframes specified below, with the exception of hormonal contraceptives and medications exempted by the Investigator on a case-by-case basis because they are judged to interfere with subject safety e.g., topical drug products without significant systemic absorption are permissible: a. Prescription medication within 14 days prior to the first dosing; b. Any medication, or treatments, that may affect the immune system such as allergy injections, immunoglobulin, interferon, immunomodulators, cytotoxic drugs, or other drugs known to be frequently associated with significant major organ toxicity within 90 days prior to enrolment; c. Any registered vaccine administered within 30 days prior to enrolment in the study, or who plan to receive any non-study vaccines within 28 days of the second dose of the study vaccine d. Any other investigational coronavirus vaccine i.e. SARS--CoV-1, SARS--CoV-2, MERS etc. at any time prior to, or during, the study.

	e. Over-the-counter products within 7 days prior to the first dosing, with the exception of the occasional use of paracetamol (up to 2 g daily) and standard dose vitamins. 12. Donation of plasma within 7 days prior to dosing. Donation or loss of blood (excluding volume drawn at screening) of 50 mL to 499 mL of blood within 30 days, or more than 499 mL within 56 days prior to the first dosing. 13. Receipt of blood products within 2 months prior to the first study treatment administration (Day 1), or planned receipt of blood products during the study period. 14. Breast-feeding subject, or subject who plans to breastfeed from the time of first dose through 60 days after last study treatment administration. 15. Presence of tattoos, scarring, skin discoloration, or any other skin disturbances at the injection site which, in the opinion of the Investigator, may inhibit the ability to effectively perform an injection site assessment. 16. Employee or immediate relative of an employee of the clinical site, any of its affiliates or partners, or Syneos Health. 17. Any reason which, in the opinion of the Investigator, would interfere with the primary study objectives or prevent the subject from participating in the study. **Part 2** Subjects to whom any of the following applies will be excluded from the study: 1. Any clinically significant abnormality or vital sign abnormality at physical examination, or uncontrolled hyertension in adults aged ≥ 56 years and older), or high random blood sugar [non-fasting]), clinically significant abnormal laboratory test results or positive test for HIV, hepatitis B, or hepatitis C found during medical screening. 2. Any acute or chronic ongoing illness which, in the judgement of the investigator, may preclude the subject's participation. 3. Any subject that has an active COVID-19 infection (positive COVID-19 test: nasal/oropharyngeal swab and/or positive serum antibody response) at screening, or Day 1, or has been in close contact with someone who has an active COVID-19 infection, or has recovered from a previous COVID-19, SARS-CoV--1, or MERS infection. 4. Positive pregnancy, urine drug screen, or alcohol breath test at screening. 5. Known history of allergic reactions or hypersensitivity to vaccines, or to any excipient in the formulation (including the adjuvant, MF59C.1). 6. Presence of a known, or suspected, impairment of the immune system including, but not limited to, HIV, autoimmune disorders, immunosuppressant therapy, and diabetes mellitus.

	7. History of a known, or suspected, or currently unstable medical condition that may expose the subject to an increased risk for severe SARS-CoV-2 disease, such as a respiratory system disorder including, but not limited to, cystic fibrosis, reactive airway disease, emphysema, chronic bronchitis, chronic obstructive pulmonary disease (COPD), or asthma, excluding childhood asthma, uncontrolled hypertension, ischemic or structural heart disease, chronic kidney disease, chronic liver disease, endocrine disorder and neurological illness. 8. History of significant alcohol abuse within 12 months year prior to screening. 9. Positive test for drugs of abuse (such as marijuana/tetrahydrocannabinol [THC] products, amphetamine, methamphetamine, methadone, barbiturates, benzodiazepines, cocaine, opiates, methylenedioxymethamphetamine [MDMA], or phencyclidine [PCP]) at screening, prior to dosing, or a history of drug abuse within 12 months prior to screening. 10. Participation in a clinical research study involving the administration of an investigational, or marketed, drug or device within 30 days prior to receiving the first treatment administration, or administration of a biological product in the context of a clinical research study within 90 days prior to the first dosing, or concomitant participation in an investigational study involving no drug, vaccine, or device administration, or intent to participate in another clinical study at any time during the conduct of the study. 11. Use of medications for the timeframes specified below, with the exception of hormonal contraceptives and medications exempted by the Investigator on a case-by-case basis because they are judged to interfere with subject safety e.g., topical drug products without significant systemic absorption are permissible: a. Prescription medication within 14 days prior to the first dosing that in the opinion of the Investigator could impact the subjects safe participation in the study; b. Any medication, or treatments, that may affect the immune system such as allergy injections, immunoglobulin, interferon, immunomodulators, cytotoxic drugs, or other drugs known to be frequently associated with significant major organ toxicity within 90 days prior to enrolment; c. Any registered vaccine administered within 30 days prior to enrolment in the study, or who plan to receive any non-study vaccines within 28 days of the second dose of the study vaccine d. Any other investigational coronavirus vaccine i.e. SARS--CoV-1, SARS--CoV-2, MERS etc. at any time prior to, or during, the study. e. Over-the-counter products within 7 days prior to the first dosing that in the opinion of the investigator could impact the subjects safe participation in the study.

	Paracetamol, (up to 2 g daily) and standard dose vitamins will be permitted. 12. Donation of plasma within 7 days prior to dosing. Donation or loss of blood (excluding volume drawn at screening) of 50 mL to 499 mL of blood within 30 days, or more than 499 mL within 56 days prior to the first dosing. 13. Receipt of blood products within 2 months prior to the first study treatment administration (Day 1), or planned receipt of blood products during the study period. 14. Breast-feeding subject, or subject who plans to breastfeed from the time of first dose through 60 days after last study treatment administration. 15. Presence of tattoos, scarring, skin discoloration, or any other skin disturbances at the injection site which, in the opinion of the Investigator, may inhibit the ability to effectively perform an injection site assessment. 16. Employee or immediate relative of an employee of the clinical site, any of its affiliates or partners, or Syneos Health. 17. Any reason which, in the opinion of the Investigator, would interfere with the primary study objectives or prevent the subject from participating in the study. 18. Permanent resident in an aged care facility (nursing or aged care home).
Study Restrictions:	Subjects will be allowed to engage in normal activity.
Sample Collection for Analysis:	Over the course of the study, a blood sample will be collected at each visit (total of no more than 36 blood samples from each subject) for screening, safety laboratory and immunological assessments. Sample volume collected will vary between 15 mL and a maximum of 73 mL with individual samples collected into multiple tubes to facilitate disparate immunological tests. A total of 8 blood samples will be collected for safety laboratory assessments from each subject, one sample at screening, pre-dose (within 30 minutes pre-dose), and 1, 7, and 14 days post dose for each dose (Days 1, 2, 8, 29, 30, 36). Each sample will consist of 15 mL of whole blood. PD samples collected for immunogenicity assessments will include 4 mL for T-cell analysis, 10 mL for IgG ELISA, virus neutralisation, and ADCC analysis, and 20 mL to isolate PBMCs for cryopreservation. The total volume of blood including that collected for eligibility screening and safety purposes should not exceed 500 mL for the whole study, with up to 400 mL collected at visits between Day 1 and Day 57±2, and up to 100 mL collected at the Day 209±5 and 394±5 visits.
Subject Monitoring:	ECG and vital signs: Day of vaccination (pre dose) and approximately 24 hours post dose. Urine pregnancy test, alcohol breath test, and urine drug screen: before each dosing.

	Clinical laboratory safety parameters, including haematology, coagulation and serum chemistry: before each dosing and Days 1, 2, 8, 29, 30, 36 and 57. Safety parameters, including laboratory parameters and vital signs will be assessed by the PI or delegate, using the clinical site's criteria for acceptance ranges as guidelines in making the medical assessment. Abnormal laboratory blood and urinalysis results will be graded as mild, moderate or severe. Safety measurements which in the opinion of the investigator are deemed clinically significant will be recorded as adverse events. Injection site evaluation: before each dosing and approximately 30 minutes, 24 hours (Days 2 and 30), and until 7 days post injection (Days 8 and 36). Subjects will be provided instructions on how to self-assess at home daily. Medical surveillance: Subjects will be monitored throughout the study by the clinical staff for adverse events, as described above. The Principal Investigator (PI) will be on site for study treatment administration and at least 30 minutes post-dose, and will be available on call for the remainder of the study. Should a subject be diagnosed with laboratory confirmed COVID-19 disease at any time throughout the duration of the study, they will be instructed to contact the study site. COVID-19 infection will be a SAE, and follow-up by a trained healthcare provider will be required to document the severity of the disease.
Study Exit Procedures (Day 394):	AE monitoring. A blood sample will be taken to assess the magnitude and duration of the immune response to the vaccine.
Analytical Methods for Humoral and Cellular Immune Response:	Analysis of the humoral response for SARS-CoV-2 at pre-dose, Days 15, 29, 43, 57, 209, and 394; (i) ELISA for antigen specific immune response (ii) virus based neutralisation assay (PBNA), and (iii) antibody dependent cellular cytotoxicity (ADCC) that will include assessment of potential correlates of protection The induction of antigen specific T-cells will be assessed through the stimulation of peripheral blood mononuclear cells (PBMCs) with a vaccine specific peptide library and analysed by multi-colour flow cytometry following surface staining for CD3, CD4, CD8, and intracellular cytokine staining for IFN-γ, TNF-α, IL-2, IL-4, IL-13, IL-17a, CD107a, and Granzyme B.
Statistical Analyses:	A complete description of the statistical analyses and methods to be performed will be presented in a statistical analysis plan (SAP) to be finalised prior to database lock. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives. The SAP will serve as a complement to the protocol and supersedes it in case of differences. An interim analysis will be performed once all Part 1 subjects (Cohorts 1, 2 and 3) have completed Day 29, and immunology assays for all samples up to Day 29 are completed. A brief study status report will be prepared and will discuss the safety, tolerability and immunogenicity data following a single vaccination dose. A further interim analysis will be performed once all Part 1 subjects (Cohorts 1, 2 and 3) have completed Day 57, and immunology assays for all samples up to Day 57 are completed. The Final CSR will be written following the completion of the Active Study Period

	Evaluation Visit (Day 57) and will discuss the safety, tolerability and immunogenicity data collected during the Active Study Period. The immunology assessments to be included for the Active Study Period in the CSR are the GMT of the serum antibody response (ELISA) to the Sclamp antigen and the serum NAb response by MN assay at Days 29 and 57 i.e. 28 days after the first and second dose respectively, the proportion of subjects with a ≥4 fold increase in titre above baseline by ELISA at Days 15, 29, 43 and 57 compared to placebo, and the proportion of subjects with a ≥4 fold increase in titre above baseline by MN assay at Days 15, 29, 43 and 57 compared to placebo. Statistical assessments will include comparisons between the four treatment groups (A-D), as appropriate to each cohort and comparison of each treatment to the placebo group. An interim analysis will be performed once all Part 2 subjects (cohorts 4,5 and 6) have completed Day 57, and immunology assays for all samples up to Day 57 are completed. An addendum to the Final CSR will be written following the completion of the Active Study Period Evaluation Visit (Day 57) for Part 2 subjects and will discuss the safety, tolerability and immunogenicity data collected during the Active Study Period. Addenda to the final study report will be prepared following the 6 month follow-up visit (Day 209) and the 12 month follow-up visit (Day 394) for Part 1 and Part 2 subjects. These addenda will discuss the safety and immunogenicity data collected at the 6 month follow-up visit (the period between the Active Study Period and the 6 month follow-up visit) and the 12 month follow-up visit (the period between the 6 month follow-up visit and the 12 month follow-up visit). Demographic parameters will be summarized descriptively. TEAEs and injection site reaction data will be tabulated by study treatment for all subjects who were dosed (Safety Population). Safety and tolerability data will be reported using descriptive statistics. Changes from baseline values in vital signs and clinical laboratory parameters will be evaluated and tabulated by study treatment. No inferential statistical analysis of safety data is planned. Descriptive statistics will be used to present all safety and immunogenicity results; number of observations (n), mean, standard deviation (SD), median, minimum (min), maximum (max), (including geometric mean, and CV% for immunogenicity data) for continuous data. For categorical variables, data will be tabulated with the number and proportion of subjects for each category by treatment group. Binary data i.e. percentages of subjects with seroconversion will be tabulated for each group using unadjusted estimates and will be reported together with two-sided exact 95% confidence intervals (CIs), Clopper-Pearson. No multiplicity adjustment to the CI levels will be implemented. The difference between the proportions of treatment groups will be determined and the corresponding two-sided 95% CIs calculated by using the exact uconditional CI based on the Farrington-Manning score statistic. Geometric means and 95% CIs will be calculated by taking the anti-logs of the means, and the 95% CI of the logtransformed immunogenicity parameters. Exact CIs based upon the binomial distribution will be calculated for percentages.

	The analysis model for the Sclamp antibody, or the MN GMTs, will be performed using a general linear model on log-transformed (base 10) post-GMT titres as the outcome variable and as covariates such as treatment groups (dose) and log-transformed pre-vaccination titre. Model adjusted differences in means (on the log scale) will be produced with 95% confidence limits. The estimated difference between treatment groups and the confidence limits will be back-transformed to obtain an *adjusted* GMT ratio with 95% confidence limits. The measure of the *unadjusted* GMT ratio based on post-vaccination GMT only will also be presented. In addition, reverse cumulative distribution plots will be generated to display the distribution of the antibody response at Days 29 and 57 for the active study phase, and will be explored for Days 209 and 396 (follow-up phase). Baseline titres for serum antibody to Sclamp, and MN titres to SARS-CoV-2 virus, will be less than or equal to the lower limit of quantitation (≤LLOQ) and will be imputed as ½ LLOQ. Bioanalysis of all samples up to, at least, Day 29 (initial status report Part 1 only) and Day 57 should be completed prior to the initiation of the immunogenicity and statistical analyses.
Safety Review Committee	A Safety Review Committee (SRC) will be implemented to review safety data during scheduled periodic reviews. For Part 1 Cohorts 1, 2 and 3 the SRC will review safety data as described in the SRC charter and in the statistical analysis plan after safety data is available up to 48 hrs after dosing of the first 2 sentinel subjects in each cohort before proceeding with vaccination of the remaining subjects in each cohort (this process will be repeated again following administration of the second dose). In addition, the SRC will review the aggregated/cumulative safety and tolerability data up to at least Day 8 for all subjects in each cohort before proceeding with vaccination of the next cohort (and similarly up to at least Day 36 following the second vaccination dose at Day 29). Once all subjects in Part 1 have completed their first vaccination and safety evaluation, dosing will commence for Part 2 subjects (Cohorts 4,5 and 6). The SRC will review the aggregated/cumulative safety and tolerability data up to at least Day 8 for all subjects in Cohorts, 4, 5 and 6 before proceeding to the second vaccination dose. Pausing rules are defined in the protocol.
Expected Start and End Dates:	The clinical portion of the study should last approximately 14 months, consisting of approximately 2 months in the active study portion and a further 12 months of follow-up. Cohort 1 is expected to start in July 2020, and Cohort 6 is expected to complete the active study portion (up to Day 57) in December 2020, with the 12 month post-second dose assessments expected to be completed for Cohort 6 in November 2021.

3. List of Abbreviations and Definition of Terms

ADCC	Antibody Dependent Cellular Cytotoxicity
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ASC	Antibody Secreting Cell
AST	Aspartate Aminotransferase
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CFR	Code of Federal Regulations
CK	Creatinine Kinase
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	Coronavirus Disease 2019
CRF	Case Report Form
CSR	Clinical Study Report
CV	Coefficient of Variation
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ELISA	Enzyme-Linked Immunosorbent Assay
EMA	European Medicines Agency
FDA	Food and Drug Administration
FIH	First In Human
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GGT	Gamma-glutamyltransferase
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GMT	Geometric Mean Titre
GP	General Practitioner
HBsAg	Hepatitis B Surface Antigen
HCV	Hepatitis C Virus
hCG	Human Chorionic Gonadotrophin
HEENT	Head, Eyes, Ears, Nose, and Throat
HIV	Human Immunodeficiency Virus
HR	Heart Rate
HREC	Human Research Ethics Committee

ICF	Informed Consent Form
IB	Investigator's Brochure
ICH	International Council for Harmonization
IFN-γ	Interferon Gamma
IgX	Immunoglobulin X i.e. Immunoglobulin A, Immunoglobulin G etc.
IL-X	Interleukin-X i.e. Interleukin-2, Interleukin-4 etc.
IM	Intramuscular
INR	International Normalized Ratio
IRB	Institutional Review Board
Kg	Kilogram
LDH	Lactate Dehydrogenase
LIMS	Laboratory Information Management System
LLN	Lower Limit of Normal
LLOQ	Lower Limit of Quantitation
MAAE	Medically Attended Adverse Event
Max.	Maximum
mcg	Microgram
MDMA	3,4-methylenedioxymethamphetamine
MERS-CoV	Middle East Respiratory Syndrome Coronavirus
mg	Milligram
Min.	Minimum
min	Minute
mL	Millilitre
mmHg	Millimetres of Mercury
MN	Microneutralisation
NAb	Neutralising Antibody
NOCD	New Onset of Chronic Disease
NTD	N-Terminal Domain
OTC	Over-The-Counter
PBMC	Peripheral Blood Mononuclear Cell
PCP	Phencyclidine
PCR	Polymerase Chain Reaction
PD	Pharmacodynamic(s)
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
RBD	Receptor Binding Domain
RT-PCR	Reverse Transcription Polymerase Chain Reaction

SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARS	Severe Acute Respiratory Syndrome
SARS-CoV-1	SARS-Coronavirus-1
SARS-CoV-2	SARS-Coronavirus-2
SD	Standard Deviation
SNMC	Significant New Medical Condition
SOP	Standard Operating Procedure
SpO_2	Peripheral Capillary Oxygen Saturation
SRC	Safety Review Committee
TEAE	Treatment-Emergent Adverse Event
T_{FH} cells	Follicle Helper T Cells
THC	Tetrahydrocannabinol
TNF-α	Tumor Necrosis Factor Alpha
ULN	Upper Limit of Normal
UQ	The University of Queensland
VMED	Vaccine Mediated Enhanced Disease
WBC	White Blood Cell
WHO	World Health Organization
WOCBP	Women of Child Bearing Potential

4. Schedule of Events

Visit Type	Screening	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5[1]	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10[18] *(Cohorts 1-2 only)*	Visit 11[2]	Visit 12[2]	*Ad Hoc* Visit
		First Dose	Safety	Safety/ Immunol.	Immunol.	Second Dose[3] / Immunol.	Safety	Safety/ Immunol.	Immunol.	Immunol.	3-4 month follow-up	6-month follow-up	12-month follow-up / EOS	Unscheduled Visit / Early Termination
Study Day (Visit window)	**Day -28 to Day -1**	**Day 1**	**Day 2[4]**	**Day 8 (±1 day)**	**Day 15 (±1 day)**	**Day 29 (±2 days)**	**Day 30[4] (±2 days)**	**Day 36 (±2 days)**	**Day 43 (±2 days)**	**Day 57 (±2 days)**	**Day 120 (+20 days)**	**Day 209 (±5 days)**	**Day 394 (±5 days)**	***Ad Hoc***
Informed consent	X													
Review of Subject Eligibility	X	X[5]												
Medical History	X													
Demographics (sex and race) and baseline characteristics including previous vaccination status	X													
Physical Examination	X	X[6]				X[6]								
Height, Weight, BMI	X													
SARS-CoV-2 Test[7]	X	X				X								
Serology (HIV, Hepatitis B and C)	X													
Injection site assessment[8]	X	X	X	X		X	X	X						(X)[9]

Visit Type	**Screening**	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5[1]**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10[18]** **(Cohorts 1-2 only)*	**Visit 11[2]**	**Visit 12[2]**	***Ad Hoc* Visit**
		First Dose	**Safety**	**Safety/ Immunol.**	**Immunol.**	**Second Dose[3] / Immunol.**	**Safety**	**Safety/ Immunol.**	**Immunol.**	**Immunol.**	**3-4 month follow-up**	**6-month follow-up**	**12-month follow-up / EOS**	**Unscheduled Visit / Early Termination**
Study Day (Visit window)	**Day -28 to Day -1**	**Day 1**	**Day 2[4]**	**Day 8 (±1 day)**	**Day 15 (±1 day)**	**Day 29 (±2 days)**	**Day 30[4] (±2 days)**	**Day 36 (±2 days)**	**Day 43 (±2 days)**	**Day 57 (±2 days)**	**Day 120 (+20 days)**	**Day 209 (±5 days)**	**Day 394 (±5 days)**	***Ad Hoc***
Vital Signs Measurements (BP, HR, RR, TT and Oxygen Saturation (SpO_2)	X	X	X			X	X							
Serum Pregnancy Test (females)	X	(X)[10]				(X)[10]								
Urine pregnancy test(females)		X				X								
FSH test (to confirm menopausal female)	X													
Subject Dosing		X				X								
ECG	X	X	X			X	X							
Urinalysis	X	X	X	X		X	X	X		X				X
Post dose Monitoring[11]		X	X	X		X	X	X						
Training for Electronic Diary Completion		X												
Review of Diary entries[12]		|					----------X----------						|	X
Electronic Diary Entry[13]		|					----------X----------						|	
Concomitant Medications	X	X	X	X	X	X	X	X	X	X				X
Adverse events[14]	X	|					----------X----------						|	X
Urine Drug Panel	X	X				X								

Visit Type	Screening	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5[1]	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10[18] *(Cohorts 1-2 only)*	Visit 11[2]	Visit 12[2]	*Ad Hoc* Visit
		First Dose	Safety	Safety/ Immunol.	Immunol.	Second Dose[3] / Immunol.	Safety	Safety/ Immunol.	Immunol.	Immunol.	3-4 month follow-up	6-month follow-up	12-month follow-up / EOS	Unscheduled Visit / Early Termination
Study Day (Visit window)	**Day -28 to Day -1**	**Day 1**	**Day 2[4]**	**Day 8 (±1 day)**	**Day 15 (±1 day)**	**Day 29 (±2 days)**	**Day 30[4] (±2 days)**	**Day 36 (±2 days)**	**Day 43 (±2 days)**	**Day 57 (±2 days)**	**Day 120 (+20 days)**	**Day 209 (±5 days)**	**Day 394 (±5 days)**	***Ad Hoc***
Alcohol Breath Test	X	X				X								
Safety Lab Blood Samples[15]	X	X	X	X		X	X	X		X				(X)[16]
Immunology Samples[17]	X	X		X	X	X		X	X	X	X	X	X	X

Abbreviations: EOS = End of Study, BMI = body mass index; BP = blood pressure; HR = heart rate; RR = respiratory rate, TT = tympanic temperature, PD = pharmacodynamic.

[1] On Day 29 immunological blood samples (test samples and retained blood samples) will be collected prior to second administration of treatment.
[2] 6 and 12 month assessments will be measured from the time of completion of the second dose i.e. 6 and 12 months post-Day 29.
[3] Some subjects in Cohort 3 will be randomised to receive placebo in place of a second dose of study vaccine.
[4] Follow-up assessments on Days 2 and 30 will be aimed to be conducted as close to 24 hours post-dose as feasible, however in order to accommodate subject schedules these assessments may be conducted at any time during Days 2 and 30. In either case the time of each assessment will be recorded.
[5] Subject eligibility will be reviewed prior to study vaccine administration on Day 1.
[6] A brief physical examination will be performed at pre-dose (each dose, Days 1 and 29).
[7] In addition to a scheduled SARS-CoV-2 test at screening, and Days 1 and 29, subjects who display symptoms of COVID-19, or have been in close proximity to someone who has tested positive, maybe administered a SARS-CoV-2 test on an *ad hoc* basis.
[8] Injection site visual assessment will be conducted and/or reviewed before each dosing, 30 minutes, 24 hours (Days 2 and 30) and until 7 days post injection (Days 8 and 36). Subjects will be provided instructions on how to self-assess at home daily (from Day 1-8 and 29-36).
[9] In the event of early study termination, or an *ad hoc* visit, scheduled within the first 7 days post-dose (first or second dose) an injection site evaluation may be conducted.
[10] A negative urine pregnancy test must be documented prior to vaccination on Day 1 for WOCBP. A serum pregnancy test will be performed to confirm pregnancy status in the event of a positive urine pregnancy test. If the serum test is negative, the subject may receive their allocated treatment.
[11] Subjects will be monitored at the clinical site for a minimum of 2 hours post-dose,and will also return after 24 hours for a further safety assessment.
[12] Diaries will be reviewed to confirm completion by subjects and administer retraining as appropriate. Diaries will also be reviewed for safety oversight, and subjects may be asked to attend an unscheduled visit if required.
[13] Entries with the electronic diary will be throughout the study up to Day 57. Post-Day 57, additional entries may be made on an *ad hoc* basis.
Study Symptoms form is completed daily from Day 1 to Day 8, and daily from Day 29 to Day 36. Other diary forms are completed as required for the duration of the study.

[14] AEs will be recorded throughout the entire duration of the study. AEs identified via subject self-reporting using the electronic diary may be investigated and characterised on a case-by-case basis.
[15] Includes haematology (complete full and differential blood count, platelet count, haemoglobin, haematocrit, RBC count, WBC count, Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils), coagulation (prothrombin time [PT] and partial thromboplastin time [APTT], Fibrinogen), and serum chemistry (albumin, amylase, AST, ALT, ALP, BUN or urea, creatinine, calcium, creatine kinase, GGT, glucose random, LDH, potassium, phosphate, sodium, total bilirubin, total protein, cholesterol, lipase). Pre-dose samples (Days 1 and 29) should nominally be drawn within 1 hour pre-dose, and post-dose samples (Days 2, 8, 30, 36 and 57) should nominally be drawn at the time of dosing on each respective day(within 30 minutes post dose)
[16] Additional safety blood samples may be drawn in the event of early termination to assist with safety assessment for subjects.
[17] Samples for immunological analyses include CD4+ and CD8+ T-cell analysis, ELISA, virus neutralisation, Luminex assay, and ADCC analysis. Day 57, 120 and Day 394 samples will be tested for cross reaction in HIV point of care and rapid diagnostic tests. Pre-dose samples (Days 1 and 29) should nominally be drawn 1 hour pre-dose, and post-dose samples (Days 8, 15, 36, 43, 57, 209, and 394) should nominally be drawn at the time of dosing on each respective day. The number of samples to be drawn varies for each visit, please refer to Table 1, Section 9.9 in the protocol for a summary of the type, and total of samples to be collected at each study visit. Ad-hoc visit samples being collected are for ELISA, and virus neutralisation.
[18] Subset of participants from Cohorts 1-2 would be invited for an additiona visit at 3 months after thier second dose (Day 120). Samples from this visit will be tested for cross reaction in HIV point of care and rapid diagnostic tests.

5. Introduction

5.1 Background Information

SARS-CoV-2 / COVID-19: In December 2019, China notified the World Health Organization (WHO) of an outbreak of human respiratory illness in the city of Wuhan. The infecting agent is a novel coronavirus, called SARS-CoV-2 which causes atypical pneumonia (COVID-19). Cases have now been reported worldwide, and the WHO declared the outbreak a pandemic in March 2020 due to the levels of global spread and severity of the virus[1].

Previous novel coronaviruses include Middle East Respiratory Syndrome (MERS)-CoV, which emerged in 2012, and Severe Acute Respiratory Syndrome (SARS-CoV), which emerged in 2003. Both viruses are known to cause severe respiratory infections and are associated with a high case fatality rate.

Although the virus is presumed zoonotic in origin, person-to-person spread is evident with a median incubation period of 3 days (range 0 to 24 days), and the time from symptom onset to developing pneumonia is 4 days (range 2 to 7 days). Transmission occurs through respiratory droplets or direct contact, other means of transmission such as faecal-to-oral transmission have not been ruled out.[2] Symptoms of COVID-19 range from asymptomatic or mild to severe, and include fever, dry cough, and fatigue. The illness may evolve over the course of a week or longer, and in some cases progresses to acute respiratory distress syndrome and septic shock, requiring lengthy hospital stays.[3]

There are currently no approved antiviral treatments or vaccinations for human coronavirus infections, although Remdesivir (Gilead) has recently been issued an Emergency Use Authorization in the U.S. for those hospitalized with severe disease. Globally, scientists are working to develop COVID-19-based vaccines. Treatment for infected individuals is symptom-directed with supportive measures consisting of supplemental oxygen and conservative fluid administration. Compassionate use and trial protocols for several antiviral agents are underway.

Vaccine technology: The University of Queensland (UQ) has developed a candidate vaccine to provide protection against SARS-CoV-2 infection and COVID-19. This candidate, SARS-CoV-2 Sclamp, consists of the recombinant viral Spike glycoprotein (S) stabilized in its trimeric form, through the incorporation of the molecular clamp (MC) stabilization domain. This form is equivalent to that expressed on the virion surface and is thought to be the main target of a protective immune response. In order to create a suitable vaccine candidate, the SARS-CoV-2 S glycoprotein was further modified during screening to identify a form that could be produced as a soluble trimer.

The research team at UQ have previously demonstrated the value of the MC for producing candidate subunit vaccines for ten different viruses in preclinical studies. In January 2019, UQ received funding from the Coalition of Epidemic Preparedness Innovations (CEPI) and commenced work to establish and validate a 'Rapid Response Vaccine Pipeline' based on the molecular clamp platform for the purpose of producing vaccine candidates in the event of a novel virus epidemic. In January 2020 in response to increasing global concern about a potential public health emergency, CEPI requested UQ to redirect their studies to generate a candidate subunit

vaccine for COVID-19 and to assess safety and effectiveness of the candidate vaccine in animal models in anticipation of accelerating progress to a Phase 1 clinical study.

The SARS-CoV-2 Sclamp protein is produced by routine biopharmaceutical technologies which involve transfection of host Chinese Hamster Ovary (CHO) cells with plasmids encoding the modified gene for the clamped Spike protein. These cells are cultivated in suspension using protein free and animal component free media for production of the secreted recombinant protein. In order to facilitate rapid isolation of high purity material, the expressed protein is purified on an affinity column using a human monoclonal antibody directed against the molecular clamp domain. The material then undergoes additional downstream purification steps resulting in a high purity bulk protein which is aseptically dispensed into vials for clinical use. This protein is combined with adjuvant immediately prior to patient injection.

Further information regarding the vaccine technology can be found in the Investigator's Brochure.

Adjuvant: To stimulate a robust and appropriate immune response, the SARS-CoV-2-S-clamp subunit protein is administered with an adjuvant. The squalene-oil-in-water adjuvant MF59C.1 (Seqirus) has been selected due to its history of safe use in licenced vaccines for over 20 years with more than 100 million doses administered globally. An MF59C.1 adjuvanted influenza vaccine, Fluad™ is currently registered in Australia for use in persons aged 65 years and over for annual vaccination against influenza. Additionally, a H5N1 Pandemic vaccine, Aflunov™ is registered for use in persons aged 18 years and older, for vaccination in the event of an influenza H5N1 pandemic being declared. Squalene-oil-in-water adjuvants have been well established to stimulate a balanced Th1/Th2 immune response that is expected to provide protection and mitigate the risk of any predisposition to enhanced disease via immunopathology. Studies have been designed and carried out using appropriate animal models, which further substantiate the safety and protective potential of SARS-CoV-2-Sclamp formulated with squalene-oil-in-water adjuvant MF59C.1 (Seqirus).

5.2 Rationale for Study Design

This will be a single centre, Phase 1, FIH, randomised, double-blind, placebo controlled, single and multiple ascending dose, 4-arm, parallel study.

The study will be conducted in two parts: Part 1 will include a young healthy adult population aged ≥ 18 - ≤ 55 years and Part 2 will include an older healthy adult population aged 56 years and over. Part 1 will be a single and multiple ascending dose, 4-arm, parallel study initiated before commencement of Part 2 so that safety can be assessed in the young adult population prior to exposure of the older adult population. Part 2 will be a multiple ascending dose, 3-arm, parallel study.

Since this is a FIH study with a novel vaccine antigen, a conservative approach to vaccine dosing will be adopted to ensure safety of study subjects. Sentinels will be used for cohorts 1, 2 and 3 such that two randomly selected subjects will receive either the first dose of SARS-CoV-2 Sclamp vaccine or placebo on Day 1 (and again on Day 29 for the second dose). After at least 24 hours from the time of administration of the first doses a review of the immediate post-vaccination safety data will be conducted by the Safety Review Committee (SRC) in accordance with the study

protocol. Should there be no safety concerns, the remaining subjects in the cohort will be dosed. The step-wise dose escalation study design is an additional precautionary measure, where the lower dose cohort will complete their first vaccination, and the cumulative safety data from the first 7 days will be evaluated by the SRC prior to initiating vaccination with sentinels of the intermediate dose of vaccine; same repeated at next (higher) dose level. After the first vaccination dose has been administered to Cohorts 1, 2 and 3 and the aggregated safety data reviewed, vaccination will be initiated for Cohorts 4, 5 and 6.

Subjects will be randomised into 1 of 4 treatment arms across 3 cohorts in Part 1 or into 1 of 3 treatment arms across 3 cohorts in Part 2, in a double-blinded manner. The double-blind will be maintained from first randomisation of an eligible subject until, at least, collection of data for all subjects is complete up to Day 57. After this day, the treatment assignment will be unblinded for all study team members, however subjects will remain blinded for the duration of the study.

Subjects will also have access to an electronic or paper diary to capture solicited and unsolicited AEs and will be instructed to advise the clinical site if they have been diagnosed with COVID-19, shown symptoms of COVID-19, or returned from overseas in the interim period. Where an acute respiratory illness, or any other relevant signs or symptoms that are clinically suspect for COVID-19, is identified and confirmed by nasal/oropharyngeal swab and SARS-CoV-2 specific PCR, subjects will be advised to contact the clinical site immediately. Subjects will be given an information sheet that defines the symptoms for COVID-19 at the time of receipt of their first study vaccination.

5.2.1 Analytes to be Measured

Analysis of the humoral response for COVID-19 will include an ELISA for the SARS-CoV-2 Sclamp antigen specific immune response, analysis of domain specificity and immunoglobulin isotype induction via Luminex Assay, analysis of microneutralisation (MN) assessed via SARS-CoV-2 virus, and ADCC that will include assessment of potential correlates of protection.

The induction of antigen specific T-cells will be assessed through the stimulation of peripheral blood mononuclear cells (PBMCs) with a vaccine specific peptide library and analysed by multi-colour flow cytometry following surface staining for CD3, CD4, CD8, and intracellular cytokine staining for IFN-γ, TNF-α, IL-2, IL-4, IL-13, IL-17a, CD107a, and Granzyme B.

5.2.2 Choice of the Dose

The planned SARS-CoV-2 Sclamp doses to be investigated in this FIH study are 5, 15, and 45 mcg. The study is designed as a dose escalation study with the safety of the 5 mcg dose to be evaluated by a Safety Review Committee prior to escalation to the 15 mcg, and similarly prior to escalation to the 45 mcg dose.

The starting dose of 5 mcg and highest dose of 45 mcg SARS-CoV-2 Sclamp are based on comparable viral subunit vaccines approved for use as outlined below and in the IB:

RECOMBIVAX HB® (Hepatitis B vaccine, recombinant, Adjuvanted)

  - Paediatric and adolescent formulation: Contains 5 mcg antigen + 0.25mg aluminium (provided as amorphous aluminium hydroxyphosphate) – Recommended 3 doses of 0.5 mL given by IM injection on a 0-, 1-, and 6-month schedule.

  - Adult (≥20 years) formulation: Contains 10 mcg antigen + 0.5mg aluminium (provided as amorphous aluminium hydroxyphosphate) - Recommended 3 doses of 0.5 mL given by IM injection on a 0-, 1-, and 6-month schedule.

- HEPLISAV-B® (Hepatitis B vaccine, recombinant, Adjuvanted)

  - Adult (≥18 years): Contains 20 mcg antigen + 3mg CPG-1018 - Recommended 2 doses of 0.5 mL given by IM injection on a 0- and 1-month schedule.

- GARDASIL®9 (Human Papillomavirus 9-valent vaccine, recombinant, Adjuvanted)

  - Children (>9 years) and adult: Contains 20 - 60 mcg antigen per strain for each of nine strains + 0.5mg aluminium (provided as amorphous aluminium hydroxyphosphate) – Recommended 3 doses of 0.5 mL given by IM injection on a 0-, 2-, and 6-month schedule.

- SHINGRIX® (Zoster Vaccine Recombinant, Adjuvanted),

  - Adult (>50 years): Reconstituted vaccine contains 50 mcg antigen + AS01b adjuvant – Recommended 2 doses of 0.5 mL given by IM injection on a 0-, 2-, and 6-month schedule.

Additionally, the choice of dose is supported by previous experience evaluating MC vaccines. Immunopathology and animal protection of SARS-CoV-2 Sclamp have investigated doses of 5 mcg per dose in mice indicating that a neutralising immune response was induced by the SARS-CoV-2 Sclamp vaccine. Further pre-clinical examinations in hamsters (also at 5 mcg per dose) and ferrets (at 20 mcg per dose), are ongoing, the results of which will be included in the SARS-CoV-2 Sclamp Investigator's Brochure.

Objectives and Endpoints

5.3 Study Objectives

Primary Safety Objective:

- To assess the safety and tolerability of SARS-CoV-2 Sclamp vaccine compared to placebo.

Primary Immunogenicity Objective:

- To assess the total serum antibody and neutralising antibody (NAb) immune responses elicited by SARS-CoV-2 Sclamp vaccine compared to placebo at Day 29 (28 days after first dose) and Day 57 (28 days after second dose).

Secondary Immunogenicity Objective:

- To compare the total serum antibody and NAb immune responses at Day 1 (baseline), Day 15, Day 29 (28 days after the first dose), Day 43, Day 57 (28 days after the second dose), Day 209 (6 months after the second dose), and Day 394 (12 months after the second dose).

Exploratory Immunogenicity Objectives:

- To follow subjects for 12 months following second study treatment administration to record infections with SARS-CoV-2 and evaluate the frequency and severity of all cases of laboratory confirmed COVID-19 disease.

- To conduct a detailed analysis of humoral and cellular immune responses elicited to Sclamp antigen upon vaccination compared to placebo and comparisons between dosing levels and across time course post-vaccination.

- Assess whether SARS-CoV-2 Sclamp vaccination can cause false positives in subsequent HIV testing. If so, assess duration and range of this response.

5.4 Study Endpoints

Primary Safety Endpoints:

- Frequency, duration, and intensity of solicited local adverse events (AEs), including pain, redness, and induration for 7 days following each study treatment (for Days 1-3, Days 4-7 and Days 1-7).

- Frequency, duration, and intensity of solicited systemic adverse events (AEs), including fever, nausea, chills, diarrhoea, headache, fatigue, and myalgia for 7 days following each study treatment (for Days 1-3, Days 4-7 and Days 1-7).

- Frequency, duration, intensity, duration, and relatedness of unsolicited AEs through to Day 57. Frequency of Serious Adverse Events (SAEs), Medically-Attended Adverse Events (MAAEs), and any AEs leading to study withdrawal (including decision by the Principal

Investigator (PI) not to proceed with the second dose) at any time during study through to Day 394. Frequency and intensity of unsolicited AEs through to Days 57, 209, and 394

Primary Immunogenicity Endpoints:

- Geometric mean titre (GMT) of the serum antibody response to the Sclamp antigen compared to placebo by antigen specific ELISA at Day 29 (28 days after first dose) and Day 57 (28 days after second dose).
- GMT of the serum NAb titres to SARS-CoV-2 virus compared to placebo by MN assay at Day 29 (28 days after first dose) and Day 57 (28 days after second dose).

Secondary Immunogenicity Endpoints:

- Proportion of subjects with ≥4 fold increase in titre above baseline by ELISA at Days 15, 29, 43, 57, 209, and 394 post-first study treatment administration compared to placebo.
- Proportion of subjects with ≥4 fold increase in titre above baseline by MN assay at Days 15, 29, 43, 57, 209, and 394 post-first study treatment administration compared to placebo.
- GMT of the serum antibody response to the Sclamp antigen compared to placebo by antigen specific ELISA at Days 1, 15, 29 (28 days after first dose), and Days 43, 57 (28 days after second dose) and Days 209 and 394 (6 and 12 months post-second dose respectively).
- GMT of the serum NAb titres to SARS-CoV-2 virus compared to by MN assay at Days 1, 15, 29 (28 days after first dose), and Days 43, 57 (28 days after second dose) and Days 209, 394.

Exploratory Immunogenicity Endpoints:

- Proportion of subjects experiencing laboratory confirmed SARS-CoV-2 infection and/or severity graded COVID-19 disease between Days 57 and 394 compared to placebo.
- Proportion of subjects with titres of ≥1:80 and ≥ 1:160 by MN assay at Days 1, 15, 29, 43, 57, 209, and 394 compared to placebo.
- Proportion of subjects with ≥10 fold increase in titre above baseline by MN assay at Days 1, 15, 29, 43, 57, 209, and 394 compared to placebo.
- Proportion of subjects showing an increase in antigen specific CD4+ T-cells at Days 15, 29, 36, 43, and 57 compared to prevaccination for vaccine antigen dose versus placebo.
- Proportion of subjects showing an increase in antigen specific CD8+ T-cell at Days 15, 29, 36, 43, and 57 compared to prevaccination for vaccine antigen dose versus placebo.
- Evaluation of antibody dependent cellular cytotoxicity (ADCC) at Days 1, 15, 29, 43, 57, 209, and 394 compared to placebo for vaccine antigen dose versus placebo.

- Evaluation of domain specificity of the elicited humoral immune response, specifically the proportion of antibodies elicited to the Receptor Binding Domain (RBD), N-Terminal Domain (NTD), and clamp trimerization domain by a custom Luminex assay and/or ELISA for vaccine antigen dose versus placebo on Days 1, 15, 29, 43, 57, 209, and 394.

- Evaluation of antigen specific humoral immune responses including isotypes IgM, IgA, IgE, and subtypes IgG1, IgG2, IgG3, and IgG4 at Days 1, 15, 29, 43, 57, 209, and 394 compared to placebo by a custom Luminex assay.

- Evaluataion of participant blood samples by a range of HIV point of care and rapid diagnostic tests to determine if the post vaccination response results in a false positive outcome, and if so, the rate of false positive detection and duration of the response.

6. Study Design

This will be a single centre, Phase 1, FIH, double-blind, randomised, placebo controlled, single and sequential ascending dose, 4-arm parallel study to evaluate the safety, tolerability, and immunogenicity of the SARS-CoV-2 Sclamp vaccine.

The study will be conducted in two parts: Part 1 will include a young healthy adult population aged ≥ 18 - ≤ 55 years and Part 2 will include an older healthy adult population aged 56 years and over. Part 1 will be a single and multiple ascending dose, 4-arm, parallel study initiated before commencement of Part 2 so that safety can be assessed in the young adult population prior to exposure of the older adult population. Part 2 will be a multiple ascending dose, 3-arm, parallel study.

The study will evaluate a single formulation of SARS-CoV-2 Sclamp protein subunit vaccine administered as a single dose or two doses of varying vaccine antigen concentrations in distinct cohorts.

Four treatments (A, B, C, and D) will be administered to subjects.

This study will consist of 6 cohorts: 2 cohorts of a lower dose (Treatment A), 2 cohorts of an intermediate dose (Treatment B), 1 cohort of a higher dose (Treatment C)(Part 2 only), and 1 cohort of a higher dose, examining both a two dose regimen (Treatment C) and a single dose vaccination regimen (Treatment D) (Part 1 only).

Cohorts 1,2 and 3 will include subjects aged ≥ 18 - ≤ 55 years of age and cohorts 4, 5 and 6 will include subjects aged 56 years and older. Cohorts 4, 5 and 6 will include an approximately equal number of subjects aged ≥ 56 - ≤ 65 years of age, and ≥ 66 years and over.

Part 1: Cohort 1 will include 32 subjects; of these 8 will receive placebo, and 24 subjects will receive Treatment A. Cohort 2 will include 32 subjects; of these 8 will receive placebo, and 24 subjects will receive Treatment B. Cohort 3 will include 56 subjects; of these 8 will receive placebo, 24 subjects will receive Treatment C, and 24 subjects will receive Treatment D.

Part 2: Cohort 4 will include 32 subjects; of these 8 will receive placebo, and 24 subjects will receive Treatment A. Cohort 5 will include 32 subjects; of these 8 will receive placebo, and

24 subjects will receive Treatment B. Cohort 6 will include 32 subjects; of these 8 will receive placebo, and 24 subjects will receive Treatment C.

Treatment	**Dose regimen**
Treatment A (Cohorts 1 & 4)	SARS-CoV-2 Sclamp vaccine 1 x 5 mcg, or placebo, administered in a two dose regimen, at least 28 days apart
Treatment B (Cohorts 2 & 5)	SARS-CoV-2 Sclamp vaccine 1 x 15 mcg, or placebo, administered in a two dose regimen, at least 28 days apart
Treatment C (Cohorts 3 & 6)	SARS-CoV-2 Sclamp vaccine 1 x 45 mcg, or placebo, administered in a two dose regiment, at least 28 days apart
Treatment D (Cohort 3 only)	SARS-CoV-2 Sclamp vaccine 1 x 45 mcg, or placebo, administered as a single dose, followed by placebo as the second dose at least 28 days apart

Sentinels will be used for cohorts 1, 2 and 3 such that the first two subjects will receive either the first dose of SARS-CoV-2 Sclamp vaccine or placebo. After at least 24 hours from the time of administration of the first doses a review of the immediate post-vaccination safety data will be conducted by the Safety Review Committee (SRC) in accordance with the study protocol. Should there be no safety concerns, the remaining subjects in each cohort will be dosed. The step-wise dose escalation study design is an additional precautionary measure, where the lower dose cohort will complete their first vaccination, and the cumulative safety data from the first 7 days will be evaluated by the SRC prior to initiating vaccination with the next higher dose of vaccine.

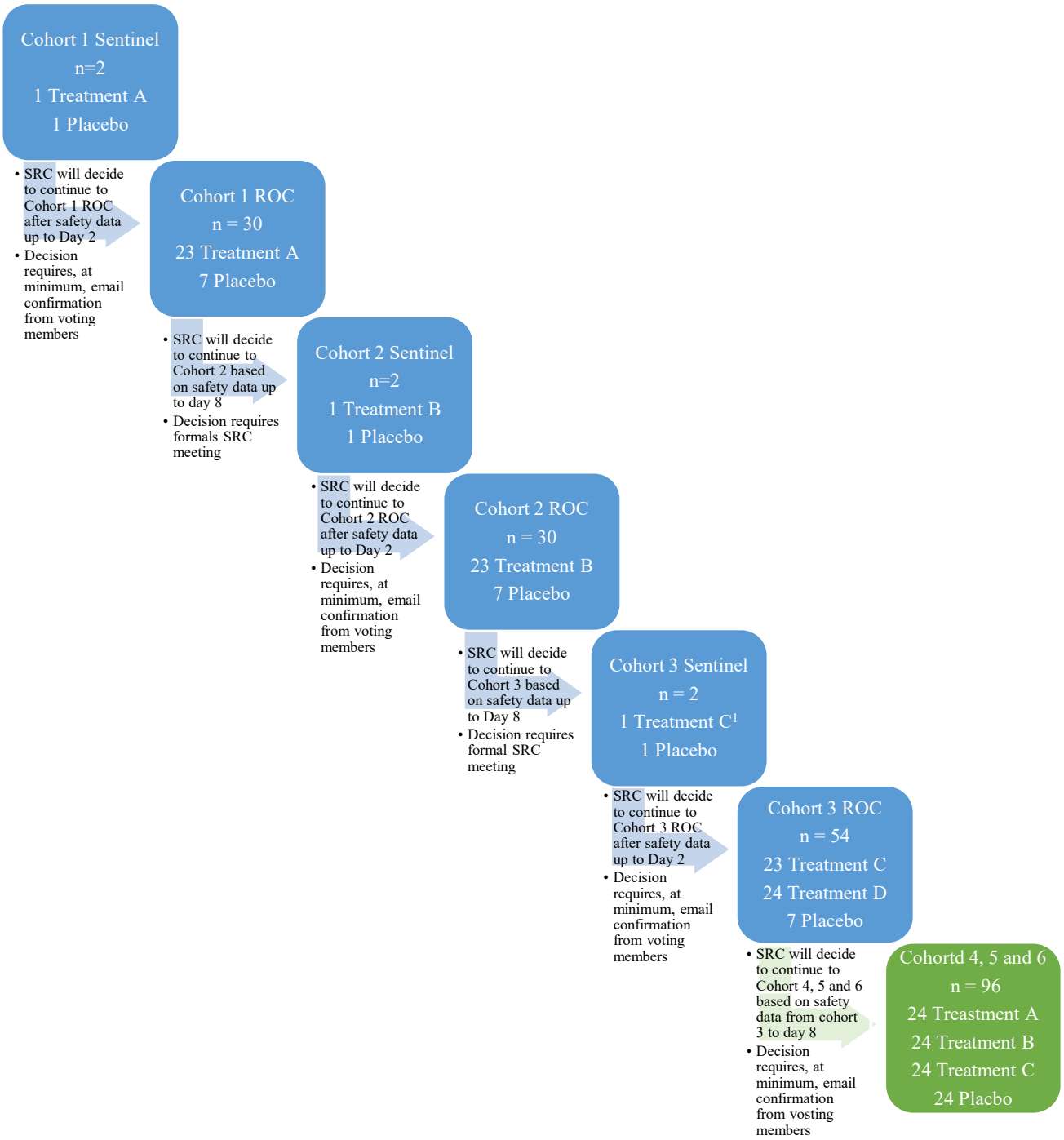
Despite consisting of 2 separate treatments, Cohort 3 will include only include 2 sentinels, 1 placebo and 1 active from Treatment C only, as Treatments C and D are functionally identical until the second dose of active or placebo (respectively) is scheduled 28 days later. The sentinel will not be randomised between Treatment C and D as Treatment D will receive placebo as a second dose, and accordingly no sentinel is required to ensure optimal safety.

Cohorts will be dosed sequentially, and escalation from Cohort 1 to Cohort 3 will be authorised by the SRC if no safety events of concern are observed in subjects up to Day 8 following review of the cumulative safety data of each Cohort.

After the first vaccination dose has been administered to Cohorts 1, 2 and 3 and the aggregated safety data reviewed by the SRC, vaccination will be initiated for Cohorts 4, 5 and 6. These Cohorts will not include sentinels, however, the SRC will review the aggregated/cumulative safety and tolerability data up to at least Day 8 post vaccination for all subjects in each of Cohorts 4, 5 and 6 by cohort before proceeding to the second vaccination dose.

The same authorisation review process will again be repeated at the second dose.

The study design is summarised in Figure 1.



[1] As Treatments C and D are functionally identical until Day 29, the active sentinel subject from Treatment C will serve as a sentinel for both treatments at first dose. At second dose, no sentinel is required for Treatment D as the placebo will be administered.

Figure 1: Visual Schematic for Study Design

6.1 Study Progression and Evaluations

The study will progress from Cohort 1 to Cohort 2, and from Cohort 2 to Cohort 3 when the cumulative safety data of the previous cohort up to Day 8 have been collected and, reviewed by the SRC, and who will provide authorisation to proceed to the next dose cohort by the process described in Section 7.1. Vaccination for Cohorts 4, 5 and 6 will be initated only once the SRC have completed their review of the aggregated safety and tolerability data from Cohorts 1, 2 and 3.

Adjustment to the currently outlined subsequent dose level, dosing regimen, and period of subjects' follow-up may be made by the SRC based on data from the prior completed dose level. However, the total dose to be administered in a given cohort will not exceed the one currently outlined in the protocol.

6.2 Starting Dose

The planned starting dose of 5 mcg administered twice in subjects has been selected based on reported dose levels of comparable viral subunit vaccines approved for use (as described in Section 5.2.2, and the IB). Of these comparable vaccines highlighted, the selected dose represents between a 3- to 18-fold decrease (compared to RECOMBIVAX HB® and GARDASIL®9 respectively) in total exposure, therefore this initial starting dose is deemed to be a suitable dose to establish initial safety information for the SARS-CoV-2 Sclamp vaccine for dose escalation purposes.

6.3 Dose Escalation Scheme

7. The proposed escalation scheme for the study consists of two three-fold dose increments. The planned dose range of 5 mcg to 15 mcg to 45 mcg administered twice 28 days apart was selected to minimize the risk to the subjects while ensuring the evaluation of an exposure range that encompasses and exceeds the expected level to achieve an immunological response. Dose Escalation Criteria

7.1 Data Review by the Safety Review Committee

The SRC will be responsible for the assessment of available safety and tolerability data for each cohort and to make decisions with regards to study progression through the three cohorts in Part 1 and prior to initiating vaccination for Part 2. The SRC will be composed of at least the PI, one Sponsor representative, and a Syneos Health Medical Monitor. Additional non-voting members of the SRC may also be included in the SRC to contribute to discussions, but will not have a vote in the decision to progress to a new cohort. The conduct of the SRC during the study will be as dictated in the SRC Charter.

In Part 1, for the purpose of progressing from sentinels to dosing the rest of cohort (ROC), an informal SRC discussion will be held after the sentinel's safety data are available for 48-hours post dose (Day 2). If no AEs of note, SAEs, or severe AEs, dosing of the ROC may be conducted

without a formal SRC meeting, and dosing may commence with email confirmation from the SRC members (this process will be repeated again following administration of the second dose).

For the purpose of progressing from Cohort 1 to Cohort 2 and from Cohort 2 to Cohort 3, a formal SRC meeting will be held after aggregated safety and tolerability data up to at least Day 8 (7 days post-first dose) are available for all eligible subjects from each cohort before proceeding with vaccination of the next cohort (and similarly up to at least Day 36 following the second vaccination dose at Day 29). As the maximal immunological response is not expected to be reached by Day 8, immunological data will not be assessed as part of the SRC decision making process.

The potential decisions of the SRC are:

1. Escalate to the next planned dose level; or
2. Suspend dose escalation until further review of study data can be made, allowing the SRC to determine whether predefined halting rules have been met. Dose escalation may resume once the SRC concludes that no halting rules have been met; or
3. Stop dose escalation;
4. Terminate the study.

The SRC will conduct a blinded review of the data; however the blind may be broken for individual subjects if judged necessary, prior to making a decision on dose escalation. Dose escalation may occur only following mutual agreement between the SRC members. Decisions taken by the SRC will be documented and submitted to the HREC overseeing the study, along with supportive data.

7.2 Dose Halting Rules

The following sections define halting rules, which are pre-defined criteria that halt the conduct of the study (either a single cohort or the entire study). These rules are to ensure the safety of study subjects. The following criteria including grading scales to be used in this study are based on the CBER (FDA) Guidance for Industry "Toxicity Grading Scale of Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials".[4] Specific safety terms and reaction grading criteria are defined in Section 9.15.

Dosing of all subjects in a cohort shall be halted for any event suggesting that there is a significant safety risk to other subjects of the cohort, or when a clinically significant pattern of toxicity is apparent in more than one subject. The following events will result in a temporary halt of dosing within that cohort:

- The occurrence of a SAE assessed, as possibly or probably related to the study vaccine;
- The occurrence of a clinically significant unsolicited severe AE (Grade 3 AE), including vital signs, and/or a laboratory abnormality assessed as possibly or probably related to the study vaccine in ≥2 subjects in the same cohort; or
- 2 or more of the subjects enrolled in each cohort experience a severe (Grade 3):

- Allergic reaction (e.g., hives, angioedema, allergic asthma, systemic anaphylaxis) that is assessed as related to study vaccine; or
- Vaccine-related injection site ulceration, abscess, or necrosis.

If any of the above halting rules are met, dosing will be suspended for all subjects in that cohort, while continuation of other cohorts at lower or equivalent dose levels will be evaluated on a case-by-case basis. The SRC will review details of the event(s) and/or additional data. If, after further review of the data, the SRC determines that no halting rules have been met e.g., AE determined to be unrelated to the study vaccine, then dosing of the cohort may resume.

The Sponsor or the Investigator (after consultation with the Sponsor) has the right to discontinue the study at any time. If the clinical study is prematurely terminated, the clinical site must promptly inform the study subjects and must ensure that appropriate treatment and follow-up for the subjects is made available. The Sponsor must notify the HREC should the study be discontinued.

8. Study Population

8.1 Rationale for the Study Population

A healthy volunteer population has been selected for Part 1 of the study because healthy subjects with no clinically significant acute or chronic diseases or conditions represent a homogenous population allowing for proper evaluation of the safety and tolerability of a vaccine while minimising the impact of additional confounding factors. No reproductive studies in animals have been conducted with the study vaccine (SARS-CoV-2 Sclamp vaccine) so far. Since the risks to a developing human foetus, or a nursing infant, following exposure to SARS-CoV-2 Sclamp vaccine are unknown at this time, only males and non-pregnant, non-lactating females will be enrolled in this study. Female subjects of childbearing potential and non-surgically-sterile male subjects with female partners of childbearing potential will be required to use a double contraceptive method for the duration of the study and for 90 days following the last administration of the study treatment. A serum pregnancy test will be performed at screening for all women of child bearing potential, and urine pregnancy tests will also be performed prior to each dosing to confirm non-pregnant status.

A healthy older adult population has been selected for Part 2 of the study because older adults have been identified to be at greatest risk of severe disease, hospitalisation and death from COVID-19 (with risk increasing continuously from 60-years of age, and much higher over 70-years). However, it is important that these older adults have no medical co-morbidities associated with an increased risk of severe COVID-19. The ability to induce a robust immune response declines with age, therefore it is important to understand the profile of the immune response between young healthy and older adult populations to evaluate the immunogenicity of the doses tested for the vaccine. The inclusion of a healthy older adult population will enable a comparison of the preliminary immunogenicity and safety characteristics between the two age groups in the study to inform the selection of dose, prior to progression of further clinical development of the vaccine.

As the study will not be assessing pharmacokinetic parameters, there is no anticipated impact of including smokers in the population, and smoker status is considered unlikely to impact the aims of the study. It is recognised, however that smokers tend to have higher rates of respiratory and

cardiovascular issues, as well as a higher chance of contracting lung and chest infections. The inclusion of smokers in the study will therefore, be limited only to social smokers, defined as those who smoke the equivalent of no more than 10 cigarettes per week. Ex-heavy smokers (heavy smoking defined as the equivalent of 25 or more cigarettes per day) may be admitted to the study if they have quit, or reduced their cigarette intake to the defined level of social smoking, for a period of at least 12 months. Further, smokers will be required to abstain from smoking for a minimum of 2 hours prior to each visit to the clinical site, and for at least 4 hours post each study treatment administration.

8.2 Sample Size

It is planned to enroll approximately 216 male and female volunteers for participation in this study.

This study will consist of 6 cohorts (2 cohorts of a lower dose, 2 cohorts of an intermediate dose and 2 cohorts of a higher dose, examining both a single and two dose vaccination regimen). Cohort 1 will include 32 subjects (8 receiving placebo and 24 subjects receiving a low-dose of SARS-CoV-2 Sclamp vaccine administered in a two dose regimen 28 days apart).

Cohort 2 will include 32 subjects (8 receiving placebo and 24 subjects receiving an intermediate dose of SARS-CoV-2 Sclamp vaccine administered in a two dose regimen 28 days apart).

Cohort 3 will include 56 subjects (8 subjects receiving placebo, 24 subjects receiving a higher dose of SARS-CoV2 Sclamp vaccine administered in a two dose regimen 28 days apart, and 24 subjects receiving a single dose of the high-dose of SARS-CoV-2 Sclamp vaccine dosed once followed by placebo 28 days later).

Cohort 4 will include 32 subjects (8 receiving placebo and 24 subjects receiving a lower dose of SARS-CoV-2 Sclamp vaccine administered in a two dose regimen 28 days apart).

Cohort 5 will include 32 subjects (8 receiving placebo and 24 subjects receiving an intermediate dose of SARS-CoV-2 Sclamp vaccine administered in a two dose regimen 28 days apart).

Cohort 6 will include 32 subjects (8 subjects receiving placebo, 24 subjects receiving a higher dose of SARS-CoV-2 Sclamp vaccine administered in a two dose regimen 28 days apart).

No prospective calculations of statistical power have been made. The sample size of 24 subjects per treatment group has been selected to provide information on safety and estimates related to the primary and secondary endpoints.

8.3 Inclusion Criteria

Subjects enrolled in this study will be members of the community at large. The recruitment advertisements may use various media types (e.g., radio, newspaper, the clinical site Web site and volunteer database).

Part 1 Subjects must meet all of the following criteria to be included in the study:

1. Healthy male or non-pregnant female, ≥18 and ≤55 years of age, with BMI >18 and <34.0 kg/m^2 and body weight ≥50.0 kg for males and ≥45.0 kg for females.

2. Healthy as defined by:

    a. The absence of clinically significant illness and surgery within 28 days prior to dosing. Subjects displaying signs or symptoms of an acute and/or febrile illness within 24 hours pre-dose (with at least 3 symptom-free pre-dose days required) will be carefully evaluated for upcoming illness/disease. Inclusion pre-dosing is at the discretion of the Investigator, and the subject may have their scheduled dosing postponed until the condition resolves.

    b. The absence of clinically significant history of neurological, endocrine, cardiovascular, respiratory, haematological, immunological, psychiatric, gastrointestinal, renal, hepatic, and metabolic disease.

3. Non-smokers or social smokers (defined as the equivalent of fewer than 10 cigarettes per week). Ex-heavy smokers (heavy smoking defined as the equivalent of 25 or more cigarettes per day) may be admitted if they have quit,or reduced their cigarette intake to the defined level of social smoking, for a period of at least 12 months.

4. Women of childbearing potential (WOCBP) or men whose sexual partners are WOCBP must be able and willing to use at least 2 highly effective methods of contraception commencing at enrolment, during the study and for 3 months after last treatment administration. A female subject is considered to be a WOCBP following menarche and until she is in a post-menopausal state for 12 consecutive months (without an alternative medical cause) or otherwise permanently sterile (for which acceptable methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy). A follicle-stimulating hormone (FSH) test may be used to confirm post-menopausal state. Examples of acceptable methods of contraceptive methods (for female subjects) to be used throughout the study include:

    a. Simultaneous use of hormonal contraceptives, started at least 28 days prior to first study treatment administration and must agree to use the same hormonal contraceptive throughout the study, and condom for the male partner;

    b. Simultaneous use of intra-uterine contraceptive device, placed at least 28 days prior to first study treatment administration, and condom for the male partner;

    c. Simultaneous use of diaphragm or cervical cap and male condom for the male partner, started at least 28 days prior to first study treatment administration;

    d. Sterile male partner (vasectomized since at least 6 months prior to first study treatment administration);

    e. True abstinence, defined as no sexual intercourse with a male partner, (for heterosexual couples) for at least 28 days prior to first study treatment administration and for at least the duration of the study. Periodic abstinence and withdrawal are not acceptable methods.

5. WOCBP must have a negative urine pregnancy test prior to receiving each dose.

6. Male subjects (including men who have had a vasectomy) with a pregnant partner, a female partner not of childbearing potential, or a same sex partner, must agree to use a condom from the first study treatment administration until at least 90 days after the last study treatment administration.

7. Male subjects must be willing not to donate sperm until 90 days following the last study treatment administration.

8. Must be able to attend all visits for the duration of the study and to comply with all study procedures according to the study schedule.

9. Capable of, and have given, written informed consent.

Part 2 Subjects must meet all of the following criteria to be included in the study:

1. Healthy male or non-pregnant female, ≥56 years of age, with BMI >18 and <34.0 kg/m^2 and body weight ≥50.0 kg for males and ≥45.0 kg for females.

2. Healthy as defined by:

    a. The absence of clinically significant illness and surgery within 28 days prior to dosing. Subjects displaying signs or symptoms of an acute and/or febrile illness within 24 hours pre-dose (with at least 3 symptom-free pre-dose days required) will be carefully evaluated for upcoming illness/disease. Inclusion pre-dosing is at the discretion of the Investigator, and the subject may have their scheduled dosing postponed until the condition resolves.

    b. The absence of clinically significant history of a pre-existing medical condition that is not stable (neurological, endocrine, cardiovascular, respiratory, haematological, immunological, psychiatric, gastrointestinal, renal, hepatic, and metabolic disease). A stable medical condition is defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 3 months before enrolment.

3. Non-smokers or social smokers (defined as the equivalent of fewer than 10 cigarettes per week). Ex-heavy smokers (heavy smoking defined as the equivalent of 25 or more cigarettes per day) may be admitted if they have quit,or reduced their cigarette intake to the defined level of social smoking, for a period of at least 12 months.

4. Women of childbearing potential (WOCBP) or men whose sexual partners are WOCBP must be able and willing to use at least 2 highly effective methods of contraception commencing at enrolment, during the study and for 3 months after last treatment administration. A female subject is considered to be a WOCBP following menarche and until she is in a post-menopausal state for 12 consecutive months (without an alternative medical cause) or otherwise permanently sterile (for which acceptable methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy). A follicle-stimulating

hormone (FSH) test may be used to confirm post-menopausal state. Examples of acceptable methods of contraceptive methods (for female subjects) to be used throughout the study include:

a. Simultaneous use of hormonal contraceptives, started at least 28 days prior to first study treatment administration and must agree to use the same hormonal contraceptive throughout the study, and condom for the male partner;

b. Simultaneous use of intra-uterine contraceptive device, placed at least 28 days prior to first study treatment administration, and condom for the male partner;

c. Simultaneous use of diaphragm or cervical cap and male condom for the male partner, started at least 28 days prior to first study treatment administration;

d. Sterile male partner (vasectomized since at least 6 months prior to first study treatment administration);

e. True abstinence, defined as no sexual intercourse with a male partner, (for heterosexual couples) for at least 28 days prior to first study treatment administration and for at least the duration of the study. Periodic abstinence and withdrawal are not acceptable methods.

5. WOCBP must have a negative urine pregnancy test prior to receiving each dose.

6. Male subjects (including men who have had a vasectomy) with a pregnant partner, a female partner not of childbearing potential, or a same sex partner, must agree to use a condom from the first study treatment administration until at least 90 days after the last study treatment administration.

7. Male subjects must be willing not to donate sperm until 90 days following the last study treatment administration.

8. Must be able to attend all visits for the duration of the study and to comply with all study procedures according to the study schedule.

9. Capable of, and have given, written informed consent.

8.4 Exclusion Criteria

Part 1:

Subjects to whom any of the following applies will be excluded from the study:

1. Any clinically significant abnormality or vital sign abnormality at physical examination (including baseline high blood pressure [140/90] after 3 repeated measurements or high random blood sugar [non-fasting]), clinically significant abnormal laboratory test results or positive test for HIV, hepatitis B, or hepatitis C found during medical screening.

2. Any acute or chronic ongoing illness which, in the judgement of the investigator, may preclude the subject's participation.

3. Any subject that has an active COVID-19 infection (positive COVID-19 test: nasal/oropharyngeal swab and/or positive serum antibody response) at screening, or Day 1, or has been in close contact with someone who has an active COVID-19 infection, or has recovered from a previous COVID-19, SARS-CoV--1, or MERS infection.

4. Positive pregnancy, urine drug screen, or alcohol breath test at screening.

5. Known history of allergic reactions or hypersensitivity to vaccines, or to any excipient in the formulation (including the adjuvant, MF59C.1).

6. Presence of a known, or suspected, impairment of the immune system including, but not limited to, HIV, autoimmune disorders, immunosuppressant therapy, and diabetes mellitus.

7. History of a known, or suspected, respiratory system disorder including, but not limited to, cystic fibrosis, reactive airway disease, emphysema, chronic bronchitis, chronic obstructive pulmonary disease (COPD), or asthma, excluding childhood asthma.

8. History of significant alcohol abuse within 12 months year prior to screening.

9. Positive test for drugs of abuse (such as marijuana/tetrahydrocannabinol [THC] products, amphetamine, methamphetamine, methadone, barbiturates, benzodiazepines, cocaine, opiates, methylenedioxymethamphetamine [MDMA], or phencyclidine [PCP]) at screening, prior to dosing, or a history of drug abuse within 12 months prior to screening.

10. Participation in a clinical research study involving the administration of an investigational, or marketed, drug or device within 30 days prior to receiving the first treatment administration, or administration of a biological product in the context of a clinical research study within 90 days prior to the first dosing, or concomitant participation in an investigational study involving no drug, vaccine, or device administration, or intent to participate in another clinical study at any time during the conduct of the study.

11. Use of medications for the timeframes specified below, with the exception of hormonal contraceptives and medications exempted by the Investigator on a case-by-case basis because they are judged to interfere with subject safety e.g., topical drug products without significant systemic absorption are permissible:

    a. Prescription medication within 14 days prior to the first dosing;

    b. Any medication, or treatments, that may affect the immune system such as allergy injections, immunoglobulin, interferon, immunomodulators, cytotoxic drugs, or other drugs known to be frequently associated with significant major organ toxicity within 90 days prior to enrolment;

    c. Any registered vaccine administered within 30 days prior to enrolment in the study, or who plan to receive any non-study vaccines within 28 days of the second dose of the study vaccine

d. Any other investigational coronavirus vaccine i.e. SARS--CoV-1, SARS--CoV-2, MERS etc. at any time prior to, or during, the study.

e. Over-the-counter products within 7 days prior to the first dosing, with the exception of the occasional use of paracetamol (up to 2 g daily) and standard dose vitamins.

12. Donation of plasma within 7 days prior to dosing. Donation or loss of blood (excluding volume drawn at screening) of 50 mL to 499 mL of blood within 30 days, or more than 499 mL within 56 days prior to the first dosing.

13. Receipt of blood products within 2 months prior to the first study treatment administration (Day 1), or planned receipt of blood products during the study period.

14. Breast-feeding subject, or subject who plans to breastfeed from the time of first dose through 60 days after last study treatment administration.

15. Presence of tattoos, scarring, skin discoloration, or any other skin disturbances at the injection site which, in the opinion of the Investigator, may inhibit the ability to effectively perform an injection site assessment.

16. Employee or immediate relative of an employee of the clinical site, any of its affiliates or partners, or Syneos Health.

17. Any reason which, in the opinion of the Investigator, would interfere with the primary study objectives or prevent the subject from participating in the study.

Part 2

Subjects to whom any of the following applies will be excluded from the study:

1. Any clinically significant abnormality or vital sign abnormality at physical examination, or uncontrolled hyertension in adults aged ≥ 56 years and older ,or high random blood sugar [non-fasting]), clinically significant abnormal laboratory test results or positive test for HIV, hepatitis B, or hepatitis C found during medical screening.

2. Any acute or chronic ongoing illness which, in the judgement of the investigator, may preclude the subject's participation.

3. Any subject that has an active COVID-19 infection (positive COVID-19 test: nasal/oropharyngeal swab and/or positive serum antibody response) at screening, or Day 1, or has been in close contact with someone who has an active COVID-19 infection, or has recovered from a previous COVID-19, SARS-CoV-1, or MERS infection.

4. Positive pregnancy, urine drug screen, or alcohol breath test at screening.

5. Known history of allergic reactions or hypersensitivity to vaccines, or to any excipient in the formulation (including the adjuvant, MF59C.1).

6. Presence of a known, or suspected, impairment of the immune system including, but not limited to, HIV, autoimmune disorders, immunosuppressant therapy, and diabetes mellitus.

7. History of a known, or suspected, or currently unstable medical condition that may expose the participant to an increased risk for severe SARS-CoV-2 disease, such as a respiratory system disorder including, but not limited to, cystic fibrosis, reactive airway disease, emphysema, chronic bronchitis, chronic obstructive pulmonary disease (COPD), or asthma, excluding childhood asthma, uncontrolled hypertension, ischemic or structural heart disease, chronic kidney disease, chronic liver disease, endocrine disorder and neurological illness.

8. History of significant alcohol abuse within 12 months prior to screening.

9. Positive test for drugs of abuse (such as marijuana/tetrahydrocannabinol [THC] products, amphetamine, methamphetamine, methadone, barbiturates, benzodiazepines, cocaine, opiates, methylenedioxymethamphetamine [MDMA], or phencyclidine [PCP]) at screening, prior to dosing, or a history of drug abuse within 12 months prior to screening.

10. Participation in a clinical research study involving the administration of an investigational, or marketed, drug or device within 30 days prior to receiving the first treatment administration, or administration of a biological product in the context of a clinical research study within 90 days prior to the first dosing, or concomitant participation in an investigational study involving no drug, vaccine, or device administration, or intent to participate in another clinical study at any time during the conduct of the study.

11. Use of medications for the timeframes specified below, with the exception of hormonal contraceptives and medications exempted by the Investigator on a case-by-case basis because they are judged to interfere with subject safety e.g., topical drug products without significant systemic absorption are permissible:

    a. Prescription medication within 14 days prior to the first dosing that in the opinion of the Investigator could impact the subjects safe participation in the study;

    b. Any medication, or treatments, that may affect the immune system such as allergy injections, immunoglobulin, interferon, immunomodulators, cytotoxic drugs, or other drugs known to be frequently associated with significant major organ toxicity within 90 days prior to enrolment;

    c. Any registered vaccine administered within 30 days prior to enrolment in the study, or who plan to receive any non-study vaccines within 28 days of the second dose of the study vaccine

    d. Any other investigational coronoavirus vaccine i.e. SARS-CoV-1, SARS-CoV-2, MERS etc. at any time prior to, or during, the study.

    e. Over-the-counter products within 7 days prior to the first dosing, that in the opinion of the investigator could impact the subjects safe participation in the study. Paracetamol (up to 2 g daily) and standard dose vitamins will be permitted.

12. Donation of plasma within 7 days prior to dosing. Donation or loss of blood (excluding volume drawn at screening) of 50 mL to 499 mL of blood within 30 days, or more than 499 mL within 56 days prior to the first dosing.

13. Receipt of blood products within 2 months prior to the first study treatment administration (Day 1), or planned receipt of blood products during the study period.

14. Breast-feeding subject, or subject who plans to breastfeed from the time of first dose through 60 days after last study treatment administration.

15. Presence of tattoos, scarring, skin discoloration, or any other skin disturbances at the injection site which, in the opinion of the Investigator, may inhibit the ability to effectively perform an injection site assessment.

16. Employee or immediate relative of an employee of the clinical site, any of its affiliates or partners, or Syneos Health.

17. Any reason which, in the opinion of the Investigator, would interfere with the primary study objectives or prevent the subject from participating in the study.

18. Permanent resident in an aged care facility (nursing or aged care home.

9. Clinical Procedures

Unless otherwise specified, procedures, data collection and evaluation will be conducted as per the clinical site SOPs.

9.1 Screening Procedures

Subject screening procedures will be performed within 28 days preceding administration of study medication. Subjects must provide written informed consent prior to initiation of any screening procedures. The consent to perform some general screening procedures may be obtained on a consent document other than the Informed Consent Form (ICF) specific to this study, and therefore, some screening test results could be obtained before signature of the ICF specific to this study. The study-specific ICF must be signed and dated by the subject before participation to study-specific procedures.

Screening procedures will include: demographic data, medical and medication histories, such as history of diabetes mellitus, hypertension and asthma, excluding childhood asthma, physical examination, body measurements, vital signs (BP, HR, RR, and TT), ECG, oxygen saturation (SpO_2), haematology, biochemistry, random blood sugar (non-fasting), coagulation (PT, APTT, and fibrinogen), serology (HIV, hepatitis B and C tests), SARS-CoV-2 test (nasal/oropharyngeal swab and RT-PCR, and serum antibodies by ELISA), urinalysis, serum pregnancy test, alcohol breath test, and urine drug screen.

Women not of childbearing potential must be post-menopausal, defined as cessation of regular menstrual periods for at least 12 months and confirmed by FSH level at screening, unless documented FSH and estradiol tests performed at the clinical site within 6 months prior to administration of the study medication are available. For women using hormone replacement

therapy and in whom FSH level have to be confirmed, this test will be performed at least one week following the withdrawal of the therapy, but before the first dosing.

For eligibility purposes, abnormal laboratory or vital signs results may be repeated at the discretion of the PI if an abnormal result is observed at the initial reading, however this discretion should be exercised on the side of caution. In the event that the participation of a subject in the study is delayed and some screening procedures had been performed outside of the prescribed screening window, outdated screening procedures may be repeated.

9.2 Clinical Visits and Follow-Up

Each subject will come for a visit to the clinical facility on Days 1 and 29 to be dosed with the study vaccine or placebo, according to their assigned randomised treatment.

Subjects will return on Days 2, 8, 29, 30, 36, and 57 for safety, including clinical laboratory safety, and immunological assessments.

Subjects will return on Days 15 and 43 for immunological assessments only.

Subjects will also return on Days 2 and 30, and 8 and 36 for a 24-hour and 7-day post-dose (respectively) safety assessment only.

In addition, subjects will be asked to return to the clinic at approximately 6 and 12 months post second dose (approximately Days 209 and 394) for a safety follow-up and blood draws for assessment of the duration of the immune response to the vaccine.

Subjects will be asked to return for an adhoc visit in early November where they will be informed of findings related to vaccine related HIV diagnostic interference. Subjects will receive written and verbal information on the potential for vaccination to elicit a reactive HIV results on some diagnostics and assured that this result does NOT indicate a HIV positive result.

A subset of subjects will also be asked to return at 3 months after their last dose (Day 120) for additional immunology assessment to evaluate the duration of HIV diagnostic cross-reactivity

9.3 Randomisation and Blinding

Subjects will be administered either a cohort specific SARS-CoV-2 Sclamp vaccine or placebo (Treatment A, B, C, or D, see Section 9.5), according to the randomisation scheme produced by Syneos Health. Eligible subjects will be allocated a randomisation number associated with a randomised treatment prior to dosing, as close to dosing as feasible (Day 1) in order to minimise the number of subject withdrawals in the period between randomisation allocation and dosing.

The subjects and the clinical personnel involved in the collection, monitoring, revision, or evaluation of AEs, or personnel who could have an impact on the outcome of the study will be blinded with respect to the subject's treatment assignment (SARS-CoV-2 Sclamp vaccine or placebo). Except for circumstances related to subject safety (see Section 7.1), blinding will be maintained at least until data collection of all subjects in each cohort up to Day 57 i.e., when reporting and evaluation of all AEs have been completed up to 28 days post-second dose.

After data is collected for all subjects up to Day 57 the collected data will be locked and the treatment assignment will be unblinded to all study team members for the purpose of data analysis and generation of the Clinical Study Report (CSR) Part 1 and Addendum to the CSR Part 2. Subjects will remain blinded for the remaining duration of the study, thus the study will adopt a single-blind design after Day 57.

Designated pharmacy personnel at the clinical site not directly involved with the clinical aspects of the trial will prepare and dispense the study medication and will be aware of the randomisation code and the treatment.

In the event of an emergency for an individual subject in which knowledge of the study treatment is critical to the subject's medical management, or for the decision of dose escalation, the Investigator, or another attending study physician, will break the blind for that subject. An envelope for each subject containing their treatment assignment will be available from the pharmacy personnel. The Investigator, or other attending study physician, will make every effort to contact the Sponsor prior to unblinding a subject's treatment assignment and will record the date and reason for unblinding in the study source documents. In the event the Sponsor cannot be contacted prior to unblinding, the Sponsor will be contacted at the earliest feasible time after the unblinding has occurred.

9.4 Allocation of Subjects to Treatment

Subjects will be randomly assigned a 4-digit randomisation number beginning by "1", "2", "3", "4", "5" and "6" for Cohorts 1, 2, 3, 4, 5 and 6 respectively. Each subject number corresponds to a treatment assignment on the generated randomisation scheme.

For Part 1 (healthy adults), the two sentinel subjects of each cohort will have the first two subject numbers of their cohort e.g. 1001 and 1002 for Cohort 1, and 2001 and 2002 for Cohort 2 and 3001 and 3002 for Cohort 3. In the case where a subject is replaced (following specifications described in Section 9.13), the replacement volunteer will take the same treatment and the same subject number added with 100. For example, if the subject number 1001 withdrew, the replacement subject will have the subject number 1101, with the treatment planned for the randomization number 1001.

For Part 2 (healthy older adults), subjects will be randomly assigned to treatment groups in a 3:1 ratio of Active to Placebo. The randomisation will be stratified by age (≥56 to ≤65 years, and ≥ 66 years respectively).

For subjects who are replaced, the replacements should take the same treatment assignment as the original subject to ensure that the planned treatment allocation ratio is retained.

9.5 Study Medication

Drug Product (DP) will be provided as separate single-use vials containing each, the SARS-CoV-2 Sclamp antigen (CSIRO Manufacturing, Clayton VIC 3168, Australia). Squalene adjuvant material, MF59C.1, will be supplied in pre-filled syringes each containing a total volume of 0.25 mL (Seqirus). DP and adjuvant will be mixed at the clinical site, and 0.5 mL of the vaccine

suspension will be drawn into a syringe for IM injection as the final investigational medicinal product (IMP).

Placebo will be provided in a single-use vial containing sterile saline for injection (Pfizer, Mulgrave VIC 3170). 0.5 mL of the placebo will be drawn into a syringe for injection.

All vaccine and placebo materials will be received and handled while observing aseptic techniques. After preparation, the vaccination dose will be transported in a blinding bag placed in a box, and unblinded dosers will be used to preserve the blinding, as physical masking of the syringe to preserve the blind is not possible.

Subjects will receive two single IM doses (5, 15, or 45 mcg) of the following 3 study treatments at 28 days apart as follows:

- Treatment A (Cohorts 1 & 4): SARS-CoV-2 Sclamp vaccine 1 x 5 mcg in 0.5 mL suspension, or placebo, administered in a two dose regimen at least 28 days apart.
- Treatment B (Cohorts 2 & 5): SARS-CoV-2 Sclamp vaccine 1 x 15 mcg in 0.5 mL suspension, or placebo administered in a two dose regimen at least 28 days apart.
- Treatment C (Cohorts 3 & 6): SARS-CoV-2 Sclamp vaccine 1 x 45 mcg in 0.5 mL suspension, or placebo administered in a two dose regimen at least 28 days apart.
- Treatment D (Cohort 3 only): SARS-CoV-2 Sclamp vaccine 1 x 45 mcg in 0.5 mL suspension, or placebo administered as a single dose, followed by placebo as the second dose, at least 28 days apart.
- Placebo: 0.5 mL solution (Sterile saline for injection)

9.6 Treatment Supplies and Accountability

It is the responsibility of the Sponsor to ensure that the study vaccine, adjuvant and placebo provided for this study are suitable for human use. The active vaccine and placebo products will be provided by the Sponsor, packed and labelled in accordance with GMP and Annex 13 requirements. The Sponsor is responsible for shipping a sufficient amount of dosage units to allow the clinical site to maintain an appropriate sampling for the study, according to TGA regulation.

Study medication will be stored at the clinical site as per applicable requirements. SARS-CoV-2 Sclamp antigen will be stored in a locked, environmentally-controlled medication room (at 2-8 °C) with restricted access, and the MF59C.1adjuvant will be stored in a locked, enviromentally-controlled medication room (at 2-8 °C) with restricted access. The individual dosage units and outer container(s) will bear a label containing at least the name of the study treatment, lot and/or batch number, and manufacturing and/or expiry/retest date. The management of investigational vaccines is under the supervision of the Investigator.

Individual doses for each subject and period will be dispensed at the clinical site, as per the appropriate local SOP. Individual doses will be dispensed according to the randomization scheme in appropriate containers indicated with at least the project number and the subject number. Whenever possible, dispensing and study treatment administration should be conducted within 3

hours of preparation of each dose, which will be stored at ambient temperature in a locked medication room prior to use. If stored refrigerated, syringes must be allowed to acclimatise to room temperature for at least 10 minutes prior to use.

All study vaccine materials received at the clinical site will be inventoried and accounted for throughout the study, and the result recorded in the drug accountability/retention record according to the clinical site appropriate SOP. Upon completion of the study, the remaining test and reference products will be maintained at the clinical site, discarded or returned to the Sponsor, as per Sponsor's request.

9.7 Study Treatment Administration

The study vaccine, or placebo, will be administered to the deltoid region of the subjects non-dominant arm(or deltoid region of other arm should a tattoo be present) via IM injection observing aseptic techniques. Detailed instructions for study vaccine administration will be included in the pharmacy manual.

Prior to treatment administration, subjects must be determined to be eligible for study vaccination and it must be clinically appropriate in the judgement of the Investigator, or another attending study physician, to vaccinate. Eligibility for study treatment administration prior to first administration is determined by evaluating the eligibility criteria outlined in Sections 8.3 and 8.4. For second dosing (Day 29), subjects who may fall outside of the bounds of eligibility criteria may still be dosed if it is deemed safe to continue in the opinion of the Investigator, or other attending study physician.Those subjects who fall outside the bounds of eligibility and who are not dosed will be withdrawn from the study and the reason for discontinuance documented.

Standard immunisation practices are to be observed, and care should be taken to administer the injection intramuscularly. Before administering vaccine, the vaccination site is to be disinfected with an appropriate skin disinfectant (e.g. 70% alcohol) and allowed to dry.

As with all injectable vaccines, trained medical personnel and appropriate medical interventions should be readily available in case of anaphylactic reactions following vaccine administration e.g. adrenaline (epinephrine), diphenhydramine, and/or other medications for treating anaphylaxis should be available).

The time of injection of each subject will be recorded in the source documents. Time of dosing will be set as the time of start of injection.

9.8 Study Restrictions

9.8.1 Food and Fluids

No food or fluid intake restrictions will be in place for the duration of the study.

9.8.2 Tobacco, Alcohol, and Illicit Drugs

Subjects will be required to abstain from using soft or hard drugs from screening and throughout the study or any tobacco or nicotine products from at least 2 hours prior to each dosing until 4 hours post-dose. Subjects will be required to abstain from food containing poppy seeds within 24 hours prior to each treatment administration.

Consumption of alcohol-based products will be prohibited from 24 hours prior to each visit on Days 1, 2, 8, 15, 29, 30, 36, 43, 57, 209, and 394.

9.8.3 Prior and Concomitant Medications

Subjects will be required to avoid using excluded prescription, over-the-counter (OTC) (other than those specified in the protocol), immunosuppressant treatments and related coronavirus vaccines i.e. SARS-CoV-1, SARS-CoV-2, MERS-CoV etc. for the periods of time specified in exclusion criterion #11 and throughout the study.

All medications and vaccinations taken by subjects after screening until the last study day will be documented as concomitant medications. Concomitant medications will be documented by treatment group, therapeutic area, and preferred drug name. Additionally, prior medical history of vaccinations, especially recent history of immunization boosters or influenza vaccinations, may be categorized as concomitant medications. If it is unclear whether a subject's use of medication is to be classified as a prior or concomitant medication i.e. falling within the screening period or periods of time specified in exclusion criterion #11, it is to be assumed that its use is concomitant.

Medications will be coded using the WHO Drug dictionary, and a listing will be presented for all concomitant medication data for all subjects.

9.8.4 Posture and Physical Activity

Subjects will be allowed to engage in normal activity.

9.9 Sample Collection and Processing

Over the course of the study, a blood sample will be collected at each visit (total of no more than 36 blood samples from each subject) for screening, safety laboratory and immunological assessments. Sample volume collected will vary between 15 mL and a maximum of 73 mL with individual samples collected into multiple tubes to facilitate disparate immunological tests (see table below for details).

A total of 8 blood samples will be collected for safety laboratory assessments from each subject, one sample at screening, pre-dose (within 60 minutes pre-dose), and 1, 7, and 14 days post dose for each dose (Days 1, 2, 8, 29, 30, 36). Each sample will consist of 15 mL of whole blood.

PD samples collected for immunogenicity assessment will 4 mL for T-cell analysis, 10 mL for ELISA, Luminex assay, virus neutralisation assay, and ADCC analysis, and 20 mL for isolation and cryopreservation of PBMCs. Pre-dose samples should be taken within 60 minutes of dosing, but all other samples may be taken within the visit window specified in Section 9.2.

Sample collections performed outside the pre-defined time windows are protocol deviations, however will be used for immunological, safety and statistical analyses. Unless otherwise specified, or for subject safety, when blood draws and other procedures coincide, blood draws will have precedence. Blood samples will be collected by direct venipuncture.

The total volume of blood including that collected for eligibility screening and safety purposes should not exceed 500 mL for the whole study, with up to 400 mL collected at visits between Day 1 and Day 57±2, and up to 100 mL collected at the Day 209±5 and 394±5 visits. All blood samples will be collected and processed as per the supplementary study specific laboratory manuals.

Table 1: Summary of all blood samples collected over the study Part 1 (Cohorts 1-3)

Visit	Total Collection Volume (mL)	Number of Samples Collected and Purpose of Sample			
		Safety Lab (15 mL)	PD (3-4 ml Whole blood)	PD (8-10 mL Serum)	PD 10-20 mL PBMCs)
Screening	29	1	1	1	0
Day 1 (first dose)	63	1	2	2	1
Day 2	15	1	0	0	0
Day 8	39	1	1	0	1
Day 15	34	0	1	1	1
Day 29 (second dose)	49	1	1	1	1
Day 30	15	1	0	0	0
Day 36	43	1	2	0	1
Day 43	34	0	1	1	1
Day 57	59	1	1	2	1
Day 120	10	0	0	1	0
Day 209	40	0	0	2	1
Day 394	20	0	0	2	0
Total volume	**450**				

Table 2: Summary of all blood samples collected over the study Part 2 (Cohorts 4-6)

Visit	Total Collection Volume (mL)	Number of Samples Collected and Purpose of Sample			
		Safety Lab (15 mL)	PD (3-4 ml Whole blood)	PD (8-10 mL Serum)	PD 10-20 mL PBMCs)
Screening	25	1	0	1	0
Day 1 (first dose)	63	1	2	2	1
Day 2	15	1	0	0	0
Day 8	39	1	1	0	1
Day 15	34	0	1	1	1
Day 29 (second dose)	45	1	0	1	1
Day 30	15	1	0	0	0
Day 36	39	1	1	0	1
Day 43	34	0	1	1	1
Day 57	55	1	0	2	1
Day 209	30	0	0	1	1
Day 394	10	0	0	1	0
Total volume	**404**				

9.9.1 Samples Storage

Samples collected for safety assessments will be retained by the central laboratory for 60 days after which they will be destroyed.

Samples collected for immunogenicity analysis will be retained by the bioanalytical labs for a maximum of 15 years after the study completion date.

9.10 Subject Monitoring

Subjects will be monitored throughout the study by the clinical staff for adverse events. A physician will be on site for treatment administration and until at least 2 hours post-dose, and available on call for the remainder of the study. If necessary, a physician, either at the clinical site or in a nearby hospital will administer treatment for any adverse event(s). A crash cart or emergency bag containing the necessary rescue material and appropriate medications will be available in the clinic to allow rapid intervention in case of emergency.

Subjects will be closely monitored by a medical team in the hours following dosing for the presence of symptoms of allergic or hypersensitivity reactions. Subjects will be also encouraged to quickly report any symptoms at any time they occur during the study period. The necessary rescue material, equipment, and appropriate medications will be available in the in the clinic to allow rapid intervention in case of emergency including, but not limited to:

- Oxygen;
- Adrenaline 1:1000 solution for IV or endotracheal injection;
- Antihistamines;
- Corticosteroids; and
- IV infusion solutions, tubing, catheters, and tape.

The following procedures will be followed in the event of a suspected anaphylactic reaction after dosing:

- Maintain an adequate airway.
- Administer antihistamines, adrenaline (epinephrine), or other medications as required by patient status and directed by the PI or a Medical Sub-Investigator.
- Continue to observe the patient and document observations.
- Emergency medical services may be called as needed.

Safety parameters, including laboratory results and ECG, will be assessed by a physician, using the clinical site's criteria for biomedical laboratory and ECG acceptance ranges as suggested guidelines in making the medical assessment. Abnormal safety laboratory results will be graded as mild, moderate or severe.

Scheduled safety measurements will be repeated according to the clinical site SOPs or upon request from a physician. Any abnormal repeated measurement will be evaluated by a physician and repeated if judged necessary. Further action may be taken upon physician's request.

Subjects will be advised to notify their health care professional(s) (e.g., physician, dentist, and/or pharmacist) that they are participating in a clinical research study on a treatment called SARS-CoV-2 Sclamp Vaccine, which is being developed for potential clinical use in the prevention of COVID-19 before taking any medicines or undergoing any medical procedure.

9.10.1 Vital Signs

BP, HR, RR, TT, and SpO_2 will be measured in a sitting position (except for safety reasons), at screening, pre-dose (each dose, Days 1 and 29), 24 hours post-dose (each dose, Days 2 and 30). Vital signs measurements should be performed before the blood collection whenever possible. Subjects should be seated for at least 5 minutes prior to taking measurements to allow for acclimatisation.

9.10.2 ECG

ECG will be performed at screening, before dosing (each dose, Days 1 and 29), and approximately 24 hours post-dose (each dose, Days 2 and 30). Subjects should recline in supine position for at least 5 minutes prior to taking measurements to allow for acclimatisation.

9.10.3 Physical Examination

A complete physical examination will be performed at screening. A complete physical examination includes assessments of the following: head, eyes, ears, nose, throat (HEENT), neck, chest, lungs, abdomen, musculoskeletal, dermatological, cardiovascular/peripheral vascular, and general neurological examination.

A brief physical examination will be done at pre-dose (each dose, Days 1 and 29). A brief physical examination includes assessments of the following: HEENT, chest, lungs, abdomen, dermatological, cardiovascular/peripheral vascular, and areas of note elicited from the subject.

9.10.4 Drug and Alcohol Screen

A urine drug screen (amphetamine, methamphetamine, methadone, barbiturates, benzodiazepines, cocaine, opiates, MDMA, PCP, and THC) and an alcohol breath test will be performed at screening and prior to each dosing.

9.10.5 Pregnancy Test

Where applicable i.e. for WOCBP, a serum pregnancy test will be performed at screening, and a urine pregnancy test will be performed pre-dose (each dose, Days 1 and 29). Where a positive urine pregnancy test is returned on Days 1 or 29, a serum pregnancy test will be undertaken for confirmation.

9.10.6 Laboratory Assessments

9.10.6.1 Tolerable Windows

Assessment value ranges, including those pertaining to haematology, biochemistry, coagulation, serology, and urinalysis are defined in Section 9.15.2. Subjects with values outside of these tolerable ranges will be assessed on a case-by-case basis by the PI to determine if follow-up is required for safety reasons.

To accommodate the various assessments a time window of ±1 hour and ±30 minutes will be allowed for pre and post-dose assessments respectively. Where applicable, blood collections will be prioritised ahead of other assessments (with an exception for vital signs, described in Section 9.10.1).

9.10.6.2 Haematology

Haematology will be performed at screening, before dosing (each dose, Days 1 and 29±2), approximately 24 hours after each dosing(Day 2, Day 30±1), Day 8±1, Day 36±2, Day 57±2. The following will be assessed: haemoglobin, haematocrit, RBC count, WBC count, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelet count.

9.10.6.3 Biochemistry

Biochemistry will be performed at screening, before dosing (each dose, Days 1 and 29±2), approximately 24 hours after each dosing(Day 2, Day 30±1), Day 8±1, Day 36±2, Day 57±2. The following will be assessed: albumin, amylase, lipase, creatine kinase, cholesterol, alkaline phosphatase, AST, ALT, GGT, urea, calcium, glucose random, magnesium, phosphate, potassium, creatinine, sodium, total bilirubin, LD, total protein, serum pregnancy (at screening and confirmation if a positive urine pregnancy test is returned on Days 1 and 29±2), urine pregnancy Days 1 and 29±2, and FSH (at screening only).

9.10.6.4 Coagulation

Coagulation tests will be performed at screening, before dosing (each dose, Days 1 and 29±2), approximately 24 hours after dosing(Day 2, Day 30±1), Days 8±1, 36±2, and 57±2. The following will be assessed: prothrombin time (PT), partial prothrombin time (APTT), and fibrinogen.

9.10.6.5 Serology

Serology will be performed at screening. The following will be assessed: HIV 1 /2 and P24 antigen and antibody, hepatitis B surface antigen (HBsAg), and hepatitis C virus (HCV) antibody.

9.10.6.6 Urinalysis

Urinalysis will be performed at screening, before dosing (each dose, Days 1 and 29±2), approximately 24 hours after each dosing(Day 2, Day 30±1), Day 8±1, Day 36±2, Day 57±2. The

following will be assessed: microscopic examination, pH, specific gravity, protein, glucose, ketones, bilirubin, occult blood, nitrite, urobilinogen, and leukocytes.

9.10.6.7 SARS –CoV-2 Test

A SARS-CoV-2 test (nasal/oropharyngeal swab and RT-PCR and serum antibodies by ELISA) will be performed at screening, and Days 1 29 (nasal/oropharyngeal swab and RT-PCR only) and may also be performed on an *ad hoc* basis for subjects displaying, or reporting, symptoms characteristic of COVID-19 i.e. fever, dry cough, shortness of breath etc. at any time up to day 394.

9.10.7 Subject Self-Reporting

Subject self-reporting will occur throughout the study and will involve subjects being provided with access to an electronic diary(eDiary), or paper diary card(Diary), an oral thermometer, and a transparent, circular measuring device to provide safety information during periods when the subject is not present at the clinical site.

The electronic diary will be used from the time of first dose (Day 1) to 28 days post-second dose (Day 57±2), but may also be used during the 12 month follow-up period (up to Day 394±5) on an *ad hoc* basis if safety events arise. Subjects are required to complete daily reporting of solicited adverse events from Day 1 to Day 8, and Day 29 to Day 36. Subjects will use the diary to report spontaneous adverse events, concomitant medication use, doctor visits, and the COVID-19 symptoms as these events arise during study participation.

The oral thermometer will be used to provide subjects oral temperature, and the transparent, circular measuring device will be used to measure any local reactogenicity events i.e. redness, swelling etc. arising around the injection site. Training for the use of the oral thermometer and measuring device, as well as the electronic diary, will be provided on Day 1 following dosing.

When measuring oral temperature, subjects will be required to abstain from eating or drinking hot or cold foods and drinks for 30 minutes prior to each reading.

Examples of information captured via self-reporting will include both local (pain, swelling, redness etc.) and systemic events (fever, nausea, diarrhoea, fatigue, headache , muscle aches), as well as a prompt for symptoms of COVID-19, or potential recent exposure to SARS-CoV-2, or acquaintances diagnosed with COVID-19.

9.10.8 Injection Site Examination

An injection site examination will be performed at screening, pre-dose (each dose, Days 1 and 29), 30 minutes, and 24 hours post-dose (each dose, Days 2 and 30) to document the appearance. Subjects will be provided instructions on how to self-assess at home daily (from Days 1-8 and 29-36). An injection site examination site at screening will consist of examining the injection site (deltoid area of the subjects non-dominant arm), and making note of any skin reactions, disturbances, tattoos (on the deltoid area of the arm), or discolourations, for subject eligibility purposes. An injection site examination pre-dose will consist of examining the injection site and making note of the presence of any skin reactions, disturbances, or discolourations to establish a

baseline for assessment. An injection site examination post-dose will consist of examining the injection site and making note of the presence of any skin reactions, disturbances, or discolourations, such that they may be compared to the pre-dose examination. For each dose at pre-dose, 30 minutes, 24 hours, and 7 days post-dose, a trained observer, whom is blinded to the randomization scheme, will check and, as appropriate, record any local dermal reactions at the application site of note and review the eDiary/Diary with the subject.. When possible, the same evaluator will follow the subject throughout the study. In the event that more than one evaluator is required to follow the subject throughout the study, then every precaution should be taken to limit the number of evaluators.

9.11 Study Exit Procedures

Blood draws for immunogenicity assessments, and AE monitoring will be performed on the last study day (Day 394±5). In the event of discontinuance of a study subject leading to withdrawal from the study, all efforts will be made to complete study exit procedures within 14 days after the last participation of the subject in the study.

9.12 Data Collection and Evaluation

The clinical study site will use a validated EDC system to enter subject data onto electronic case report forms (eCRFs). Data will be collected using the EDC system and entered into a quality controlled clinical database. Prior to the commencement of the study, items to be included in the clinical database will be determined, and suitable paper source documents will be created to ensure the appropriate collection of all required data.

Clinical staff conducting the study will enter the required data promptly, accurately, legibly, and indelibly onto source documents. All entries, corrections, and alterations will be made by the Investigator or other authorized study personnel, and all data entries will be verified for accuracy and correctness. The EDC system is optimized for manual keying and review (including review by independent monitors) and maintains a full audit trail. All source documents will be conserved in order to maintain data integrity.

Clinical laboratory, PD, safety, and/or immunogenicity data will be transmitted electronically from external vendors to Data Management and reconciled against the clinical database. Further details of data management processes will be detailed in the data management plan.

9.13 Subject Withdrawal and Replacement

Subjects will be advised that they are free to withdraw from the study at any time. Over the course of the study, the Sponsor and the Investigator or a delegate may withdraw any subject from the study for one of the reasons described below; subject withdrawal will be done in accordance with the clinical site's SOP:

- Safety reason;
- Non-compliance with protocol requirements;
- Significant protocol deviation; or

- Positive alcohol breath test, urine drug screen, or pregnancy test;

Haematology, coagulation, and biochemistry results will be reviewed by the Investigator prior to dosing; subjects will be withdrawn from the study if it is deemed that the subject's safety may be at risk on the basis of these test results.

Subjects who withdraw, or are withdrawn, from the study prior to dosing, but after randomization, may be replaced. Subjects who withdraw, or are withdrawn, from the study after dosing will not be replaced. However, in the event that individual subjects drop out early into the study or the number of drop-outs exceeds initial expectations, subjects who withdraw, or are withdrawn, may be replaced at the discretion of the Sponsor. Such replacement resulting in dosing more subjects than planned in this protocol would be documented in a protocol amendment.

Subjects who withdraw, or are withdrawn, will be asked to remain at the clinic until the Investigator or a delegate agrees that the subject is fine and can be discharged. As soon as subject withdrawal is confirmed, blood sampling will be stopped. A PD blood draw may be collected at the time of withdrawal if deemed required by the Investigator. Study exit procedures will be performed at the time of withdrawal from the study, or as soon as possible thereafter.

9.14 Early Termination Visit

In the event that a subject withdraws, or is withdrawn, from the study, the PI will notify the Sponsor and, when possible, will invite the subject to return to the clinical site for an early termination visit. When applicable, the visit will include the procedures listed below:

- Review the subject's solicited and unsolicited safety data;
- Perform an injection site inspection (if terminated within the reactogenicity reporting period for either dose);
- Review of concomitant medications/vaccinations since last visit; and
- Draw blood samples for safety laboratory and immunogenicity assessments;

9.15 Adverse Events

9.15.1 Definition of Adverse Events

An AE is any symptom, physical sign, syndrome, or disease that either emerges during the study or, if present at screening, worsens during the study, regardless of the suspected cause of the event. All medical and psychiatric conditions (except those related to the indication under study) present at screening will be documented in the medical history eCRF. Changes in these conditions and new symptoms, physical signs, syndromes, or diseases should be noted on the AE eCRF during the rest of the study. Clinically significant laboratory abnormalities should also be recorded as AEs. Surgical procedures that were planned before the subject enrolled in the study are not considered AEs if the conditions were known before study inclusion; the medical condition should be reported in the subject's medical history.

Adverse events are collected as either solicited or unsolicited AEs. Solicited events are those collected in the eDiary Study Symptoms Form, which subjects are prompted to enter daily for 7 days following each vaccinaton. Unsolicited AEs are those that are reported spontaneously by the subject, either in the eDiary Adverse Events form, during a study visit, or by contacting the study site between visits.

Any vital sign abnormality that is judged to be clinically significant by the investigator must be recorded as an AE.

Any abnormal laboratory test finding that is judged by the investigator as clinically significant must be recorded as an AE or an SAE, if it meets the definition of an SAE (Section 9.15.3).

9.15.2 Recording of Adverse Events

Adverse events will be recorded and evaluated for their seriousness, severity, and relationship to the study medication. Adverse events will be collected and documented during the course of the study by appropriately trained and delegated medical staff in the clinic, as well as via self-reporting from subjects using the electronic diary. For a period of 12 months following the last study vaccine administration, adverse events will also be documented, if reported. Adverse events will be followed-up until complete resolution, or until the Investigator judges it to be safe to discontinue follow-up.

The term “reactogenicity” refers to solicited signs and symptoms (“solicited AEs”) occurring in the hours and days following vaccination, to be collected by the subject or legal representative(s) for 7 consecutive days, using an electronic Diary (eDiary) or paper Diary card (Diary).

The following solicited local and systemic AEs are included in the e-Diary. Solicited local reactions include erythema, swelling, and pain at the injection site. Solicited systemic reactions include fatigue, fever, headache, myalgia/arthralgia, chills, diarrhoea, nausea/vomiting.

Upon review of the subject ediary, if a solicited local or systemic AE has been reported with a severity Grade=3 (severe), then the site is to confirm with the subject whether medical assistance was sought, was concomitant medication taken, and collect information around the event and outcome to document a safety assessment. In the event that the additional information leads to a determination that the solicited AE is deemed a Serious Adverse Event (SAE), the site will record the solicited AE as an SAE and report the event following the SAE reporting guidelines and time frames.

Each solicited AE is to be assessed using the toxicity grading provided in the scoring system adapted from the FDA Guidance for Industry -Toxicity Grading Scale for Healthy Adults and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials.[4] Solicited AEs will be recorded as mild, moderate or severe by study subjects.

Table 2. Toxicity Grading for Solicited Local (Administration Site) Adverse Events

Local Reactions to Injection	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Pain (at the vaccination site)	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
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest
Erythema/Redness	2.5 – 5 cm	5.1 – 10 cm	>10 cm
Induration/Swelling	2.5 – 5 cm and does not interfere with activity	5.1 – 10 cm or interferes with activity	>10 cm or prevents daily activity

Table 3. Toxicity Grading Scales for Solicited Systemic Adverse Events

Systemic Solicited Adverse Event	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Fever °C (Oral*)	38.0 – 38.4 .	38.5 – 38.9	39.0 - 40
Chills	Present, but does not interfere with activity	Interferes with activity	Prevents daily activity
Nausea	Nausea present but not interfering with daily activity	Nausea present leading to decreased oral intake	Nausea present leading to minimal to no oral intake
Vomiting	No interference with activity or 1 – 2 episodes in 24 hours	Some interference with activity or >2 episodes in 24 hours	Prevents daily activity, ≥4 episodes in 24 hours, or 2 or more per day prolonged on several days
Muscle pain	Present, but does not interfere with activity	Interferes with activity, or some use of non-narcotic pain reliever	Prevents daily activity; use of narcotic pain reliever
Joint pain	Present, but does not interfere with activity	Interferes with activity, or some use of non-narcotic pain reliever	Prevents daily activity; use of narcotic pain reliever
Headache	Present, but does not interfere with activity	Interferes with activity, or some use of non-narcotic pain reliever	Prevents daily activity; use of narcotic pain reliever

Systemic Solicited Adverse Event	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Fatigue/Somnolence	Present, but does not interfere with activity	Interferes with activity,	Prevents daily activity;
Diarrhoea	2 – 3 loose stools or <400 g / 24 hours	4 – 5 stools or 400 – 800 g / 24 hours	6 or more watery stools or >800 g / 24 hours or requires outpatient IV hydration
Malaise (general discomfort)	No interference with activity	Some interference with usual and social activity, no treatment	Significant, prevents usual daily and social, activity or requires treatment

* Oral temperature; no recent hot or cold beverages or smoking

Subjects will be instructed to report the local and systemic solicited AEs in the electronic Diary (eDiary)/Diary card on a daily basis, preferably about the same time each day. The eDiary/Diary card will be reviewed and the subject interviewed by the investigator or designee at each study visit regarding the AEs. All AEs are to be followed up until resolution or a stable clinical endpoint is reached. Any solicited AE that meets the following criteria must be entered into the Adverse Event eCRF:

- Solicited local or systemic AEs leading to a subject withdrawing or being withdrawn from the study by the PI,
- Solicited local or systemic AEs that last beyond 7 days duration,
- Solicited local or systemic AEs that lead to the decision not to further vaccinate a subject,
- Solicited local or systemic AEs that meet the definition of an SAE.

Each AE is to be documented in the eCRF with reference to date of onset, duration, frequency, severity, relationship to study treatment, action taken with study treatment, treatment of event, and outcome. Furthermore, each AE is to be classified as being serious or non-serious. Changes in AEs and resolution dates are to be documented on the eCRF.

For the purposes of this study, the period of observation for collection of AEs extends from the time the subject gives informed consent until the last follow-up visit (Day 394). Follow-up of the AE, even after the date of therapy discontinuation, is required if the AE persists until the event resolves or stabilizes at a level acceptable to the investigator. An AE that occurs in the period from informed consent until vaccination is a non-treatment emergent AE. An AE that occurs in the period from vaccination until study exit is a Treatment Emergent AE (TEAE).

When changes in the intensity of an AE occur more frequently than once a day, the maximum intensity for the event should be noted. If the intensity category changes over a number of days, then those changes should be recorded separately (with distinct onset dates).

Specific guidelines for classifying AEs by intensity and relationship to study drug are given in Table 4 and Table 5.

Table 4. Classification of Adverse Events by Intensity

MILD: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
MODERATE: An event that is sufficiently discomforting to interfere with normal everyday activities.
SEVERE: An event that prevents normal everyday activities.

Table 5. Classification of Adverse Events by Relationship to Study Vaccine

UNRELATED: This category applies to those AEs that are clearly and incontrovertibly due to extraneous causes (disease, environment, etc.)
UNLIKELY: This category applies to those AEs that are judged to be unrelated to the test vaccine but for which no extraneous cause may be found. An AE may be considered unlikely to be related to study vaccine if or when it meets 2 of the following criteria: (1) it does not follow a reasonable temporal sequence from administration of the test vaccine; (2) it could readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; (3) it does not follow a known pattern of response to the test vaccine; or (4) it does not reappear or worsen when the study vaccine is readministered.
POSSIBLY: This category applies to those AEs for which a connection with the test vaccine administration appears unlikely but cannot be ruled out with certainty. An AE may be considered possibly related if or when it meets 2 of the following criteria: (1) it follows a reasonable temporal sequence from administration of the vaccine; (2) it could not readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; or (3) it follows a known pattern of response to the test vaccine.
PROBABLY: This category applies to those AEs that the investigator feels with a high degree of certainty are related to the test vaccine. An AE may be considered probably related if or when it meets 3 of the following criteria: (1) it follows a reasonable temporal sequence from administration of the vaccine; (2) it could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; (3) it disappears or decreases on cessation or reduction in dose (note that there are exceptions when an AE does not disappear upon discontinuation of the vaccine, yet treatment-relatedness clearly exists; for example, as in bone marrow depression, fixed drug eruptions, or tardive dyskinesia); or (4) it follows a known pattern of response to the test vaccine.

Abbreviation: AE = adverse event.

9.15.2.1 Unsolicited Adverse Events

An unsolicited AE is an AE that was not solicited using the subject's eDiary and that was spontaneously reported by a subject. Unsolicited AEs include serious and non-serious AEs.

9.15.2.2 Medically-Attended Events and Significant New Medical Conditions

Potentially unsolicited AEs may be medically attended. The subjects will be instructed to contact the site as soon as possible to report any Medically Attended AE (MAAE) or significant new medical condition (SNMC). Details about all unsolicited AEs will be collected by qualified study personnel, reviewed by the investigator and documented in the subject's source document.

The subject e-diary will include prompts for symptoms of respiratory disease that could be COVID-19 (table below), to encourage subjects to contact the site or their medical practitioner for a confirmatory COVID-19 laboratory test (see Section 9.10.6.7).

Table 6: COVID-19 Symptoms Prompt

Systemic Solicited Adverse Event
Fever ≥37.5°C (Oral*) Or history of fever eg. Night sweats, chills
Cough
Sore throat
Shortness of Breath

* Oral temperature; no recent hot or cold beverages or smoking

In the event that a laboratory confirmation of COVID-19 is not undertaken and a diagnosis of COVID-19 is suspect, a tool to aid diagnosis of COVID-19 in subjects is included in Appendix I Checklist for Medical History Follow-Up for Persons Who Meet the Protocol Defined COVID-19 Case Definition. Study personnel will follow-up to assess the medical history against the COVID-19 diagnostic categories, signs and symptoms that meet the COVID-19 case definition as per Appendix I.

9.15.3 Serious Adverse Events

A serious AE (SAE) is any untoward medical occurrence, in the view of either the investigator or Sponsor, that:

- Results in death;
- Is life-threatening;
- Results in inpatient hospitalization or prolongation of existing hospitalization;

- Results in persistent or significant disability/incapacity; and/or
- Is a congenital anomaly/birth defect.

Other important medical events that may not be immediately life-threatening or result in death or hospitalization, based upon appropriate medical judgment, are considered serious AEs (SAEs) if they are thought to jeopardize the subject and/or require medical or surgical intervention to prevent one of the outcomes defining an SAE. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, or convulsions that do not result in in-patient hospitalization. Events which could have led to the above outcomes had they occurred with greater severity are not SAEs, but should be reported as AEs, MAAEs, or SNMCs, as appropriate.

Serious AEs are critically important for the identification of significant safety problems; therefore, it is important to take into account both the investigator's and the Sponsor's assessment. If either the Sponsor or the investigator believes that an event is serious, the event must be considered serious and evaluated by the Sponsor for expedited reporting.

Any serious adverse event (SAE) will be reported to the Sponsor via telephone, fax, e-mail, or in person, within 24 hours of occurrence or knowledge by the Investigator or designee. The notification must be directed to:

Syneos Health Safety and Pharmacovigilance

Fax Number: 001-877-464-7787
Local Toll-Free Fax Number Australia: 1800 256 952
Email: safetyreporting@syneoshealth.com

Information on SAEs will be recorded on the SAE Report Form. Blank copies are included in the study Investigator's file. It is not acceptable for the Investigator to send photocopies of the patient's medical records to the Sponsor company or its representative in lieu of completion of the appropriate AE eCRF page or SAE Report Form. However, there may be instances when copies of medical records for certain cases are requested by the Sponsor or its representative. In this instance, all subject identifiers will be blinded on the copies of the medical records before submission to the Sponsor or its representative.

The completed SAE Form and SAE cover sheet should be sent via fax or e-mail immediately upon completion to Syneos Health Safety and Pharmacovigilance. If the Investigator does not have all information regarding an SAE, they will not wait to receive additional information before completing and sending the form.

Additional relevant information or clinical follow-up should be sent via fax or e-mail to Syneos Health Safety and Pharmacovigilance as soon as it becomes available. The Investigator should follow the subject with the event until resolution or stabilization of the condition. Follow-up reports (as many as required) should be completed and faxed/e-mailed following the same procedure above.

A final report is required once the condition is resolved or stabilized and no more information about the event is expected. The final report should be completed and faxed/e-mailed following the same procedure above.

The Investigator must keep a copy of all documentation related to the event in the study site's files.

If the Investigator learns of any SAE, including death, at any other time after a subject completes the study, and they consider the event reasonably related to the study drug, the Investigator will promptly notify the Sponsor/Medical Monitor.

9.15.4 Suspected Unexpected Serious Adverse Reactions

AEs that meet all of the following criteria will be classified as suspected unexpected serious adverse reactions (SUSARs) and reported to the appropriate regulatory authorities in accordance with applicable regulatory requirements for expedited reporting:

- Serious;
- Unexpected (i.e., the event is not consistent with the safety information in the IB); or
- There is at least a reasonable possibility that there is a causal relationship between the event and the study treatment

The investigator will assess whether an event is causally related to study treatment. The Sponsor (or Syneos Health) will consider the investigator's assessment and determine whether the event meets the criteria for being reportable as a 7-day or 15-day safety report. SUSARs that are fatal or life-threatening must be reported to the regulatory authorities and the HREC(where required) within 7 days after the Sponsor (or Syneos Health) has first knowledge of them, with a follow-up report submitted within a further 8 calendar days. Other SUSARs must be reported to the relevant regulatory authorities and the HREC within 15 calendar days after the Sponsor (or Syneos Health) first has knowledge of them.

The Sponsor (or Syneos Health) is responsible for reporting SUSARs and any other events required to be reported in an expedited manner to the regulatory authorities and for informing investigators of reportable events, in compliance with applicable regulatory requirements within specific timeframes. Investigators will notify the relevant HREC of reportable events within the applicable timeframes.

9.16 Pregnancy

In the event a dosed female subject (or the female partner of a dosed male subject) becomes pregnant during or shortly after participation in the study, this pregnancy will be reported to the Sponsor within 24 hours of first knowledge of the event. Any subject who becomes pregnant during the study will be immediately withdrawn. Follow-up information regarding the course and outcome of the pregnancy will be documented (after obtaining the consent of the female partner, when applicable) as per clinical site's SOP. If the outcome of the pregnancy meets the criteria for classification as an SAE, reporting of the event to the HREC and regulatory agency(ies) will be performed as per clinical site's SOP.

Any pregnancy will be reported to the Sponsor via telephone, fax, e-mail, or in person, within 24 hours of knowledge by the Investigator or designee. The notification must be directed to:

Syneos Health Safety and Pharmacovigilance

Fax Number: 001-877-464-7787
Local Toll-Free Fax Number Australia: 1800 256 952
Email: safetyreporting@syneoshealth.com

Information on the pregnancy will be recorded on the Pregnancy Report Form.

9.17 Reportable Disease

In the case a subject has, or manifests, any clinical signs characteristic of a reportable disease or condition (e.g., HIV, tuberculosis, SARS, COVID-19), it is the responsibility of the Principal Investigator to notify the Sponsor after becoming aware of the information.

9.18 Premature Termination of the Study

The study may be prematurely terminated by the Investigator following consultation with the Sponsor, by the Sponsor or by the regulatory authorities. Following a decision to discontinue the trial, the Investigator will promptly inform the active study subjects and the HREC responsible for this trial, stating the reasons for discontinuation of the study and, furthermore, advise them in writing of any potential risks to the health of study subjects or other persons. It is the Sponsor's responsibility to report the premature termination of the study to the regulatory authority(ies), when required by the applicable regulatory requirement(s).

10. Analytical Methodology

When applicable, samples will be transported to the bioanalytical facilities in at least two separate shipments, with each set of aliquots in separate shipments. Once the bioanalytical laboratory confirms receipt of the first shipment, the second set of aliquots may be sent. The samples should be packed on sufficient dry ice to keep them frozen for at least 72 hours.

Tetra-Q will analyse SARS-CoV-2 specific antigen in serum samples using a validated method.

The Peter Doherty Institute for Infection and Immunity will analyse live virus neutralisation in serum samples using a validated method.

The University of Queensland will perform T-cell analysis via multi-colour cell cytometry which will include assessment of markers of a Th2 immune response (CD3, CD4, CD8, TFN-γ, TNF-α, IL-2, IL-4, IL-13, IL-17a, CD107a, and Granzyme B) in whole blood samples and cryopreserved peripheral blood mononuclear cells (PBMCs) using a validated method.

The bioanalytical work in support of the study will be conducted in compliance with the GCP, using the SOPs in place each respective laboratory. These SOPs are in accordance with applicable regulations in the industry: Guidelines on Bioanalytical Method Validation, Good Laboratory Practice (GLP), and Guideline for GCP ICH E6 (R2).

Samples from subjects included in the Safety Population (see Section 11.4.3) and from subjects who were withdrawn from the study due to adverse events will be analysed.

11. Statistical Analyses

A complete description of the statistical analyses and methods to be performed will be presented in a statistical analysis plan (SAP) to be finalised prior to database lock. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives. The SAP will serve as a complement to the protocol and supersedes it in case of differences.

An interim analysis will be performed once all Part 1 subjects (Cohorts 1,2 &3) have completed Day29, and immunology assays for all samples up to Day 29 are completed. A brief study status report will be prepared and will discuss the safety, tolerability and immunogenicity data following a single vaccination dose. A further interim analysis will be performed once all Part 1 subjects (Cohorts 1,2 &3) have completed Day 57, and immunology assays for all samples up to Day 57 are completed. The Final CSR will be written following the completion of the Active Study Period Evaluation Visit (Day 57) and will discuss the safety/tolerability and immunogenicity data collected during the Active Study Period.

The immunology assessments to be included for the Active Study Period in the CSR are the GMT of the serum antibody response (ELISA) to the Sclamp antigen and the serum NAb response by MN assay at Days 29 and 57 i.e. 28 days after the first and second dose respectively, the proportion of subjects with a ≥4 fold increase in titre above baseline by ELISA at Days 15, 29, 43 and 57 compared to placebo, and the proportion of subjects with a ≥4 fold increase in titre above baseline by MN assay at Days 15, 29, 43 and 57 compared to placebo.

Statistical assessments will include comparisons between the four treatment groups (A-D), as appropriate for each cohort and comparison of each treatment to the placebo group.

An interim analysis will be performed once all Part 2 subjects (cohorts 4,5 and 6) have completed Day 57, and immunology assays for all samples up to Day 57 are completed. An addendum to the Final CSR will be written following the completion of the Active Study Period Evaluation Visit (Day 57) for Part 2 subjects and will discuss the safety, tolerability and immunogenicity data collected during the Active Study Period.

Addenda to the final study report will be prepared following the 6 month follow-up visit (Day 209) and the 12 month follow-up visit (Day 394). These addenda will discuss the safety, tolerability, and immunogenicity data collected at the 6 month follow-up visit (the period between the Active Study Period and the 6 month follow-up visit) and the 12 month follow-up visit (the period between the 6 month follow-up visit and the 12 month follow-up visit).

Demographic parameters will be summarized descriptively. TEAEs and injection site reaction data will be tabulated by study treatment for all subjects who were dosed (Safety Population). Safety and tolerability data will be reported using descriptive statistics. Changes from baseline values in vital signs and clinical laboratory parameters will be evaluated and tabulated by study treatment. No inferential statistical analysis of safety data is planned.

Descriptive statistics will be used to present all safety and immunogenicity results; number of observations (n), mean, standard deviation (SD), median, minimum (min), maximum (max), (including geometric mean, and CV% for immunogenicity data) for continuous data. For categorical variables, data will be tabulated with the number and proportion of subjects for each category by treatment group.

Binary data i.e. percentages of subjects with seroconversion, will be tabulated for each group using unadjusted estimates and will be reported together with two-sided exact 95% confidence intervals (CIs), Clopper-Pearson. No multiplicity adjustment to the CI levels will be implemented.

The difference between the proportions of treatment groups will be determined and the corresponding two-sided 95% CIs calculated using the exact uconditional CI based on the Farringont-Manning score statistic. Geometric means and 95% CIs will be calculated by taking the anti-logs of the means and the 95% CI of the log-transformed immunogenicity parameters. Exact CIs based upon the binomial distribution will be calculated for percentages.

The analysis model for the Sclamp antibody, or the MN GMTs, will be performed using a general linear model on log-transformed (base 10) post-GMT titres as the outcome variable and as covariates such as treatment groups (dose) and log-transformed pre-vaccination titre. Model adjusted differences in means (on the log scale) will be produced with 95% confidence limits. The estimated difference between treatment groups and the confidence limits will be back-transformed to obtain an *adjusted* GMT ratio with 95% confidence limits.

The measure of the *unadjusted* GMT ratio based on post-vaccination GMT only will also be presented.

In addition, reverse cumulative distribution plots will be generated to display the distribution of the antibody response at Days 29 and 57 for the active study phase, and will be explored for Days 209 and 396 (follow-up phase). Baseline titres for serum antibody to Sclamp, and MN titres to SARS-CoV-2 virus, will be less than or equal to the lower limit of quantitation (≤LLOQ) and will be imputed as ½ LLOQ.

Bioanalysis of all samples up to, at least, Day 57 should be completed prior to the initiation of the immunogencity and statistical analyses.

As the SARS-CoV-2 Sclamp study vaccine does not contain novel adjuvants nor excipients, and it is not administered via a novel delivery system nor route of administraition, no pharmacokinetic analyses will be conducted in agreement with the EMA Guideline on Clinical Evaluation of New Vaccines.[5]

11.1 Safety Measurements

Safety will be assessed by measuring the frequency and intensity of local and systemic solicited adverse events (AEs), unsolicited AEs, serious adverse events (SAEs), and safety laboratory data for all subjects. All solicited adverse events will be summarised according to the protocol defined severity grading scales. The proportion of subjects experiencing each adverse event will be presented for each symptom severity. Summary tables showing the occurrence of any local or systemic adverse event overall and at each time point will be presented.

Reactogenicity will be assessed by the proportion of subjects with solicited local and solicited systemic AEs up to 7 days after each vaccination and calculated for 3 time intervals after each vaccination: Days 1--3, Days 4--7, and Days 1--7. Post-administration solicited adverse events reported from Days 1-7 will be summarised by time interval, maximal severity and by vaccine group. The severity of solicited local adverse events, including injection site redness, swelling and induration will be summarised according to categories based on linear measurement: 2.5 to 5.0 cm, 5.1 to 10.0 cm and >10 cm.

Injection site pain and systemic reactions (except fever) occurring up to 7 days after each vaccination dose will be summarised according to "mild", "moderate" or "severe". Body temperature will be summarised by 0.5 °C increments from 36.0 °C up to ≥40 °C and will be reported by route of measurement.

Unsolicited AEs will be assessed by the proportion of subjects with any unsolicited AEs for 28 days after each vaccination.

The proportion of subjects with SAEs, TEAS, non-scheduled GP visits, unsolicited medically attended AEs, unsolicited AEs leading to study withdrawal or decision by the PI to discontinue with the second dose, will be collected from study start until study completion.

All spontaneously reported adverse events occurring during the study assessed by the Investigator as probably related, possibly related, or not related to vaccination will be recorded.

The original terms used by the Investigator in the CRFs will be assigned to preferred terms using the MedDRA dictionary. The adverse events will then be grouped by MedDRA preferred terms into frequency tables according to system organ class and preferred terms within each system organ class then presented by vaccination group. Where an adverse event occurs more than once for a subject, the maximal severity and strongest relationship to the vaccine group will be counted.

Separate summaries will be prepared as follows:

- Serious adverse events
- Adverse events that are probably or possibly related to the vaccine
- Adverse events leading to a medically attended visit

Safety parameters, ie.laboratory parameters, ECG and vital signs, will be assessed by the PI or delegate, using the clinical site's criteria for acceptance ranges as guidelines in making the medical assessment. Abnormal safety blood and urinalysis laboratory measurements will be assessed for severity in accordance with the scoring system described in the FDA Guidance for Industry – Toxicity Grading Scale for Healthy Adults and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials(4) using the reference ranges specified by the testing laboratory, SydPath in accordance with the Laboratory Manual.

Safety measurements which in the opinion of the investigator are deemed clinically significant will be recorded as adverse events

11.2 Immunogenicity

Various approaches will be used in this study to assess the immunogenic response of the SARS--CoV--2 Sclamp vaccine in subjects: analysis of SARS-CoV-2 specific immune response via ELISA, analysis of domain specificity and immunoglobulin isotype induction via Luminex Assay, analysis of MN assessed via virus neutralisation, and ADCC via a bioluminescent reporter assay. Additionally, induction of poly-functional T-cells will be assessed via stimulation of PBMCs with vaccine specific antigen, and further analysed via various staining techniques coupled with multi-flow cytometry. While analysis of safety and tolerability is the primary outcome of this study, the combination of immunogenicity data collected will provide some indication of the potential efficacy of the vaccine for future studies to investigate further.

Seroconversion rate is defined as a minimum 4-fold rise in post-vaccination titre at Days 29 and 57 relative to Day 1. The baseline titres for serum antibody to Sclamp and MN titres to SARS-CoV-2 virus will be ≤ LLOQ and will be imputed as ½ LLOQ.

Blood samples will be collected at specified visits according to the Schedule of Assessments included in Section 4, and blood volumes will be collected according to Section 9.9.

The immunogenicity analyses will evaluate immunogenicity of SARS-CoV-2 Sclamp vaccine as measured by ELISA and MN assay.

Additional immunologic assays, including ADCC reporter assay and Luminex assay will be used to conduct further exploratory analysis to determine antibody isotypes, domain specificities and functions that may be correlated with protection.

Potential for seroconversion to trigger false positives on HIV testing will be assessed by assessing blood samples in a panel of point of care and investigative HIV detection diagnostics.

Serum samples will be analysed by Sponsor designated qualified laboratory personnel blinded to the treatment assignment and the visit. Please see Laboratory Manual for complete details.

11.3 Success Criteria

In the absence of formal statistical hypotheses, the study will not be declared positive or negative according to pre-determined rules. The selection of an appropriate vaccine dosage and regimen for future studies will be determined by the joint evaluation of the safety and immunogenicity profiles of each dosage group and dosage regimen.

11.4 Analysis Populations

11.4.1 Intent-to-Treat (ITT) Population (Full Analysis Set, FAS)

Includes all trial subjects that:

- Provide consent; and
- Are randomized.

The ITT Population will be used for all listings and demographic summaries, and will be listed according to the planned treatment.

11.4.2 Safety Population

Includes all trial subjects that:

- Provide consent; and
- Are randomized; and
- Receive at least one dose of the study treatment, and
- Provided any evaluable safety data.

The Safety Population will be used for all safety analyses and will be analysed as actually treated.

11.4.3 Immunogenicity Population up to Day 57

Includes all subjects in the Safety Population that:

- Have immunological results for Days 1, 15, 29, 36, 43, and 57 (subjects who withdraw early and do not complete all assessment days will still be included for analyses); and
- Did not experience a laboratory confirmed COVID-19 illness between Day 1 and Day 57; and
- Did not receive any prohibited medication during the study to Day 57 that is medically assessed to potentially impact the immune response (and immunogenicity results); and
- Have no major protocol deviations affecting the primary immunogenicity outcomes as determined by the Sponsor prior to database lock and unblinding.

The Immunogenicity Population will be the primary population used for immunogenicity analyses for the Day 57 analyses for each of Part 1 and Part 2.

11.4.4 Full Immunogenicity Population

Includes all subjects in the Immunogenicity Population that:

- Have also completed follow-up examinations on Days 209 and 394; and
- Did not experience a laboratory confirmed COVID-19 illness between Day 1 and Day 394.

The Full Immunogenicity Population will be the primary population used for follow-up analyses.

11.5 Immunogenicity Analysis

For the evaluation of immunogenicity, vaccine antibody titres will be analysed using the Immunogenicity Population and the methodology described previously in Section 11:

- Geometric Mean Titres (GMT) on Days 1, 15, 29, 43 and 57, and 209 and 394 will be summarized using descriptive statistics by treatment group compared to placebo;
- Seroconversion on Days 15, 29, 43, 57, 209 and 394, compared to placebo. Seroconversion is defined as the percentage of subjects with a ≥4 fold increase in post-vaccination titre compared to Day 1;
- Geometric Mean Fold increases on Day 15 / Day 1, Day 29 / Day 1, Day 43 / Day 1, and Day 57 / Day 1, Day 209 / Day 1, and Day 394 / Day 1, compared to placebo;
- Fold increase in antigen specific CD4+ T-cells at Days 8, 15, 29, 36, 43, and 57 compared to Day 1 for vaccine antigen dose versus placebo;
- Fold increase in antigen specific CD8+ T-cells at Days 8, 15, 29, 36, 43, and 57 compared to Day 1 for vaccine antigen dose versus placebo;
- Fold increase in antibody dependent cellular cytotoxicity (ADCC) at Days 15, 29, 43, 57, 209, and 394 compared to Day 1 for vaccine antigen dose versus placebo;
- Fold increase in antibodies elicited to the Receptor Binding Domain (RBD), N-Terminal Domain (NTD), and clamp trimerization domain on Days 15, 29, 43, 57, 209, and 394 compared to Day 1 for vaccine antigen dose versus placebo; and
- Fold increase in antigen specific humoral immune responses including isotypes IgM, IgA, IgE, and subtypes IgG1, IgG2, IgG3 and IgG4 at Days 15, 29, 43, 57, 209, and 394 compared to Day 1 for vaccine antigen dose compared to placebo.

Once all subjects have completed Day 57, an interim analysis will be performed. The immunogenicity analysis will be included as part of this interim analysis.

12. Final Report

A final report including clinical, bioanalytical, and statistical sections will be the responsibility of Delve Medical Writing and will be signed and approved by at least the Sponsor.

An interim analysis will be performed once all Part 1 subjects (Cohorts 1,2 &3) have completed Day 29, and immunology assays for all samples up to Day 29 are completed. A brief study status report will be prepared and will discuss the safety, tolerability and immunogenicity data following a single vaccination dose. A further interim analysis will be performed once all Part 1 subjects (Cohorts 1,2 & 3) have completed Day 57, and immunology assays for all samples up to Day 57 are completed. The Final CSR will be written in an unblinded manner following the completion of the Active Study Period Evaluation Visit (Day 57) and will discuss the safety, tolerability and immunogenicity data collected during the Active Study Period. (The period from first dose up until completion of the Day 57 assessments defines the Active Study Period). The immunology assessments to be included for the Active Study Period in the CSR are the GMT of the serum antibody response (ELISA) to the Sclamp antigen and the serum NAb response by MN assay at Days 29 and 57 i.e. 28 days after the first and second dose respectively, the proportion of subjects with a ≥4 fold increase in titre above baseline by ELISA at Days 15, 29, 43 and 57 compared to

placebo, and the proportion of subjects with a ≥4 fold increase in titre above baseline by MN assay at Days 15, 29, 43 and 57 compared to placebo.

An interim analysis will be performed once all Part 2 subjects (cohorts 4,5 and 6) have completed Day 57, and immunology assays for all samples up to Day 57 are completed. An addendum to the Final CSR will be written following the completion of the Active Study Period Evaluation Visit (Day 57) for Part 2 subjects and will discuss the safety, tolerability and immunogenicity data collected during the Active Study Period.

Addenda to the final study report will be written following the 6 month follow-up visit (Day 209) and the 12 month follow-up visit (Day 394). These addenda will discuss the safety and immunogenicity data collected at the 6 month follow-up visit (the period between the Active Study Period and the 6 month follow-up visit) and the 12 month follow-up visit (the period between the 6 month follow-up visit and the 12 month follow-up visit).

In the event that the study is prematurely terminated, Delve Medical Writing will produce an abbreviated safety report. In such an event, raw data will not be submitted with the abbreviated report but will be archived at the clinical site, unless requested by the Sponsor.

13. Regulatory Considerations and Quality Assurance

13.1 Independent Ethics Committee Approval of Protocol and Other Study Documents

The Investigator(s) agree to provide the HREC with all appropriate documents, including a copy of the protocol/amendments, ICFs, advertising text (if any), Investigator's Brochure and any other written information provided to study subjects. The trial will not begin until the Investigators have obtained the HREC favourable written approvals for the above-mentioned study documents. A properly executed written ICF shall be read, signed, and dated by each subject prior to entering the trial or prior to performing any study procedure. The original signed and dated ICF will be kept at the clinical site, and a copy will be given to the subject.

In the event that the protocol is amended, the revised protocol must be approved by the HREC prior to its implementation, unless the changes involve only logistical or administrative aspects of the trial. If a revised ICF is introduced during the study, each subject's further consent must be obtained. The new version of the ICF must be approved by the HREC, prior to subsequently obtaining each subject's consent.

The Investigator and the Sponsor's representative must sign the protocol and its amendments (if any) before initiating the study.

It is the Sponsor's responsibility to submit the protocol and its amendments (if any), and the ICFs to regulatory authorities when necessary.

13.2 Compliance

This study will be conducted in compliance with the protocol, GCP, the requirements of Directive 2001/83/EC Annex I, as amended by Directive 2003/63/EC and Directive 2001/20/EC, and all applicable regulations. The study will also be conducted in compliance with the recommendations

laid down in the most recent version of the Declaration of Helsinki, with the exception that registration of such Phase 1 trials in a publicly accessible database is not mandatory.

13.3 Quality Assurance Program

Syneos Health has established Quality Control (QC) and Quality Assurance (QA) systems with written SOPs to ensure that the study will be conducted and data will be generated, recorded, and reported in compliance with the protocol, GCP, and applicable regulatory requirements. A rigorous QC program is applied to ensure accuracy of all data and reports. QA oversees a complementary risk-based program of audits to assure compliance with applicable regulations and Syneos Health's prescriptive documentation.

13.4 Audits, Inspections and Monitoring

In accordance with the principles of GCP and GLP, the study may be inspected by regulatory authorities, the Sponsor and Syneos Health. The Sponsor is entitled to access information about the status of the study and to review the original documents of the study.

14. Confidentiality and Retention of Study Records

This document contains trade secrets and commercial information that is confidential and may not be disclosed to third parties. Persons to whom this study protocol is disclosed must be informed that all the information herein is confidential and may not be further divulged. These restrictions will apply as well to all future communications if deemed privileged or confidential. Publication of the study results may only be allowed with written permission from the Sponsor.

All information on a subject obtained during the conduct of the study will be kept confidential. Subjects will be identified by an anonymized identifier on all samples and study records provided to the Sponsor or designee. In compliance with ICH GCP, the Sponsor’s authorized representatives, monitor(s), auditor(s), HREC, and regulatory authority(ies) will be granted direct access to the subject’s original trial-related records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations. Consent from the subject for disclosure of such information will be obtained in writing in the ICF. In addition, should a subject require medical care or hospitalization during the course of the study, the clinical site may contact the treating physician with the subject’s consent, except that consent may not be requested if there is an emergency situation. If the results of the study are published, the subject’s identity will remain confidential.

15. References

1 World Health Organisation: Coronavirus Disease 2019 (SARS-CoV-2): Situation Report--51. WHO website. Published March 11, 2020. Accessed March 27, 2020. https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200311-sitrep-51-covid-19.pdf

2 Guan, WJ. et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020. 382; 1708-1720.

3 Huang, C. et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020. 395(10223); 497–506.

4 FDA Guidance for Industry – Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials. Revised date 17 May 2019. Accessible online: https://www.fda.gov/media/73679/download

5 Committee for Medicinal Products for Human Use (CHMP), EMA. Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products. EMEA/CHMP/SWP/28367/07 Rev. 1. 20 July 2017. Accessible online: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-strategies-identify-mitigate-risks-first-human-early-clinical-trials-investigational_en.pdf

Appendix I Checklist for Medical History Follow-Up for Persons Who Meet the Protocol Defined COVID-19 Case Definition.

Clinical Diagnostic Category	Sign/symptom	Outcome (please check box)	
A. At least one sign or symptom of lower respiratory tract disease:	New onset persistent dry (non-productive) cough		
	New onset tachypnoea or dyspnoea or low oxygen saturation		
		At least one sign/symptom for Category A	☐
B. Fever or history of fever (defined as body temperature of >38.0 °C irrespective of method)	Fever as per definition	Fever as defined in Category B	☐
C. At least one sign or symptom of viral illness:	New onset myalgia		
	New onset chills		
	Sore throat		
	New onset loss of smell or taste		
	Diarrhoea		
		At least one sign/symptom for Category C	☐
Meets Criteria for COVID-19 Clinical Disease		At least 2 of 3 clinical diagnostic categories checked	☐