A Phase 1b, Randomized, Double-blind, Placebo-controlled, Dose-escalation Study to Evaluate the Safety and Immunogenicity of the ID93 + GLA-SE Vaccine in BCG-Vaccinated Healthy Adults

Investigational Product: **ID93 + GLA-SE**

IDRI Protocol Number: **IDRI-TBVPX-114**

US FDA IND Number: **BB-IND 15101**

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I, the undersigned, have reviewed this protocol and agree to conduct this protocol in accordance with Good Clinical Practices (ICH-GCP), the ethical principles set forth in the Declaration of Helsinki, and with local regulatory requirements.

Signature Date

Printed Name

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LIST OF ABBREVIATIONS

βHCG	beta human chorionic gonadotropin
µg	microgram(s)
Ab	antibody
AE	adverse event(s)
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BCG	bacillus Calmette-Guérin
BMI	body mass index
BUN	blood urea nitrogen
CBC	complete blood count
CFR	Code of Federal Regulations (US)
CIOMS	Council for International Organizations of Medical Sciences
CRF	case report form(s)
CRO	contract research organization
CRP	C-reactive protein
EDC	electronic data capture
ELISA	enzyme-linked immunosorbent assay
ELISPOT	enzyme-linked immunospot
FDA	United States Food and Drug Administration
GCP	good clinical practices
GMP	good manufacturing practices
HIV	human immunodeficiency virus
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICS	intracellular cytokine staining
IEC	Independent Ethics Committee
IFN-γ	interferon gamma
IL-2	interleukin-2
IM	intramuscular
IND	Investigational New Drug Application
IRB	Institutional Review Board
IUD	intrauterine device
MAF	medical assessment form
MDR	multidrug-resistant
MedDRA	Medical Dictionary for Regulatory Activities
mL	milliliter(s)
Mtb	*Mycobacterium tuberculosis*
PBMC	peripheral blood mononuclear cell(s)
PI	principal investigator
PPD	purified protein derivative
PRBC	packed red blood cells
PT	preferred term

QFT	QuantiFERON®-TB Gold
RNA	ribonucleic acid
SAE	serious adverse event(s)
SAER	supplemental serious adverse event report
SE	stable emulsion
SMC	Safety Monitoring Committee
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction(s)
TB	tuberculosis
TLR	toll-like receptor
TNF-α	tumor necrosis factor alpha
ULN	upper limit of normal
US	United States
WBC	white blood cell
WHO	World Health Organization

STUDY ABSTRACT

TITLE:

A Phase 1b, Randomized, Double-blind, Placebo-controlled, Dose-escalation Study to Evaluate the Safety and Immunogenicity of the ID93 + GLA-SE Vaccine in BCG-Vaccinated Healthy Adults

RATIONALE:

The initial target population for the vaccine is previously BCG-vaccinated adults who may be latently infected with *Mtb*. With the demonstration of initial safety in non-BCG-vaccinated, QFT-negative adults, safety and immunogenicity data in BCG-vaccinated adults are needed prior to further studies in *Mtb*-exposed populations.

OBJECTIVES:

Primary Objective

To describe the safety profile of ID93 + GLA-SE in BCG-vaccinated, QuantiFERON TB-Gold (QFT) negative and positive healthy adults.

Secondary Objective(s)

To describe the immunogenicity of ID93 + GLA-SE in BCG-vaccinated, QFT negative and positive healthy adults.

To identify one or more ID93 + GLA-SE vaccination regimens for further evaluation in BCG-vaccinated, QFT negative and positive healthy adults.

DESIGN:

This is a Phase 1b, randomized, double-blind, placebo-controlled, dose-escalation evaluation of two dose levels of the ID93 antigen administered intramuscularly (IM) in combination with two dose levels of the GLA-SE adjuvant. This study will be conducted in 66 HIV-negative, healthy South African adults with previous BCG vaccination. For safety reasons, participants who are QFT negative (not latently infected with *Mtb*) at screening will be enrolled first; successive cohorts will enroll both QFT negative and positive participants. The study will be conducted at one or more clinical research sites in South Africa. Participants will be followed for 6 months following the last study injection. Solicited and unsolicited adverse events (AEs) will be recorded for 28 days following each study injection; serious adverse events and adverse events of special interest will be recorded for the duration of the study. Immune responses (cellular and antibody) will be assessed at baseline and periodically after study injections.

Table 0-1 shows the dose cohorts and treatment regimen. Entry of participants in successive cohorts will occur after the principal investigator(s) and the local medical monitor have reviewed cumulative safety data following the first two study injections (up to and including Study Day 35) of all participants in the preceding cohort(s).

Table 0-1 Dose Cohorts and Treatment Regimen

Cohort/ QFT status	Group	Number of participants	Study injections	ID93 Dose	GLA-SE Dose	Dosing Schedule
1 (QFT-)	1	9	ID93 + GLA-SE	10 µg	2 µg	Days 0, 28, 112
	2	3	Placebo (saline)	-	-	
2 (QFT -/+)	3	15	ID93 + GLA-SE	2 µg	2 µg	Days 0, 28, 112
	4	3	Placebo (saline)	-	-	
3 (QFT -/+)	5	15	ID93 + GLA-SE	10 µg	2 µg	Days 0, 28, 112
	6	3	Placebo (saline)	-	-	
4 (QFT -/+)	7	15	ID93 + GLA-SE	10 µg	5 µg	Days 0, 28, 112
	8	3	Placebo (saline)	-	-	
Total number of participants	**66 (54 receiving ID93 + GLA-SE, 12 receiving saline placebo)**					

ANALYSIS OF IMMUNOLOGY

The primary variables of interest for assessment of the immune response to the vaccine will be the percentage of CD4+ and CD8+ T cells that produce any of selected cytokines following stimulation with peptide pools derived from and representing the entire amino acid sequences of the mycobacterial antigens Rv2608, Rv3619, Rv3620, and Rv1813. Response will be measured using PBMCs by flow cytometry in the intracellular cytokine staining (ICS) assay, and will be presented using median DMSO-subtracted cytokine responses and associated 95% CIs by treatment regimen. Positivity of T cell responses from the ICS assay will be determined according to a pre-specified methodology, to be described in the statistical analysis plan, and will be summarized as number (percentage) of responders by treatment regimen. Separate summaries will also be presented by treatment regimen and by baseline QFT status.

ANALYSIS OF SAFETY

The primary variable for evaluation of the safety profile will be the number and percentage of unsolicited and solicited adverse events recorded at all available post-vaccination time points, summarized by MedDRA system organ class (SOC) and preferred term (PT). Additional summaries will present the number (percentage) of participants with adverse events by severity and by relationship to study injection.

1 INTRODUCTION

1.1 Background

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis* (*Mtb*). Despite progress in reducing the number of deaths due to TB, the global burden of disease remains enormous, with an estimated 8.7 million new cases and 1.4 million deaths from TB in 2011. Worldwide, 3.7% of new cases and 20% of previously treated cases were estimated to have multidrug-resistant (MDR) TB, with 60% of those cases in India, China, or South Africa; extensively drug resistant TB has been reported in 84 countries (1).

BCG is the only TB vaccine currently licensed for use in humans and appears to be effective at preventing severe disseminated disease in newborns and young children, but fails to protect against pulmonary TB in adults (2). Even though variable efficacy has been shown with BCG vaccination in human trials, BCG is unlikely to be replaced in the near future and is the reference standard to which all other experimental vaccines are compared. A number of countries with a lower incidence of TB, including the United States, have not adopted or have withdrawn from routine BCG vaccination, preferring to screen for and treat TB with antibiotics. Therefore, ID93 + GLA-SE is being developed as a TB vaccine that is safe and efficacious for the prevention of pulmonary TB in both BCG- and non-BCG-primed individuals.

1.2 Description of ID93 + GLA-SE

Protective immunity to TB may be conferred by Th1 CD4 and CD8 T cells (3), and TB animal models have demonstrated that an effective vaccine requires the generation of a T cell-mediated immune response. *Mtb* antigens have been identified which are recognized by human T cells and are capable of eliciting dominant Th1 responses associated with reduced bacterial burden in a mouse model of TB (4). A recombinant subunit vaccine antigen, called ID93, has been developed in response to these findings. ID93 combines four antigens belonging to families of *Mtb* proteins associated with virulence (Rv2608, Rv3619, Rv3620) and latency (Rv1813) (4, 5, 6).

As recombinant proteins are known to demonstrate poor immunogenicity alone and require an adjuvant to elicit adaptive immune responses, a synthetic Toll-like Receptor (TLR) 4 adjuvant has been developed and formulated in a stable oil-in-water emulsion (GLA-SE) (7). This adjuvant system has been successfully combined with recombinant protein antigens for the induction of high antibody titers (8, 9) and of Th1 immune responses that have been associated with protection in *Mtb* and *Leishmania* challenge models (10, 11).

1.3 Nonclinical Experience with ID93 + GLA-SE

Several nonclinical studies in human cells, mice, guinea pigs, non-human primates, and rabbits have demonstrated the safety and immunogenicity of ID93 + GLA-SE.

Observed effects of ID93 + GLA-SE in toxicity and safety studies in nonhuman primates and rabbits include:

- Elevation of CRP and fibrinogen levels; and,
- Changes in hematologic values

These mild and reversible effects are considered related to treatment and the intramuscular injection route of administration. Previous toxicity studies with other vaccine antigens and GLA-SE have indicated the potential for mild and reversible injection site reactogenicity. Further details can be found in the ID93 + GLA-SE Investigator's Brochure, and in the GLA-SE Investigator's Brochure (attached as an appendix to the ID93 + GLA-SE Investigator's Brochure).

1.4 Clinical Experience with ID93 + GLA-SE

Aeras (a non-profit organization dedicated to the development of new TB vaccines) is partnering with IDRI in the clinical development of ID93 + GLA-SE. A Phase 1 study is currently being conducted at Johnson County Clin-Trials in Lenexa, Kansas, USA. Sixty BCG-naïve, HIV-negative, QuantiFERON®-TB Gold (QFT)-negative healthy adults are being randomized to receive ID93 + GLA-SE or ID93 alone given intramuscularly on Days 0, 28, and 56 and are being followed through Day 420. Four dose cohorts will escalate ID93 from 2 µg to 10 µg and GLA-SE from 2 µg to 5 µg. To date, vaccinations in Cohort 1 (2 µg ID93 with or without 2 µg GLA-SE) and Cohort 2 (10 µg ID93 with or without 2 µg GLA-SE) have been well tolerated. Local reactogenicity has been mostly mild pain and swelling and related systemic AEs have been mostly mild. See the ID93 + GLA-SE Investigator's Brochure for further details.

1.5 Clinical Experience with GLA-SE

GLA-SE has been used in clinical trials of vaccines targeting schistosomiasis, malaria, leishmaniasis, and influenza. Dose levels of GLA-SE have ranged from <2 to 10 µg, with up to 3 injections administered. Injections of vaccines containing GLA-SE have generally been well-tolerated, adverse events have been mostly mild, and no serious adverse events related to GLA-SE have been observed. See the GLA-SE Investigator's Brochure for further details.

1.6 Rationale for Study

The initial target population for the vaccine is remotely BCG-vaccinated adults (i.e., vaccinated as infants) who may be latently infected with *Mtb*. With the demonstration of initial safety in non-BCG-vaccinated, QFT-negative adults, safety and immunogenicity data in BCG-vaccinated adults are needed prior to further studies in *Mtb*-exposed populations. The current study, to be conducted in South Africa, will begin with QFT-negative adults (who are less likely to be latently infected with *Mtb*) at a dosing level shown to be safe in US adults. If no safety issues are identified, successive cohorts will enroll both QFT-negative and positive adults beginning with a lower dose and separately escalating both ID93 and GLA-SE. The dose levels of the ID93 antigen and the GLA-SE adjuvant and the intramuscular route of administration chosen for this clinical protocol have been selected based on the initial safety data in the US Phase 1 study, pre-clinical studies of ID93 + GLA-SE in animals, and clinical trials of other vaccines adjuvanted with GLA-SE. In this study vaccinations will be administered at Study Days 0, 28, and 112; the longer interval between the 2nd and 3rd doses of vaccine, as compared to the Phase 1 study, may

increase the boosting effect of the third dose. If safety and immunogenicity are demonstrated in QFT-negative and positive, BCG-vaccinated adults, subsequent studies using either a 2 or 3-dose regimen will evaluate safety in adults recently treated for tuberculosis (Phase 2a), and efficacy against pulmonary tuberculosis (Phase 2b). Data from the Phase 1 (US adults) and Phase 1b (South African adults) studies will be used for selection of the dose and regimen to be taken forward in clinical development.

2 STUDY OBJECTIVES AND DESIGN

2.1 Objectives

Primary Objective

To describe the safety profile of ID93 + GLA-SE in BCG-vaccinated, QuantiFERON TB-Gold (QFT) negative and positive healthy adults.

Secondary Objective(s)

To describe the immunogenicity of ID93 + GLA-SE in BCG-vaccinated, QFT negative and positive healthy adults.

To identify one or more ID93 + GLA-SE vaccination regimens for further evaluation in BCG-vaccinated, QFT negative and positive healthy adults.

2.2 Design

This is a Phase 1b, randomized, double-blind, placebo-controlled, dose-escalation evaluation of two dose levels of the ID93 antigen administered intramuscularly (IM) in combination with two dose levels of the GLA-SE adjuvant. This study will be conducted in 66 HIV-negative, healthy South African adults with previous BCG vaccination. For safety reasons, participants who are QFT negative (not latently infected with *Mtb*) at screening will be enrolled first; successive cohorts will enroll both QFT negative and positive participants. The study will be conducted at one or more clinical research sites in South Africa.

Participants will be sequentially assigned to a dose cohort based on timing of completion of screening and on QFT status at screening. Participants will be randomized in a 3:1 ratio (Cohort 1) or 5:1 ratio (Cohorts 2–4) to receive ID93 + GLA-SE or saline placebo on Days 0, 28, and 112. Participants and site personnel involved in observing the participants will be blinded as to treatment regimen. Participants will be followed for 6 months following the last study injection. Solicited and unsolicited adverse events (AEs) will be recorded for 28 days following each study injection; serious adverse events and adverse events of special interest will be recorded for the duration of the study. Immune responses (cellular and antibody) will be assessed at baseline and periodically after study injections. Primary endpoints will be the frequency and severity of AEs. Secondary endpoints will be cellular responses to the vaccine antigens as assessed by intracellular cytokine staining (ICS).

Table 2-1 shows the dose cohorts and treatment regimens. The first 4 participants vaccinated in any dose cohort must be evaluated at their second post-vaccination follow-up visit (Study Day 3)

before any additional participants in that cohort may be vaccinated. If the principal investigator determines that there is no reason to pause the study, based on the study suspension rules as outlined in Section 6.2, then the site may proceed to enroll the remainder of the participants in the cohort. Entry of participants in successive cohorts will occur after the principal investigator(s) and the local medical monitor have reviewed cumulative safety data following the first two study injections (up to and including Study Day 35) of all participants in the preceding cohort(s).

Table 2-1 Dose Cohorts and Treatment Regimen

Cohort/ QFT status	Group	Number of participants	Study injections	ID93 Dose	GLA-SE Dose	Dosing Schedule
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	8	3	Placebo (saline)	-	-	
Total number of participants	**66 (54 receiving ID93 + GLA-SE, 12 receiving saline placebo)**					

3 STUDY PROCEDURES

3.1 Schedule of Participant Evaluations

A Summary Schedule of Evaluations depicting all visit-specific procedures is provided in Table 3-1. See Appendix A for a more detailed description of the evaluations.

Table 3-1 Summary Schedule of Participant Evaluations

Study Visit Day →	Scr[a]	0	1	3	7	14	28	29	31	35	42	56	112	113	115	119	126	140	196	294
Written informed consent	X																			
Eligibility criteria verification	X	X																		
Medical history	X																			
Physical examination	X																			
Urine toxicology screen	X																			
Urine βHCG (all females)	X	X					X						X							
QuantiFERON®-TB Gold (mL)	3																			3
Hepatitis B, C (mL)	3																			
HIV (mL)[e]	3																			
Urinalysis	X																			
Serum chemistry (mL)[b]	5				5					5						5				
CBC, differential (mL)[c]	5				5					5						5				
Study injection administration		**X**					**X**						**X**							
Study Day 0 site of injection examination and photograph[d]		X	X	X	X	X	X													
Study Day 28 site of injection examination and photograph[d]							X	X	X	X	X	X								
Study Day 112 site of injection examination and photograph[d]													X	X	X	X	X	X		
Vital signs		X					X						X							
Interval history		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Focused physical examination		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Whole blood (mL) for: - Primary immuno PBMCs (Flow cytometry, ICS) - Exploratory immuno PBMCs (IFN-γ ELISPOT)		30				30					30		30				30		30	30
Whole blood (mL) for: - Exploratory immuno (ICS)		10				10					10		10				10		10	10
Serum (mL) for: - Exploratory immuno (antigen-specific IgG ELISA)		4															4			4
Serum (mL) for: - Exploratory immuno (autoimmune Ab ELISA)		2																		2
Whole blood (mL) for: - Exploratory RNA extraction (microarray)		2.5	2.5	2.5	2.5												2.5			

Study Visit Day →	Scr[a]	0	1	3	7	14	28	29	31	35	42	56	112	113	115	119	126	140	196	294
Solicited adverse events (incl. con. meds.)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Unsolicited adverse events (incl. con. meds.)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Serious adverse events and adverse events of special interest (incl. con. meds.)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Per visit phlebotomy volume (mL)	19	48.5	2.5	2.5	12.5	40	0	0	0	10	40	0	40	0	0	10	46.5	0	40	49
Cumulative phlebotomy volume (mL)	19	67.5	70	72.5	85	125	125	125	125	135	175	175	215	215	215	225	271.5	271.5	311.5	360.5

a. Screening evaluations must be completed within 30 days prior to randomization.
b. Serum chemistry includes AST, ALT, alkaline phosphatase, total bilirubin, creatinine, and BUN.
c. Includes hemoglobin, hematocrit, white blood cell count with differential, and platelet count.
d. Site of injection will be photographed only if there is a visible injection-site abnormality; on vaccination days, the photograph will be taken (if applicable) at 60 minutes post-vaccination.
e. Rapid test with ELISA confirmation

3.2 Participant Selection

3.2.1 Recruitment and Informed Consent

Various methods of recruitment may be used such as advertising, referrals, or solicitation of participants previously known to the clinical site. Interested potential participants will be invited to participate in the informed consent process. Informed consent will be obtained by the use of a written consent form approved by the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) and signed and dated by the participant at the time of consent. Potential participants will be interviewed to ensure that they meet all entry criteria relating to history. The clinical investigator or designee will conduct the consent discussion on an individual basis with each participant and will allow adequate time for all questions to be addressed. Written informed consent will be obtained prior to conducting any study-related procedures. A copy of the signed consent form shall be given to the participant prior to Study Day 0.

3.2.2 Screening

After informed consent is obtained, a screening number will be assigned to each participant for identification purposes, and the participant will be screened to assess eligibility for the study. A screening log will be maintained by the site that records all participants for whom consent was obtained and who entered the screening process. At a minimum, the screening log will document the participant's date of consent, screening number, initials, and date of birth. For screened participants who do not subsequently enter the study, the screening log will provide details as to why the participant did not enter the study (e.g., ineligibility due to screening laboratory abnormality, new illness, or new clinical finding; withdrawal of consent; or failure to return to the study site). For screened participants who subsequently enter the study, the date of study entry (date participant is assigned to a study group) will also be recorded. Abnormal results and findings resulting in ineligibility will be discussed with the participant, who will be referred for follow-up care with their healthcare provider if necessary.

Eligibility for entry into the study will be based on the inclusion and exclusion criteria described below. The investigator must document confirmation of eligibility prior to randomization.

3.2.3 Inclusion Criteria

Participants must meet <u>all</u> of the following criteria:

1. Has completed the written informed consent process prior to start of screening evaluations
2. Male or female who is ≥18 years and ≤50 years of age at the time of randomization
3. Agrees to stay in contact with the study site for the duration of the study, provide updated contact information as necessary, and has no current plans to move from the study area for the duration of the study
4. Agrees to avoid elective surgery for the full duration of the study
5. For female participants: agrees to avoid pregnancy from 21 days prior to Study Day 0 and for the full duration of the study. Women physically capable of pregnancy (not sterilized and still menstruating or within 1 year of the last menses if menopausal) in sexual relationships with men must use an acceptable method of avoiding pregnancy during this period. Acceptable methods of avoiding pregnancy include a sterile sexual partner, sexual abstinence

(not engaging in sexual intercourse), hormonal contraceptives (oral, injection, transdermal patch, or implant), vaginal ring, intrauterine device (IUD), or the combination of a condom or diaphragm with spermicide gel
6. Has general good health, confirmed by medical history and physical examination
7. Has body mass index (BMI) between 19 and 33 (weight/height^2) by nomogram
8. Had BCG vaccination at least 5 years ago, documented through medical history or presence of scar

3.2.4 Exclusion Criteria

Participants must have <u>none</u> of the following:

1. Acute illness at the time of randomization
2. Oral temperature ≥37.5°C at the time of randomization
3. Clinically significant abnormal laboratory values for any of the following screening laboratory parameters, per local laboratory normal ranges from blood collected within **30 days** prior to Study Day 0 randomization as follows:
   - hemoglobin, hematocrit, absolute neutrophil count, absolute lymphocyte count, or platelet count below lower limit of normal (LLN)
   - white blood cell count above upper limit of normal (ULN) or below LLN (i.e., must be within normal limits)
   - ALT, AST, total bilirubin, alkaline phosphatase, creatinine, or blood urea nitrogen (BUN) above ULN
4. Evidence of systemic or local disease process on screening urinalysis
5. Evidence of significant active infection
6. History of treatment for active or latent tuberculosis or evidence of active tuberculosis
7. Shared a residence within the last year prior to randomization with an individual on anti-tuberculosis treatment or with culture or smear positive tuberculosis
8. History of autoimmune disease or immunosuppression
9. Used immunosuppressive medication within 42 days before randomization (inhaled and topical corticosteroids are permitted)
10. Received immunoglobulin or blood products within 42 days before randomization
11. Received any investigational drug therapy or investigational vaccine within 182 days before randomization, or planned participation in any other investigational study during the study period
12. Received investigational *Mtb* vaccine at any time prior to randomization
13. Received a live vaccine within past 4 weeks or a killed vaccine within past 2 weeks prior to randomization.
14. Unable to discontinue current chronic prescription drug therapy that can be hepatotoxic or toxic to the bone marrow or kidneys.
15. History or laboratory evidence of immunodeficiency state including but not limited to any laboratory indication of HIV-1 infection
16. History of allergic disease or reactions (including allergy to kanamycin-related antibiotics, allergic reaction to eggs, and severe eczema), likely to be exacerbated by any component of the study vaccine

17. Previous medical history that may compromise the safety of the participant in the study, including but not limited to: severe impairment of pulmonary function from pulmonary disease; chronic illness with signs of cardiac or renal failure; suspected progressive neurological disease; or uncontrolled epilepsy
18. Evidence of chronic hepatitis (e.g., hepatitis B surface antigen or hepatitis C antibody)
19. Chronic heavy ethanol intake which, in the opinion of the investigator, may compromise the safety of the participant or interfere with the evaluation of the safety of the vaccine
20. Cannabis smoking 3 or more days per week
21. Positive urine test for illicit drugs (opiates, cocaine, amphetamines)
22. History or evidence on physical examination of any systemic disease or any acute or chronic illness that, in the opinion of the investigator, may interfere with the evaluation of the safety or immunogenicity of the vaccine
23. All female participants: currently pregnant or lactating/nursing; or positive urine pregnancy test during screening or on the day of study injection
24. Received a tuberculin skin test within 3 months (90 days) prior to Study Day 0
25. Any current medical, psychiatric, occupational, or substance abuse problems that, in the opinion of the investigator, will make it unlikely that the participant will comply with the protocol or may compromise the safety of the participant

3.2.5 Screening Clinical Assessments and Laboratory Tests

Unless noted otherwise, the window period within which all screening evaluations must be completed, and the results reviewed by the investigator to confirm eligibility of participants, is 30 days prior to Study Day 0.

Participants will provide a detailed medical history and will undergo a physical examination. The assessment will include the determination of any surgeries or medically significant procedures planned to occur during the entire study period. Demographic characteristics (date of birth, gender, and race/ethnicity) will also be collected. Any new abnormal findings will be discussed with the participant and referral will be made for follow-up care if necessary.

Screening laboratory tests (hemoglobin, hematocrit, white blood cell count with differential, platelet count, AST, ALT, alkaline phosphatase, total bilirubin, creatinine, BUN, urinalysis, hepatitis B and C, HIV, QFT) will be performed during the screening process. Results from these laboratory tests will serve as study-entry baseline values. Abnormal results and findings that make the participant ineligible will be discussed with the participant and the participant will be referred for follow-up care with their healthcare provider if necessary. All screening laboratory specimens will be processed according to laboratory SOPs available from the clinical laboratory(ies) designated for the study. Information about the laboratory(ies), including any instructions for performing and interpreting specific tests, will be maintained in the investigator's study files.

3.3 Study Randomization

Participants will be sequentially assigned to a Dose Cohort based on time of completion of screening and then randomized within each Dose Cohort to a treatment regimen based on a

sequential series of two-digit randomization numbers linked to a randomly-generated sequence of treatment assignments (randomization schedule). The subject identification number consists of the screening number plus the randomization number, which allows for linking of results and samples obtained before randomization.

In order to maintain the blind of the team at the study site(s), the study vaccine manager must be a designated study team member who will have no clinical or regulatory responsibilities associated with the conduct of the study during the entire study period, other than managing the vaccine.

A participant is considered randomized when the study vaccine manager assigns that participant to the treatment group corresponding to the participant's assigned randomization number. If a participant does not meet all study entry criteria, randomization of the participant should not occur on that day. If the situation permits, participants may be reconsidered for randomization at a later date, e.g., pending resolution of an acute illness or after a repeated clinical laboratory evaluation result is shown to be within normal limits, within the allowed time frame for complete screening evaluations.

For each randomization number on the randomization schedule there will be a corresponding "back-up" randomization number to be used in the event that a participant needs to be replaced. If a participant withdraws consent or is removed from the study AFTER being randomized but BEFORE receiving any study injection, that participant will be replaced; the next participant randomized will be assigned the "back-up" randomization number and thus the same treatment assignment as the participant who was replaced. If a participant withdraws consent or is removed from the study AFTER receiving any study injection, that participant will not be replaced and that participant's "back-up" randomization number will not be used.

3.4 Blinding

Personnel at the study site(s) will be blinded to participant treatment assignments, with the exception of the study vaccine manager (and designee, if appointed) and QA/QC site staff responsible for reviewing pharmacy records (if appointed). In addition, since ID93 + GLA-SE and saline for injection (comparator) have different appearances, the study injection administrator (the study team member in the clinic who will be administering the injections) will also be unblinded. To avoid unblinding of the study participants, the syringes containing study vaccine or comparator will be masked. All unblinded persons must take care to not reveal individual participant treatment regimen assignments to any other member of the study team, including the immunologists. Unblinded study personnel must not participate in the evaluation of adverse events. A Delegation of Authority Log will be maintained by the site and will identify the individual(s) authorized to function as the study vaccine manager and study injection administrator, i.e., individuals with access to study blinding information. The pharmacy reconciliation monitor(s) and the Aeras investigational product manager will also have access to unblinded information.

The randomization schedule will be provided by the unblinded statistician to the study vaccine manager in a sealed tamper-evident envelope, or randomization will be administered via a

validated IVRS/IWRS (interactive voice/web response system). Access to the randomization schedule during the study will be provided to the study vaccine manager (and designee) and the unblinded pharmacy reconciliation monitor(s). The randomization schedule and all pharmacy source documents and dose preparation records that can link a subject identification number with a treatment assignment must remain secure (e.g., in the pharmacy with access limited to only authorized unblinded persons) until notification from the sponsor or its designee that the study has been unblinded.

3.4.1 Unblinding for Clinical Emergencies

If there is an urgent clinical requirement to know a participant's treatment assignment, the investigator (in consultation with the local medical monitor, if possible) will make a written request to the vaccine manager for urgent unblinding of a participant's treatment. The request must include the subject identification number, the date, a brief justification of the clinical requirement for unblinding, and the investigator's signature. The request will be kept in the study file.

Upon receipt of proper written request, the vaccine manager or designee will disclose the treatment group to the investigator. Aeras must be notified immediately of any clinically required break of the study blind on an Immediately Reportable Event Form.

3.5 Study Injection Administration

On Study Day 0, participants will receive their study injection as soon as possible after assignment of a subject identification number, and after their baseline immunology blood collection. On Study Day 28, participants who have not met any of the criteria for discontinuation of study injections (see Section 6.1) will receive a second study injection. In cases of short term, reversible conditions, such as acute febrile or respiratory illness or evidence of significant active infection, the second study injection should be deferred until the participant has recovered; the allowable time period for deferral of the second dose is 5 days (i.e., Study Day 28+5 days; see Appendix A). On Study Day 112, participants who have not met any of the criteria for discontinuation of study injections (see Section 6.1) will receive a third study injection. Again, in cases of short term, reversible conditions, such as acute febrile or respiratory illness or evidence of significant active infection, the third study injection should be deferred until the participant has recovered; the allowable time period for deferral of the third dose is 14 days (i.e., Study Day 112+14 days).

The study vaccine manager will send the study injection to the clinic as a unit-dose syringe, which will be identified with the subject identification number, participant's initials, date and time of dose preparation, and the volume prepared. The syringe will contain 0.5 mL of the study vaccine or saline placebo (the comparator). A medically qualified study team member must be present in the clinic at the time of all study injection administrations.

Before administering the injection, the study injection administrator must inspect the syringe and vaccine volume, checking that the syringe is identified with the correct subject identification number and initials and checking the date and time the dose was prepared. The vaccine must be

administered within 6 hours of being prepared. If circumstances result in a delay of administration beyond the allotted time, an explanation must be entered into the source documents and the expired syringe must be returned to the study vaccine manager, who will prepare a replacement syringe using a new vial(s).

The study injection will be administered IM by the study injection administrator into the deltoid area using standard aseptic technique. The Study Day 28 injection should be administered in the opposite arm to the Study Day 0 injection. The Study Day 112 injection can be administered in either arm.

The study vaccine manager will refer to the IDRI-TBVPX-114 Vaccine Management Manual (provided under separate cover) for detailed instructions for study vaccine storage and preparation.

3.6 Study Evaluations

3.6.1 Immunology Laboratory Evaluations

A summary of immunologic assays to be performed on blood specimens is shown in Table 3-2. Staff at the clinical research site will refer to the most current version of the Specimen Management Manual (provided under separate cover) for further instructions and additional information on specimen collection and processing.

Table 3-2 Summary of Immunology Laboratory Evaluations

Sample type	Location	Assay	Purpose of Assay	Study Days
Primary Immunology: Peripheral Blood Mononuclear Cells (PBMCs)	Aeras	Flow cytometry, Intracellular cytokine staining (ICS)	Determine cellular immune response to study vaccine	Days 0, 14, 42, 112, 126, 196, 294
Exploratory Immunology Cells (PBMCs)	Aeras	IFN-γ ELISPOT	Determine cellular immune response to study vaccine	Days 0, 14, 42, 112, 126, 196, 294
Exploratory Immunology Whole Blood	Study site	Whole blood ICS	Determine cellular immune response to study vaccine	Days 0, 14, 42, 112, 126, 196, 294
Exploratory Immunology Serum	Aeras or designee	Antigen-specific IgG	Determine humoral response to study vaccine	Days 0, 126, 294
Exploratory Immunology Serum	NA (to be stored)	Autoimmune antibodies (ELISA)	Determination of vaccine-induced autoimmunity	Days 0, 294
Exploratory Immunology Whole Blood for RNA Extraction	Aeras or designee	Microarray transcriptional profiling or RNA sequencing	Determine immune response to study vaccine	Days 0, 1, 3, 7, 126

A 13-color ICS assay using frozen PBMC will be performed at Aeras' immunology laboratory in the US, where the reagents, equipment, and training of personnel have all been standardized to provide consistent results. The IFN-γ ELISpot assay using frozen PBMC will also be conducted at Aeras' immunology laboratory using a qualified assay. Conducting both the ICS and IFN-γ ELISpot assays in the same laboratory using the same material will reduce the assay variability, particularly when determining the correlation between the 2 assays. The whole blood assay is an exploratory assay and will be conducted at the study site(s) if the capacity exists to conduct the assay there.

3.6.2 Safety Evaluations

3.6.2.1 Pre-vaccination and Post-vaccination Monitoring of Participants

Participants will have vital signs taken prior to each study vaccination. Participants will remain in the clinic under close observation for at least 60 minutes after receiving each study injection. Vital signs will be repeated before participants leave the clinic. Allergic reactions to vaccination are possible, therefore, appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available and a medically qualified study team member trained to recognize and treat anaphylaxis must be present in the clinic during the entire vaccination procedure and post-vaccination monitoring period.

3.6.2.2 Clinical Assessments and Laboratory Tests

Clinical assessments and laboratory tests are summarized in Appendix A.

Assessment of Abnormal Clinical Laboratory Test Results

Results from clinical laboratory tests obtained on the study must be reviewed by the investigator (or a designee who is a medically qualified study team member) within 72 hours of receiving the results to determine if abnormalities exist. If the laboratory value is abnormal and has increased in toxicity grade (see Appendix C for toxicity grading scales) from pre-vaccination values, it must be reported as an adverse event and repeated promptly to demonstrate resolution. Additional laboratory tests may be performed if the investigator deems them to be necessary to fully evaluate an adverse event. In the event that the investigator elects to order non-protocol-specified laboratory tests, the investigator must record the rationale for the tests and a determination of clinical significance of the result in the source documents. The investigator must keep the local medical monitor informed of adverse events of clinical significance.

Abnormal results and findings will be discussed with the participant, and the participant will be referred for follow-up with their healthcare provider if necessary.

3.6.2.3 Adverse Events

The collection periods for adverse events are:

Unsolicited adverse events:	28 days post-vaccination
Solicited adverse events:	28 days post-vaccination
Serious adverse events:	Entire study period (i.e., 294 days)

Adverse events of special interest: Entire study period (i.e., 294 days)

Solicited adverse events to be collected include the following: pain, redness (erythema) and swelling (induration) at the site of injection; fever; myalgia (muscle pain); arthralgia (joint pain); fatigue; headache; anorexia (loss of appetite); hives; chills.

Adverse events of special interest (see Appendix D) will be collected passively during participant safety evaluations.

3.6.2.4 Concomitant Medications

The collection of information on concomitant medications used by participants following vaccination will coincide with the collection period of adverse events. The collection period for concomitant medications associated with the treatment of adverse events will be 28 days following each vaccination. The collection period for concomitant medications associated with the treatment of serious adverse events will be Study Days 0-294.

Concomitant medication includes prescription and non-prescription drugs or other treatments, and any vaccines other than the study vaccine. The name of the medication, treatment start and stop dates (or 'ongoing'), route of administration, and indication must be recorded on the Concomitant Medications case report form (CRF). The indication recorded on the Concomitant Medications CRF must correspond to a medical term/diagnosis recorded on the adverse event (AE) CRF, or to a pre-existing condition noted in the participant's medical history, or be noted as prophylaxis, e.g., dietary supplement.

3.6.3 Participant Follow-up and Contact

All participants who are assigned a subject identification number and receive study injection(s) will be followed according to the protocol unless consent is withdrawn.

Participants will be instructed to contact a study team member to report new diagnoses or new or worsening adverse events and to come to the study clinic if medical attention is needed, provided the urgency of the situation permits. For emergencies and other unscheduled visits to a medical facility other than the study clinic, medical records will, to the extent possible, be obtained by the investigator.

During each clinic visit, participants will be reminded to notify a study team member of the following:

- The occurrence of AEs and SAEs during the respective reporting periods
- Receipt of any concomitant medications during the applicable reporting period
- Plans to move or if contact information changes
- If participant has decided to withdraw from the study
- Change in general health status
- Any other change in status that may affect the participant's continuation (e.g., plan to participate in another investigational study)

All deviations from protocol procedures, evaluations, and/or visits must be categorized and documented as they occur. Each deviation must be documented on a Protocol Deviation Form. When possible, missed visits and procedures must be rescheduled and performed at the nearest possible time point to the original schedule. In cases where the visit at which the second or third study injection is to be administered (i.e., Study Day 28 or 112) would fall outside of the allowable visit window (see Appendix A), scheduling of the visit should be done in consultation with the sponsor or designee.

3.6.4 Loss to Follow-up

If the site's study team members are unable to establish contact with participant who misses a scheduled study visit, the clinical site must make every possible effort to re-establish contact and document such efforts. If contact is re-established, then the participant will resume participation in the study.

If contact with the participant cannot be re-established by the participant's calculated Study Day 294 visit date, then a determination of "lost to follow-up" should be made.

4 STUDY VACCINES

4.1 Supplies

ID93 antigen, GLA-SE adjuvant, and SE (stable emulsion) will be supplied by IDRI in separate vials for admixture at the site.

ID93 recombinant protein is produced by fermentation and purified following cGMP guidelines at the University of Iowa Center for Biocatalysis and Bioprocessing (Iowa City, Iowa). The ID93 Purified Bulk Protein is formulated and lyophilized following cGMP guidelines at the University of Iowa Pharmaceuticals (Iowa City, Iowa) to yield the final vaccine fusion antigen, ID93 for Injection. ID93 for Injection is formulated as a lyophilized solid and appears as a white to off-white cake.

GLA-SE is manufactured at IDRI. SE, also referred to as EM060G in the ID93 + GLA-SE Investigator's Brochure, contains the same components as GLA-SE but without GLA and is also manufactured at IDRI. SE will be used to dilute the GLA-SE to the appropriate dose for the clinical study while maintaining the 2% oil concentration in the final dose. Both GLA-SE and SE were formulated by IDRI under cGMP guidelines. Bulk GLA was manufactured for IDRI by Avanti Polar Lipids (Alabaster, Alabama).

Further details regarding clinical supplies, including the composition of ID93 for Injection and GLA-SE, are provided in the ID93 + GLA-SE Investigator's Brochure and/or the Vaccine Management Manual.

The normal saline placebo (comparator) will be sourced by the study vaccine manager in sterile 10 mL vials. A separate vial will be used for each participant in order to ensure sterility.

4.2 Accountability

The study vaccine manager is required to maintain accurate study vaccine accountability records. Instructions and forms to be completed and kept for accountability will be provided to the study vaccine manager. If the study vaccine manager wishes to use site-specific accountability forms, these must be reviewed and approved in advance by the sponsor or its designee. Upon completion of the study, all study vaccine management records will be copied and the copies returned to the sponsor or its designee. The originals must be maintained at the clinical site with the rest of the study records.

4.3 Receipt and Storage

Upon receipt of study vaccine supplies, the study vaccine manager must immediately inspect all vials for damage. ID93 antigen, GLA-SE adjuvant, and SE will be shipped with a continuous temperature-monitoring device. Any damage or discrepancies from the packing list must be documented and promptly discussed with the sponsor or its designee and the study monitor to determine the appropriate action.

Lyophilized ID93 for Injection, GLA-SE adjuvant, and SE must be stored at 2-8°C in a monitored secure location with no access for unauthorized personnel. The normal saline placebo will be stored at room temperature in the study pharmacy.

Refer to the most recent version of the Vaccine Management Manual for detailed instructions regarding study vaccine storage.

4.4 Vaccine Preparation

The procedure for reconstitution and admixture of ID93 + GLA-SE for each treatment regimen is described in the Vaccine Management Manual. Refer to the most recent version of the Vaccine Management Manual for detailed instructions regarding study vaccine preparation. **The antigen/adjuvant mixture is stable for 6 hours at room temperature**; hence, the antigen/adjuvant mixture must be freshly prepared at the beginning of each injection time point.

4.5 Disposal of Unused Supplies

Upon completion of the study, the sponsor or its designee must provide authorization for any unused study vaccine and supplies to be disposed of or returned to the sponsor. Any disposal of study vaccine conducted at the clinical site must be done according to the facility's SOPs for destruction and documented in the study file.

5 SAFETY

5.1 Responsibilities for Ensuring the Safety of Trial Participants

The national regulatory authority, the study sponsor or its designee, the institution through which the research is performed and all members of the principal investigator's clinical team share

responsibility for ensuring that participants in this trial are exposed to the least possible risk of adverse events that may result from participation in this trial.

5.1.1 Principal Investigator

The principal investigator has a personal responsibility to closely monitor trial participants and an inherent authority to take whatever measures necessary to ensure their safety. The principal investigator has the authority to terminate, suspend or require changes to a clinical trial for safety concerns and may delay an individual's study injection administration or pause study injection administration in the whole trial if the investigator has some suspicion that the study injection might place a participant at significant risk. The principal investigator determines severity and causality with respect to the study injection for each adverse event. For blinded studies the principal investigator is blinded.

5.1.2 Study Sponsor

The sponsor or its designee also has an institutional responsibility to ensure participant safety. This responsibility is vested in the local medical monitor and a safety monitoring committee (SMC).

5.1.3 Local Medical Monitor

The local medical monitor is the sponsor's representative and is a credentialed physician or surgeon in their country of residence with the necessary expertise to act in such capacity. The local medical monitor reviews the safety of the product for protocols in a specific region and determines expectedness of the adverse event. The local medical monitor may make a sponsor's assessment of severity and causality for adverse events that may upgrade the degree of severity and causality determined by the principal investigator. The local medical monitor, like the principal investigator, is blinded for a blinded study.

5.1.4 Safety Monitoring Committee

A Safety Monitoring Committee (SMC) will be formed and its composition will be described in an SMC charter. If study injection administration is paused (see rules for suspension of entire study in Section 6.2) by the principal investigator or the local medical monitor, the SMC will be convened. The voting members cannot be directly involved with the conduct of the study. Voting members cannot be employees of the sponsor or the sponsor's designee (e.g., CRO). Additional subject area experts may be present to provide expertise if requested by the SMC. The SMC may review an individual SAE or it may choose to review adverse events, serious adverse events, solicited adverse events, and laboratory and vital signs data. The SMC may unblind any amount of safety information needed to conduct their assessment. All procedures associated with this review, including objectives, data handling, and elements to be included for review will be documented in SMC minutes.

Based on its review and the protocol stopping rules (Section 6) the SMC will make recommendations in the SMC minutes to the sponsor or its designee regarding further conduct of the study and further administration of study injections. The conclusions of the SMC, along with

the final decision of the sponsor or its designee, will be communicated to the investigators and the Institutional Review Boards and the national regulatory authority. The sponsor or its designee agrees to abide by any directives issued by the national regulatory authority or the Institutional Review Board.

5.1.5 Institutional Review Boards and Ethics Committees

The Institutional Review Board or Ethics Committee has institutional responsibility for the safety of research participants. The Institutional Review Board or Ethics Committee has the authority to terminate, suspend or require changes to a clinical trial.

5.1.6 National Regulatory Authority

Since the national regulatory authority (such as the Food and Drug Administration [FDA] and Medicines Control Council [MCC]) receives all expedited safety reports it also has the authority to terminate, suspend or require changes to a clinical trial.

5.2 Safety Surveillance During the Study

Participants will be evaluated on Days 1, 3, 7, 14, and 28 after each vaccination. Safety data will be collected by way of clinical interviews and examinations, and through evaluation of laboratory results. Time points and the specific data collected for each of these evaluations are described in Section 3 and the protocol appendices.

5.3 Definition of Adverse Event

Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An *adverse event* (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, and does not imply any judgment about causality. An adverse event can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.

All conditions that exist prior to administration of the study injection (pre-existing conditions) will be recorded in the participant's medical history to establish baseline. Day-to-day fluctuations in pre-existing conditions that do not represent a clinically significant change in the participant's status will not necessarily be reported as adverse events.

Any adverse change from the participant's baseline condition (determined from screening evaluations conducted to confirm study eligibility) that occurs following the administration of the study injection will be considered an adverse event. This includes the occurrence of a new adverse event or the worsening of a baseline condition, whether or not considered related to the study injection. Intermittent conditions such as headaches in adults or irritability in infants may be present on Study Day 0 but may represent an adverse event if the intensity or duration of the event is worse than usual following receipt of study injection. Adverse events include but are not limited to: adverse changes from baseline that represent increases in toxicity grade according

to the Toxicity Table (see protocol appendices), adverse changes in the general condition of the participant, signs and symptoms noted by the participant, concomitant disease with onset or increased severity after study injection administration, and changes in laboratory safety parameters occurring after study injection administration.

The reporting period for all adverse events is specified in Section 3. Adverse events will be reported on the Adverse Event CRF using a recognized medical term or diagnosis that accurately reflects the event. Adverse event evaluations will be reviewed by the principal investigator or by a designated medically qualified practitioner. Adverse event CRF pages are to be completed by members of the study team designated in writing by the principal investigator. The onset and resolution dates of the event and action taken in response to the event will be documented. All adverse events must be followed until resolution is demonstrated. The resolution date will be recorded on the CRF as the last date on which the participant experienced the adverse event. If an adverse event resolution date is uncertain the principal investigator should estimate the completion date based on medical judgment and interview of the participant. Approximate dates of resolution from interviews may be taken as adverse event resolution dates. Some examples of estimation of adverse event resolution are: 1) an asymptomatic laboratory abnormality on one visit that has not been followed-up between visits but has resolved by the next visit may be assumed to have resolved by the midpoint of the inter-visit interval; 2) A resolved adverse event that was treated may be assumed to have been resolved by the end of treatment. Adverse events that are still present at the end of the trial should be recorded as ongoing. Information recorded on the CRF must be substantiated in the source documents. If an adverse event evolves into a condition that becomes "serious," it will be designated as serious on the Adverse Event CRF and a Supplemental SAE Report (SAER) form will be completed.

5.4 Assessing Severity

The safety concepts of "severity" and "seriousness" are distinct concepts (see Section 5.8). Severity refers to a degree of clinical manifestation. "Seriousness" refers to defined outcomes from an adverse event. A severe adverse event is not always serious and a serious adverse event is not always severe.

For all adverse events, the investigator (or designee, who is a healthcare professional; is someone the investigator deems qualified to review adverse event information, to provide a medical evaluation of the event, and to classify the event based upon medical judgment and the severity categories described below) is responsible for assessing the severity of the event and the causal relationship of the event to the study injection.

The **severity** of all adverse events, including clinical findings and abnormal laboratory values, will be classified as one of the following grades:

1. **Mild**
2. **Moderate**
3. **Severe**

A Toxicity Table is provided in the protocol appendices for the assessment of severity of specified adverse events. The Toxicity Table Adverse Event Grades do not correlate directly

with the classical severity grades of mild, moderate and severe. For the purposes of recording events on the CRF, Toxicity Table Grade 1 events will be considered mild in severity, Toxicity Table Grade 2 events will be considered moderate in severity, and both Toxicity Table Grade 3 and 4 events will be considered as severe. In the Toxicity Table certain local reactions such as erythema (redness) and swelling (induration) are graded according to size. Laboratory values are graded according to level of deviation from the normal range.

For adverse events not listed in the Toxicity Table determination of severity requires some level of interpretation as outlined below. The degree of incapacity caused by the adverse event and the level of medical intervention required for treatment may be helpful in assessing the overall severity of the adverse event.
For example:

- "Mild" events are generally regarded as noticeable but have no impact on normal activities; they may or may not require over-the-counter treatment managed by the participant.
- "Moderate" events generally have some impact on an individual's normal activities and may require general symptomatic medical intervention by a healthcare professional or by the participant.
- "Severe" adverse events may be incapacitating, leading to suspension of normal daily activities, and would generally require more immediate medical evaluation and intervention by a healthcare professional.

A change in severity of an adverse event will not be recorded as a new adverse event. Only the highest severity level that occurs during the entire period of the adverse event will be recorded on the CRF with the onset and resolution dates encompassing the entire duration of the event.

5.5 Assessing Causal Relationship (Relatedness)

For all adverse events, the investigator will determine a **causal relationship** to the study injection without knowledge, for blinded studies, of whether ID93 + GLA-SE or placebo was administered. A number of factors will be considered in making this assessment, including: 1) the temporal relationship of the event to the administration of the study injection 2) whether an alternative etiology has been identified and 3) biological plausibility. The investigator will use the following guidelines to assess the causal relationship of an adverse event to study injection:

- **Not Related** to study injection (i.e., there is no evidence of a causal relationship; another etiology is known to have caused the adverse event. The alternative etiology should be documented in the participant's study record).
- **Unlikely Related** to study injection (i.e., there is less than a reasonable possibility that the adverse event was caused by study injection).
- **Possible** relationship to study injection (i.e., there is a reasonable possibility that the adverse event was caused by study injection. There must be a plausible mechanism for the event to be related to study injection. The evidence is inadequate to accept or reject, or favors rejection of, a causal relationship; an association exists between the event and the study injection but there may also be an alternative etiology, such as characteristics of the participant's clinical status or underlying condition).

- **Probable** relationship to study injection (i.e., it is likely that the adverse event was caused by administration of the study injection. The evidence favors acceptance of a causal relationship; an association exists between the event and receipt of the study injection and there is a plausible mechanism for the event to be related to the study injection, and an alternative etiology is not apparent).
- **Definite** relationship to study injection (i.e., the study injection is known to be the cause of the adverse event. The evidence establishes a causal relationship; an association exists between the event and receipt of the study injection and there is a plausible mechanism for the event to be related to the study injection, and causes other than the study injection have been ruled out).

Definite, probable and possible are considered to be related to study injection. Not related and unlikely related are considered to be unrelated.

For adverse events requiring immediate reporting, the principal investigator and the local medical monitor both determine causality. It is expected that communication and consultation may occur in the assessment of the causality of adverse events. The greatest degree of causal relationship (definite > probable > possible > unlikely related > not related) determined by either the investigator or local medical monitor after their discussions will determine the ultimate classification of the adverse event.

Every effort should be made by the investigator to determine the existence of any pre-existing conditions (e.g., headache in adults or rashes in infants on Study Day 0 with onset prior to study vaccination) that must be taken into consideration when assessing causal relationship of an adverse event. Pre-existing conditions should be recorded in the CRF as baseline history and substantiated by appropriate source documentation. Intermittent conditions such as headaches in adults or irritability in infants may not be present on Study Day 0 but may represent an adverse event if the intensity or duration of the event is worse than usual following study injection.

5.6 Definition of Adverse Reaction

An adverse reaction is an adverse event judged to be related to study injection (see Section 5.3 for adverse event definition).

Related adverse events (adverse reactions) are defined as those judged by the investigator or local medical monitor to be possibly, probably, or definitely related to study injection.

5.7 Solicited Adverse Events and Injection Site Reactions

Solicited adverse events are events the participant is specifically asked about. These adverse events are commonly observed soon after receipt of vaccines. For this study, solicited adverse events to be collected include: pain, redness and swelling at the site of injection; fever; myalgia; arthralgia; fatigue; headache; anorexia, hives, chills. Solicited adverse events of local injection site reactions (i.e., pain at injection site, redness at injection site, or swelling at injection site) will be considered causally related to study injection (adverse reaction).

The reporting period during which *solicited* adverse events will be evaluated is specified in Section 5.2. The solicited adverse event reporting period begins with the day of vaccination.

Adverse events and solicited adverse events including assessment of local injection site reactions will be assessed by the investigator for severity, causal relationship to the study injection, possible etiologies, and whether the event meets criteria as a serious adverse event (and therefore requires immediate notification to the local medical monitor).

Presence of ulceration and/or scarring at the site of injection and axillary lymphadenopathy of the injection arm(s) are considered to be adverse events that are causally related to the study injection and are of special interest. Site of injection ulceration (including presence of drainage) and axillary lymphadenopathy will be actively evaluated during each clinic visit through the end of the study. These events will be recorded on the Adverse Event CRF.

In the event that the clinical presentation meets the definition of a serious adverse event, an SAER form must be completed and the event reported per protocol instructions.

5.8 Adverse Events of Special Interest (AESIs)

Adverse events of special interest (AESIs) are clinical events which are potentially immune mediated, and are listed in Appendix D.

5.9 Assessing "Seriousness" and Serious Adverse Events

Seriousness refers to the outcome of an adverse event. Seriousness is determined by both the principal investigator and the local medical monitor. If either principal investigator or local medical monitor determines an event to be serious, it will be classified as such. If any of the following outcomes are present then the adverse event is serious:

- It results in **death** (i.e., the AE caused or led to the fatality). Serious does not describe an event which hypothetically might have caused death if it were more severe.
- It was immediately **life-threatening** (i.e., the AE placed the subject at immediate risk of dying. It does not refer to an event which hypothetically may have led to death if it were more severe).
- It required inpatient **hospitalization** or prolonged hospitalization beyond the expected length of stay. Hospitalizations for scheduled treatments and elective medical/surgical procedures related to a pre-existing condition that did not increase in severity or frequency following receipt of study injection, are **not** serious by this criterion. Hospitalization is defined as either 1) a hospital admission, or 2) an emergency room visit for a period greater than 24 hours.
- It resulted in a persistent or significant **disability/incapacity** (i.e., substantial reduction of the subject's ability to carry out activities of daily living).
- It resulted in a **congenital anomaly or birth defect** (i.e., an adverse finding in a child or fetus of a subject exposed to the study vaccine prior to conception or during pregnancy).
- Other **medically important conditions** that may not result in death, threaten life or require hospitalization (i.e., the AE does not meet any of the above serious criteria) may be

considered a serious adverse event when, based on appropriate medical judgment, they may jeopardize the subject and require medical or surgical intervention to prevent one of the serious outcomes listed in these criteria (e.g., allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in hospitalization, or the development of drug dependency or drug abuse).

A **serious adverse event** is an adverse event meeting the outcome criteria for seriousness regardless of relationship to an administered medicinal product.

5.10 Assessing Expectedness

Expected adverse events are adverse events consistent with the applicable product information provided by the sponsor (the investigator's brochure for an investigational product). The sponsor, in the person of the local medical monitor, determines expectedness. If the assessment is that the adverse event is **expected** no further action is required. If the local medical monitor's assessment is that the adverse event is **unexpected,** then the event may represent a SUSAR or expedited SAE (see Sections 5.11 and 5.12).

5.11 Definition of Suspected Unexpected Serious Adverse Reaction (SUSAR)

When an adverse event is judged to be related to an investigational product, such as ID93 + GLA-SE, and also is judged to be serious and unexpected, it is a SUSAR (suspected unexpected serious adverse reaction) and is subject to expedited reporting.

5.12 Reporting of Serious Adverse Events

Serious adverse events, **which include SUSARs, are reported to the sponsor or its designee and to the World Wide Safety Center for the entire study period (see Appendix B). SUSARs are reported even after the trial is over, if the sponsor or its designee, local medical monitor or principal investigator becomes aware of them.** The site will be provided with specific reporting procedures including the Adverse Event CRF and any supplemental reporting forms to be used. Serious adverse events will be reported on the Adverse Event CRF using a recognized medical term or diagnosis that accurately reflects the event.

Serious adverse events will be assessed by the investigator and the local medical monitor according to their roles (as described in Sections 5.1.1 and 5.1.3) for severity, causal relationship to the study injection, and expectedness. The onset and resolution dates of the event and the action taken in response to the event will be documented. If the event has not resolved by the final study visit, it will be documented as "ongoing" on the CRF, however, follow-up of the SAE must continue until resolved. Information recorded on the CRF must be substantiated in the source documents.

The SAE Report form completed for that event must be scanned and emailed, or faxed, by the principal investigator or his/her designee, within one business day of the clinical site becoming aware of the event, to the local medical monitor, study monitor, and the World Wide Safety Center. The AE CRF should be completed with all information known at the

time; the SAE Report (paper form) should be completed and both forms scanned and emailed, or faxed (even if all information concerning the event is not yet known) within one business day of awareness of the event.

Fatal or life-threatening serious adverse events that the investigator suspects are related to the study injection should be telephoned to the local medical monitor immediately upon the investigator's awareness of the event. If the local medical monitor is required by the protocol or chooses to suspend enrollment s/he shall immediately create a written memorandum for record to the study file and telephonically notify the sponsor or its designee of this act.

Contact information for all safety personnel are contained in the Team Contact List which will be stored on site in the Site Regulatory Binder and maintained by the study sponsor or its designee.

Investigators must not wait to collect additional information to fully document the event before notifying the local medical monitor and World Wide Safety Center of a serious adverse event. The initial notification should include the following (at minimum):

- Protocol number and name and contact number of the investigator
- Subject ID number (and initials and date of birth, if available)
- Date(s) participant received study injection(s)
- Serious adverse event(s) and date of event onset
- Current status of participant

The sponsor or its designee has authorized the World Wide Safety Center to execute its responsibilities for safety report submission to the appropriate regulatory authorities within specific time periods of being notified of the event (within 7 or 15 calendar days depending the character of the SUSAR); therefore, it is important that the investigator submit additional information requested as soon as it becomes available.

The sponsor or its designee will notify the SMC of all SUSARs within 3 working days of becoming aware of an event and will provide all follow-up information in a timely manner.

5.13 Other Events Requiring Immediate Reporting

The investigator must report the following events by scanning and emailing, or faxing, the appropriate form to the local medical monitor within one business day of becoming aware of the event:

- Emergency unblinding (Immediately Reportable Event Form)
- Protocol violation affecting the safety of a participant or involving the vaccination process (Immediately Reportable Event Form)
- Any event that, according to the protocol or in the opinion of the investigator, precludes further administration of the study injections (Immediately Reportable Event Form, unless meets SAE criteria)
- Pregnancy (Immediately Reportable Event Form, and Pregnancy Notification Form)

5.14 Adverse Event Treatment, Follow-up, and Outcome

Treatment of any adverse events will be determined by the investigator using his/her best medical judgment and according to local clinical practice guidelines. All applied measures as well as follow-up will be recorded in the appropriate CRF.

Adverse events will be considered resolved when the condition returns to normal or returns to the participant's baseline status as established on Study Day 0, or when the condition has stabilized with the expectation that it will remain chronic.

The investigator will continue follow-up on adverse events, including laboratory abnormalities and solicited adverse events, until the event has resolved, is otherwise satisfactorily explained, or the participant completes the study.

Follow-up for serious adverse events must continue until resolution and the outcome reported to Aeras, even if this extends beyond the serious adverse event reporting period (i.e., after the final study visit). For analysis purposes, the outcome for serious adverse events will be determined on the final study visit.

Outcome of all adverse events will be classified as one of the following:

- Resolved
- Resolved with sequelae
- Ongoing
- Death

If at any time after completion of the serious adverse event reporting period (the final study visit) the investigator becomes aware of a serious adverse event that is suspected by the investigator to be related to the study injection, the event must be reported to Aeras.

5.15 Follow-up of Participants Who Become Pregnant

If a participant becomes pregnant during the study, she will not receive any further study injections but should be encouraged to continue in the study for safety follow-up. Follow-up should continue for pregnancy outcome including premature terminations, and data are to be included in the safety reports.

The investigator must notify the local medical monitor and the World Wide Safety Center of the pregnancy immediately (even if already known to have resulted in spontaneous or elective abortion) by emailing the scanned copy or faxing the Pregnancy Notification Form. At a minimum, the estimated date of conception, the estimated due date, and the date the participant received the study injection(s) should be provided.

If a participant becomes pregnant, she will not have any interventions done as normally mandated by the protocol. The participant will undergo all other evaluations according to the Summary Schedule(s) of Evaluations.

The health status of the mother and child, the date of delivery, and the child's sex, birth weight and parity should be reported to the safety monitor after delivery, using a Pregnancy Notification Form. If delivery occurs before the final study visit, the participant should continue to be followed for SAEs through the final study visit unless withdrawal of consent has occurred. If delivery occurs after the final study visit, the investigator should attempt to maintain contact with the participant to obtain information after delivery.

Pregnancy will not be recorded as an adverse event. However, pregnancy outcomes will be recorded in the World Wide Safety Database. If the pregnancy results in a miscarriage or a planned termination, the event (spontaneous abortion or elective abortion) will be reported as an adverse event or serious adverse event per the investigator's judgment (e.g., if it was a medically important or life-threatening event that meets the definition of a serious adverse event).

A congenital anomaly or birth defect (i.e., an adverse finding in a child or fetus of a participant exposed to the study vaccine before conception or during pregnancy) must be reported as a serious adverse event.

If it is determined after completion of the study that a participant became pregnant during the study, the participant should notify the investigator. The pregnancy must be reported to the local medical monitor and the World Wide Safety Center and the status of the mother and child after delivery will be obtained and reported, when possible.

5.16 Dose Escalation

Entry of participants into the next dose cohort may be permitted after the completion and review by the principal investigator and local medical monitor of cumulative safety data, including the specified post-vaccination adverse event reporting period for the most recently completed dose cohort, and the local medical monitor has confirmed:

- That rules for suspension of the entire study (Section 6.2) have not been met

  AND

- The absence of a pattern of significant symptoms, physical findings or laboratory abnormalities (adverse events) that, although individually minor, collectively represent a safety concern in the opinion of the investigator or the local medical monitor for the most recently completed randomized blinded dose cohort.

If the above confirmation occurs, dose escalation to the next dose cohort may take place following completion and review of safety data by the local medical monitor from the specified post-vaccination adverse event reporting period. The local medical monitor will confirm this in a memorandum to the study file and inform the principal investigator(s) before enrollment of the next dose cohort proceeds.

If rules for suspension are met or an adverse event pattern of concern is determined to be related to study injection, enrollment and study injection administration will be paused pending review by the SMC.

6 CRITERIA FOR INTERRUPTING THE TRIAL

6.1 Rules for Discontinuing Study Injections in an Individual Participant

Administration of additional study injections will be discontinued for an individual participant if he/she has any of the following immediately reportable adverse events:

- A clinical or laboratory parameter change which meets Grade 3 or Grade 4 severity, as defined in the protocol toxicity table, AND is judged to be possibly, probably, or definitely related to study injection
- Fever (oral temperature ≥102.1˚F/39˚C) within 1 week following study injection which is associated with constitutional symptoms (myalgia, arthralgia, fatigue, headache, anorexia, hives, chills) AND is judged to be possibly, probably, or definitely related to study injection
- Injection site reactogenicity that involves Grade 3 or Grade 4 induration (swelling), or pain as defined in the protocol toxicity table
- Adverse event occurring within 4 hours of injection thought to be an allergic reaction to the study injection, including anaphylaxis or bronchospasm
- Any extensive rash (>40% body surface) on the thorax, abdomen, or limbs, including but not limited to urticaria, generalized petechiae, or erythema multiforme judged to be possibly, probably, or definitely related to study injection
- Development of active tuberculosis
- Development of autoimmune disease or immunosuppression, or an adverse event of special interest
- Receipt of investigational drug therapy or investigational vaccine (other than study injections received as part of this study)
- Missed study injection
- Any event that in the opinion of the principal investigator precludes administration of any further study injections
- Pregnancy

6.2 Rules for Suspension of the Entire Study

The study will be immediately suspended and no additional study injections administered pending review and discussion by the SMC of all appropriate safety data in the event of any of the following immediately reportable adverse events **judged to be possibly, probably, or definitely related to study injection**:

- One or more SAE(s)
- Two or more participants in any dose cohort experience the same Grade 2 or higher laboratory abnormality, or one or more participants in any dose cohort experience a toxicity Grade 3 systemic AE lasting more than 24 hours or toxicity Grade 3 laboratory abnormality

- Anaphylaxis or bronchospasm within 4 hours of injection, indicative of an immediate hypersensitivity reaction to the study injection
- Any extensive rash (>40% body surface) on the thorax, abdomen, or limbs, including but not limited to urticaria, generalized petechiae, or erythema multiforme

The study will also be immediately suspended and no additional study injections administered pending SMC review and discussion of all appropriate safety data if 3 or more participants fulfill the criteria for discontinuation of further injections due to an AE or SAE.

If the principal investigator or medical monitor interrupts administration of study injections in the study, he or she will record this in a memorandum to the study file and notify the sponsor or its designee who will then convene the Safety Monitoring Committee (SMC). The administration of study injections may resume only after SMC review of safety data. Any changes to the protocol recommended by the SMC as a condition of study injection resumption must be approved by the Institutional Review Board or Independent Ethics Committee.

7 STATISTICAL CONSIDERATIONS

The planned statistical analyses for this study are outlined below. A detailed statistical analysis plan will be created and finalized prior to database lock and preparation of any unblinded preliminary data review and for preparation of the final study report.

7.1 Participant Populations

The safety population will consist of all randomized participants who received at least one study injection.

7.2 Demographics and Protocol Compliance

Demographic parameters (age, gender, and race/ethnicity) and other baseline characteristics will be summarized by treatment group for all participants in the safety population.

As participant enrollment to each dose cohort will be conducted based on timing of completion of study eligibility requirements, any imbalance in baseline characteristics between dose cohorts will also be examined.

Listings of randomized participants who missed any study injection and of participants with protocol deviations (to be defined in the statistical analysis plan) will be provided.

7.3 Efficacy Analyses

There will be no efficacy analyses performed in this study.

7.4 Immunology Analyses

7.4.1 Primary Immunology Analyses

The primary variables of interest for assessment of the immune response to the vaccine will be the percentage of CD4+ and CD8+ T cells that produce any of selected cytokines following stimulation with peptide pools derived from and representing the entire amino acid sequences of the mycobacterial antigens Rv2608, Rv3619, Rv3620, and Rv1813. Response will be measured using PBMCs by flow cytometry in the intracellular cytokine staining (ICS) assay, and will be presented using median DMSO-subtracted cytokine responses and associated 95% CIs by treatment regimen. DMSO (background) values in vaccine recipients with respective antigen-stimulated responses and responses in the placebo recipients will be presented for comparison. Separate summaries will be presented by treatment regimen and by baseline QFT status.

Positivity of T cell responses from the ICS assay will be determined according to a pre-specified methodology (12), to be described in the statistical analysis plan, and will be summarized as number (percentage) of responders by treatment regimen. Separate summaries will also be presented by treatment regimen and by baseline QFT status.

7.4.2 Exploratory Immunology Analyses

Immune sera will be analyzed for the presence of antigen-specific IgG antibodies by enzyme-linked immunosorbent assay (ELISA) techniques. Responses will be summarized using geometric mean titers and associated 95% CIs by treatment regimen and by baseline QFT status, at all available time points.

A qualified enzyme-linked immunospot (ELISPOT) assay will be used to detect and quantify the number of antigen-specific IFN-γ-secreting cells in the peripheral blood mononuclear cells collected from patients prior to and following vaccination. Positivity of T cell responses from the ELISPOT assay will be determined according to pre-specified methodologies and will be summarized as described above for the ICS assay.

Cellular responses will also be assessed using a whole blood assay and RNA will be obtained for microarray transcriptional profiling or RNA sequencing.

7.5 Safety Analyses

The safety profile will be described by treatment regimen for all participants who received at least one study injection. Listings will be provided for all participants with adverse events (AEs), serious adverse events (SAEs) and adverse events of special interest (AESIs). All AEs and clinically relevant laboratory results will be summarized to examine the relationship between treatment regimen and key safety endpoints including number (percentage) of participants with solicited and unsolicited adverse events and number (percentage) of participants with newly abnormal post-vaccination laboratory values based on predefined toxicity criteria. Adverse events will also be summarized by severity and by relationship to study injection, by treatment regimen, and by baseline QFT status.

7.5.1 Adverse Events

The safety profile of the dose levels of ID93 + GLA-SE will be described. The primary variable for evaluation of the safety profile will be the number and percentage of unsolicited and solicited adverse events recorded at all available post-vaccination time points. For all presentations of adverse events, additional summaries based on reporting period of adverse events following each study injection may also be presented.

The number (percentage) of participants with adverse events will be summarized by MedDRA system organ class (SOC) and preferred term (PT). Additional summaries will present the number (percentage) of participants with adverse events by severity and by relationship to study injection; each participant will be counted once per preferred term at the greatest severity or most related state recorded for that term.

Separate summaries of the number (percentage) of participants with solicited adverse events will also be presented. Solicited adverse events will also be summarized by severity and relationship to study injection; each participant will be counted once per preferred term at the greatest severity or most related state recorded for that term.

Separate summaries of the number (percentage) of participants with adverse events of special interest will also be presented.

Listings will be provided for participants with adverse events.

Serious adverse events will be recorded through the final study visit for all participants. Listings will be provided for participants with serious adverse events.

Listings will be provided for participants who have discontinued prematurely due to an adverse event.

7.5.2 Clinical Laboratory and Vital Sign Parameters

For each clinical laboratory parameter and vital sign parameter pre-specified in the protocol, summary statistics for continuous parameters will be presented by treatment regimen for all pre- and post-vaccination assessments and for change from pre-vaccination to post-vaccination assessments.

The number (percentage) of participants with post-vaccination clinical laboratory values or vital sign values recorded as newly abnormal following study injection and meeting toxicity mild criteria (Grade 1) or above as specified in the Toxicity Table (Appendix C) will be tabulated at each post-vaccination time point and overall. Clinical laboratory and vital sign abnormalities will also be reported as adverse events and will be included in the summary of adverse events.

7.6 Sample Size Considerations

The sample size for this study was selected as adequate to detect frequent adverse events. Given a total sample size of 54 participants receiving ID93 + GLA-SE at any dose level, the study will

have an 80 percent chance of observing at least one adverse event which occurs at a rate of 3 percent. Alternatively, if no events are observed in 54 participants who receive ID93 + GLA-SE at any dose level, the upper bound of the one-sided 95 percent confidence interval on the rate of event occurrence is approximately 5.4 percent.

Given the dose-escalation design (15 participants in Cohorts 2, 3, and 4), there is nearly 80% probability of observing an event that occurs at a rate of 10 percent in each individual ID93 + GLA-SE antigen/adjuvant study group/cohort. Additionally, if the single-stage procedure proposed by Sobel and Huyett were to be used for the dose response analysis of immunogenicity data based on number of vaccine responders, given 15 participants per vaccine dose group, this study will allow for selection of the correct dose group with the largest true response rate with an 85% confidence if the observed difference in response rate between the highest response dose group and the next best is at least 25 percentage points (13).

7.7 Plan for Statistical Summaries and Analyses

7.7.1 Preliminary Data Reviews

A preliminary unblinded review of Th-1 and Th-2 cytokine response, based on ICS data, may be conducted following completion of Study Day 42 (i.e., 14 days after the second study injection) for each dose cohort. The purpose of these preliminary reviews is to obtain preliminary immunogenicity data for use in the decision-making process regarding vaccine dose level and dosing regimens to be employed in future studies of the vaccine. Study procedures and monitoring practices will not change following the unblinded preliminary data reviews. No decision cut points or stopping rules will be stipulated. No hypothesis testing will be performed. Personnel involved in assessment of adverse events and at the immunology laboratories will remain blinded to all study results and to treatment assignments until after the Study Day 294 data have been collected, reviewed and queries resolved.

7.7.2 Dose response

A dose response analysis of safety and immunogenicity data from Cohorts 2-4 will also be performed. The details on the statistical method for the dose response analysis will be provided in the statistical analysis plan.

7.7.3 Final Study Report

The final study report will include all available safety data, primary immunogenicity data, clinical assessments, and concomitant medications through the final study visit. The database will be locked prior to preparation of the final study report when all of the above data have been entered, reviewed, and all queries related to the data have been addressed.

Modifications or additions to the analyses described above will be included in the relevant statistical analysis plan(s). Any decisions to deviate from the planned analyses described in the protocol and in the statistical analysis plan will be described in detail in the final study report.

7.8 Computer Methods

Statistical analyses will be performed using SAS® version 9.1.3 or later under a Windows operating system.

8 DATA COLLECTION, MONITORING, AND RECORD RETENTION

For the purpose of monitoring and auditing the study, source documentation will consist of existing medical records and/or study records developed and maintained by the investigator. Any source document templates provided by Aeras or its designee will serve as supplements to the participant's study record.

Data recorded on source documents will be transcribed onto case report forms (CRFs) provided by Aeras or entered using electronic case report forms (eCRFs) using an Electronic Data Capture (EDC) system provided and approved by Aeras. Completed, original CRFs will be retrieved by Aeras or its designee and a copy of each completed CRF will be retained at the clinical site as part of the study records.

The study will be monitored regularly by Aeras or its designee throughout the study period. For studies of unapproved investigational products, all study records (source documents, signed informed consent forms, copies of CRFs, IRB/IEC correspondence and approval letters, national regulatory authority correspondence and approval letters, study vaccine management records) will be kept secured for a minimum of 2 years following the marketing of the investigational product or for 2 years after the discontinuation of the IND (or CTA, etc.). Records will be kept for longer than 2 years if required by local regulations. The investigator will ensure that study records are not disposed of or removed from the clinical site without prior notification and approval from Aeras or its designee.

9 HUMAN SUBJECTS

9.1 Ethics and Regulatory Considerations

The study will be conducted according to the ethical principles set forth in the Declaration of Helsinki, ICH-GCP, Protection of Human Subjects (21 CFR 50), Institutional Review Boards (21 CFR 56), Obligations of Clinical Investigators (21 CFR 312), Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants in South Africa, and local regulatory requirements.

The protocol and informed consent form will be reviewed and approved by the local national regulatory authority and the IRB or IEC of each participating clinical site prior to any protocol-specified procedures being conducted. The investigator will inform the IRB/IEC as to the progress of the study on a regular basis, or at minimum, once a year.

Written informed consent will be obtained from each participant prior to any protocol-specified procedures being conducted.

To maintain confidentiality, subject identification numbers will be used to identify the participant's laboratory specimens, source documents, CRF, study reports, etc. All study records will be maintained in a secured location. Clinical information will not be released without written permission from the participant except as necessary for monitoring or auditing of the study by Aeras or its designee or applicable regulatory authorities.

After the study has been unblinded, the participant should be informed which treatment (ID93 + GLA-SE or placebo) the participant received.

9.2 Institutional Review Board or Independent Ethics Committee

All the documents the IRB/IEC may need to fulfill its responsibilities, such as the protocol, protocol amendments, informed consent forms, information concerning participant recruitment, payment or compensation procedures, etc., will be submitted to the IRB/IEC by the investigator. The IRB's/IEC's written, unconditional approval of the study protocol and the informed consent form will be in the possession of the investigator/clinical site staff prior to the conduct of any protocol-specified procedures.

Modifications to the protocol may not be implemented without prior written IRB/IEC approval except when necessary to eliminate immediate hazards to the participants or when the modification involves only logistical or administrative aspects of the study. Such logistical or administrative modifications will be submitted to the IRB/IEC in writing by the investigator, and a copy of the correspondence to verify the submission will be maintained.

The investigator must inform the IRB/IEC of modifications to the informed consent form or any other documents previously submitted for review/approval, of any new information that may adversely affect the safety of the participants or the conduct of the study, provide an annual update and/or request for re-approval according to local requirements, and advise the IRB/IEC when the study has been completed.

Any documents or forms to be provided to the participant (e.g., information cards, form letters from the investigator), and all forms of study advertising (flyers, brochures, print advertisements, radio or television scripts, etc.) must be approved by Aeras or its designee prior to the clinical site submitting them to the IRB/IEC. Approval from the IRB/IEC must be obtained prior to providing the documents or forms to the participant.

9.3 Informed Consent

The principles of informed consent in the current edition of the Declaration of Helsinki, ICH-GCP/21 CFR 50.25, South Africa GCP, and local regulations should be implemented prior to any protocol-specified procedures being conducted. Informed consent will be documented in writing on a consent form approved by the IRB/IEC.

All relevant information should be provided in both oral and written form in a way that is understandable to the participant. Ample time and opportunity must be given for the participant to inquire about details of the study. The written consent document will embody the elements of

informed consent as described in the Declaration of Helsinki and will also comply with local regulations.

The investigator or the investigator's qualified designee will explain the nature of the study and inform the participant that participation is voluntary and that he or she can leave the study at any time, without penalty or loss of benefits to which they are otherwise entitled. The participant must be informed about the study's purpose including why the participant was selected to participate, study goals, expected benefits and risks, potential risks, and that some potential risks are unforeseeable. The participant must be provided with a description of the procedures and the estimated duration of time required for participation in the study, as well as alternative interventions or courses of treatment, if applicable.

The participant must receive an explanation as to whether any compensation and any medical treatments are available if injury occurs and, if so, what they are, where further information may be obtained, and who to contact in the event of a study-related injury. Participants must be told who to contact for answers to any questions related to the study. The extent of the confidentiality of participant records must be defined and the participant must be informed that applicable data protection legislation applies.

The participant must be informed that the monitor(s), auditor(s), IRB/IEC members, and the applicable regulatory authorities will be granted direct access to the participant's original study medical records for verification of protocol-specified procedures and/or data, without violating the confidentiality of the participant to the extent permitted by the applicable laws and regulations. The participant must be informed that his/her signature on the informed consent form indicates that he/she has decided to participate in the study, having read and discussed the information presented.

Modifications made by the investigator to an informed consent form template provided to the investigator by Aeras or its designee will be reviewed and approved by Aeras or its designee prior to being submitted to the IRB/IEC.

The original, signed informed consent form for each participant will be maintained by the investigator as part of the participant's study records. A copy of the signed informed consent form will be provided to each participant.

10 STUDY COMPLETION

At the discretion of the sponsor or its designee, all materials and supplies provided to the investigator will be returned or disposed of in compliance with local regulatory requirements upon authorization from Aeras, upon study completion. The investigator or designated clinical site staff will notify the IRB/IEC when the study has been completed.

11 PUBLICATIONS

All information contained in this clinical study protocol and accompanying documents is confidential. All data collected during the course of this study are confidential and considered the sole property of IDRI. The investigators agree to use this information and data only in accomplishing this study, including for benchmarking and other analytical purposes in future clinical trials, and will not use it for other purposes without the written permission of IDRI. IDRI encourages publication in peer-reviewed medical journals and will not unduly withhold permission to publish. However, all proposed publications, papers, abstracts, or written materials related to the study, or an outline or poster of any oral presentation, shall be submitted to and coordinated by IDRI for review not less than eight (8) weeks in advance of the planned submission date or presentation. In regard to all proposed public disclosures, IDRI has the right to do the following: request changes to the manuscript in accordance with scientific custom; request changes for patent purposes and/or inadvertent disclosure of IDRI's confidential information; request changes that could reasonably be expected to materially or negatively impact IDRI's intellectual property rights; and access patentability of any invention disclosed and delay submission for up to sixty (60) days to allow IDRI to file a patent.

IDRI may request in writing that the proposed publication or presentation be delayed or modified, specifying in reasonable detail the reasons for the request. If IDRI objects to a proposed publication or presentation on the basis that it would disclose confidential information, the investigator shall remove the objectionable information from such proposed publication or presentation. If the parties disagree concerning whether certain information should be deleted or modified, the parties agree to meet for the purpose of making good faith efforts to discuss and resolve any such issues or disagreements. IDRI will work with the Institution in a collaborative manner to make certain that the clinical study results contained within such presentation or publication (whether positive or negative) are accurate.

If IDRI determines that the proposed presentation or publication contains patentable subject matter that requires protection, IDRI may require an additional delay and the Institution shall delay such publication or presentation for an additional period (not to exceed sixty (60) days) for the purpose of filing a patent application(s). In no event shall IDRI unreasonably delay such publication or presentation.

All publications and presentations must acknowledge IDRI's sponsorship of the clinical study.

12 CHANGES IN THE PROTOCOL

The protocol may not be modified without written approval from the sponsor or its designee. All changes to the protocol must be submitted to the IRB/IEC and must be approved by the IRB/IEC prior to their implementation.

13 REFERENCES

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APPENDIX A Detailed Description of Study Visits

Screening Visit(s)

1. Written informed consent process
2. Assignment of screening number
3. Verify study entry eligibility criteria are met
4. Medical history
5. Physical examination
6. Urine collection for urinalysis, toxicology screen, and (for females) βHCG
7. Blood collection for
   - QuantiFERON®-TB Gold In-Tube
   - Hepatitis B, C
   - HIV-1
   - Serum chemistry (AST, ALT, alkaline phosphatase, total bilirubin, creatinine, BUN)
   - Hematology (hemoglobin, hematocrit, white cell count with differential and platelet count)

Study Day 0

Pre- injection:

1. Urine collection (females) for βHCG
2. Obtain pre-immunization vital signs (blood pressure, pulse, oral temperature)
3. Interval medical history and focused physical examination. Note: focused physical examination to include axillary lymph node examination.
4. Verify study entry eligibility criteria are met
5. Assign subject ID number (randomize)
6. Blood collection for
   - PBMCs for flow cytometry, ICS, and ELISPOT
   - Serum for antigen-specific IgG ELISA
   - Whole blood for exploratory immunology (ICS)
   - Serum for autoimmune Ab ELISA
   - Whole blood for RNA extraction (microarray)

Injection:

7. Administer study injection by intramuscular injection into deltoid area. Record date and time of injection and which arm was injected.

Post-injection:

8. Monitor participant for solicited, unsolicited, and serious adverse events (including adverse events of special interest) for at least 60 minutes after injection; record concomitant medications
9. Obtain 30±5-minute and 60±5-minute post-immunization vital signs
10. Complete Study Day 0 study injection site examination (with photograph at 60±5 minutes post-injection if there is a visible injection-site abnormality)

Study Day 1 - *Allowable window for clinic visit is 1±0 days from Study Day 0.*

1. Interval medical history and focused physical examination. Note: focused physical examination to include axillary lymph node examination.
2. Monitor participant for solicited, unsolicited, and serious adverse events (including adverse events of special interest), and record concomitant medications
3. Complete Study Day 0 study injection site examination (with photograph if there is a visible injection-site abnormality)
4. Blood collection for

- Whole blood for RNA extraction (microarray)

Study Day 3 - *Allowable window for clinic visit is 3+1 days from Study Day 0.*

1. Interval medical history and focused physical examination. Note: focused physical examination to include axillary lymph node examination.
2. Monitor participant for solicited, unsolicited, and serious adverse events (including adverse events of special interest), and record concomitant medications
3. Complete Study Day 0 study injection site examination (with photograph if there is a visible injection-site abnormality)
4. Blood collection for
   - Whole blood for RNA extraction (microarray)

Study Day 7 - *Allowable window for clinic visit is 7±1 days from Study Day 0.*

1. Interval medical history and focused physical examination. Note: focused physical examination to include axillary lymph node examination.
2. Monitor participant for solicited, unsolicited, and serious adverse events (including adverse events of special interest), and record concomitant medications
3. Complete Study Day 0 study injection site examination (with photograph if there is a visible injection-site abnormality)
4. Blood collection for
   - Serum chemistry (AST, ALT, alkaline phosphatase, total bilirubin, creatinine, BUN)
   - Hematology (hemoglobin, hematocrit, white cell count with differential and platelet count)
   - Whole blood for RNA extraction (microarray)

Study Day 14 - *Allowable window for clinic visit is 14±2 days from Study Day 0.*

1. Interval medical history and focused physical examination. Note: focused physical examination to include axillary lymph node examination.
2. Monitor participant for solicited, unsolicited and serious adverse events (including adverse events of special interest), and record concomitant medications
3. Complete Study Day 0 study injection site examination (with photograph if there is a visible injection-site abnormality)
4. Blood collection for
   - PBMCs for flow cytometry, ICS, and ELISPOT
   - Whole blood for exploratory immunology (ICS)

Study Day 28 - *Allowable window for clinic visit is 28-2/28+5 days from Study Day 0.*

Pre- injection:

1. Urine collection (females) for βHCG
2. Obtain pre-immunization vital signs (blood pressure, pulse, oral temperature)
3. Interval medical history and focused physical examination. Note: focused physical examination to include axillary lymph node examination.
4. Monitor participant for solicited, unsolicited, and serious adverse events (including adverse events of special interest), and record concomitant medications

Injection:

5. Administer study injection by intramuscular injection into deltoid area of opposite arm from Study Day 0 injection. Record date and time of injection and which arm was injected.

Post-injection:

6. Monitor participant for solicited, unsolicited, and serious adverse events (including adverse events of special interest) for at least 60 minutes after injection; record concomitant medications
7. Obtain 30±5-minute and 60±5-minute post-immunization vital signs

8. Complete Study Day 0 study injection site examination
9. Complete Study Day 28 study injection site examination (with photograph at 60±5 minutes post-injection if there is a visible injection-site abnormality)

Study Day 29 - *Allowable window for clinic visit is 1±0 days from Study Day 28.*

1. Interval medical history and focused physical examination. Note: focused physical examination to include axillary lymph node examination.
2. Monitor participant for solicited, unsolicited, and serious adverse events (including adverse events of special interest), and record concomitant medications
3. Complete Study Day 28 study injection site examination (with photograph if there is a visible injection-site abnormality)

Study Day 31 - *Allowable window for clinic visit is 3+1 days from Study Day 28.*

1. Interval medical history and focused physical examination. Note: focused physical examination to include axillary lymph node examination.
2. Monitor participant for solicited, unsolicited, and serious adverse events (including adverse events of special interest), and record concomitant medications
3. Complete Study Day 28 study injection site examination (with photograph if there is a visible injection-site abnormality)

Study Day 35 - *Allowable window for clinic visit is 7±1 days from Study Day 28.*

1. Interval medical history and focused physical examination. Note: focused physical examination to include axillary lymph node examination.
2. Monitor participant for solicited, unsolicited, and serious adverse events (including adverse events of special interest), and record concomitant medications
3. Complete Study Day 28 study injection site examination (with photograph if there is a visible injection-site abnormality)
4. Blood collection for
   - Serum chemistry (AST, ALT, alkaline phosphatase, total bilirubin, creatinine, BUN
   - Hematology (hemoglobin, hematocrit, white cell count with differential and platelet count)

Study Day 42 - *Allowable window for clinic visit is 14±2 days from Study Day 28.*

1. Interval medical history and focused physical examination. Note: focused physical examination to include axillary lymph node examination.
2. Monitor participant for solicited, unsolicited and serious adverse events (including adverse events of special interest), and record concomitant medications
3. Complete Study Day 28 study injection site examination (with photograph if there is a visible injection-site abnormality)
4. Blood collection for
   - PBMCs for flow cytometry, ICS, and ELISPOT)
   - Whole blood for exploratory immunology (ICS)

Study Day 56 - *Allowable window for clinic visit is 28±5 from Study Day 28.*

1. Interval medical history and focused physical examination. Note: focused physical examination to include axillary lymph node examination.
2. Monitor participant for solicited, unsolicited, and serious adverse events (including adverse events of special interest), and record concomitant medications
3. Complete Study Day 28 study injection site examination (with photograph if there is a visible injection-site abnormality)

Study Day 112 – *Allowable window for clinic visit is 112-2/112+14 days from Study Day 0.*

Pre- injection:

1. Urine collection (females) for βHCG
2. Obtain pre-immunization vital signs (blood pressure, pulse, oral temperature)
3. Interval medical history and focused physical examination. Note: focused physical examination to include axillary lymph node examination.
4. Blood collection for
   - PBMCs for flow cytometry, ICS, and ELISPOT
   - Whole blood for exploratory immunology (ICS)

Injection:

5. Administer study injection by intramuscular injection into deltoid area of either arm. Record date and time of injection and which arm was injected.

Post-injection:

6. Monitor participant for solicited, unsolicited, and serious adverse events (including adverse events of special interest) for at least 60 minutes after injection; record concomitant medications
7. Obtain 30±5-minute and 60±5-minute post-immunization vital signs
8. Complete Study Day 28 study injection site examination
9. Complete Study Day 112 study injection site examination (with photograph at 60±5 minutes post-injection if there is a visible injection-site abnormality)

Study Day 113 - *Allowable window for clinic visit is 1±0 days from Study Day 112.*

1. Interval medical history and focused physical examination. Note: focused physical examination to include axillary lymph node examination.
2. Monitor participant for solicited, unsolicited, and serious adverse events (including adverse events of special interest), and record concomitant medications
3. Complete Study Day 112 study injection site examination (with photograph if there is a visible injection-site abnormality)

Study Day 115 - *Allowable window for clinic visit is 3+1 days from Study Day 112.*

1. Interval medical history and focused physical examination. Note: focused physical examination to include axillary lymph node examination.
2. Monitor participant for solicited, unsolicited, and serious adverse events (including adverse events of special interest), and record concomitant medications
3. Complete Study Day 112 study injection site examination (with photograph if there is a visible injection-site abnormality)

Study Day 119 - *Allowable window for clinic visit is 7±1 days from Study Day 112.*

1. Interval medical history and focused physical examination. Note: focused physical examination to include axillary lymph node examination.
2. Monitor participant for solicited, unsolicited, and serious adverse events (including adverse events of special interest), and record concomitant medications
3. Complete Study Day 112 study injection site examination (with photograph if there is a visible injection-site abnormality)
4. Blood collection for

- Serum chemistry (AST, ALT, alkaline phosphatase, total bilirubin, creatinine, BUN)
- Hematology (hemoglobin, hematocrit, white cell count with differential and platelet count)

Study Day 126 - *Allowable window for clinic visit is 14±2 days from Study Day 112.*

1. Interval medical history and focused physical examination. Note: focused physical examination to include axillary lymph node examination.
2. Monitor participant for solicited, unsolicited and serious adverse events (including adverse events of special interest), and record concomitant medications
3. Complete Study Day 112 study injection site examination (with photograph if there is a visible injection-site abnormality)
4. Blood collection for
   - PBMCs for flow cytometry, ICS, and ELISPOT
   - Serum for antigen-specific IgG ELISA
   - Whole blood for exploratory immunology (ICS)
   - Whole blood for RNA extraction (microarray)

Study Day 140 - *Allowable window for clinic visit is 28±5 days from Study Day 112.*

1. Interval medical history and focused physical examination. Note: focused physical examination to include axillary lymph node examination.
2. Monitor participant for solicited, unsolicited and serious adverse events (including adverse events of special interest), and record concomitant medications
3. Complete Study Day 112 study injection site examination (with photograph if there is a visible injection-site abnormality)

Study Day 196 - *Allowable window for clinic visit is 196±14 from Study Day 0.*

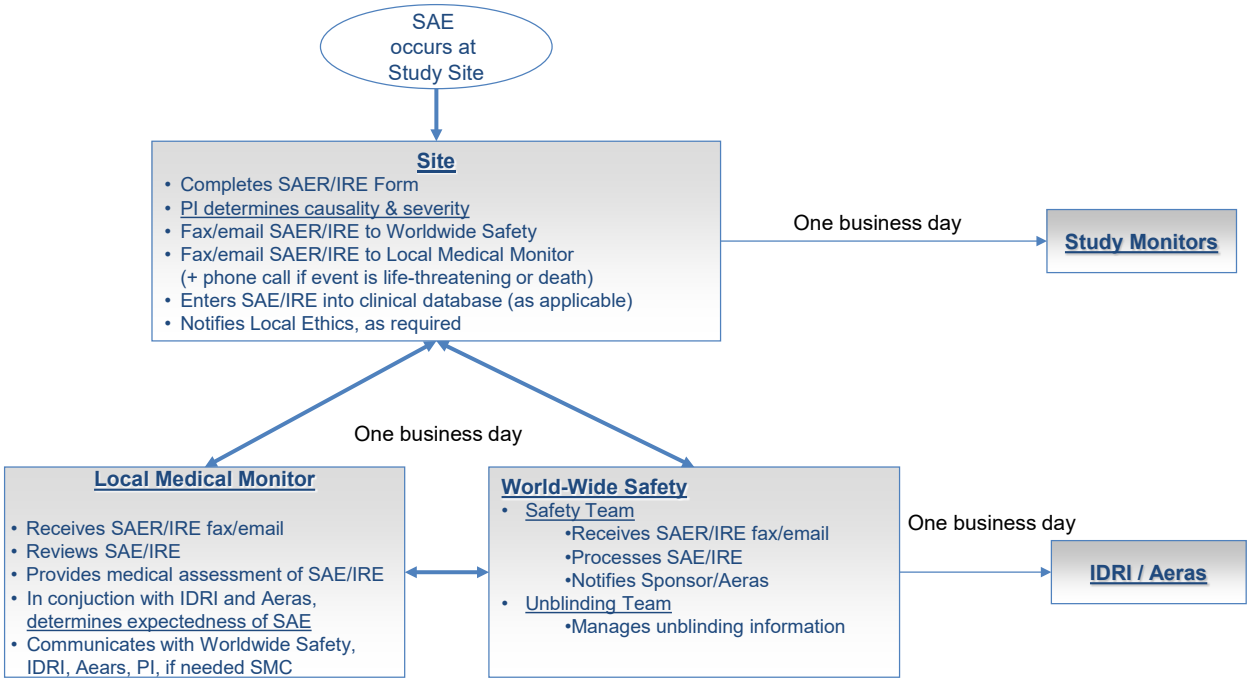
1. Interval medical history and focused physical examination. Note: focused physical examination to include axillary lymph node examination.
2. Monitor participant for serious adverse events (including adverse events of special interest), and record concomitant medications
3. Blood collection for
   - PBMCs for flow cytometry, ICS, and ELISPOT
   - Whole blood for exploratory immunology (ICS)

Study Day 294 - *Allowable window for clinic visit is 294±14 days from Study Day 0.*

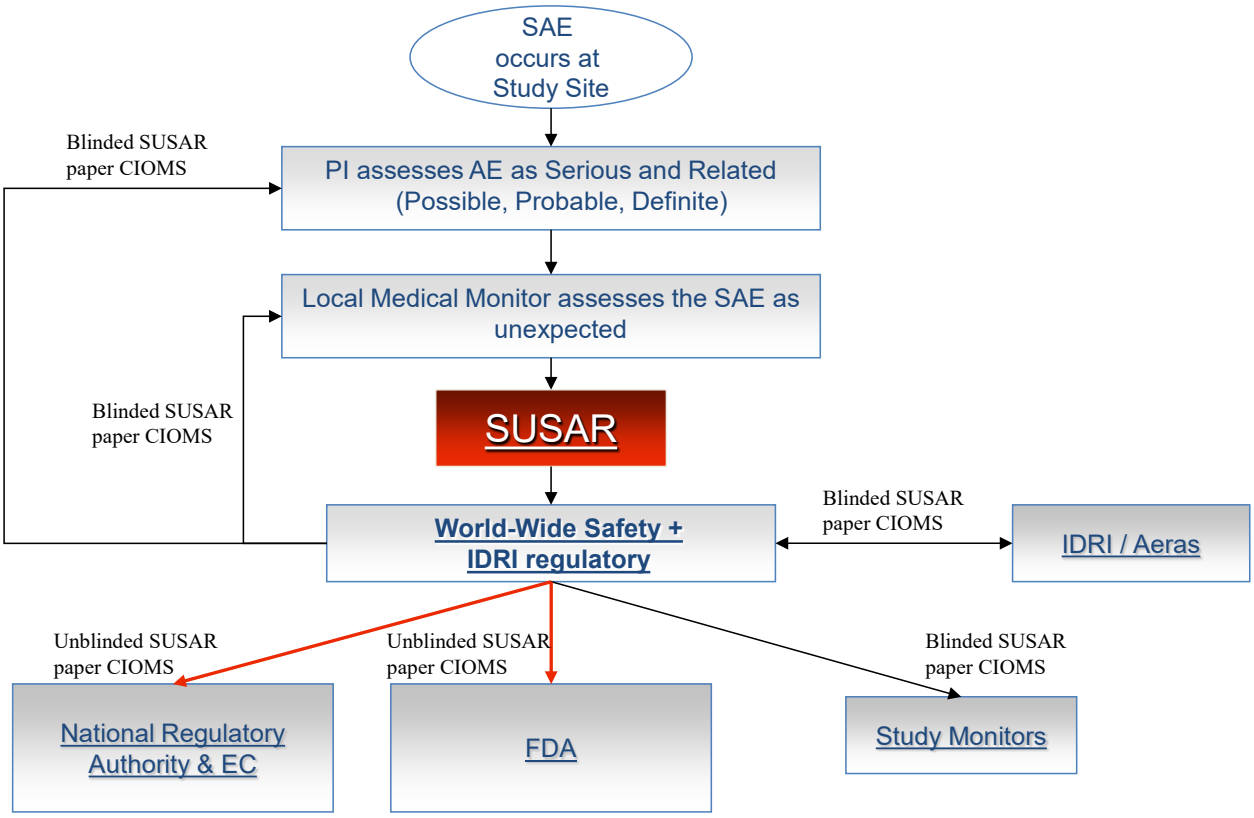
1. Interval medical history and focused physical examination. Note: focused physical examination to include axillary lymph node examination.
2. Monitor participant for serious adverse events (including adverse events of special interest), and record concomitant medications
3. Blood collection for
   - QuantiFERON®-TB Gold In-Tube
   - PBMCs for flow cytometry, ICS, and ELISPOT
   - Whole blood for exploratory immunology (ICS)
   - Serum for antigen-specific IgG ELISA
   - Serum for autoimmune Ab ELISA

APPENDIX B Reporting Schemes for SAEs, Immediately Reportable Events, and SUSARs

Reporting Scheme for SAEs and Immediately Reportable Events (IREs)



Reporting Scheme for SUSARs



APPENDIX C Toxicity Table

Note: From final US FDA guidance: Toxicity Grading Scale for Healthy Adult and Adolescent Subjects Enrolled in Preventive Vaccine Clinical Trials (September 2007); laboratory values are in conventional and SI units. The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

Local Site of Injection Symptoms	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Erythema/Redness *	2.5 - 5 cm	5.1 - 10 cm	>10 cm	Necrosis (ulceration) or exfoliative dermatitis
Induration/Swelling *	2.5 - 5 cm	5.1 - 10 cm	>10 cm	Necrosis (ulceration)

* In addition to grading the local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.

Vital Signs*	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Fever**	38.0 – 38.4°C 100.4 – 101.1°F	38.5 - 38.9°C 101.2 - 102.0°F	39.0 - 40°C 102.1 - 104°F	>40°C >104°F
Tachycardia – beats per minute	101 – 115	116 – 130	>130	ER visit or hospitalization for arrhythmia
Bradycardia – beats per minute	50 – 54	45 – 49	<45	ER visit or hospitalization for arrhythmia
Hypertension (systolic) – mm Hg	141 – 150	151 – 155	>155	ER visit or hospitalization for malignant hypertension
Hypertension (diastolic) – mm Hg	91 – 95	96 – 100	>100	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) – mm Hg	85 - 89	80 – 84	<80	ER visit or hospitalization for hypotensive shock
Respiratory rate – breaths per minute	17 – 20	21 – 25	>25	Intubation

* Subject should be at rest for all vital sign measurements. ** Oral temperature; no recent hot or cold beverages or smoking.

Systemic (General)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Nausea/vomiting	No interference with activity or 1 - 2 episodes/24 hours	Some interference with activity or >2 episodes/24 hours	Prevents daily activity, requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Diarrhea	2 - 3 loose stools or < 400 grams/ 24 hours	4 - 5 stools or 400 - 800 grams/24 hours	6 or more watery stools or > 800 grams/24 hours or requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Headache	No interference with activity	Repeated use of non-narcotic pain reliever > 24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Myalgia (muscle pain)	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Illness or clinical adverse event (as defined according to applicable regulations)	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	ER visit or hospitalization

Serum	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Blood urea nitrogen (BUN) – mg/dL: mmol/L:	23 – 26 8.3 – 9.5	27 – 31 9.6 – 11.2	>31 >11.2	Requires dialysis
Creatinine – elevated mg/dL: umol/L:	1.5 – 1.7 121 - 145	1.8 – 2.0 146 – 170	2.1 – 2.5 171 – 208	>2.5 or requires dialysis >208 or requires dialysis
Alkaline phosphatase (ALP) – increased	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	>10 x ULN
Liver Function Tests (LFT): AST, ALT – increased	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	>10 x ULN
Bilirubin (with any increase in LFT) - increased	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	>1.75 x ULN
Bilirubin (with normal LFT) - increased	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 3.0 – x ULN	>3.0 x ULN

ULN (upper limit of normal) dependent on normal reference ranges per institutional parameters.

Hematology	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Hemoglobin (Female) – g/dL: g/L:	11.0 – 12.0 110 – 120	9.5 – 10.9 95 – 109	8.0 – 9.4 80 – 94	<8.0 <80
Hemoglobin (Male) – g/dL: g/L:	12.5 – 13.5 125 – 135	10.5 – 12.4 105 - 124	8.5 – 10.4 85 – 104	<8.5 <85
WBC – increased cells/mm^3: cells x 10^9/L:	10,800 – 15,000 10.8 – 15.0	15,001 – 20,000 15.1 – 20.0	20,001 – 25,000 20.1 – 25.0	>25,000 >25.0
WBC – decreased cells/mm^3: cells x 10^9/L:	2,500 – 3,500 2.5 – 3.5	1,500 – 2,499 1.5 – 2.4	1,000 – 1,499 1.0 – 1.4	<1,000 <1.0
Lymphocytes – decreased cells/mm^3: cells x 10^9/L:	750 – 1,000 0.8 – 1.0	500 – 749 0.5 – 0.7	250 – 499 0.3 – 0.4	<250 <0.3
Neutrophils – decreased cells/mm^3: cells x 10^9/L:	1,500 – 2,000 1.5 – 2.0	1,000 – 1,499 1.0 – 1.4	500 – 999 0.5 – 0.9	<500 <0.5
Platelets – decreased cells/mm^3: cells x 10^9/L:	125,000 – 140,000 125 – 140	100,000 – 124,000 100 – 124	25,000 – 99,000 25 – 99	<25,000 <25

ULN (upper limit of normal) dependent on normal reference ranges per institutional parameters.

APPENDIX D Adverse events of Special Interest

Adverse events of special interest (AESIs) are events which are potentially immune mediated and include:

Acute disseminated encephalomyelitis (ADEM)
Addison's Disease
Anti-neutrophil Cytoplasmic Antibody (ANCA)-associated Vasculitis
Ankylosing Spondylitis
Anti-phospholipid Syndrome
Autoimmune Bullous Skin Diseases
Autoimmune Hemolytic Anemia
Autoimmune Hepatitis
Basedow's Disease
Behcet's Syndrome
Bell's Palsy
Carditis
Celiac Disease
Crohn's Disease
Cutaneous Lupus
Demyelinating Disease
Dermatomyositis
Diabetes Mellitus, Insulin Dependent (IDDM)
Erythema Nodosum
Glomerulonephritis
Guillain Barre Syndrome
Grave's Disease
Idiopathic Thrombocytopenic Purpura (ITP)
Inflammatory Bowel Disease (non-specific)
Juvenile Rheumatoid Arthritis
Mixed Connective Tissue Disease
Multiple Sclerosis
Myasthenia Gravis
Myelitis/Transverse Myelitis
Myocarditis
Nephritis
Optic neuritis
Pericarditis
Polymyalgia Rheumatica
Polymyositis
Primary Biliary Cirrhosis
Primary Sclerosing Cholangitis
Psoriasis
Psoriatic Arthritis

Raynaud's Phenomenon
Rheumatoid Arthritis
Sarcoidosis
Scleroderma
Sjogren's Syndrome
Spondylo-arthropathy
Stevens-Johnson Syndrome
Systemic Lupus Erythematosus
Temporal Arteritis
Thyroiditis
Ulcerative Colitis
Ulcerative Proctitis
Uveitis
Vasculitis
Vitiligo
Wegener's Granulomatosis