**A PHASE 2a, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, CLINICAL TRIAL TO EVALUATE THE SAFETY AND IMMUNOGENICITY OF THE ID93 + GLA-SE VACCINE IN HIV UNINFECTED ADULT TB PATIENTS AFTER TREATMENT COMPLETION**

**Protocol Number: IDRI-TBVPX-203**

**Sponsor: Infectious Disease Research Institute (IDRI)**

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**U.S. FDA IND Number: BB-IND #15101**

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**Protocol Version Number: 1.3**

**Date: 14 January 2016**

STATEMENT OF COMPLIANCE and Signature Page

**Principal Investigator Agreement**

Protocol Number: IDRI-TBVPX-203

I, the undersigned, have reviewed this protocol, including all attached information.

I agree to conduct this clinical study in accordance with the ethical principles set forth in the Declaration of Helsinki, the E6 Guidance of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) “Good Clinical Practice: Consolidated Guidance”, and the U.S. Code of Federal Regulations governing the protection of human subjects (21 CFR 50), Institutional Review Boards (21 CFR 56), the 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. Furthermore, I agree to maintain all study documentation for the time specified in Section 15.2.

|  |  |  |  |
| --- | --- | --- | --- |
| **Site Principal Investigator:** | | | |
| Signed: |  | Date: |  |
|  |  |  |  |
| Printed Name: |  |  |  |
|  |  |  |  |

# TABLE OF CONTENTS

[TABLE OF CONTENTS 3](#_Toc440906235)

[LIST OF TABLES 6](#_Toc440906236)

[LIST OF ABBREVIATIONS 6](#_Toc440906237)

[PROTOCOL SUMMARY 9](#_Toc440906238)

[1 Key Roles 11](#_Toc440906239)

[2 Background Information and Scientific Rationale 12](#_Toc440906240)

[2.1 Background Information 12](#_Toc440906241)

[2.1.1 Preclinical Data for ID93 + GLA-SE 12](#_Toc440906242)

[2.1.2 Clinical Data for ID93 + GLA-SE 14](#_Toc440906243)

[2.2 Rationale 19](#_Toc440906244)

[2.3 Potential Risks and Benefits 21](#_Toc440906245)

[2.3.1 Potential Risks 21](#_Toc440906246)

[2.3.2 Known Potential Benefits 22](#_Toc440906247)

[2.3.3 Route of Administration, Dose, and Dose Regimen 22](#_Toc440906248)

[3 Objectives 23](#_Toc440906249)

[3.1 Study Objectives 23](#_Toc440906250)

[3.2 Study Outcome Measures 23](#_Toc440906251)

[3.2.1 Primary Outcome Measures 23](#_Toc440906252)

[3.2.2 Secondary Outcome Measures 24](#_Toc440906253)

[4 Study Design 25](#_Toc440906254)

[4.1 Study Phases 25](#_Toc440906255)

[4.2 Evaluation of Safety Outcomes 27](#_Toc440906256)

[4.3 Evaluation of Immunogenicity Outcomes 27](#_Toc440906257)

[4.4 Evaluation of TB Disease Recurrence 28](#_Toc440906258)

[5 Study Enrollment and Withdrawal 29](#_Toc440906259)

[5.1 Subject Inclusion Criteria 29](#_Toc440906260)

[5.2 Subject Exclusion Criteria 30](#_Toc440906261)

[5.3 Treatment Assignment Procedures 31](#_Toc440906262)

[5.3.1 Randomization Procedures 31](#_Toc440906263)

[5.3.2 Masking Procedures 32](#_Toc440906264)

[5.3.3 Reasons for Withdrawal 33](#_Toc440906265)

[5.3.4 Handling of Withdrawals 33](#_Toc440906266)

[5.3.5 Subject Replacement 33](#_Toc440906267)

[5.3.6 Termination of Study 33](#_Toc440906268)

[6 Study Intervention/Investigational Product 35](#_Toc440906269)

[6.1 Study Product Description 35](#_Toc440906270)

[6.1.1 Acquisition 35](#_Toc440906271)

[6.1.2 Formulation, Packaging, and Labeling 35](#_Toc440906272)

[6.1.3 Product Storage and Stability 36](#_Toc440906273)

[6.2 Dosage, Preparation and Administration of Study Intervention/Investigational Product 36](#_Toc440906274)

[6.3 Modification of Study Intervention/Investigational Product for a Participant 36](#_Toc440906275)

[6.4 Accountability Procedures for the Study Intervention/Investigational Product(s) 36](#_Toc440906276)

[6.5 Assessment of Subject Compliance with Study Intervention/Investigational Product 37](#_Toc440906277)

[6.6 Concomitant Medications/Treatments 37](#_Toc440906278)

[7 Study Schedule 38](#_Toc440906279)

[7.1 Screening 38](#_Toc440906280)

[7.2 Study Injection Phase 39](#_Toc440906281)

[7.3 Final Study Visit 39](#_Toc440906282)

[7.4 Early Termination Visit 40](#_Toc440906283)

[7.5 Unscheduled Visit 40](#_Toc440906284)

[8 Study Procedures/Evaluations 41](#_Toc440906285)

[8.1 Screening Visit 41](#_Toc440906286)

[8.1.1 First Screening Visit 41](#_Toc440906287)

[8.1.2 Second Screening Visit 41](#_Toc440906288)

[8.1.3 Third Screening Visit 42](#_Toc440906289)

[8.2 Study Injection Phase Visits 42](#_Toc440906290)

[8.2.1 Day 0 (within 28 days of the end of TB treatment date, *and* within 28 days of the 3rd screening visit evaluation) 42](#_Toc440906291)

[8.2.2 Day 3 43](#_Toc440906292)

[8.2.3 Day 7 (±1) 43](#_Toc440906293)

[8.2.4 Day 14 (± 1) 43](#_Toc440906294)

[8.2.5 Day 28 (± 3) Cohorts 1 and 2 44](#_Toc440906295)

[8.2.6 Day 28 (± 3) Cohort 3 only 44](#_Toc440906296)

[8.2.7 Day 31 (3 days from Day 28 visit) Cohort 3 only 44](#_Toc440906297)

[8.2.8 Day 35 (7 days ±1 from Day 28 visit) Cohort 3 only 45](#_Toc440906298)

[8.2.9 Day 42 (14 days ±1 from Day 28 visit) Cohort 3 only 45](#_Toc440906299)

[8.2.10 Day 56 (± 3) 45](#_Toc440906300)

[8.2.11 Day 59 (3 days from Day 56 visit) 46](#_Toc440906301)

[8.2.12 Day 63 (7 days ±1 from Day 56 visit) 46](#_Toc440906302)

[8.2.13 Day 70 (14 days ±1 from Day 56 visit) 46](#_Toc440906303)

[8.2.14 Day 84 (±3) 47](#_Toc440906304)

[8.2.15 Day 112 (±5) Field Visit 47](#_Toc440906305)

[8.2.16 Day 168 (±10) Field Visit 47](#_Toc440906306)

[8.2.17 Day 224 / EOS visit (±10) 48](#_Toc440906307)

[8.2.18 Unscheduled visits 48](#_Toc440906308)

[8.3 Laboratory Evaluations 48](#_Toc440906309)

[8.3.1 Clinical Laboratory Evaluations 48](#_Toc440906310)

[8.3.2 Immunology Laboratory Evaluations 49](#_Toc440906311)

[8.3.3 Specimen Preparation, Handling, and Shipping 51](#_Toc440906312)

[9 Assessment of Safety 52](#_Toc440906313)

[9.1 Specification of Safety Parameters 52](#_Toc440906314)

[9.2 Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters 52](#_Toc440906315)

[9.3 Adverse Events 53](#_Toc440906316)

[9.3.1 Definitions 53](#_Toc440906317)

[9.3.2 Assessment of Severity (Grading) 55](#_Toc440906318)

[9.3.3 Assessment of Causality (Relatedness to Study Injection) 56](#_Toc440906319)

[9.3.4 Evaluation of Expectedness 57](#_Toc440906320)

[9.4 Reactogenicity 57](#_Toc440906321)

[9.5 Serious Adverse Events 57](#_Toc440906322)

[9.5.1 Procedures to be Followed in the Event of Abnormal Laboratory Test Values or Abnormal Clinical Findings 58](#_Toc440906323)

[9.6 Reporting Procedures 58](#_Toc440906324)

[9.6.1 Serious Adverse Events 58](#_Toc440906325)

[9.6.2 Regulatory Reporting 59](#_Toc440906326)

[9.6.3 Other Adverse Events (if applicable) 60](#_Toc440906327)

[9.6.4 Reporting of Pregnancy 61](#_Toc440906328)

[9.7 Type and Duration of Follow-up of Subjects after Adverse Events 61](#_Toc440906329)

[9.8 Halting Rules 62](#_Toc440906330)

[9.8.1 Rules for Dose Escalation 62](#_Toc440906331)

[9.8.2 Rules for Discontinuing Study injection in an Individual Subject 63](#_Toc440906332)

[9.8.3 Rules for Suspension of the Entire Study 64](#_Toc440906333)

[9.9 Safety Oversight (LMM plus DSM) 65](#_Toc440906334)

[10 Clinical Monitoring 66](#_Toc440906335)

[10.1 Site Monitoring 66](#_Toc440906336)

[11 Statistical Considerations 67](#_Toc440906337)

[11.1 Study Hypotheses 67](#_Toc440906338)

[11.2 Sample Size Considerations 67](#_Toc440906339)

[11.3 Planned Interim Analyses 67](#_Toc440906340)

[11.4 Final Analysis Plan 67](#_Toc440906341)

[12 Source Documents and Access to Source Data/Documents 70](#_Toc440906342)

[13 Quality Control and Quality Assurance 71](#_Toc440906343)

[14 Ethics/Protection of Human Subjects 72](#_Toc440906344)

[14.1 Ethical Standard 72](#_Toc440906345)

[14.2 Institutional Review Board 72](#_Toc440906346)

[14.3 Informed Consent Process 73](#_Toc440906347)

[14.3.1 Informed Consent/Assent Process (in Case of a Minor) 74](#_Toc440906348)

[14.4 Exclusion of Women, Minorities, and Children (Special Populations) 74](#_Toc440906349)

[14.5 Subject Confidentiality 74](#_Toc440906350)

[14.6 Future Use of Stored Specimens 74](#_Toc440906351)

[14.7 Modification of Protocol 75](#_Toc440906352)

[14.8 Departure from Protocol 75](#_Toc440906353)

[14.9 Suspension of Study 75](#_Toc440906354)

[14.10 Study Termination by the Sponsor 75](#_Toc440906355)

[15 Data Handling and Record Keeping 76](#_Toc440906356)

[15.1 Direct Access to Source Data/Documents and Study Monitoring 76](#_Toc440906357)

[15.2 Record Retention 76](#_Toc440906358)

[16 Publication Policy 77](#_Toc440906359)

[17 Literature References 78](#_Toc440906360)

[Appendix 1: Schedule of study visits and procedures 79](#_Toc440906361)

[Appendix 2: Schedule of blood draws and volumes 80](#_Toc440906362)

[Appendix 3: Schedule of physical exam, directed physical exam, TB screen and sputum sampling tests 81](#_Toc440906363)

[Appendix 4: Grading scale for clinical laboratory values 82](#_Toc440906364)

[Appendix 5: Grading scale for local (injection site) reactions by investigator 83](#_Toc440906365)

[Appendix 6: Toxicity grading scale¹ for determining the severity of clinical AEs 84](#_Toc440906366)

[Appendix 7: Toxicity grading scale for determining the severity of clinical AEs not in Appendix 6 85](#_Toc440906367)

[Appendix 8: List of AESIs 86](#_Toc440906368)

# LIST OF TABLES

[Table 1: IDRI-TBVPX-113: Treatment Groups](#_Toc440906399)

[Table 2: IDRI-TBVPX-113: Incidence of Local and Systemic Reactogenicity Adverse Events](#_Toc440906400)

[Table 3: IDRI-TBVPX-113: Incidence of Systemic Reactogenicity Adverse Events](#_Toc440906401)

[Table 4: IDRI-TBVPX-113: Incidence of All Other Adverse Events and Laboratory Abnormalities Occurring in at Least 3 Subjects](#_Toc440906402)

[Table 5: IDRI-TBVPX-114: Treatment Groups](#_Toc440906403)

[Table 6: IDRI-TBVPX-114: Incidence of Local Reactogenicity Adverse Events](#_Toc440906404)

[Table 7: IDRI-TBVPX-114: Incidence of Systemic Reactogenicity Adverse Events](#_Toc440906405)

[Table 8: IDRI-TBVPX-114: Incidence of All Other Adverse Events and Laboratory Abnormalities Occurring in at Least 3 Subjects](#_Toc440906406)

[Table 9: IDRI-TBVPX-203: Treatment Assignments](#_Toc440906407)

[Table 10: Summary of Immunology Laboratory Evaluations](#_Toc440906408)

# LIST OF ABBREVIATIONS

|  |  |
| --- | --- |
| AE | Adverse event/adverse experience |
| AESI | Adverse event of special interest |
| ALT | Alanine aminotransferase |
| AST | Aspartate aminotransferase |
| BCG | Bacille Calmette-Guérin |
| BHCG | Beta human chorionic gonadotropin |
| CFR | Code of Federal Regulations |
| CRA | Clinical research associate |
| CRF | Case report form |
| CRP | C-reactive protein |
| CXR | Chest X-ray |
| DLT | Dose limiting toxicity |
| DSM | Data and Safety Monitor |
| DTHC | Desmond Tutu HIV Centre |
| eCRF | Electronic case report form |
| ELISA | Enzyme-linked immunosorbent assay |
| EOS | End of study |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| GLA-SE | Glucopyranosyl Lipid A – Stable Emulsion |
| GLP | Good Laboratory Practice |
| HIV | Human immunodeficiency virus |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonisation |
| ICS | Intracellular cytokine staining |
| IDRI | Infectious Disease Research Institute |
| IEC | Independent or institutional ethics committee |
| IM | Intramuscular |
| IND | Investigational new drug application |
| INH | Isoniazid |
| IRB | Institutional review board |
| LMM | Local medical monitor |
| LTFU | Lost to follow up |
| MCC | Medicines Control Council |
| MDR-TB | Multiple drug resistant tuberculosis |
| MedDRA® | Medical Dictionary for Regulatory Activities |
| MGIT | Mycobacteria growth indicator tube (Becton-Dickinson, USA) |
| MOP | Manual of Procedures |
| Mtb | Mycobacterium tuberculosis |
| N | Number (typically refers to subjects) |
| PBMC | Peripheral blood mononuclear cells |
| PI | Principal Investigator |
| PID # | Participant identification number (randomization ID) |
| QFT | QuantiFERON®-TB Gold |
| RIF | Rifampicin |
| SAE | Serious adverse event |
| SATVI | South African Tuberculosis Vaccine Initiative |
| SID # | Screening identification number |
| SMC | Safety monitoring committee |
| SMV | Site monitoring visit |
| SOP | Standard operating procedure |
| SUSAR | Suspected unexpected serious adverse reaction |
| TASK | TASK Applied Science |
| TB | Tuberculosis |
| UCT | University of Cape Town |
| US | United States |
| WBC | White blood cell |
| WHO | World Health Organization |
| XDR-TB | Extensively drug resistant tuberculosis |
| Xpert MTB/RIF | Detection kit for Mtb and rifampin-resistance mutations (Cepheid, USA) |

# PROTOCOL SUMMARY

The purpose of this study is to evaluate the safety and immunogenicity of ID93 + GLA-SE vaccine when administered to HIV uninfected adult pulmonary TB patients in either two doses 56 days apart or three doses 28 days apart, following successful completion of TB treatment with confirmed bacteriologic cure, in preparation for a future Phase 2b prevention of TB recurrence trial in the same population.

Formulation of the vaccine, identified as ID93 + GLA-SE, consists of the recombinant four-antigen *Mycobacterium tuberculosis* fusion protein ID93 in combination with GLA-SE (Glucopyranosyl Lipid A-Stable Emulsion) as adjuvant.

**Primary Objectives:**

* To evaluate the safety of ID93 + GLA-SE at three increasing dose levels compared to saline placebo, following intramuscular administration on either Days 0 and 56 or Days 0, 28 and 56.
* To assess the immunogenicity of ID93 + GLA-SE at three increasing dose levels following intramuscular administration on Days 0 and 56 or Days 0, 28 and 56, by evaluating IgG antibody and T-cell responses to ID93 + GLA-SE at specified time points.

**Secondary Objective:**

* To assess whether gene expression signatures can predict IgG antibody and T-cell responses to ID93 + GLA-SE, following successful treatment of TB (identify correlates of immunogenicity for ID93 + GLA-SE).

Design: A Phase 2a, randomized, double-blind, placebo controlled clinical trial to evaluate the safety and immunogenicity of the ID93 + GLA-SE vaccine following intramuscular administration on Days 0 and 56 or Days 0, 28 and 56 in HIV uninfected adults, following successful completion of standard treatment for bacteriologically confirmed, drug-susceptible pulmonary TB.

**Study Population**: BCG immunized, HIV negative, TB patients aged 18 – 60 years of age, who have completed a course of TB treatment, as per the current South African national guidelines, for drug-sensitive, culture confirmed pulmonary TB. Patients will be recruited from TB clinics at up to three recruiting sites in the Western Cape region of South Africa.

**Randomization:** Following successful completion of TB treatment and bacteriologic confirmation of cure, defined as two consecutive negative Xpert MTB/RIF (taken at least 14 days apart at the end of month 4 and during month 5 of TB treatment), or if Xpert MTB/RIF remains positive, negative MGIT liquid culture on the same two occasions, subjects will be randomized to either study vaccine or saline placebo. Sixty subjects will be enrolled into three consecutive dose-escalating cohorts. Subjects who develop a positive MGIT liquid culture at, or after, the end of treatment will be excluded from receiving further study injections.

Main Inclusion Criteria: Male or female TB patients aged ≥ 18 to ≤ 60 years, who have successfully completed a standard course of TB treatment for drug-sensitive pulmonary TB with bacteriologic confirmation of cure, who are willing to avoid pregnancy, and provide informed consent.

Main Exclusion Criteria: HIV positive, incomplete or non-standard TB drug regimen, poor adherence to TB treatment, TB treatment failure, diabetes mellitus, autoimmune condition, or other medical or surgical condition likely to affect the safety or immunogenicity of the study vaccine.

Treatment Assignments: Progression through Cohorts 1-3 will depend on demonstration of safety.

|  |  |  |  |
| --- | --- | --- | --- |
| Cohort | N | Treatment Assignment | Timing of Study Injections |
| **1** | 15 | 2 μg ID93 + 2 μg GLA-SE | Day 0, Day 56 |
| 5 | Saline placebo | Day 0, Day 56 |
| **2** | 9 | 10 μg ID93 + 2 μg GLA-SE | Day 0, Day 56 |
| 3 | Saline placebo | Day 0, Day 56 |
| **3** | 12 | 2 μg ID93 + 5 μg GLA-SE  Saline placebo\* | Day 0, Day 56  Day 28\* |
| 12 | 2 μg ID93 + 5 μg GLA-SE | Day 0, Day 28, Day 56 |
| 4 | Saline placebo | Day 0, Day 28, Day 56 |

\*Saline placebo injection to be administered at Day 28 to retain blinding in Cohort 3.

**Study follow-up**: Each subject will be followed up for safety, immunogenicity, and recurrent TB disease outcomes for 224 days after the first study injection.

Statistical Considerations: The sample size is based on what is deemed reasonable for a safety study to observe common adverse events. The sample size will allow the Sponsor to define a safety profile for the ID93 + GLA-SE vaccine in pulmonary TB patients upon completion of treatment, and to evaluate immunogenicity specific to the vaccine following one, two or three injections in this study population.

# Key Roles

|  |  |
| --- | --- |
| **Study Sites:** | South African Tuberculosis Vaccine Initiative (SATVI), University of Cape Town (UCT), South Africa  Desmond Tutu HIV Centre (DTHC), University of Cape Town (UCT), South Africa  TASK Applied Science (TASK), Cape Town, South Africa |
| **Site Personnel:** | **SATVI**  Mark Hatherill, MD (National PI)  Thomas Jens Scriba, PhD (Deputy Director, Immunology)  Angelique Kany Kany Luabeya, MD (Site PI)  **DTHC**  Linda-Gail Bekker, PhD (Site PI)  **TASK**  Andreas Diacon, MD (Site PI) |
| **Sponsor:** | **Infectious Disease Research Institute (IDRI)** |
| **Sponsor Personnel:** | Rhea Coler, PhD (Clinical Immunology Director)  Anna Marie Beckmann, PhD (Project/Regulatory Director)  Stuart Kahn, MD (Medical Advisor)  Jill Ashman, MS (Project Manager)  Aude Frevol, RN, PMP (Project Coordinator)  Zachary Sagawa, MS (Regulatory Specialist)  Tracey Day, PhD (Clinical Immunology Coordinator) |

# Background Information and Scientific Rationale

## Background Information

IDRI has developed a tetravalent candidate tuberculosis (TB) vaccine antigen, ID93, formulated in a synthetic nano-emulsion adjuvant, GLA-SE. Prophylactic immunization with ID93 + GLA-SE limited experimental infection of both drug-sensitive and drug-resistant *Mycobacterium tuberculosis* (Mtb)in both mice and guinea pig models. Therapeutic immunization with ID93 + GLA-SE shortened the course of Mtb infection when administered in combination with existing first-line chemotherapeutics rifampicin (RIF) and isoniazid (INH). These studies used a mouse model of fatal TB as well as the established cynomolgus monkey model in studies that combined ID93 + GLA-SE with the standard antibiotic chemotherapy (i.e., an immuno-chemotherapeutic strategy). In addition to demonstrating excellent safety profiles, this combined approach reduced the duration of conventional chemotherapy required for survival, induced robust and durable multifunctional antigen-specific Th1 cells, decreased bacterial burden, and decreased Mtb-induced lung pathology, as compared to animals receiving chemotherapy alone.

These results have demonstrated the ability of therapeutic immunization to significantly enhance the efficacy of chemotherapy against TB, with implications for reduced treatment times, lower recurrence rates and reduced transmission to new patients, as well as expanded resource allocation. ID93 + GLA-SE is currently in Phase 1 testing; preliminary results indicate that it is safe and well tolerated in both BCG naïve and BCG immunized, TB-negative volunteers.

### Preclinical Data for ID93 + GLA-SE

Multiple preclinical studies in human cells, mice, guinea pigs, non-human primates, and a GLP toxicity study in rabbits have demonstrated the safety and immunogenicity of ID93 + GLA-SE (see Investigator’s Brochure).

ID93 elicits a cytokine response in *ex vivo* assays of peripheral blood mononuclear cells (PBMC) from humans with prior exposure to Mtbor Bacille Calmette-Guérin (BCG), a childhood TB vaccine made of attenuated *M. bovis*, indicating it has relevant antigenic qualities.

Mice immunized with the ID93 + GLA-SE vaccine candidate displayed antigen-specific Th1-type immune responses, characterized by high antigen-specific IgG levels and robust production of pro-inflammatory cytokines by restimulated T-cells. A high proportion of the ID93-specific T-cells are polyfunctional, producing the Th1 cytokines IL-2, IFN-γ, and TNF rather than the Th2 cytokines IL-5, IL-10, and/or IL-17. Upon challenge with Mtb, mice immunized with ID93 + GLA-SE showed significantly lower bacterial burdens in lungs and/or spleens compared with mice injected with saline, antigen alone, or adjuvant alone. Analysis of lung cellular infiltrates showed that vaccinated animals responded to challenge with Mtb with a greater proportion of CD4 T-cells expressing both IFN-γ and TNF, relative to controls. There were no safety issues noted.

The ID93 + GLA-SE vaccine candidate was evaluated in both naïve and BCG-exposed guinea pigs. In these animals, the vaccine induced increased antibody levels, ID93-specific Th1 cytokine responses, and protection from challenge as shown by reduced mortality and histopathological findings. No significant local or systemic toxicity was observed.

A safety and immunogenicity study in non-human primates demonstrated that administration of ID93 + GLA-SE was well-tolerated and immunogenic in male cynomolgus monkeys. No vaccine-related mortality occurred and no vaccine-related changes in clinical observations, food consumption, body weights, rectal temperature, and injection site reactions were identified. Vaccine-related findings were limited to a mild acute phase response following each injection associated with modest increases in neutrophils, white blood cells, fibrinogen, and C-reactive protein (CRP). Maximal levels of response occurred in an adjuvant (GLA-SE)-dependent manner. Increases in neutrophils and white blood cells were similar with each consecutive dosing; the magnitude of fibrinogen and CRP responses progressively increased with each consecutive dosing; and, all findings resolved within 14 to 15 days after each dosing. None of the identified vaccine-related changes were considered adverse. Immunogenicity analysis revealed a mixed Th1 and Th2 cell-mediated response to ID93 + GLA-SE, a complex reaction observed with other vaccines.

In a GLP repeated-dose toxicity study, male and female New Zealand White rabbits were given four weekly intramuscular (IM) doses of ID93 + GLA-SE. All test articles were well-tolerated and immunogenic. Observations were generally mild and reversible, including increases in globulin, fibrinogen, blood cells (WBCs, heterophils, and monocytes), and microscopic findings of mixed or mononuclear cell infiltrates. These findings are consistent with the administration of immunogenic substances (i.e., the ID93 antigen and the GLA-SE adjuvant formulation). Some of these observations were likely secondary to local effects at the injection sites as evidenced by the observation of inflammation in injection site histopathology.

A study in mice and cynomolgus monkeys demonstrated that therapeutic immunization with ID93 + GLA-SE, administered in combination with existing first-line chemotherapeutics rifampicin and isoniazid, is an effective adjunct to antibiotic treatment [[1](#_ENREF_1)]. A mouse model of fatal tuberculosis and the established cynomolgus monkey model was used to design an immuno-chemotherapeutic strategy to increase long-term survival and reduce bacterial burden, compared with standard antibiotic chemotherapy alone. This combined approach induced robust and durable pluripotent antigen-specific Th1-type immune responses, decreased bacterial burden, reduced the duration of conventional chemotherapy required for survival, and decreased Mtb induced lung pathology, compared with chemotherapy alone. These results demonstrated the ability of therapeutic immunization to significantly enhance the efficacy of chemotherapy against tuberculosis and other infectious diseases, with implications for treatment duration, patient compliance, and more optimal resource allocation.

### Clinical Data for ID93 + GLA-SE

#### Protocol IDRI-TBVPX-113

This is a phase 1 randomized clinical trial to evaluate the safety, tolerability, and immunogenicity of ID93 + GLA-SE in healthy adult subjects naïve to BCG and QFT negative. This study has completed enrollment of a total of 60 subjects as listed in Table 1. All subjects have completed the study and the data is being cleaned prior to database lock.

Table 1: IDRI-TBVPX-113: Treatment Groups

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Cohort | N | Treatment Assignment | Injection Route | Timing of Study Injections |
| #1 | 12 | 2 μg ID93 + 2 μg GLA-SE | IM | Days 0, 28, and 56 |
| 3 | 2 μg ID93 alone |
| #2 | 12 | 10 μg ID93 + 2 μg GLA-SE |
| 3 | 10 μg ID93 alone |
| #3 | 12 | 2 μg ID93 + 5 μg GLA-SE |
| 3 | 2 μg ID93 alone |
| #4 | 12 | 10 μg ID93 + 5 μg GLA-SE |
| 3 | 10 μg ID93 alone |

Subjects received a total of three intramuscular (IM) study injections at the Day 0, Day 28, and Day 56 visits. Safety assessments were performed 1, 3, 7, 14, and 28 days after each study injection. Subjects remained in follow-up for one year after the last study injection. This study is being conducted at Johnson County Clin-Trials in Lenexa, Kansas (Clinicaltrials.gov identifier: NCT01599897).

Although all subjects have completed the study as of 30MAY2014, as of the data cutoff date of 05MAY2014, subjects in Cohorts 1 and 2 had completed the study and subjects in Cohorts 3 and 4 only had the final follow-up phone call to complete. The preliminary safety data is summarized below.

The safety data is blinded within each cohort with respect to whether the adjuvanted vaccine or the antigen alone was administered. Each column in the tables that follow is headed with the Cohort number and the dose of ID93 plus or minus (±) the dose of GLA-SE; the “n” for each group is 15.

There were no Grade 4 adverse events, SAEs, AESIs, or deaths. Five subjects withdrew consent prior to receiving all three injections. No subjects withdrew because of safety-related reasons (e.g., an adverse event).

Local injection site adverse events (AEs) are tabulated in Table 2. The most frequent local reaction was injection site pain, followed by induration and erythema. One Grade 3 self-limiting erythema was noted in a Cohort 1 subject three days after the third dose. This event caused no discomfort to the subject and resolved by the next day. The Safety Monitoring Committee reviewed the case along with all other available injection site reactions and recommended continuing study as is without modifications. There were no Grade 4 local reactions.

Table 2: IDRI-TBVPX-113: Incidence of Local and Systemic Reactogenicity Adverse Events

|  |  | **Cohort 1** | **Cohort 2** | **Cohort 3** | **Cohort 4** |
| --- | --- | --- | --- | --- | --- |
| **Finding** | **Grade** | **2 µg ID93 ±**  **2 µg GLA-SE (n=15)** | **10 µg ID93 ±**  **2 µg GLA-SE (n=15)** | **2 µg ID93 ±**  **5 µg GLA-SE (n=15)** | **10 µg ID93 ±**  **5 µg GLA-SE (n=15)** |
| Injection site erythema | 1 | 1 (6.7%) | 0 | 0 | 0 |
|  | 3 | 1 (6.7%) | 0 | 0 | 0 |
| Injection site hematoma | 1 | 0 | 1 (6.7%) | 0 | 0 |
| Injection site pain | 1 | 12 (80.0%) | 9 (60.0%) | 10 (66.7%) | 9 (60.0%) |
|  | 2 | 0 | 3 (20.0%) | 1 (6.7%) | 2 (13.3%) |
| Injection site reaction | 1 | 1 (6.7%) | 0 | 0 | 0 |
| Injection site induration | 1 | 1 (6.7%) | 1 (6.7%) | 1 (6.7%) | 0 |

Note: Highest severity per subject reported for each event

Solicited systemic reactogenicity AEs are summarized in Table 3. The most frequent systemic reaction was headache, followed by fatigue and myalgia. There were no Grade 3 or Grade 4 systemic reactions.

Table 3: IDRI-TBVPX-113: Incidence of Systemic Reactogenicity Adverse Events

|  |  | **Cohort 1** | **Cohort 2** | **Cohort 3** | **Cohort 4** |
| --- | --- | --- | --- | --- | --- |
| **Finding** | **Grade** | **2 µg ID93 ±**  **2 µg GLA-SE (n=15)** | **10 µg ID93 ±**  **2 µg GLA-SE (n=15)** | **2 µg ID93 ±**  **5 µg GLA-SE (n=15)** | **10 µg ID93 ±**  **5 µg GLA-SE (n=15)** |
| Anorexia | 1 | 2 (13.3%) | 0 | 1 (6.7%) | 1 (6.7%) |
| Arthralgia | 1 | 0 | 0 | 0 | 1 (6.7%) |
|  | 2 | 0 | 0 | 1 (6.7%) | 0 |
| Chills | 1 | 2 (13.3%) | 0 | 0 | 0 |
| Fatigue | 1 | 4 (26.7%) | 1 (6.7%) | 3 (20.0%) | 3 (20.0%) |
|  | 2 | 1 (6.7%) | 0 | 0 | 1 (6.7%) |
| Headache | 1 | 5 (33.3%) | 3 (20.0%) | 2 (13.3%) | 4 (26.7%) |
|  | 2 | 0 | 1 (6.7%) | 1 (6.7%) | 1 (6.7%) |
| Myalgia | 1 | 3 (20.0%) | 0 | 0 | 1 (6.7%) |
|  | 2 | 0 | 0 | 1 (6.7%) | 1 (6.7%) |

Note: Highest severity per subject reported for each event

All other AEs and laboratory abnormalities occurring in at least 3 subjects are summarized in Table 4. The Grade 3 laboratory findings of increased blood potassium and decreased neutrophils were considered not related to study injections.

Table 4: IDRI-TBVPX-113: Incidence of All Other Adverse Events and Laboratory Abnormalities Occurring in at Least 3 Subjects

|  |  | **Cohort 1** | **Cohort 2** | **Cohort 3** | **Cohort 4** |
| --- | --- | --- | --- | --- | --- |
| **System Organ Class**  **Preferred Term** | **Grade** | **2 µg ID93 ±**  **2 µg GLA-SE (n=15)** | **10 µg ID93 ±**  **2 µg GLA-SE (n=15)** | **2 µg ID93 ±**  **5 µg GLA-SE (n=15)** | **10 µg ID93 ±**  **5 µg GLA-SE (n=15)** |
| **Infections and infestations** |  |  |  |  |  |
| Cellulitis | 1 | 1 (6.7%) | 0 | 0 | 0 |
|  | 2 | 2 (13.3%) | 0 | 0 | 0 |
| Sinusitis | 1 | 0 | 1 (6.7%) | 0 | 1 (6.7%) |
|  | 2 | 0 | 0 | 1 (6.7%) | 0 |
| **Investigations** |  |  |  |  |  |
| ALT increased | 1 | 0 | 3 (20.0%) | 1 (6.7%) | 0 |
| AST increased | 1 | 0 | 3 (20.0%) | 0 | 1 (6.7%) |
| Blood potassium increased | 1 | 1 (6.7%) | 0 | 2 (13.3%) | 0 |
|  | 2 | 1 (6.7%) | 0 | 0 | 0 |
|  | 3 | 4 (26.7%) | 1 (6.7%) | 0 | 0 |
| Blood sodium increased | 1 | 3 (20.0%) | 3 (20.0%) | 4 (26.7%) | 8 (53.3%) |
|  | 2 | 2 (13.3%) | 4 (26.7%) | 2 (13.3%) | 1 (6.7%) |
| Hemoglobin decreased | 1 | 2 (13.3%) | 2 (13.3%) | 2 (13.3%) | 0 |
|  | 2 | 0 | 1 (6.7%) | 0 | 0 |
| Neutrophil count decreased | 1 | 2 (13.3%) | 1 (6.7%) | 1 (6.7%) | 2 (13.3%) |
|  | 2 | 0 | 0 | 1 (6.7%) | 0 |
|  | 3 | 0 | 0 | 0 | 1 (6.7%) |

Note: Highest severity per subject reported for each event.

#### Protocol IDRI-TBVPX-114

This clinical trial is a Phase 1b, randomized, double-blind, placebo-controlled, dose-escalation evaluation of two dose levels of the ID93 antigen administered intramuscularly in combination with two dose levels of the GLA-SE adjuvant. The intended study population is 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 were enrolled first; successive cohorts will enroll both QFT negative and positive participants. This study has completed enrollment of the first two cohorts of subjects as listed in Table 5.

Table 5: IDRI-TBVPX-114: Treatment Groups

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Cohort | N | Treatment Assignment | QFT status | Injection Route | Timing of Study Injections |
| #1 | 9 | 10 μg ID93 + 2 μg GLA-SE | Negative | IM | Days 0, 28, and 112 |
| 3 | Placebo (saline) |
| #2 | 15 | 2 μg ID93 + 2 μg GLA-SE | Positive or negative |
| 3 | Placebo (saline) |
| #3 | 15 | 10 μg ID93 + 2 μg GLA-SE |
| 3 | Placebo (saline) |
| #4 | 15 | 10 μg ID93 + 5 μg GLA-SE |
| 3 | Placebo (saline) |

Subjects will receive a total of three intramuscular study injections at the Day 0, Day 28, and Day 112 visits. Safety assessments will be performed 1, 3, 7, 14, and 28 days after each study injection. Subjects will remain in follow-up for six months after the last study injection. This study is being conducted at the South African Tuberculosis Vaccine Initiative (SATVI) located in Worcester, South Africa (Clinicaltrials.gov identifier: NCT01927159).

As of the data cut-off date of 05MAY2014, 8 of 12 subjects in Cohort 1 have completed the Day 112 visit (received all three injections) and 17 of 18 subjects in Cohort 2 have completed the Day 28 visit (received two of the three injections). Enrollment of Cohort 3 is pending review of all safety data through the Day 35 visit for Cohort 2. The preliminary safety data is summarized below.

The safety data is blinded within each cohort with respect to whether the vaccine or saline placebo was administered; each column in the tables that follow is headed with the Cohort number and the dose of ID93 + GLA-SE or placebo.

There have been no Grade 3 or 4 adverse events and no AESIs or deaths. No subjects have withdrawn for any reason.

One SAE was reported for a subject who experienced a pregnancy with abnormal outcome. The subject revealed to the PI at Day 119 that she had a miscarriage on 23APR2014 (Study Day 100) followed by dilation and curettage at her private physician’s office. The subject had negative pregnancy tests on Days 0, 28, and 112 and received all three study injections on those days. The PI made a final diagnosis of incomplete spontaneous abortion that is unlikely to be related to the investigational product, due to prior history of ectopic pregnancy, dysmenorrhea, and menorrhagia.

Local injection site adverse events are tabulated in Table 6. Local reactions included mild to moderate injection site pain and induration. No erythema was noted. There were no Grade 3 or 4 local reactions.

Table 6: IDRI-TBVPX-114: Incidence of Local Reactogenicity Adverse Events

|  |  | **Cohort 1** | **Cohort 2** | **Cohort 3** | **Cohort 4** |
| --- | --- | --- | --- | --- | --- |
| **Finding** | **Grade** | **10 µg ID93 +**  **2 µg GLA-SE**  **or placebo (QFT-)**  **(n=12)** | **2 µg ID93 +**  **2 µg GLA-SE**  **or placebo (QFT+/-)**  **(n=18)** | **10 µg ID93 +**  **2 µg GLA-SE**  **or placebo (QFT+/-)**  **(n= )** | **10 µg ID93 +**  **5 µg GLA-SE**  **or placebo (QFT+/-)**  **(n= )** |
| Injection site erythema | - | 0 | 0 |  |  |
| Injection site pain | 1 | 5 (41.7%) | 12 (66.7%) |  |  |
|  | 2 | 1 (8.3%) | 3 (16.7%) |  |  |
| Injection site induration | 1 | 0 | 2 (11.1%) |  |  |
|  | 2 | 0 | 3 (16.7%) |  |  |

Note: Highest severity per subject reported for each event

Solicited systemic reactogenicity AEs are summarized in Table 7. The most frequent systemic reaction was myalgia, followed by headache and fatigue/malaise. There were no Grade 3 or Grade 4 systemic reactions.

Table 7: IDRI-TBVPX-114: Incidence of Systemic Reactogenicity Adverse Events

|  |  | **Cohort 1** | **Cohort 2** | **Cohort 3** | **Cohort 4** |
| --- | --- | --- | --- | --- | --- |
| **Finding** | **Grade** | **10 µg ID93 +**  **2 µg GLA-SE**  **or placebo (QFT-)**  **(n=12)** | **2 µg ID93 +**  **2 µg GLA-SE**  **or placebo (QFT+/-)**  **(n=18)** | **10 µg ID93 +**  **2 µg GLA-SE**  **or placebo (QFT+/-)**  **(n= )** | **10 µg ID93 +**  **5 µg GLA-SE**  **or placebo (QFT+/-)**  **(n= )** |
| Anorexia | 2 | 1 (8.3%) | 0 |  |  |
| Fatigue/malaise | 2 | 1 (8.3%) | 1 (5.6%) |  |  |
| Fever | 1 | 1 (8.3%) | 0 |  |  |
| Headache | 1 | 1 (8.3%) | 0 |  |  |
|  | 2 | 2 (16.7%) | 0 |  |  |
| Myalgia | 1 | 1 (8.3%) | 3 (16.7%) |  |  |
|  | 2 | 0 | 1 (5.6%) |  |  |

Note: Highest severity per subject reported for each event

All other AEs and laboratory abnormalities occurring in at least 3 subjects are summarized in Table 8. The two Grade 2 lab findings of decreased neutrophils within the same treatment group triggered a protocol-defined pausing rule. After review by the SMC, it was determined that the study may continue unmodified.

Table 8: IDRI-TBVPX-114: Incidence of All Other Adverse Events and Laboratory Abnormalities Occurring in at Least 3 Subjects

|  |  | **Cohort 1** | **Cohort 2** | **Cohort 3** | **Cohort 4** |
| --- | --- | --- | --- | --- | --- |
| **System Organ Class**  **Preferred Term** | **Grade** | **10 µg ID93 +**  **2 µg GLA-SE**  **or placebo (QFT-)**  **(n=12)** | **2 µg ID93 +**  **2 µg GLA-SE**  **or placebo (QFT+/-)**  **(n=18)** | **10 µg ID93 +**  **2 µg GLA-SE**  **or placebo (QFT+/-)**  **(n= )** | **10 µg ID93 +**  **5 µg GLA-SE**  **or placebo (QFT+/-)**  **(n= )** |
| **Investigations** |  |  |  |  |  |
| ALT increased | 1 | 2 (16.7%) | 1 (5.6%) |  |  |
| Blood pressure diastolic increased | 1 | 1 (8.3%) | 2 (11.1%) |  |  |
|  | 2 | 1 (8.3%) | 0 |  |  |
| Hemoglobin decreased | 1 | 2 (16.7%) | 1 (5.6%) |  |  |
|  | 2 | 0 | 1 (5.6%) |  |  |
| Neutrophil count decreased | 1 | 2 (16.7%) | 3 (16.7%) |  |  |
|  | 2 | 0 | 2 (11.1%) |  |  |

Note: Highest severity per subject reported for each event.

## Rationale

The rationale for this trial is to establish safety and immunogenicity of the ID93 + GLA-SE vaccine in HIV uninfected adult pulmonary TB patients upon completion of treatment, in preparation for a planned Phase 2b prevention of TB recurrence trial in this study population. The rationale for the proposed Phase 2b trial is based on 1) the potential of post-treatment ID93 + GLA-SE vaccination to reduce the rate of recurrent TB disease, and thus improve MDR-TB control efforts; 2) the need for a proof-of-concept efficacy signal for this novel TB vaccine, in a study population with very high incidence of the TB disease endpoint, which could justify expansion to Phase 3 trials; and 3) the need for safety data in TB patients who have recently completed TB treatment, prior to testing ID93 + GLA-SE as a therapeutic vaccine in TB patients receiving active treatment.

The emergence of drug resistant strains of MTB presents a significant threat to global TB control efforts and international health. In 2010, it is estimated that there were 490,000 incident cases of MDR-TB, an increase of 80% from estimates in 2000 [[2](#_ENREF_2)]. It is estimated that global MDR-TB prevalence is between 1 and 1.5 million. From 1990 to 2009, incidence of TB in South Africa has risen from 302/100,000 persons to 970/100,000 persons, among the highest in the world. Eighteen thousand recurrent TB cases were reported in South Africa in 2010 [[2](#_ENREF_2)]. Retreatment TB drug regimens may be long, complex, and associated with poor adherence [[3](#_ENREF_3)]; and retreatment patients account for almost half of MDR-TB cases, carrying a massive burden of morbidity, mortality and cost of healthcare. South Africa spends half its TB budget on MDR-TB and XDR-TB control; and TB control strategies for patients with recurrent TB are aimed at prevention of MDR-TB. Effective post-treatment vaccination of TB patients against recurrent disease would be a simple intervention, which would not need expensive new infrastructure in resource-poor countries, but which would have a major global health impact on the burden of TB control.

Patients with pulmonary TB, who have successfully completed treatment through to cure, remain epidemiologically and/or immunologically more susceptible to subsequent, recurrent TB than persons without prior disease [[4](#_ENREF_4)]. Our data indicate that the incidence of culture-confirmed, recurrent TB within 12 months of completing standard regimen TB treatment, under optimal research conditions, is approximately 5% in the Cape Town region of South Africa (five-fold higher than community TB incidence). It would be expected that recurrent disease occurring immediately following treatment completion would be due predominantly to reactivation (true relapse), whereas recurrent disease occurring more distant from treatment completion would be more likely due to reinfection [[4-6](#_ENREF_4)].

Globally, the incidence of culture-confirmed, recurrent TB within 12 months of completing treatment ranges from 2-8% under research conditions [[4](#_ENREF_4), [6-8](#_ENREF_6)]. A systematic review of 15 trials showed that 91% of all recurrent TB occurred within 12 months after treatment completion [[7](#_ENREF_7)], although the 8% recurrence rate is inflated by sub-optimal treatment arms [[7](#_ENREF_7)]. Poor adherence increases the rate of reactivation TB, yet adequately treated patients remain at risk of recurrence [[6](#_ENREF_6), [8](#_ENREF_8)]. Lower recurrence rates (2-3%) have been found in low TB burden countries, where transmission is least, but these rates are still many times higher than national background incidence [[8](#_ENREF_8)]. For example, data from Cape Town for the 5-year period 1993-1998, when annual community TB incidence was 0.3%, showed cumulative 14% culture-confirmed recurrence, equivalent to an annual rate almost ten-fold greater than the community TB incidence [[6](#_ENREF_6)]. Recurrent TB disease rates in high burden countries should be estimated for standard-of-care, directly observed treatment, short course (DOTS) regimens, in which optimal adherence has been assured under research conditions [[5](#_ENREF_5), [6](#_ENREF_6)]. Twelve-month incidence of recurrent TB in the standard-of-care arm of a treatment shortening trial at our SATVI Worcester research site was 5.7%. Similarly, 2-year cumulative incidence of recurrent TB at the SUN research site in Cape Town was 10.4%. For comparison, annual incidence of new TB cases in South Africa is 0.98% [[9](#_ENREF_9)].

The relatively high incidence rate of recurrent TB may be leveraged to carry out proof-of-principle efficacy trials. Large-scale Phase 3 trials will not be feasible or affordable for all the candidate TB vaccines in the development pipeline and TB case accrual, key to determination of vaccine efficacy, is the primary driver of trial sample size, duration, and cost. This Phase 2a study is the immediate precursor to a planned Phase 2b trial that will maximize TB case accrual with optimal cost efficiency, to facilitate evidence-based progression of the vaccine candidate to Phase 3 efficacy trials.

The tetravalent candidate TB vaccine antigen, ID93, is formulated in a synthetic nano-emulsion adjuvant, GLA-SE. GLA is a synthetic compound similar to the major active species of the naturally derived TLR4 agonist MPL [[10](#_ENREF_10)]. ID93 is a fusion of four Mtb proteins associated with virulence or latency: Rv2608 (PE/PPE family), Rv3619 and Rv3620 (both EsX family), and the hypoxia-associated protein Rv1813. Immunization with ID93 + GLA-SE produces robust poly-functional Th1 responses in mice and is protective against aerosolized Mtbinfection in mouse, guinea pig and non-human primate challenge models [[11](#_ENREF_11), [12](#_ENREF_12)]. Importantly, ID93 + GLA-SE vaccination also protects against MDR-TB challenge and boosts the protective efficacy of the BCG vaccine [[12](#_ENREF_12)].

This Phase 2a trial will test the safety and immunogenicity of the ID93 + GLA-SE TB vaccine, in HIV uninfected, previously BCG vaccinated, adult TB patients who have successfully completed treatment with bacteriologic confirmation of cure. We hypothesize that ID93 + GLA-SE is safe and immunogenic in HIV uninfected, BCG vaccinated adults, after successful completion of treatment for pulmonary TB.

This study will advance the development of a vaccine that might be used ultimately for a prophylactic indication, to reduce the incidence of recurrent and drug-resistant TB disease, or for a therapeutic indication, in conjunction with chemotherapy to shorten treatment time.

## Potential Risks and Benefits

### Potential Risks

There are potential known and unknown risks associated with vaccination with ID93 + GLA-SE. ID93 + GLA-SE vaccination in BCG naïve, QuantiFERON®-TB Gold (QFT) negative (i.e., Mtb uninfected) adults has shown an acceptable safety profile. No significant safety issues have been observed in BCG vaccinated, QFT negative and positive adults in an ongoing study in South Africa [see Section 2.1.2 above for safety data from the IDRI-TBVPX-113 and IDRI-TBVPX-114 studies and the Investigator’s Brochure for complete details].

Known risks from these studies include mild to moderate local reactogenicity including injection site pain and induration, and systemic effects such as headache, fatigue, and myalgia. Possible adverse events include general reactions to vaccines or severe allergic reactions that may be unpredictable.

The risks associated with ID93 + GLA-SE vaccination of persons with active or previous TB disease are not known. This Phase 2a study will evaluate the safety profile of ID93 + GLA-SE vaccination in BCG vaccinated, HIV uninfected, South African adult TB patients upon successful completion of treatment and cure.

Theoretical risks of ID93 + GLA-SE vaccination of persons with previous TB disease may include exacerbation of local reactogenicity, compared to persons without previous TB disease, and the Koch reaction. The Koch reaction is a severe cell-mediated hypersensitivity response to administration of Mtb antigens characterized by tissue necrosis at the injection site. The phenomenon was described by Robert Koch following administration of old tuberculin to TB patients, but has not been observed in any subjects, including persons with latent Mtb infection and prior TB disease, who have participated in clinical trials of 6 different TB vaccines at our research sites. However, in order to minimize these theoretical risks, subjects will undergo stringent safety monitoring; will be subject to limits on the rate of randomization; and will be subject to rules governing the demonstration of safety in prior dose levels before written authorization to proceed with randomization and administration of study injections in subsequent higher dosing cohorts is given.

Other known risks of participation include mild discomfort associated with phlebotomy. The volume of blood sampling is not deemed clinically significant in this adult population at the end of successful TB treatment, and in whom bacteriologic cure has been demonstrated.

HIV testing will be performed with appropriate pre- and post-test counseling, optimal measures to protect confidentiality, and referral to health services for medical care including access to antiretroviral treatment.

### Known Potential Benefits

Although not a study intervention, support of patient adherence to TB chemotherapy will be a consideration when identifying potential patients for study enrollment. Optimal adherence would be expected to reduce rates of treatment failure and relapse. During the study screening phase (last two months of standard TB treatment) staff may detect side effects of TB chemotherapy, allowing for effective intervention and referral.

Study staff will perform study-specific sputum sampling during the last two months of TB treatment, including drug susceptibility testing, the results of which will be shared with health services to improve patient care. Further, since subjects will be screened for symptoms of recurrent TB disease at regular intervals after the end of treatment, participation will allow early diagnosis and referral for treatment of recurrent TB disease.

Additional screening tests, including testing for HIV infection, and other previously undiagnosed medical conditions, such as diabetes mellitus, will allow early detection and referral for appropriate medical care.

### Route of Administration, Dose, and Dose Regimen

The route of administration (intramuscular), dose (2 or 10 µg ID93 + 2 or 5 µg GLA-SE), and dose regimen (one injection on each of Days 0 and 56 or on each of Days 0, 28 and 56) for the ID93 + GLA-SE vaccine to be used in this clinical trial have been selected based on pre-clinical and clinical studies in order to optimize the safety, immunogenicity, and potential efficacy of the vaccine.

# Objectives

## Study Objectives

The purpose of this study is to evaluate the safety and immunogenicity of ID93 + GLA-SE vaccine when administered to HIV uninfected adult pulmonary TB patients in two doses 56 days apart following successful completion of TB treatment with confirmed bacteriologic cure, in preparation for a future collaborative Phase 2b prevention of TB recurrence trial in the same population.

**Primary Objectives:**

* To evaluate the safety of ID93 + GLA-SE at three increasing dose levels, compared to saline placebo, following intramuscular administration on either Days 0 and 56 or Days 0, 28 and 56.
* To assess the immunogenicity of ID93 + GLA-SE at three increasing dose levels following intramuscular administration on Days 0 and 56 or Days 0, 28 and 56, by evaluating IgG antibody and T-cell responses to ID93 + GLA-SE at specified time points.

**Secondary Objective:**

* To assess whether gene expression signatures can predict IgG antibody and T-cell responses to ID93 + GLA-SE, following successful treatment of TB (identify correlates of immunogenicity for ID93 + GLA-SE).

## Study Outcome Measures

Assessment of safety will include clinical laboratory tests, vital signs, and physical exam findings.

Although not statistically powered to detect prevention of recurrent cases, patients will be followed and evaluated throughout the course of the study for recurrence of TB disease as a safety endpoint.

### Primary Outcome Measures

#### Safety Outcomes

Safety outcomes will include solicited adverse events within 7 days and unsolicited adverse events within 28 days after each study injection; and serious adverse events after the first study injection until end of study follow-up.

#### Clinical Assessments and Laboratory Tests

Clinical assessments and laboratory tests are summarized in Appendix 1. Any abnormal laboratory values, abnormal vital signs, or abnormal physical examination findings will be documented by the Investigator as adverse events. The safety assessments will be based on reported adverse events, changes in laboratory values, and changes in vital signs. The severity and relationship to treatment will be recorded for all adverse events. Adverse events will be coded for summary and analysis using standardized preferred terms and system organ class.

#### Immunology Outcomes

Antigen-specific IgG and PBMC T-cell responses will be assessed for subjects at Days 0, 14, 28, 42, 56, 70, 84, and 224.

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.

Immunology analyses will also involve assessment of the immune response to the vaccine by measurement of the frequency of CD4+ and CD8+ T-cells that produce any of selected cytokines following stimulation with whole ID93 protein and peptide pools derived from and representing the entire amino acid sequences of the ID93 component 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.

### Secondary Outcome Measures

#### Secondary Immunology Outcomes

Exploratory analysis of T-cell responses measured in whole blood will be assessed for subjects at Days 0, 14, 28, 42, 56, 70, 84, and 224.

In addition, samples will be collected and stored for future exploratory analyses of gene signatures and RNA-Seq to determine biological correlates of protective response induced through vaccination that may prevent recurrent TB disease. A small sample of whole blood will also be collected and used to quantitate whole blood cellular subsets. This data will be used to deconvolute transcriptomic signatures obtained from whole blood.

# Study Design

A Phase 2a, randomized, double-blind, placebo controlled clinical trial to evaluate the safety and immunogenicity of the ID93 + GLA-SE vaccine following intramuscular administration on Days 0 and 56 or Days 0, 28 and 56 in HIV uninfected, previously BCG vaccinated adults, following successful completion of standard treatment and cure for Mtb culture-confirmed, drug-susceptible pulmonary TB. A total of 60 subjects will be randomized and injected.

## Study Phases

*Screening Phase:* TB patients with MTB liquid culture (MGIT system, Becton-Dickinson, USA) or Xpert MTB/RIF (Cepheid, USA) confirmed pulmonary TB will be recruited from local TB health facilities approximately 4 months after starting a standard course of TB treatment. Adequate TB treatment adherence must be demonstrated by regular attendance and completion of treatment at the local clinic. Adequate adherence is defined as having completed 24 weeks (-1/+4 weeks) of TB treatment from the start date of treatment. Response to TB treatment and sputum bacteriologic culture conversion will be assessed on two successive occasions at least 14 days apart, at approximately 4 and 5 months after starting treatment.

A TB symptom questionnaire will be administered by study staff as part of study screening, and two consecutive sputum samples will be collected for Xpert MTB/RIF and MTB liquid culture. Since a false positive Xpert MTB/RIF may occur during treatment due to the presence of non-viable, killed bacilli, MGIT culture will also be performed on sputum samples collected at the 1st screening visit (approximately the end of month 4), 2nd screening visit (14 to 28 days after 1st screening) and 3rd screening visit at the end of TB treatment. Subjects with new or worsening symptoms judged consistent with TB treatment failure will be excluded.

Bacteriologic confirmation of cure by negative Xpert MTB/RIF, or if Xpert MTB/RIF positive, MTB liquid culture on two successive occasions at least 14 days apart, at approximately the end of 4 months after starting TB treatment (16 weeks +/-1 week) and 14 to 28 days later, will be required for eligible subjects to be randomized to receive the first study injection with either ID93 + GLA-SE vaccine or saline placebo. All subjects must also complete the full course of scheduled TB treatment as per the prevailing current South African National Tuberculosis Management Guidelines (2009 Guideline: 2 months isoniazid, rifampicin, pyrazinamide, and ethambutol [intensive phase], followed by 4 months isoniazid and rifampicin).

Subjects must receive their first study injection within 28 days after their last day of TB treatment. An end of treatment sputum sample will be collected at either the 3rd screening visit, or on Day 0 prior to administration of study injection, for both Xpert MTB/RIF and MGIT MTB liquid culture. Development of a positive MTB liquid culture at end of treatment, despite two prior negative cultures, will constitute a late exclusion criterion and such subjects will be excluded from receiving further study injections but remain in follow-up for safety evaluation through Day 168.

*Study Injection Phase:* Subjects in all treatment groups will receive a total of either two or three intramuscular study injections, one injection on each of Days 0 and 56 or Days 0, 28 and 56.

*Follow-up Phase*: Post study injection phase all subjects will continue to be evaluated for recurrent TB disease as a safety endpoint.

A total of 60 subjects will be randomized in an overall ratio of 4:1 to receive vaccine or saline placebo. A total of 20, 12 and 28 subjects in each of 3 sequential dose-escalation cohorts, respectively, will be randomized 3:1 to receive vaccine or saline placebo on Days 0 and 56 (Cohorts 1 and 2) and 3:3:1 to receive vaccine on Days 0 and 56 (with a saline injection at Day 28 to preserve blinding), vaccine on Days 0, 28 and 56 or saline placebo with escalating vaccine dose as follows: 2 µg ID93 + 2 µg GLA-SE (Cohort 1), 10 µg ID93 + 2 µg GLA-SE (Cohort 2), and 2 µg ID93 + 5 µg GLA-SE (Cohort 3), see Table 9. Safety at the lower doses must be demonstrated prior to dose-escalation to the next cohort. If no stopping rules are observed following injection at a lower dose, written permission to proceed to the next cohort level will be provided by the local Medical Monitor (LMM) before proceeding to randomization of Cohort 2 and Cohort 3.

To ensure subject safety prior to increasing the *rate of randomization*, no more than one subject in Cohort 1 will be randomized and dosed per day (see Rules for Suspension).

To ensure subject safety prior to *dose escalation*, the next Cohort will not be randomized and injected with a higher dose if a significant safety signal has been observed at a lower dose (see Rules for Suspension).

To ensure subject safety prior to *administering a 2nd injection at a given dose level,* a 2nd injection will not be administered if a significant safety signal has been observed after the first injection in that Cohort (see Rules for Suspension).

To ensure subject safety prior to *administering a 2nd injection at a higher dose level*, a 2nd injection at a higher dose level will not be administered if a significant safety signal has been observed after the 2nd injection at a lower dose level.

Table 9: IDRI-TBVPX-203: Treatment Assignments

|  |  |  |  |
| --- | --- | --- | --- |
| Cohort | N | Treatment Assignment | Timing of Study Injections |
| **1** | 15 | 2 μg ID93 + 2 μg GLA-SE | Day 0, Day 56 |
| 5 | Saline placebo | Day 0, Day 56 |
| **2** | 9 | 10 μg ID93 + 2 μg GLA-SE | Day 0, Day 56 |
| 3 | Saline placebo | Day 0, Day 56 |
| **3** | 12 | 2 μg ID93 + 5 μg GLA-SE  Saline placebo | Day 0, Day 56  Day 28 |
| 12 | 2 μg ID93 + 5 μg GLA-SE | Day 0, Day 28, Day 56 |
| 4 | Saline placebo | Day 0, Day 28, Day 56 |

## Evaluation of Safety Outcomes

For each subject, general safety will be evaluated at baseline and on Days 0, 28, 56, 84, 112, 168, and 224. Selected safety assessments will also be conducted in the clinic at 30 minutes, three and seven days after each injection (i.e., on Days 0, 3, and 7, Days 28, 31, and 35, and Days 56, 59, and 63). Blood will be obtained at baseline, Day 28 pre-injection, Day 56 pre-injection, and 7 days after each injection for safety assessments. Safety laboratory results from 7 days post injection (and any follow-up labs necessary) will be reviewed prior to the next scheduled study injection.

Safety through 7 days after the first injection must be demonstrated for all subjects in Cohort 1 prior to randomizing and administering the first injection to subjects in Cohort 2 (i.e., no rules for suspension are met). Similarly, safety through 7 days after the first injection must be demonstrated for all subjects in Cohort 2, prior to randomizing and administering the first injection to subjects in Cohort 3.

Safety through 7 days after the 2nd injection must be demonstrated for all subjects in Cohort 1, prior to administering the 2nd injection to subjects in Cohort 2..

## Evaluation of Immunogenicity Outcomes

Blood for immunogenicity assessments will be obtained on Days 0, 3, 14, 28, 42, 56, 70, 84, and 224. Immunogenicity evaluations will include quantification of T-cell cytokine responses from whole blood and PBMC samples and IgG serum antibody responses to ID93. Samples for gene expression signatures (RNA) will be obtained and stored for future analyses on Days 0, 3, 7, 28, 31, 35, 56, 59, 63, and if relevant, at time of TB disease recurrence.

## Evaluation of TB Disease Recurrence

Subjects will be assessed for possible recurrent TB disease at each post injection study visit. Additionally, subjects will be asked to contact the study team if they develop symptoms suggestive of recurrent TB disease.

Subjects who present with respiratory symptoms should be evaluated for TB disease at the discretion of the investigator on clinical grounds. A course of antibiotic therapy may be appropriate to rule out a bacterial respiratory infection before starting TB investigations. Subjects will be screened for persistent (14 days or longer) or unexplained symptoms of suspected TB disease, including productive cough, fever, weight loss, fatigue, chest pain, or any hemoptysis. In addition, subjects will be educated to contact study staff if any symptoms of suspected TB occur in the interim. Presence of persistent and unexplained symptoms should trigger investigation for recurrent TB disease, including at least two sputum collections for MTB liquid culture and speciation, and Xpert MTB/RIF. Subjects with confirmed recurrent TB disease will also be investigated for possible HIV infection. Investigation of subjects who are sputum liquid MTB culture negative and Xpert MTB/RIF test negative, or who have suspected extra-pulmonary TB, may include additional sputum induction, chest radiography, other radiological imaging, aspiration, biopsy, or other additional investigations as clinically indicated.

# Study Enrollment and Withdrawal

## Subject Inclusion Criteria

Subjects must meet ALL of the following inclusion criteria to be eligible:

1. Males and females ≥18 years and ≤60years of age.
2. Subjects must have been successfully treated, i.e., completed the scheduled course of TB treatment as per the prevailing South African national guidelines, for MTB culture-confirmed, drug sensitive pulmonary TB, as evidenced by a record of positive liquid MTB culture with formal drug sensitivity testing (DST) and/or by Xpert MTB/RIF test at baseline.
3. Must have two separate samples showing bacteriologic confirmation of cure - defined in the first instance as Xpert MTB/RIF test negative, or, if Xpert MTB/RIF positive, as MTB liquid culture negative - on two successive occasions at least 14 days apart. Subjects who are sputum unproductive will be deemed Xpert MTB/RIF and MTB liquid culture negative [[14](#_ENREF_14)].
4. Female subjects of childbearing potential must have a negative serum pregnancy test at screening and a negative urine pregnancy test on the day of each study injection, must not be breast-feeding, and be willing to avoid pregnancy for 3 months following first study injection. 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. These precautions are necessary due to unknown effects that ID93 + GLA-SE might cause in a fetus or newborn infant.
5. The following screening laboratory values must be within the laboratory reference range or, if abnormal, deemed not clinically significant and less than Grade 2 severity on the FDA Toxicity Scale, as determined by the PI and LMM or Sponsor Medical Advisor: ALT, AST, total bilirubin, creatinine, total WBC count, hemoglobin, and platelet count. Note: creatinine, AST, ALT, and bilirubin values lower than the normal range are acceptable (not graded on the Toxicity Table).
6. The HIV 1/2 antibody serology tests must be negative.
7. Must give informed consent, be able and willing to make all evaluation visits, be reachable by telephone or personal contact by the study site personnel, and be willing to remain in the study area for the duration of the trial.

## Subject Exclusion Criteria

Subjects who meet ANY of the following criteria will be excluded from the study (ineligible):

1. TB treatment failure, as evidenced by clinical diagnosis or a positive MTB liquid culture at approximately month 4 or month 5 after starting treatment. A positive MTB liquid culture at, or after, end of treatment would exclude subjects from receiving further study injections.
2. Previous course of TB treatment completed within 5 calendar years prior to obtaining baseline diagnostic sputum samples.
3. Receipt of any investigational products or investigational drug in the past 6 months or investigational vaccine ever.
4. Treatment with immunosuppressive drugs (e.g., oral or injected steroids, such as prednisone; high dose inhaled steroids) in the past 6 months. Topical steroids would be allowable.
5. Received incomplete or investigational, or non-standard TB drug regimen, other than the prevailing current South African national guideline as reference standard, or poor adherence to TB treatment regimen. An incomplete regimen or poor adherence to TB treatment is defined as having completed less than 23 weeks of TB treatment from the start date of treatment, or taken longer than 28 weeks to complete treatment.
6. Diagnosed with rifampicin-resistant MTB strain (by Xpert MTB/RIF and/or culture and formal DST).
7. History of autoimmune disease or other causes of immunosuppressive states.
8. History or evidence of any acute or chronic illness (including diabetes mellitus, asthma), medical or surgical condition, or chronic heavy ethanol or drug use, or use of medication that, in the opinion of the Principal Investigator, may interfere with the evaluation of the safety or immunogenicity of the vaccine.
9. Subjects with a history of previous anaphylaxis or severe allergic reaction to vaccines, eggs, or unknown allergens.
10. Subjects who are unlikely to cooperate with the requirements of the study protocol.

## Treatment Assignment Procedures

### Randomization Procedures

Subjects will be screened for eligibility for randomization upon successful completion of a course of standard TB treatment. The investigator will assess subjects for eligibility for randomization, document the randomization inclusion and exclusion criteria, and refer eligible subjects to the study vaccine manager for randomization.

A randomization list will be generated by the IDRI biostatistician or designee in blocks of appropriate size resulting in a ratio of 3:1 (ID93 + GLA-SE vaccine to saline placebo) for Cohorts 1 and 2, and in a ratio of 3:3:1 (ID93 + GLA-SE vaccine at Days 0 and 56: ID93 + GLA-SE vaccine at Days 0, 28 and 56: saline placebo). The randomization list (or opaque, sealed, randomization envelopes) will be provided to the designated site sub-investigator responsible for study injection preparation. The list (or individual envelopes) will have study Participant ID number (PID #) and corresponding study injection assignment. The list (or envelopes) must be maintained under the control of the study personnel responsible for study injection preparation.

Each subject will be assigned a unique seven digit study PID # after eligibility is confirmed and prior to baseline immunology blood draw on Day 0. This PID # will be assigned in sequential order and must be recorded in the Screening Log and linked to the subject’s screening identification number (SID #). The first three digits of the PID # identify the country (first digit: 9 = South Africa) and site (next two digits, where 01 = SATVI, 02 = DTHC, and 03 = TASK). The next four digits of the PID # identify the cohort and study subject. Subjects enrolled into Cohort 1 of the study at the SATVI site will be assigned the PID # 901-1001, 901-1002 and so on. Subjects enrolled into Cohort 2 of the study at the SATVI site will be assigned the PID # 901-2001, 901-2002 and so on. Subjects enrolled into Cohort 3 at the SATVI site will be assigned the PID # 901-3001, 901-3002, etc. Similarly, subjects enrolled at the DTHC site will be assigned PID # 902-1001, etc., for Cohort 1, 902-2001, etc., for Cohort 2, and 902-3001, etc., for Cohort 3.

The study PID # and subject initials will be given to the study vaccine manager responsible for preparation of the study injection on Day 0. He/she will match this PID # to the study injection assignment in the randomization list (or by opening the sealed envelope). Separate vials of ID93 and GLA-SE will be provided. The study vaccine manager will mix the contents of the vials and prepare the syringes just prior to each injection based on the assigned treatment for that individual.

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, usually the study pharmacist, 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. In addition, in order to maintain blinding, subjects in Cohort 3 who are assigned to ID93 + GLA-SE vaccine at Days 0 and 56, will receive a saline study injection at Day 28.

A subject is considered randomized when the study vaccine manager assigns that subject to the treatment group corresponding to the participant’s assigned PID #. If a subject does not meet all eligibility criteria, randomization should not occur on that day. Subjects may be reconsidered for randomization at a later date if the reason for ineligibility appears self-limiting, e.g., pending resolution of an acute illness or after a repeated clinical laboratory evaluation result is shown to be within normal limits, but within the allowed time frame for complete screening evaluations.

IDRI will closely monitor enrollment numbers across all sites for each cohort in order to assure the correct treatment allocations are met. In the event that the rate of enrollment is slower than anticipated at one or more sites, the IDRI biostatistician will provide instructions to ensure the correct enrollment quota and treatment assignments are met across all sites for any given cohort.

### Masking Procedures

Personnel at the study site(s) will be blinded to subject treatment assignments, with the exception of the study vaccine manager (and designee, if appointed). In addition, since ID93 + GLA-SE and saline for injection (placebo) have a different appearance, the study injection administrator (the study team member in the clinic who will be administering the injections) will also be unblinded. Unblinded study personnel must not participate in safety or immunogenicity evaluations.

All unblinded persons must not reveal individual subject treatment regimen assignments to any other member of the study team. A Delegation of Authority Log will be maintained by the site(s) 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 unblinding information. The designated unblinded pharmacy monitor(s) and the Sponsor biostatistician will also have access to unblinded information.

The randomization schedule (or individual opaque, sealed, randomization envelopes) will be provided to the study vaccine manager by the unblinded statistician in a sealed tamper-evident envelope. The randomization schedule (or randomization envelopes) 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.

If there is an urgent clinical need to know a subject’s treatment assignment, the investigator (in consultation with the LMM and Sponsor if possible) will make a written request (may be by e-mail) to the study vaccine manager (and/or the unblinded IDRI biostatistician) for urgent Emergency Unblinding of a subject’s treatment allocation. The request must include the subject identification number (PID #), 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.

The Sponsor must be notified immediately of any break of the study blind, whether accidental or a clinically indicated Emergency Unblinding.

### Reasons for Withdrawal

Subjects are free to withdraw from participating in the study at any time upon request. Subjects wishing to withdraw from participation only in certain study activities may remain on study at the discretion of the investigator, so that whenever possible, an End-of-Study (EOS) visit may be conducted.

The investigator may discontinue a subject from the study if any clinical AE, laboratory abnormality, intercurrent illness, or other medical condition occurs such that continued participation in the study would not be in the best interest of the subject.

### Handling of Withdrawals

Subjects will be free to withdraw from the study at any time, for any reason, and without prejudice to further treatment. Subjects who wish to withdraw before their second study injection will be encouraged to continue safety evaluations and be given appropriate care under medical supervision until any AE has resolved or become static. Subjects should be encouraged to attend an EOS visit for evaluation of safety, and screening for possible recurrent TB disease. Any subject who withdraws from the study, regardless of reason, will not be allowed to re-enroll in the study.

If the study team is unable to establish contact with a subject who misses a scheduled study visit(s), the study team must make every possible effort to re-establish contact and document such efforts. If contact is re-established, then the subject will resume participation in the study. A minimum of 3 attempts on separate days should be made. If contact with the subject cannot be re-established by the scheduled Day 224 EOS visit date, then a determination of “lost to follow-up (LTFU)” should be made.

Subjects who have withdrawn from the study or who have been classified as LTFU will be included in the intent-to-treat analysis. Reasons for withdrawal will be recorded on the appropriate CRF. The final report will include reasons for withdrawal and any necessary treatment when applicable.

### Subject Replacement

There will be no subject replacements in this study.

### Termination of Study

The study may be terminated by a decision of the national regulator, institutional ethics committee(s), PI, Data and Safety Monitor (DSM), or Sponsor. A decision to terminate the study should only be reached after consultation, and ideally consensus agreement, among these parties. Possible reasons for termination of the study include if one or more subjects in any treatment group experience any of the following related AEs:

* Anaphylaxis or bronchospasm within 4 hours of study injection indicative of an immediate hypersensitivity reaction to the vaccine and not attributable to another cause.
* Any systemic rash, including but not limited to urticaria, generalized petechiae, or erythema multiforme, related to the vaccine and not attributable to another cause.
* Tissue necrosis at the injection site.
* Any other SAE deemed to be possibly, probably, or definitely attributable to the study injection by the Principal Investigator, IDRI Medical Advisor, Local Medical Monitor, or DSM, based on close temporal relationship or other factors.

The study will also be immediately suspended and no additional study injections administered pending review and discussion of all appropriate safety data if three or more subjects fulfill the criteria for discontinuation of study injections in an individual subject and if the dose-limiting AEs are determined to be possibly, probably, or definitely related to study injection (see Section 9.8.3).

# Study Intervention/Investigational Product

## Study Product Description

ID93 is a recombinant subunit vaccine antigen, which combines four antigens belonging to families of Mtbproteins associated with virulence (Rv2608, Rv3619, Rv3620) or latency (Rv1813). ID93 is a lyophilized formulation containing 100 μg ID93 and excipients (mannitol, sucrose, and polysorbate 80).

Glucopyranosyl Lipid A (GLA) is a synthetic Toll-like Receptor 4 (TLR4) agonist. GLA is formulated in a stable oil-in-water emulsion (SE) to yield the adjuvant formulation GLA-SE. Due to the TLR4 activity of the GLA molecule, the combination of GLA-SE with a recombinant protein antigen (ID93) results in a Th1-type T-cell response, which is important for protection from infection with Mtb. GLA-SE appears as a milky-white liquid.

EM060G is a diluent that has the same components as GLA-SE, but without the GLA. EM060G appears as a milky-white liquid.

Normal saline for injection (0.9% sodium chloride) will be used as a placebo control. Water for injection will be used to reconstitute the lyophilized ID93.

### Acquisition

Vaccine components will be shipped under refrigerated conditions and must be stored upon arrival at the site in a monitored refrigerator maintained at 2-8ºC (36-46ºF) in a secure, controlled location. Unused product will be returned or destroyed per instructions from IDRI.

The clinical site(s) will source their own supply of normal saline for injection and water for injection.

### Formulation, Packaging, and Labeling

Each vaccine component is supplied in glass vials labeled in accordance with South African regulations.

The investigational products to be utilized in this study are listed below.

**ID93 for Injection**

Part # 0193 Lot # 13-993F-001

100 µg/vial lyophilized

Manufactured by Aeras

**GLA-SE Adjuvant**

Part # 0194 Lot # 12H002

Concentration: 20 µg/mL Fill volume: 0.4 mL/vial

Manufactured by Infectious Disease Research Institute

### Product Storage and Stability

ID93, GLA-SE must be stored in a monitored refrigerator maintained at 2-8ºC (36-46ºF) in a secure, controlled location. The vials should be stored in the labeled boxes in which they were shipped.

Stability of clinical lots of ID93 and GLA-SE, is monitored in real time in accordance with ICH recommendations.

## Dosage, Preparation and Administration of Study Intervention/Investigational Product

All study injections will be prepared within 2 hours of administration. Complete details for dose preparation and administration are described in the Pharmacy and Study Injection Preparation section of the Study Specific Procedures Manual.

The study personnel assigned to administer the study injections will be supplied with a loaded syringe labeled with the PID #. Study injections will be given on Day 0, 28 and Day 56. All injections will be given intramuscularly into the deltoid muscle.

All used vials for each participant should be placed in a sealable plastic bag labeled with the PID # and the date of injection. The used vials must be kept in a secured location. Used vials may be kept at room temperature or refrigerated until drug accountability is completed by the study monitor.

## Modification of Study Intervention/Investigational Product for a Participant

Not applicable. No dose modifications are planned. If toxicity is noted, study injections may be discontinued as described in Section 9.8.2.

## Accountability Procedures for the Study Intervention/Investigational Product(s)

Study products will be shipped by the Sponsor to the clinical site(s). After receipt, the site PI is responsible for cold-chain distribution and storage of these study products and has ultimate responsibility for drug accountability. Logs of receipt, storage temperature, transportation cold-chain (when applicable), maintenance, and documentation of vaccine preparation and disposal must be maintained in the study file.

Used and unused vials of vaccine antigen and adjuvant will be retained until monitored by the designated unblinded monitor for accountability and released for disposition. Study product will be returned or destroyed per instructions from the Sponsor.

## Assessment of Subject Compliance with Study Intervention/Investigational Product

All study injections will be administered by the designated injection administrator(s) and documented in the participant’s source documentation and Case Report Form.

## Concomitant Medications/Treatments

Administration of any medications, therapies, or vaccines will be documented in the participant’s source documentation and Case Report Form. Concomitant medications will include all medications, vitamins, and supplements taken within the 28 days before randomization and through 28 days after the last injection (approximately Day 84) or early termination, whichever occurs first. After Day 84, concomitant medications will only be documented for SAEs and AESIs.

Medications that might interfere with the evaluation of the investigational product should not be used unless absolutely necessary. Medications in this category include, but are not limited to, glucocorticoids (i.e., oral, parenteral and high-dose inhaled steroids), and immunosuppressive or cytotoxic drugs.

Standard-of-care TB treatment received prior to and during screening, as well as any subsequent TB treatment that may be started post-randomization, will be documented in the appropriate source document and summarized in the TB Medical History and Treatment Summary CRF (prior to randomization) and TB Treatment Medications Taken On Study CRF (for post-randomization).

# Study Schedule

## Screening

Recently diagnosed TB patients who have completed approximately 4 months standard-of-care treatment for pulmonary TB will be identified at local clinics and hospitals by review of medical registers and laboratory records, and liaison with health service staff, and invited to participate in the informed consent process. Adequate TB treatment adherence, prior to signing informed consent must be assessed (either through review of the patient’s medical records or confirmed by the TB clinic staff). 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 subject at the time of consent.

Potential subjects will be interviewed to ensure that they meet all entry criteria relating to medical history. The study staff member delegated to perform the informed consent process will conduct the consent discussion on an individual basis with each subject, allow adequate time for all questions to be addressed, and document any questions in the source documents. 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.

After informed consent has been obtained, a screening number (SID #) will be assigned to each subject for identification purposes, and the subject will be screened to assess eligibility for enrollment in the study. A screening log will be maintained by the site that records all subjects for whom consent was obtained and who entered the screening process. At a minimum, the screening log will document the subject’s date of consent, screening number, initials, and year of birth. The screening log will provide details of screen failure as to why a subject did not enter the study (e.g., ineligibility due to screening laboratory abnormality, drug-resistant TB, new illness, or new clinical finding; withdrawal of consent; or failure to return to the study site). Abnormal results and findings resulting in ineligibility will be discussed with the subject, who will be referred for follow-up care with their healthcare provider if necessary.

After signing informed consent, a TB symptom questionnaire will be administered by study staff and sputum samples will be collected for Xpert MTB/RIF and MTB liquid culture (see Appendix 3). Subjects with new or worsening symptoms consistent with TB treatment failure during screening evaluations will be excluded. Subjects who are not eligible for randomization, for example due to TB treatment failure, will be referred for appropriate management by the health services.

Bacteriologic cure will be assessed on a minimum of 2 sequential occasions at least 14 days apart. Since a false positive Xpert MTB/RIF may occur due to the presence of non-viable, killed bacilli, MGIT culture will also be performed. Bacteriologic cure will be defined as two consecutive (at least 14 days apart) negative Xpert MTB/RIF, or if Xpert MTB/RIF remains persistently positive, as negative MGIT culture.

Subjects with bacteriologic confirmation of cure at approximately 4 and 5 months after starting treatment (as defined above), and meeting all other inclusion and exclusion criteria described in Sections 5.1 and 5.2, will be eligible to be randomized within 28 days of completing TB treatment to receive the first study injection with either ID93 + GLA-SE vaccine, or saline placebo.

All subjects must also complete the full course of scheduled TB treatment prior to Day 0 as per the prevailing current South African National Tuberculosis Management Guidelines (2009 Guideline: 2 months isoniazid, rifampicin, pyrazinamide, and ethambutol [intensive phase], followed by 4 months isoniazid and rifampicin).

An end of treatment sputum sample will be collected for MTB liquid culture at the 3rd screening visit (at or shortly after the end of treatment) or on Day 0 prior to study injection. Development of a positive MTB liquid culture at, or after, end of treatment will constitute a late exclusion criterion and such subjects will be excluded from receiving further study injections.

Eligibility will be based on the inclusion and exclusion criteria described in Sections 5.1 and 5.2 above. The investigator must document confirmation of eligibility prior to randomization.

Upon determination of eligibility for randomization, a subject will be assigned the next consecutive subject PID # immediately prior to baseline immunology blood draw and first study injection. Subjects will be considered randomized into the study upon issue of the PID #. Subjects who develop any late exclusion criterion after randomization will be excluded from receiving further study injections, have no further immunology blood draws, remain in reduced visit follow-up through Day 168 for safety evaluations of AEs, SAEs or AESIs, and be referred for the appropriate medical management.

## Study Injection Phase

After randomization, subjects in Cohorts 1 and 2 will receive a total of two intramuscular study injections, one injection on each of Days 0 and 56, and subjects in Cohort 3 will receive a total of three intramuscular study injections, one injection on each of Days 0, 28 and 56. All subjects will be followed for safety and immunogenicity through 224 days after the first study injection.

Each subject will be evaluated on Days 0, 3, 7,14, 28, 31, 35, 42, 56, 59, 63, 70, 84, 112, 168, and 224 (EOS).

See Appendix 1 for the Schedule of Visits and Procedures**.**

## Final Study Visit

All subjects remaining on study should have an EOS visit at Day 224. Every effort should be made to perform an EOS visit for all subjects.

Subjects will be assessed for resolution of any ongoing AEs and screened for possible recurrent TB disease. Every effort should be made to obtain at least 2 EOS sputum samples for any subject with suspected recurrent TB disease. Subjects with ongoing AEs at the EOS visit will be referred to the appropriate health care provider for ongoing management.

## Early Termination Visit

Subjects who permanently discontinue participation on the study prior to the Day 224 visit should have an EOS Early Termination Visit for assessment of resolution of any ongoing AEs, referral for ongoing medical care if appropriate, and screening for possible recurrent TB disease as above.

## Unscheduled Visit

Subjects may attend an unscheduled visit in the event of safety concerns, or reported symptoms consistent with suspected recurrent TB disease. Additional clinical and laboratory investigations may be requested at the discretion of the investigator.

# Study Procedures/Evaluations

## Screening Visit

More than one clinic visit will be required to complete screening. Screening will begin at approximately 4 months (16 weeks +/- 1 week) after initiation of standard TB treatment.

### First Screening Visit

The following procedures will take place approximately 4 months (16 weeks +/- 1 week) after initiation of standard TB treatment:

* Obtain written informed consent process.
* Assign initial screening SID #.
* Review the clinic medical records.
* Confirm MTB diagnosis by Xpert or MGIT
* Assess treatment adherence and document the start of TB treatment and the total number of weeks or days TB treatment received to date.
* Obtain screening history including TB symptoms (confirm methods of contraception for females).
* Obtain two sputum samples (Xpert MTB/RIF and MGIT culture) to assess cure.
* Provide HIV counselling.
* HIV serology.
* Pregnancy test (serum BHCG).
* Perform symptom directed physical exam including vital signs
* Concomitant medications.
* Upon receipt of sputum and serology results, verify eligibility criteria.

### Second Screening Visit

Note on timing of 2nd screening visit: sufficient time must be allowed to obtain a confirmatory MGIT culture result, if necessary, prior to the anticipated end of TB treatment + 28 days.

The following procedures will take place 14 to 28 days after the first screening evaluation:

* Screen for TB symptoms and confirm TB treatment adherence.
* Pregnancy test (urine BHCG).
* Perform symptom directed physical exam including vital signs
* Concomitant medications.
* Two sputum samples for Xpert MTB/RIF and MGIT culture to assess cure.
* Upon receipt of sputum results review and reconfirm study eligibility criteria are met.

### Third Screening Visit

The following procedures will take place at, or shortly after, end of TB treatment, and within 28 days of Day 0:

* Screen for TB symptoms and confirm TB treatment adherence. Adherence is defined as having completed 24 weeks (-1/+4 weeks) of TB treatment from the start date of treatment.
* Perform symptom directed physical exam including vital signs.
* Concomitant medications.
* Draw safety blood (hematology and chemistry: total WBC count, hemoglobin, platelet count, total bilirubin, creatinine, ALT, AST and CRP).
* Pregnancy test (serum BHCG).
* Obtain Chest X-Ray (CXR).
* Obtain two sputum samples for Xpert MTB/RIF and MGIT culture to rule out ‘late exclusion’ after enrollment (may be obtained on Day 0).
* Upon receipt of sputum and lab results review and reconfirm study eligibility criteria are met.

## Study Injection Phase Visits

### Day 0 (within 28 days of the end of TB treatment date, *and* within 28 days of the 3rd screening visit evaluation)

***Pre-injection:***

* Review TB treatment record and results of treatment phase sputum samples to confirm treatment completion and cure.
* Obtain medical history including TB symptoms (reconfirm methods of contraception for females).
* Vital signs (axillary temperature must be <38.0°C).
* Perform physical exam, including height, weight, and assessment of clinical response to TB treatment by evaluating unexplained persistent or productive cough, fever, weight loss, fatigue, chest pain, or hemoptysis including chest radiography as indicated. Investigation for extra-pulmonary TB may include aspiration, biopsy, or radiological imaging, as clinically indicated.
* Obtain two sputum samples for MGIT culture if not already done so at the 3rd screening visit.
* Concomitant medications.
* BMI.
* Pregnancy test (urine BHCG).
* Confirm eligibility and assign the next sequential PID # if eligible.
* Document PID # in Screening/Enrollment Log *before* baseline immunology sample collection.
* Immunology blood: gene signatures, whole blood absolute count, whole blood ICS, PBMCs, serum for IgG ELISA including serum to store.

***Injection:***

* Inspect syringe and vaccine volume, confirm PID #, subject initials, and the date and time of dose preparation.
* Administer study injection intramuscularly into deltoid. Record date and time of injection, and which arm was injected.

***30 minute evaluation post-injection (at least 30 minutes):***

* Obtain vital signs.
* Injection site checks (pain, erythema, induration) and specific solicited systemic symptoms (arthralgia, chills, nausea, fever, fatigue, myalgia).
* Record any adverse events.

### Day 3

* Concomitant medications.
* Vital signs.
* Immunology blood: gene signatures and whole blood absolute count.
* Injection site check (pain, eryrthema, induration) and specific solicited systemic symptoms (arthralgia, chills, nausea, fever, fatigue, myalgia).
* Adverse events, including SAEs and AESIs.

### Day 7 (±1)

* Concomitant medications.
* TB symptom screen and two sputum samples for Xpert MTB/RIF and MGIT culture if symptom directed.
* Vital signs.
* Hematology and chemistry: total WBC count, hemoglobin, platelet count, total bilirubin, creatinine, and ALT.
* Immunology blood: gene signatures and whole blood absolute count.
* Injection site check (pain, erythema, induration) and specific solicited systemic symptoms (arthralgia, chills, nausea, fever, fatigue, myalgia).
* Adverse events, including SAEs and AESIs.

### Day 14 (± 1)

* Concomitant medications.
* Immunology blood: whole blood ICS, PBMCs, serum for IgG ELISA.
* TB symptom screen and two sputum samples for Xpert MTB/RIF and MGIT culture if symptom directed.
* Adverse events, including SAEs and AESIs.

### Day 28 (± 3) Cohorts 1 and 2

* Concomitant medications.
* Immunology blood: whole blood ICS, PBMCs, serum for IgG ELISA.
* TB symptom screen and two sputum samples for Xpert MTB/RIF and MGIT culture if symptom directed.
* Adverse events, including SAEs and AESIs.

### Day 28 (± 3) Cohort 3 only

***Pre-injection:***

* Concomitant medications.
* Vital signs (axillary temperature must be <38.0°C).
* Directed physical exam including weight and assessment of unexplained persistent (14 days or longer) or productive cough, fever, weight loss, fatigue, chest pain, or any hemoptysis, including chest radiography as indicated, to screen for suspected recurrent TB. Investigation for suspected extra-pulmonary TB may include aspiration, biopsy, or radiological imaging, as clinically indicated.
* TB symptom screen and two sputum samples for Xpert MTB/RIF and MGIT culture if symptom directed.
* Pregnancy test (urine BHCG).
* Hematology and chemistry: total WBC count, hemoglobin, platelet count, total bilirubin, creatinine, and ALT.
* HIV counselling and serology if confirmed TB.
* Immunology blood: whole blood ICS, PBMCs, serum for IgG ELISA, gene signatures and whole blood absolute count.
* Confirm continued eligibility for study injection.

***Injection:***

* Inspect syringe and vaccine volume, confirm PID #, subject initials, and the date and time of dose preparation.
* Administer study injection by intramuscular injection into deltoid area of arm. Record date and time of injection and which arm was injected.

***30 minute evaluation post-injection***(at least 30 minutes)*:*

* Injection site checks (pain, erythema, induration) and specific solicited systemic symptoms (arthralgia, chills, nausea, fever, fatigue, myalgia).
* Adverse events, including SAEs and AESIs.

### Day 31 (3 days from Day 28 visit) Cohort 3 only

* Injection site checks (pain, erythema, induration) and specific solicited systemic symptoms (arthralgia, chills, nausea, fever, fatigue, myalgia).
* Concomitant medications.
* Vital signs.
* TB symptom screen and two sputum samples for Xpert MTB/RIF and MGIT culture if symptom directed.
* Immunology blood: gene signatures and whole blood absolute count.
* Adverse events, including SAEs and AESIs.

### Day 35 (7 days ±1 from Day 28 visit) Cohort 3 only

* Concomitant medications.
* TB symptom screen and two sputum samples for Xpert MTB/RIF and MGIT culture if symptom directed.
* Vital signs.
* Hematology and chemistry: total WBC count, hemoglobin, platelet count, total bilirubin, creatinine, and ALT.
* HIV counselling and serology if confirmed TB.
* Immunology blood: gene signatures and whole blood absolute count.
* Injection site check (pain, erythema, induration) and specific solicited systemic symptoms (arthralgia, chills, nausea, fever, fatigue, myalgia).
* Adverse events, including SAEs and AESIs.

### Day 42 (14 days ±1 from Day 28 visit) Cohort 3 only

* Concomitant medications.
* TB symptom screen and two sputum samples for Xpert MTB/RIF and MGIT culture if symptom directed.
* Adverse events, including SAEs and AESIs.
* Immunology blood: whole blood ICS, PBMCs, serum for IgG ELISA.

### Day 56 (± 3)

***Pre-injection:***

* Concomitant medications.
* Vital signs (axillary temperature must be <38.0°C).
* Directed physical exam including weight and assessment of unexplained persistent (14 days or longer) or productive cough, fever, weight loss, fatigue, chest pain, or any hemoptysis, including chest radiography as indicated, to screen for suspected recurrent TB. Investigation for suspected extra-pulmonary TB may include aspiration, biopsy, or radiological imaging, as clinically indicated.
* TB symptom screen and two sputum samples for Xpert MTB/RIF and MGIT culture if symptom directed.
* Pregnancy test (urine BHCG).
* Hematology and chemistry: total WBC count, hemoglobin, platelet count, total bilirubin, creatinine, and ALT.
* HIV counselling and serology if confirmed TB.
* Immunology blood: whole blood ICS, PBMCs, serum for IgG ELISA, gene signatures and whole blood absolute count.
* Confirm continued eligibility for study injection.

***Injection:***

* Inspect syringe and vaccine volume, confirm PID #, subject initials, and the date and time of dose preparation.
* Administer study injection by intramuscular injection into deltoid area of arm. Record date and time of injection and which arm was injected.

***30 minute evaluation post-injection***(at least 30 minutes)*:*

* Injection site checks (pain, erythema, induration) and specific solicited systemic symptoms (arthralgia, chills, nausea, fever, fatigue, myalgia).
* Adverse events, including SAEs and AESIs.

### Day 59 (3 days from Day 56 visit)

* Injection site checks (pain, erythema, induration) and specific solicited systemic symptoms (arthralgia, chills, nausea, fever, fatigue, myalgia).
* Concomitant medications.
* Vital signs.
* TB symptom screen and two sputum samples for Xpert MTB/RIF and MGIT culture if symptom directed.
* Immunology blood: gene signatures and whole blood absolute count.
* Adverse events, including SAEs and AESIs.

### Day 63 (7 days ±1 from Day 56 visit)

* Concomitant medications.
* TB symptom screen and two sputum samples for Xpert MTB/RIF and MGIT culture if symptom directed.
* Vital signs.
* Hematology and chemistry: total WBC count, hemoglobin, platelet count, total bilirubin, creatinine, and ALT.
* HIV counselling and serology if confirmed TB.
* Immunology blood: gene signatures and whole blood absolute count.
* Injection site check (pain, erythema, induration) and specific solicited systemic symptoms (arthralgia, chills, nausea, fever, fatigue, myalgia).
* Adverse events, including SAEs and AESIs.

### Day 70 (14 days ±1 from Day 56 visit)

* Concomitant medications.
* TB symptom screen and two sputum samples for Xpert MTB/RIF and MGIT culture if symptom directed.
* Adverse events, including SAEs and AESIs.
* Immunology blood: whole blood ICS, PBMCs, serum for IgG ELISA.

### Day 84 (±3)

* Concomitant medications.
* Vital signs.
* Directed physical exam including weight and assessment of unexplained persistent (14 days or longer) or productive cough, fever, weight loss, fatigue, chest pain, or hemoptysis, including chest radiography as indicated, to screen for suspected recurrent TB. Investigation for suspected extra-pulmonary TB may include aspiration, biopsy, or radiological imaging, as clinically indicated.
* TB symptom screen and two sputum samples (MGIT culture and XPert MTB/RIF for suspected recurrent TB if symptom directed).
* Immunology blood: whole blood ICS, PBMCs, serum for IgG ELISA.
* HIV counselling and serology if confirmed TB.
* Immunology blood for gene signatures and whole blood absolute count if TB confirmed.
* Adverse events, including SAEs and AESIs.

**Follow up Phase Visits (Day 112 and Day 168 may be field visits with referral to clinic if symptomatic for TB)**

### Day 112 (±5) Field Visit

* TB symptom screen (referral to clinic if symptomatic for TB).
* Vital signs
* Directed physical exam including weight and assessment of unexplained persistent (14 days or longer) or productive cough, fever, weight loss, fatigue, chest pain, or hemoptysis, including chest radiography as indicated, to screen for suspected recurrent TB. Investigation for suspected extra-pulmonary TB may include aspiration, biopsy, or radiological imaging, as clinically indicated.
* Sputum samples (MGIT culture and XPert MTB/RIF for suspected recurrent TB if symptom directed).
* HIV serology if confirmed TB.
* Immunology blood for gene signatures and whole blood absolute count if TB confirmed.
* SAEs/AESIs (and concomitant medications if taken for SAE or AESI).

### Day 168 (±10) Field Visit

* TB symptom screen (referral to clinic if symptomatic for TB).
* Vital signs
* Directed physical exam including weight and assessment of unexplained persistent (14 days or longer) or productive cough, fever, weight loss, fatigue, chest pain, or hemoptysis, including chest radiography as indicated, to screen for suspected recurrent TB. Investigation for suspected extra-pulmonary TB may include aspiration, biopsy, or radiological imaging, as clinically indicated.
* Sputum samples (MGIT culture and XPert MTB/RIF for suspected recurrent TB if symptom directed).
* HIV counselling and serology if confirmed TB.
* Immunology blood for gene signatures and whole blood absolute count if TB confirmed.
* SAEs/AESIs (and concomitant medications if taken for SAE or AESI).

### Day 224 / EOS visit (±10)

* TB symptom screen.
* Vital signs
* Directed physical exam including weight and assessment of unexplained persistent (14 days or longer) or productive cough, fever, weight loss, fatigue, chest pain, or hemoptysis, including chest radiography as indicated, to screen for suspected recurrent TB. Investigation for suspected extra-pulmonary TB may include aspiration, biopsy, or radiological imaging, as clinically indicated.
* Sputum samples (MGIT culture and XPert MTB/RIF for suspected recurrent TB if symptom directed).
* Immunology blood: whole blood ICS, serum for IgG ELISA including serum to store.
* HIV counselling and serology if confirmed TB.
* Immunology blood for gene signatures if TB confirmed.
* SAEs/AESIs (and concomitant medications if taken for SAE or AESI).

### Unscheduled visits

* Unscheduled visits may occur for investigation of adverse events/SAEs/AESIs or for further investigation of participant reported TB symptoms.
* Such visits should be documented on the unscheduled visit source document and CRF.

## Laboratory Evaluations

### Clinical Laboratory Evaluations

*Screening and Study Injection Phase Safety Evaluations* will include:

Hematology: hemoglobin, white blood cells (WBC) with differential count, platelet count.

Chemistry: creatinine, total bilirubin, alanine aminotransferase (ALT), and aspartate aminotransferase (AST). Note: after screening only ALT will be documented in the CRF and followed for liver transaminase AEs.

Pregnancy test: serum pregnancy test required at screening for eligibility; urine pregnancy test to be done within 24 hours prior to study injections and results must be available prior to administration of study product.

HIV rapid antibody test: to be performed using two test kits from different manufacturers. Discordant or indeterminate test results to be confirmed by laboratory HIV PCR.

*TB Disease Laboratory Evaluations* will include:

Microbiology: Sputum Xpert MTB/RIF (Cepheid, USA) and MGIT culture (Becton-Dickinson, USA). Samples from additional sites may be requested for investigation of extrapulmonary TB at the discretion of the investigator.

### Immunology Laboratory Evaluations

A summary of immunologic assays to be performed on blood specimens is shown in Table 10. 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 10: Summary of Immunology Laboratory Evaluations

| **Sample type** | **Location** | **Assay** | **Purpose of Assay** | **Study Days**  **Cohorts 1 and 2** | **Study Days Cohort 3** |
| --- | --- | --- | --- | --- | --- |
| Primary Immunology: PBMC | IDRI | Flow cytometry, intracellular cytokine staining (ICS) | Determine cellular immune response to study vaccine | Days 0, 14, 28, 56, 70, 84, 224 | Days 0, 14, 28, 42, 56, 70, 84, 224 |
| Primary Immunology: Serum | IDRI or designee | Antigen-specific IgG | Determine humoral response to study vaccine | Days 0, 14, 28, 56, 70, 84, 224 | Days 0, 14, 28, 42, 56, 70, 84, 224 |
| Exploratory Immunology Whole blood ICS | SATVI | ICS | Determine cellular immune response to study vaccine | Days 0, 14, 28, 56, 70, 84, 224 | Days 0, 14, 28, 42, 56, 70, 84, 224 |
| Exploratory Immunology Serum | NA (to be stored) | Autoimmune antibodies (ELISA) | Determination of vaccine-induced autoimmunity | Days 0, 224 | Days 0, 224 |
| Exploratory Immunology Whole blood for gene signatures | TBD | Microarray transcriptional profiling or RNA sequencing | Determine immune response to study vaccine | Days 0, 3, 7, 59, 63 and if TB is confirmed | Days 0, 3, 7, 28, 31, 35, 56, 59, 63 and if TB is confirmed |
| Exploratory Immunology Whole blood absolute count | SATVI | Whole blood absolute count | Deconvolution of transcriptional data | Days 0, 3, 7, 59, 63 and if TB is confirmed | Days 0, 3, 7, 28, 31, 35, 56, 59, 63 and if TB is confirmed |

#### Primary Immunology Evaluations:

Both PBMC and whole blood will be collected in this study, to allow measurement of CD4 and CD8 T-cell responses to vaccine antigens by ICS. PBMC will be analyzed by IDRI as the primary immunological outcome, and data generated will be used to inform dose selection decisions for future safety and efficacy trials.

Immunology analyses will involve assessment of the immune response to the vaccine by measurement of the frequency of CD4+ and CD8+ T-cells that produce any of selected cytokines following stimulation with whole ID93 protein and peptide pools derived from and representing the entire amino acid sequences of the ID93 component 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 medianDMSO-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. Positivity of T-cell responses from the ICS assay will be determined according to a pre-specified methodology [[13](#_ENREF_13)] to be described in the statistical analysis plan, and will be summarized as number (percentage) of responders by treatment regimen.

Additionally, immune sera will be analyzed for the presence of antigen-specific IgG antibodies by ELISA. 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.

#### Exploratory Immunology Analyses

A 13-color ICS assay using whole blood will be performed at SATVI’s immunology laboratory, where the reagents, equipment, and training of personnel have all been standardized to provide consistent results.

Samples will be stored for future transcriptomic analysis of whole blood and PBMC subsets, as well as RNA-Seq. RNA samples may be used for validation studies of existing candidate gene expression correlates. Whole blood will be collected in PAXgene tubes to allow for future analyses including transcriptomic profiling at early time point following vaccine priming. Whole blood will also be collected for absolute counts and analysis of cellular subsets to allow deconvolution of transcriptomic data according to peripheral blood cellularity. These outcomes will allow identification of innate response gene signatures that correlate with the magnitude and/or character of the ID93-induced T-cell response.

We will also collect PBMC samples to allow correlates of protection to be determined at a later time point, by looking at antigen specific responses in specific cellular subsets, in assays that are yet to be defined.

An exploratory analysis may also seek to identify innate response gene signatures that correlate with the magnitude of the ID93-induced IgG response.

Furthermore, serum will be collected and stored for future proteomic analysis, including cytokine measurement with ELISA and/or Luminex or other multiplex techniques. Serum will also be used for microRNA measurement with microRNA arrays. These analyses will include the measurement of soluble host marker biosignatures (up to 10 markers) and microRNA signatures (up to 40 markers) in sera of patients as correlates of risk for TB recurrence.

Serum samples will be banked for autoimmune antibody analysis, if indicated by a clinical safety signal.

### Specimen Preparation, Handling, and Shipping

#### Instructions for Specimen Preparation, Handling, and Storage

Instructions for the correct preparation, handling, and storage of samples for safety, immunology, and protection evaluations are described in the Specimen Management Manual.

#### Specimen Shipment

Instructions for shipment of immunology samples (where relevant) are described in the Specimen Management Manual.

# Assessment of Safety

## Specification of Safety Parameters

Safety outcome measures (AEs) include local site of injection reactions (pain, induration, and erythema), and systemic symptoms (arthralgia, chills, nausea, fever, fatigue, myalgia), and laboratory measurements (hematology and chemistry); and AEs that meet the criteria for seriousness (SAEs) and adverse events of special interest (AESIs).

## Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

For all subjects, the reporting periods for AEs will be as follows:

* For unsolicited adverse events, 28 days after each study injection (Day 0-28 and Day 56-84 for Cohorts 1 and 2, and Day 0-27, Day 28-55 and Day 56-84 for Cohort 3 );
* For solicited adverse events, 7 days after each study injection (Day 0-7 and Day 56-63 for Cohorts 1 and 2, and Day 0-7, Day 28-35 and Day 56-63 for Cohort 3); and
* For SAEs and AESIs, from Day 0 until end of study.

Acute injection site reactogenicity and specific solicited systemic reactions will be assessed at 30 minutes, 3 days, and 7 days following each study injection. Assessment will include local site of injection reactions (pain, induration, and erythema) and systemic symptoms (arthralgia, chills, nausea, fever, fatigue, myalgia).

Local reactions will be graded as adverse events following the grading scale provided in Appendix 5 , solicited systemic reactions will be graded according to the FDA AE Grading Table shown in Appendix 6 and clinical and laboratory AEs will be graded following the FDA Toxicity Tables shown in Appendix 4, Appendix 6, and Appendix 7, and their relationship to study injection assessed based on the clinical judgment of the study clinician according to protocol definitions described below in Section 9.3.3 .

Subjects reporting new onset or significant worsening of existing respiratory symptoms, including, but not limited to persistent [14 days or longer] and/or productive cough, shortness of breath, or wheeze, in the 224 days following first study injection will undergo repeat chest radiography. Additional investigations, including, but not limited to chest CT scan and pulmonary function testing may be requested at the discretion of the attending clinician, based upon clinical and radiological assessment.

For all subjects, unsolicited adverse events will be obtained by retrospective review at clinic visits and/or field visits. All unsolicited adverse events will be collected for 28 days following each study injection (Days 0-28 and Days 56-84 for Cohorts 1 and 2, and Day 0-27, Day 28-55 and Day 56-84 for Cohort 3).

During the follow-up period after Day 84, serious adverse events (SAEs) and adverse events of special interest (AESIs) will continue to be collected. AESIs are a predefined list of disorders of possible or known autoimmune etiology that are required of clinical trials involving vaccines with novel adjuvants (see Appendix 8 for the list of AESIs). These unsolicited AESIs will be recorded and reported in the same way as SAEs, regardless of their attributed relationship to study injections.

## Adverse Events

### Definitions

***Adverse Event:*** Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug or study injection 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 may be present on Study Day 0, but may represent an adverse event if the frequency, 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.

A***suspected adverse reaction***is any adverse event for which there is a *reasonable possibility* that the study injection caused the event. Suspected adverse reactions are a subset of all adverse events. For example: headache or fever following study injection.

An ***adverse reaction*** is any adverse event *definitely* caused by the study injection. Adverse reactions are a subset of all suspected adverse reactions. For example: local site of injection erythema or pain at the site of injection.

***Unexpected Adverse Event:*** An adverse event is considered “unexpected” if it is not listed in the Investigator’s Brochure or is not listed at the specificity or severity that has been observed.

***Serious Adverse Event:*** An adverse event is considered to be a *serious* adverse event (SAE) if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

* death,
* a life-threatening adverse event,
* inpatient hospitalization or prolongation of existing hospitalization,
* persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions,
* a congenital anomaly/birth defect in the offspring of a study subject.

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

**NOTE:** A distinction should be drawn between serious and severe events. A severe event is a major experience of its type. A severe event does not necessarily need to be serious. For example, nausea, which persists for several hours, may be considered severe nausea but not a serious adverse event. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a serious adverse event.

***Life-threatening Event:*** An adverse event is considered “life-threatening” if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event that, had it occurred in a more severe form, might have caused death.

***Adverse Events of Special Interest (AESIs)****:* FDA requires monitoring for specified known or suspected autoimmune disorders when testing novel adjuvants. AESIs will be recorded and reported in the same way as SAEs, regardless of their attributed relationship to study injections. AESIs consist of any of the diagnoses listed in Appendix 8 observed in study injection recipients during the course of the study follow-up period.

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 PI 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 PI. 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 the subject cannot recall the date of resolution, then the resolution date will be visit date on which the study staff determines the AE to be resolved.

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 an SAE Report will be completed.

### Assessment of Severity (Grading)

The safety concepts of “severity” and “seriousness” are distinct concepts. 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 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

4. Potentially life-threatening

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 Grading Scale for local reactions Appendix 5 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 Tables 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 daily 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.

### Assessment of Causality (Relatedness to Study Injection)

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 including the toxicity profile of any concomitant medication, 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).
* **Possibly Related** 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).
* **Probably Related** 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).
* **Definitely Related** 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 adverse events are considered related to study injection. Not related and unlikely related adverse events are considered to be unrelated.

For adverse events requiring immediate reporting, the PI and the LMM 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 LMM after their discussions will determine the ultimate classification of the adverse event. Adverse events where the causality is not assessable, will be considered related to the study injection.

Every effort should be made by the investigator to determine the existence of any pre-existing conditions 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 may not be present on Study Day 0 but may represent an adverse event if the frequency, intensity or duration of the event is worse than usual following study injection.

### Evaluation of 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 LMM and/or sponsor medical advisor, determines expectedness. If the assessment is that the adverse event is expected no further action is required. If the LMM’s assessment is that the adverse event is unexpected, then the event may represent a suspected unexpected serious adverse reaction (SUSAR) or expedited SAE. In the event that the LMM and sponsor Medical Advisor disagree the event will be treated as unexpected in order to be conservative in the assessment.

## Reactogenicity

Local site of injections reactions (pain, erythema/redness and induration/hardness) will be graded according to Appendix 5. Specific solicited systemic reaction (arthralgia, chills, nausea, fever, fatigue, myalgia) will be graded according to the FDA AE Grading Table shown in Appendix 6.

## Serious Adverse Events

**Assessment of Seriousness**

Seriousness refers to the outcome of an adverse event. Seriousness is determined by both the PI and the LMM. If either PI or LMM 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 the study injection.

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 and is subject to expedited reporting.

### Procedures to be Followed in the Event of Abnormal Laboratory Test Values or Abnormal Clinical Findings

Investigation, treatment, follow-up and medical referral 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.

## Reporting Procedures

### Serious Adverse Events

Serious adverse events, which include SUSARs, are reported to the sponsor or its designee for the entire study period. SUSARs are reported even after the trial is over, if the sponsor or its designee, LMM, or PI 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 LMM 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 PI or his/her designee, within one business day of the clinical site becoming aware of the event, to the LMM, and Sponsor or designee. The AE CRF should be completed with all information known 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 LMM and Sponsor or designee immediately upon the investigator’s awareness of the event. If the LMM or Sponsor 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 investigators of this act.

Investigators must not wait to collect additional information to fully document the event before reporting a serious adverse event. The initial notification should include the following (at minimum):

* Protocol number and name and contact number of the investigator
* Subject PID 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 may authorize its designee 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 LMM and DSM of all SUSARs within 3 working days of becoming aware of an event and will provide all follow-up information in a timely manner.

### Regulatory Reporting

All AEs, regardless of severity or presumed relationship to study injection, will be documented on the AE form. Specific guidelines for grading out-of-range laboratory results are provided in Appendix 4. All SAEs, AESIs, and Grade 3 and 4 AEs, must be reported by the PI (or designee) directly to IDRI Pharmacovigilance within 24 hours by e-mail or telephone. The reporting sequence for all SAEs, AESIs, Grade 3 AEs, and Grade 4 AEs will be as follows:

1. The Principal Investigator (or designee) must report the event immediately (within 24 hours of knowledge of the event) to IDRI Pharmacovigilance.
2. IDRI Pharmacovigilance will then complete and forward an incident report by e-mail, containing all relevant information about the subject to the LMM, IDRI Medical Advisor (MA), and the Data and Safety Monitor (DSM) within 48 hours of receipt of the report of the event.
3. The Principal Investigator will meet his/her IRB/IEC reporting requirements.
4. The LMM must provide a written report by e-mail to the DSM and IDRI Pharmacovigilance within 2 working days of receipt of the initial incident report. This report must provide a recommendation as to whether the individual subject may continue to receive study injections (if more injections are scheduled).
5. IDRI Pharmacovigilance will forward the LMM’s written report and recommendation by e-mail to the Principal Investigator within 2 working days of receipt.

All SUSARs will be reported to the appropriate regulatory authorities within 7 or 15 days of receipt of the report of the event, depending on the nature of the SUSAR. In addition, all other SAEs and AESIs will be reported annually to the FDA and semi-annually to the MCC in a dedicated tabulation by MedDRA coding term and relationship to study vaccine.

### Other Adverse Events (if applicable)

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

* Emergency unblinding (Reportable Adverse Event Form)
* Protocol violation affecting the safety of a participant or involving the study injection process (Reportable Adverse Event Form)
* Any event that, according to the protocol or in the opinion of the investigator, precludes further administration of the study injections (Reportable Adverse Event Form, unless meets SAE criteria)
* Pregnancy (Pregnancy Alert Report Form)

### Reporting of Pregnancy

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 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 Sponsor. Pregnancy will not be recorded as an adverse event. However, 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.

## Type and Duration of Follow-up of Subjects after Adverse Events

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, 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

## Halting Rules

### Rules for Dose Escalation

Entry of participants into the next dose cohort may be permitted after the completion and review by the PI, Sponsor, and LMM of cumulative safety data for the most recently completed dose cohort, and the LMM has confirmed:

* That rules for suspension of the entire study (Section 9.8.3) 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 LMM for the most recently completed randomized blinded dose cohort.

Dose escalation to the next dose cohort may take place following completion and review of safety data by the LMM as follows:

To ensure subject safety prior to increasing the *rate of randomization*, no more than one subject in Cohort 1 will be randomized and dosed per day (see Rules for Suspension).

To ensure subject safety prior to *dose escalation*, the next Cohort will not be randomized and injected with a higher dose if a significant safety signal has been observed at a lower dose (see Rules for Suspension).

To ensure subject safety prior to *administering a 2nd injection at a given dose level,* a 2nd injection will not be administered if a significant safety signal has been observed after the first dose in that Cohort (see Rules for Suspension).

To ensure subject safety prior to *administering a 3rd injection in Cohort 3* a 3rd injection will not be administered if a significant safety signal has been observed after the second dose in Cohort 3 (see Rules for Suspension).

To ensure subject safety prior to *administering a 2nd injection at a higher dose level (Cohort 2)*, a 2nd injection at a higher dose level will not be administered if a significant safety signal has been observed after the 2nd injection at the lower dose level in Cohort 1.

The LMM will confirm their recommendation to proceed to the next cohort in a memorandum to the study file and inform the principal investigator(s) before randomization 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 DSM.

### Rules for Discontinuing Study injection in an Individual Subject

Administration of additional study injections will be discontinued for an individual if he/she has any of the following reactions:

* Changes in laboratory parameters which meet Grade 3 or Grade 4 severity as defined in the Laboratory Toxicity Grading Table recommended by FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adults Enrolled in Preventive Vaccine Clinical Trials, September 2007 (Appendix 4).
* High fever (axillary temperature ≥ 38.5˚C) within 1 week following study injection associated with constitutional symptoms and not attributable to another cause.
* Severe injection site reactogenicity that involves Grade 3 or Grade 4 local pain, induration, or erythema as defined in Appendix 5.
* Sputum culture result from end of TB treatment is *Mtb* positive (late exclusion).
* Development of active TB.
* Pregnancy.

Subjects for whom study injections are discontinued will remain in limited visit follow-up for 6 months after their first injection for safety evaluations of AEs (28 days post first study injection), SAEs, and AESIs, and have no further immunology blood draws.

**The reporting sequence for AEs that require discontinuation of study injections in an individual subject will be as follows:**

1. The Principal Investigator (or designee) must report the event immediately (within 24 hours) to IDRI Pharmacovigilance.
2. IDRI Pharmacovigilance will then complete and forward an incident report by e-mail, containing all relevant information about the subject, to the LMM, IDRI MA, and the DSM within 48 hours of receipt of the report of the event.
3. The Principal Investigator will meet local EC reporting requirements.
4. The LMM must provide a written report by e-mail to the DSM and IDRI Pharmacovigilance within 2 working days of receipt of the initial incident report. This report must provide a recommendation as to whether the individual subject may continue to receive study injections (if any additional injections are scheduled).
5. IDRI Pharmacovigilance will forward the written report and recommendation by e-mail to the Principal Investigator within 2 working days of receipt.

All subjects who are discontinued from study injections due to one of the above dose-limiting reactions will be followed until the resolution or stabilization of the event.

### Rules for Suspension of the Entire Study

The study will be immediately suspended (paused) and no additional study injections administered, pending review and discussion of all appropriate safety data by the DSM, if one or more subjects in any treatment group experience any of the following adverse events (dose-limiting reactions):

* Anaphylaxis or bronchospasm within 4 hours of study injection indicative of an immediate hypersensitivity reaction to the vaccine and not attributable to another cause.
* Any systemic rash, including but not limited to urticaria, generalized petechiae, or erythema multiforme, not attributable to another cause.
* Tissue necrosis at the study injection site.
* Any other serious adverse event deemed to be possibly, probably, or definitely attributable to the study injection by the Principal Investigator, IDRI MA, LMM, or DSM, based on close temporal relationship or other factors.

The study will also be immediately suspended (paused) and no additional study injections administered pending review and discussion of all appropriate safety data by the DSM if three or more subjects fulfill the criteria in Section 9.8.2 for discontinuation of study injections in an individual subject and if the dose-limiting AEs are determined to be possibly, probably, or definitely related to study injection.

**The reporting sequence for AEs that require suspension of study injections in all subjects enrolled in the study will be as follows:**

1. The Principal Investigator (or designee) must report immediately (within 24 hours) any occurrence of one or more of the above events to IDRI Pharmacovigilance.
2. IDRI Pharmacovigilance will then complete and forward an incident report by e-mail, containing all relevant information about the subject(s) to the IDRI MA, LMM, and the DSM within 48 hours of receipt of the report of the event.
3. In case of SAE possibly related to the Investigational Product that resulted in death or is life-threatening, follow reporting requirements listed in Section 9.6.2.
4. Within 15 working days of the initial report of the event, the IDRI MA, LMM, the DSM, FDA, and the Principal Investigator must reach a consensus to either re-start or terminate the study. This process will be coordinated by the IDRI Project Director.

The Principal Investigator must report the incident(s) and the final decision to re-start or terminate the study to the local Ethics Committee.

Study suspension or termination will only apply to additional study injections. Subjects for whom their second study injections are discontinued will remain in limited visit follow-up for 6 months after their first injection for safety evaluations of AEs (28 days post first study injection), SAEs and AESIs, and have no further immunology blood draws. Subjects who have received two study injections will continue to be followed at all scheduled evaluation visits. Any subject(s) experiencing one or more of the adverse events as identified in this section must be followed closely until resolution.

## Safety Oversight (LMM plus DSM)

An independent Data and Safety Monitor (DSM), whose primary purpose will be to review the safety data for this study, will operate under charter. Information on each episode of dose limiting toxicity (DLT), each episode of a Grade 3 or 4 adverse event, and each SAE or SUSAR will be provided and assessed within 5 working days by the DSM.

Meetings between the Sponsor, the Co-PIs, the LMM, and the DSM will be scheduled at the discretion of the DSM to review individual adverse events and/or accumulated safety data.

# Clinical Monitoring

## Site Monitoring

The Sponsor CRA or a consulting CRA will be responsible for monitoring the study sites, including the adherence to study schedules and scientific requirements of the study.

Site monitoring visits (SMVs) for the study will include a site initiation visit, regular monitoring visits, and a study close-out visit. After each site visit, the CRA will prepare a visit report and follow-up letter.

Source document verification will be performed on 100% *all* safety data, for *all* subjects, through the final visit; 100% *all* data, for *all* subjects, through Day 63 visit; and 100% *all* data for random 30% study subjects on Days 84, 168, and final visits.

Other CRA responsibilities will include:

Keep the Sponsor informed of study progress through regular verbal and written communication including status reports, e-mail and phone contact as needed.

* Identify potential issues and risks that could affect the project and development of contingency plans.
* Manage prompt resolution of identified problems with the appropriate team members.
* Assist in day to day management of the study site, under the direction of the Sponsor.
* Schedule and confirm SMVs with the study Site Coordinator in writing in advance.
* Review storage and daily temperature monitoring for investigational product.
* Review proper storage of study specimens and temperature monitoring of freezer if applicable.
* Assure sufficient and appropriate resources are assigned and maintained.
* Ensure that the PI submits any amendments and reports to the IRB.
* Maintain documentation of all project correspondence, meetings, status reports, monthly reports, and telephone communications.
* Ensure that work carried out is in accordance with Sponsor SOPs and GCP guidelines.

The CRA will ensure that the following are filed on site prior to study initiation:

* Protocol (approved version)
* Amendments, if any
* Investigator’s Brochure (current edition)
* Informed Consent Form and HIV consent

# Statistical Considerations

## Study Hypotheses

We hypothesize that ID93 + GLA-SE is safe and immunogenic in BCG vaccinated, HIV uninfected adults, after successful completion of treatment for pulmonary TB

## Sample Size Considerations

The sample size (60 subjects) is based upon the statistical power to evaluate safety outcomes (severe local reactogenicity events and related SAEs). If no severe local reactogenicity events or related SAEs are observed in any of the 48 subjects receiving ID93 + GLA-SE vaccine, the upper limit of the 95% confidence interval for the true proportion of such events is 7.9%. This sample size has 95% probability of detecting a severe local reactogenicity event or SAE with a true occurrence rate of 2% in subjects receiving ID93 + GLA-SE vaccine.

This sample size will allow the Sponsor to define a safety profile for the ID93 + GLA-SE vaccine in pulmonary TB patients upon completion of treatment, and to evaluate immunogenicity specific to the vaccine, in order to select the dose to be evaluated in the planned Phase 2b trial in this study population.

## Planned Interim Analyses

No interim analyses of immunogenicity or protection outcomes are planned *a priori*.

## Final Analysis Plan

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.

**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-injection laboratory values based on predefined toxicity criteria. Adverse events will also be summarized by severity and by relationship to study injection, and by treatment regimen.

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-injection 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. 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-injection assessments and for change from pre-injection to post-injection assessments. The number (percentage) of participants with post-injection 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 will be tabulated at each post-injection 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.

**Immunology Analyses**

The evaluation of vaccine-induced immunity will be based on the development of circulating antibody and T-cell responses directed against the ID93 protein. IgG responses will be assessed at Days 0, 14, 28, 42, 56, 70, 84, and 224. T-cell responses will be assessed for all subjects at Days 0, 14, 28, 42, 56, 70, 84, and 224.

The primary immunology analyses involve assessment of the immune response to the vaccine by measurement of the frequency 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. Positivity of T-cell responses from the ICS assay will be determined according to a pre-specified methodology [[13](#_ENREF_13)], to be described in the statistical analysis plan, and will be summarized as number (percentage) of responders by treatment regimen.

Immune sera will be analyzed for the presence of antigen-specific IgG antibodies by ELISA. 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.

# Source Documents and Access to Source Data/Documents

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 the Sponsor 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) or entered using electronic case report forms (eCRFs) using an Electronic Data Capture (EDC) system. Completed, original CRFs will be retained at the clinical site as part of the study records.

# Quality Control and Quality Assurance

Ongoing detection, analysis, review, intervention and preventive action for protocol non-compliances and other quality issues is essential.

Quality Management is an integrated system of standardized tools and procedures that are applied to monitor trial activities, to ensure participant protection, and to minimize errors in documentation and data collection.

A Quality Management Plan will be developed by the site to allow prompt recognition of quality trends, early identification of protocol non-compliances, facilitation of corrective action plans, and to provide a formal mechanism for review by the investigator and feedback of preventive actions, including timelines and measures of compliance, to the study team, and to the Sponsor.

# Ethics/Protection of Human Subjects

## Ethical Standard

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.

## Institutional Review Board

The protocol and informed consent form will be reviewed and approved by 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 at applicable intervals as defined by IRB/IEC policy.

All the documents the IRB/IEC may need to fulfill its responsibilities, such as the protocol, protocol amendments, information concerning subject 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 subjects 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 subjects or the conduct of the study, provide an annual update and/or request for re-approval, 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 the Sponsor 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.

## Informed Consent Process

The principles of informed consent in the current edition of the Declaration of Helsinki and ICH-GCP/21 CFR 50.25 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 subject 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 subject records must be defined and the subject 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 subject’s original study medical records for verification of protocol-specified procedures and/or data, without violating the confidentiality of the subject 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 the Sponsor or its designee will be reviewed and approved by the Sponsor or its designee prior to being submitted to the IRB/IEC.

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

### Informed Consent/Assent Process (in Case of a Minor)

Not applicable. The age of majority in South Africa is 18 years.

## Exclusion of Women, Minorities, and Children (Special Populations)

Adolescents and children are excluded from participation in this study. The safety and immunogenicity of ID93 + GLA-SE has not been demonstrated in age groups younger than 18 years. Further, TB disease in children is often pauci-bacillary and difficult to diagnose. Therefore, confirmation of TB disease, ascertainment of bacteriologic cure, and determination of reactivation versus reinfection TB disease would be difficult in this study population.

HIV infected persons and other immune-compromised individuals are excluded from participation. The safety and immunogenicity of ID93 + GLA-SE has not been demonstrated in this study population. Further, TB disease in HIV infected individuals is often pauci-bacillary and difficult to diagnose. Therefore, confirmation of TB disease at baseline, ascertainment of bacteriologic cure, and determination of reactivation versus reinfection TB disease would be difficult in this study population.

## Subject Confidentiality

To maintain confidentiality, subject identification numbers will be used to identify the subject’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 the Sponsor or its designee or applicable regulatory authorities.

## Future Use of Stored Specimens

Human subject samples collected during the study will be used for the assays described in the protocol, including exploratory immunological assays and techniques that become available to address the objectives stated in the protocol prior to study closure.

MTB monocultures derived from sputum or other subject samples will not be considered human subject material for the purposes of future use of stored samples.

Subjects will be asked to consent separately for storage of their human subject material and future use of these samples for TB research. The samples from subjects who decline consent for storage and future use of their human subject material will be destroyed upon study closure.

## Modification of Protocol

No deviations from the protocol may be made. IDRI may approve minor exceptions on a case-by-case basis. If modification of the protocol is necessary, the modification must be initiated and confirmed in writing by IDRI, and the Investigator will inform the IRB and not institute the change until approved by the IRB.

## Departure from Protocol

When an emergency occurs that requires a departure from the protocol for an individual, a departure will be only for that individual. The Investigator or other physician in attendance in such an emergency will, if circumstances and time permit, contact IDRI immediately by telephone. The CRFs will completely describe the departure from the protocol and state the reasons for such departure. The IRB must be notified immediately if the departure from the protocol affects the safety or rights of the subject; otherwise, annually.

## Suspension of Study

If safety concerns arise during the study, the LMM or DSM may recommend to the Sponsor that the study be suspended, amended, or terminated. The study may be suspended by the Sponsor until the situation or safety concern has been resolved.

## Study Termination by the Sponsor

IDRI retains the right to terminate the study for any cause, suspending subject enrollment, and removing all investigational products and related study materials from the study site at any time. Specific instances, which may precipitate such termination at a site, are as follows:

* Deviation from protocol requirements.
* Inaccurate and/or incomplete data recording on a recurrent basis.
* Unauthorized use of investigational products or administration to any subject not enrolled as part of the protocol.
* Delinquent fulfillment of obligation on the part of the Investigator with regard to adverse reaction reporting, unacceptable subject enrollment, or other responsibilities as outlined in this protocol.

# Data Handling and Record Keeping

## Direct Access to Source Data/Documents and Study Monitoring

The study will be monitored regularly by the Sponsor or its designee throughout the study period. The Investigator will allow representatives of IDRI (or their designee) to periodically audit, at mutually convenient times during and after the study, all CRFs and corresponding source documents for each subject. It is important that the Investigator and/or other staff are available at these visits. The monitoring visits provide IDRI with the opportunity to evaluate the progress of the study, to verify the accuracy and completeness of CRFs, to resolve any inconsistencies in the study records, as well as assuring that all protocol requirements, applicable regulations, and Investigator's obligations are being fulfilled. The Investigator must maintain source documents such as laboratory and consultation reports, history and physical examination reports, etc., for possible review.

The IDRI monitor will record the date of each visit together with a summary of the status and progress of the study. Proposed actions will be confirmed with the Investigator in writing.

Telephone contact will be made as necessary during the data collection period and during the data and report writing periods.

## Record Retention

The Investigator shall retain the clinical study records until such time as directed by IDRI. Records are to be kept secured for at least two years after regulatory approval or longer if required by local regulations, or if not approved, until two years after shipment and delivery of drug for investigational use are discontinued. The investigator will ensure that study records are not disposed of or removed from the clinical site without prior notification and approval from the Sponsor or its designee.

# Publication Policy

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.

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# Appendix 1: Schedule of study visits and procedures

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Screening** | | | **Schedule for Study Injection Phase** | | | | | | | | | | | | | **Follow-up Visits** | | |
| **1st screen** | **2nd Screen** | **3rd Screen** |
|  | 16 weeks (+/- 1 week) of TBRx | 14 – 28 days after 1st screen | Within  -28 days of Day 0 | **Day 0**1 | Day  3 | Day  7  (±1) | Day 14 (±1) | **Day**  **28**  **(±3)** | Day  31 | Day  35  (±1) | Day 42 (±1) | **Day**  **56**  **(±3)** | Day  59 | Day  63  (±1) | Day  70  (±1) | **Day**  **84**  **(±3)** | **Day**  **112**7  **(±5)** | **Day**  **168**7  **(±10)** | **Day**  **224  (±10)** |
| Informed Consent(s) | X |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Inclusion/Exclusion Criteria | X | X | X | X |  |  |  |  |  |  |  | X |  |  |  |  |  |  |  |
| Medical History | X | X | X | X |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| TB Symptom screen | X | X | X | X |  | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Concomitant Medications | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |  |  |  |
| Full Physical Exam |  |  |  | X |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Directed Physical Exam | X | X | X |  |  |  |  | X |  |  |  | X |  |  |  | X | X2 | X2 | X |
| Weight |  |  |  | X |  |  |  |  |  |  |  | X |  |  |  | X | X | X | X |
| BMI |  |  |  | X |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Chest X-ray |  |  | X |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Sputum Samples (x2) | X | X | X | [X] |  | X3 | X3 | X3 | X3 | X3 | X3 | X3 | X3 | X3 | X3 | X3 | X3 | X3 | X3 |
| Vital Signs | X | X | X | X | X | X |  | X | X | X |  | X | X | X |  | X |  |  |  |
| Hematology/Chemistries |  |  | X |  |  | X |  | X |  | X |  | X |  | X |  |  |  |  |  |
| HIV Counselling and Serology | X |  | X |  |  |  |  |  |  |  |  | X4 |  | X4 |  | X4 | X4 | X4 | X4 |
| Pregnancy Testing5 | X | X | X | X |  |  |  | X |  |  |  | X |  |  |  |  |  |  |  |
| Immunology Blood6 |  |  |  | X | X | X | X | X | X | X | X | X | X | X | X | X | X7 | X7 | X |
| Study Injection |  |  |  | **X** |  |  |  | **X** |  |  |  | **X** |  |  |  |  |  |  |  |
| Injection Site Checks |  |  |  | X | X | X |  | X | X | X |  | X | X | X |  |  |  |  |  |
| Adverse Events |  |  |  | X | X | X | X | X | X | X | X | X | X | X | X | X |  |  |  |
| SAEs/AESIs |  |  |  | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

1 Must be within end of TB treatment date + 28 days. Assign PID # *prior* to baseline immunology blood draw. 2 Directed physical exam in-clinic if indicated by presence of unexplained or persistent symptoms for 14 days or longer, or any hemoptysis.3 Sputum Xpert MTB/RIF and MGIT culture for suspected recurrent TB only (symptom directed, unexplained or persistent symptoms for 14 days or longer, or any hemoptysis). 4 HIV testing for confirmed TB only. 5 Serum BHCG at 1st screening and End of Rx; all other timepoints urine BHCG. 6 See Appendix 2 for volumes of immunology blood. 7Days 112 and 168 may be field based visits unless symptomatic of TB recurrence. NOTE: Yellow denotes Cohort 3 only visits and procedures.

# Appendix 2: Schedule of blood draws and volumes

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **1st Screen** | **3rd Screen** | **Day**  **0** | **Day**  **3** | **Day**  **7**  **(± 1)** | **Day**  **14**  **(± 1)** | **Day**  **28**  **(±3)** | **Day**  **31** | **Day**  **35**  **(± 1)** | **Day**  **42**  **(± 1)** | **Day**  **56**  **(±3)** | **Day**  **59** | **Day 63**  **(± 1)** | **Day 70**  **(± 1)** | **Day 84**  **(± 3)** | **Day 112**  **(± 5)** | **Day 168**  **(± 10)** | **Day 224**  **(± 10)** |
| Hematology/Chemistries |  | 101 |  |  | 10 |  | 10 |  | 10 |  | 10 |  | 10 |  |  |  |  |  |
| HIV Serology and βHCG | 52 | 52 |  |  |  |  |  |  |  |  | 53 |  | 53 |  | 53 | 53 | 53 | 53 |
| **Clinical Blood Volume** | 5 | 15 |  |  | 10 |  | 10 |  | 10 |  | 10 |  | 10 |  |  |  |  |  |
| Gene signatures (PaxGene (2.5 mL) and Absolute Blood Count (0.5 mL) |  |  | 3 | 3 | 3 |  | 3 | 3 | 3 |  | 3 | 3 | 3 |  |  | 33 | 33 | 33 |
| Whole Blood / ICS |  |  | 8 |  |  | 8 | 8 |  |  | 8 | 8 |  |  | 8 | 8 |  |  | 8 |
| PBMCs |  |  | 30 |  |  | 30 | 30 |  |  | 30 | 30 |  |  | 30 | 30 |  |  | 30 |
| Serum for IgG ELISA |  |  | 6.5 4 |  |  | 4 | 4 |  |  | 4 | 4 |  |  | 4 | 4 |  |  | 6.5 4 |
| **Immunology Blood Volume** |  |  | 47.5 | 3 | 3 | 42 | 45 | 3 | 3 | 42 | 45 | 3 | 3 | 42 | 42 |  |  | 44.5 |
| **Total Visit Volume** | 5 | 15 | 47.5 | 3 | 13 | 42 | 55 | 3 | 13 | 42 | 55 | 3 | 13 | 42 | 42 |  |  | 44.5 |
| **Cumulative Volume5** | 5 | 20 | 67.5 | 70.5 | 83.5 | 125.5 | 180.5 | 183.5 | 196.5 | 238.5 | 293.5 | 296.5 | 309.5 | 351.5 | 393.5 |  |  | 438 |

1 Includes CRP at baseline only.

2 HIV serology only if discordant rapid HIV test. βHCG at screening only for females of child bearing potential

3 HIV PCR and gene signatures in cases of TB recurrence.

**4** Includes additional 2.5 mL to be banked for autoimmune testing if indicated.

5 Excluding footnote 3 volumes.

NOTE: Yellow denotes Cohort 3 only visits and procedures

# Appendix 3: Schedule of physical exam, directed physical exam, TB screen and sputum sampling tests

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Screening** | | | **Schedule for Study Injection Phase** | | | | | | | | | | | | | **Follow-up Visits** | | |
| **1st Screen** | **2nd Screen** | **3rd Screen** |
|  | 16 weeks (+/- 1 week) ofTBRx | 14 - 28 days after 1st screen | Within  -28 days of Day 0 | **Day**  **0** | Day 3 | Day  7  (±1) | Day  14  (±1) | **Day 28 (±3)** | Day 31 | Day  35  (±1) | Day  42  (±1) | **Day 56 (±3)** | Day 59 | Day 63 (±1) | Day 70  (±1) | **Day 84 (±3)** | **Day 112 (±5)** | **Day 168 (±10)** | **Day 224  (±10)** |
| TB Symptoms Screen | X | X | X | X |  | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Full Physical Exam |  |  |  | X |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Symptom Directed Physical Exam and vital signs | X | X | X |  |  |  |  | X |  |  |  | X |  |  |  | X | X1 | X1 | X |
| Sputum Samples (x2) | X2 | X2 | X2 | X3 |  | X4 | X4 | X4 | X4 | X4 | X4 | X4 | X4 | X4 | X4 | X4 | X4 | X4 | X4 |

1 Directed physical exam in-clinic if indicated by presence of unexplained or persistent symptoms for 14 days or longer, or any hemoptysis.

2 Sputum Xpert MTB/RIF and MGIT culture.

3 Sputum Xpert MTB/RIF and MGIT culture if not already done so at the 3rd screening visit.

4 Sputum Xpert MTB/RIF and MGIT culture for suspected recurrent TB only (symptom directed, unexplained or persistent symptoms for 14 days or longer, or any hemoptysis).

Sputum sampling will always include two samples.

The tests to be performed on sputum samples at different time points will be as follows:

**First Screening Visit (**at 16 weeks (+/- 1 week) of Rx**):** Sputum Xpert MTB/RIF and MGIT culture.

**Second Screening Visit (**at 18 weeks (+ 3 weeks) of Rx and ≥ 14 days after first screen**):** Sputum Xpert MTB/RIF and MGIT culture.

**Third Screening Visit (or on Day 0):** Sputum Xpert MTB/RIF and MGIT culture

**On study after Day 0**: Sputum Xpert MTB/RIF and MGIT culture for suspected recurrent TB only (symptom directed by presence of unexplained or persistent TB symptoms for 14 days or longer, or any hemoptysis).

NOTE: Yellow denotes Cohort 3 only visits and procedures

# Appendix 4: Grading scale for clinical laboratory values

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Grade for Abnormal Results (Value or Change from Reference)\*** | | | | |
| **Parameter** | **Mild**  **(Grade 1)** | **Moderate**  **(Grade 2)** | **Severe**  **(Grade 3)** | **Potentially Life-threatening (Grade 4)** | |
| Creatinine (mg/dL) | >1.5 - 1.7 mg/dL | 1.8 - 2.0 mg/dL | 2.1 - 2.5 mg/dL | | >2.5 mg/dL or requires dialysis |
| Total Bilirubin (mg/dL) | >ULN - 1.5 x ULN\*  \*\*>ULN - 1.25 x ULN | >1.5 - 2.0 x ULN\*  \*\*> 1.25 - 1.5 x ULN | >2.0 - 3.0 x ULN \*  \*\*> 1.5 - 1.75 x ULN | > 3.0 x ULN \*  \*\*> 1.75 x ULN | |
| ALT (SGPT) (IU/L) | >ULN - 2.5 x ULN | >2.5 - 5.0 x ULN | >5.0 - 10 x ULN | >10 x ULN | |
| AST (SGOT) (IU/L) | >ULN - 2.5 x ULN | >2.5 - 5.0 x ULN | >5.0 - 10 x ULN | >10 x ULN | |
| WBC (K/µL or 109/L) | >12.0 - 15.0 K/µL  2.5 - <4.0 K/µL | >15.0 - 20.0 K/µL  1.5 - <2.5 K/µL | >20.0 - 25.0 K/µL  1.0 - <1.5 K/µL | >25.0 K/µL  <1.0 K/µL | |
| Hemoglobin (g/dL) | M: <LLN - 11.5 g/dL  F: <LLN - 10.0 g/dL | M: 11.4 - 9.5 g/dL  F: 9.9 - 8.5 g/dL | M: 9.4 - 8.5 g/dL  F: 8.4 - 8.0 g/dL | <8.5 g/dL  <8.0 g/dL | |
| Platelet count (K/µL or 109/L) | 100 - 149 K/µL | 50 - 99 K/µL | <50 K/µL |  | |

FDA Guidance for Industry Toxicity Grading Scale for Healthy Adults Enrolled in Preventive Vaccine Clinical Trials, 2007. ULN=upper limit of normal; LLN=lower limit of normal. \*Tox Grading for total bilirubin when liver transaminases are normal. \*\*Tox Grading for total bilirubin when accompanied by increased transaminases. **NOTE: If subject has a Grade 3 or Grade 4 lab toxicity do NOT administer study injections. See Section 9.8.2.**

# Appendix 5: Grading scale for local (injection site) reactions by investigator

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Local Finding** | **Grade 0**  **(None)** | **Grade 1**  **(Mild)** | **Grade 2**  **(Moderate)** | **Grade 3**  **(Severe)** | **Grade 4**  **(Potentially Life-threatening)** |
| Pain | None | Does not interfere with activity | Repeated use of non-narcotic pain reliever >24 hours or interferes with activity | Any use of narcotic pain reliever or prevents daily activity | Emergency room (ER) visit or hospitalization |
| Erythema/Redness | <2.5cm | 2.5 – 5.0 cm | 5.1 – 10 cm | >10 cm | Necrosis or exfoliative dermatitis |
| Induration/Swelling | <2.5cm | 2.5 – 5.0 cm | 5.1 – 10 cm | >10 cm | Necrosis |

**NOTE:** **Local injection site reaction grading should not be confused with general AE grading**.

In addition to grading the measured local reaction at the greatest single diameter, the measurements of the widest diameter and the diameter perpendicular to it should be recorded in the CRF as a continuous variable.

# Appendix 6: Toxicity grading scale¹ for determining the severity of clinical AEs

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **VITAL SIGNS** | | | | | |
|  | **Grade 1 Mild** | **Grade 2 Moderate** | **Grade 3\* Severe** | **Grade 4\*\* Potentially Life-threatening** | |
| Fever: axillary (˚C) | 37.5 – 37.9 | 38.0 – 38.4 | 38.5 – 39.5 | > 39.5 | |
| Tachycardia - bpm | 101 - 115 | 116 - 130 | >130 | 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 | |
| **SYSTEMIC (GENERAL)** | | | | | |
| Nausea/Vomiting | No interference with activity or 1 - 2 episode in 24 hours | Some interference with activity or >2 episodes in 24 hours | Prevents daily activity or requires outpatient IV hydration | | ER visit or hospitalization for hypotensive shock |
| Diarrhea | 2-3 loose stools in 24 hours | 4-5 loose stools in 24 hours | > 5 watery stools in 24 hours or outpatient IV hydration | | Requiring significant/urgent medical care or hospitalization |
| Headache | No interference with activity | Repeated use of  non-narcotic pain reliever > 24 hours or some interference with activity | Significant; use of narcotic pain reliever or prevents daily activity | | Requiring significant/urgent medical care or hospitalization |
| Malaise/fatigue, myalgia (muscle pain), arthralgia (joint pain), chills, anorexia (loss of appetite), self-reported symptoms of ‘fever’ (no temperature taken) | No interference with activity | Some interference with activity | Significant; prevents daily activity | | Requiring significant/urgent medical care or hospitalization |
| Allergic reaction | Pruritus without rash | Localized urticaria (rash) | Generalized urticaria; angioedema | | Requiring significant/urgent medical care or hospitalization |
| Hives (urticaria) | Urticarial lesions covering <10% BSA; topical intervention indicated | Urticarial lesions covering 10 -30% BSA; oral ntervention indicated | Urticarial lesions covering >30% BSA; IV intervention indicated | |  |
| Illness or clinical adverse event | No interference with activity. | Some interference with activity but does not require medical intervention | Prevents daily activity and requires medical intervention | | Requiring significant/urgent medical care or hospitalization |

1 = FDA Guidance for Industry Toxicity Grading Scale for Healthy Adults Enrolled in Preventive Vaccine Clinical Trials, 2007. \*Report Grade 3 AEs to Pharmacovigilance by e-mail within 24 hours. \*\*Grade 4 AE constitutes an SAE; report to the Pharmacovigilance Team by e-mail within 24 hours.

# Appendix 7: Toxicity grading scale for determining the severity of clinical AEs not in Appendix 6

|  |  |
| --- | --- |
| **Grade 1 Mild** | Transient or mild discomfort (< 48 hr); no medical intervention/therapy required |
| **Grade 2 Moderate** | Mild to moderate limitation in activity – some assistance may be needed; no or minimal medical intervention/therapy required |
| **Grade 3 Severe** | Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization possible |
| **Grade 4 Potentially Life-threatening** | Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable |

# Appendix 8: List of AESIs

This list is current as of December 2013. It is provided by FDA/CBER and is subject to periodic update. Any updates will be implemented via a Note to File.

**Gastrointestinal disorders**

* Celiac disease
* Crohn’s disease
* Ulcerative colitis
* Ulcerative proctitis

**Liver disorders**

* Autoimmune cholangitis
* Autoimmune hepatitis
* Primary biliary cirrhosis
* Primary sclerosing cholangitis

**Metabolic diseases**

* Addison’s disease
* Autoimmune thyroiditis (including Hashimoto thyroiditis)
* Diabetes mellitus type I
* Grave's or Basedow’s disease

**Musculoskeletal disorders**

* Antisynthetase syndrome
* Dermatomyositis
* Juvenile chronic arthritis, (including Still’s disease)
* Mixed connective tissue disorder
* Polymyalgia rheumatic
* Polymyositis
* Psoriatic arthropathy
* Relapsing polychondritis
* Rheumatoid arthritis
* Scleroderma, including diffuse systemic form and CREST syndrome
* Spondyloarthritis, including ankylosing spondylitis, reactive arthritis (Reiter's Syndrome) and undifferentiated spondyloarthritis
* Systemic lupus erythematosus
* Systemic sclerosis

**Neuroinflammatory disorders**

* Acute disseminated encephalomyelitis, including site specific variants: e.g.

non-infectious encephalitis, encephalomyelitis, myelitis, myeloradiculomyelitis

* Cranial nerve disorders, including paralyses/paresis (e.g. Bell’s palsy)
* Guillain-Barré syndrome, including Miller Fisher syndrome and other variants
* Immune-mediated peripheral neuropathies and plexopathies,(including chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy and polyneuropathies associated with monoclonal gammopathy).
* Multiple sclerosis
* Narcolepsy
* Optic neuritis
* Transverse Myelitis

**Skin disorders**

* Alopecia areata
* Autoimmune bullous skin diseases (including pemphigus, pemphigoid and dermatitis herpetiformis)
* Cutaneous lupus erythematosus
* Erythema nodosum
* Morphoea
* Lichen planus
* Psoriasis
* Sweet’s syndrome
* Vitiligo

**Vasculitides**

* Large vessels vasculitis including: giant cell arteritis such as Takayasu's arteritis and temporal arteritis.
* Medium sized and/or small vessels vasculitis including: polyarteritis nodosa, Kawasaki's disease, microscopic polyangiitis, Wegener's granulomatosis, Churg–Strauss syndrome (allergic granulomatous angiitis), Buerger’s disease thromboangiitis obliterans), necrotizing vasculitis and anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified), Henoch- Schonlein purpura, Behcet's syndrome, leukocytoclastic vasculitis.

**Others**

* Antiphospholipid syndrome
* Autoimmune hemolytic anemia
* Autoimmune glomerulonephritis (including IgA nephropathy, glomerulonephritis rapidly progressive, membranous glomerulonephritis, membranoproliferative glomerulonephritis, and mesangioproliferative glomerulonephritis)
* Autoimmune myocarditis/cardiomyopathy
* Autoimmune thrombocytopenia
* Goodpasture syndrome
* Idiopathic pulmonary fibrosis
* Pernicious anemia
* Raynaud’s phenomenon
* Sarcoidosis
* Sjögren’s syndrome
* Stevens-Johnson syndrome
* Uveitis