IMPAACT P1113 / Aeras C-015-404

PHASE I/II, SAFETY AND IMMUNOGENICITY STUDY OF A RECOMBINANT PROTEIN TUBERCULOSIS VACCINE (AERAS-404) IN BCG-PRIMED INFANTS

A Limited Center, International Trial of the International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT)

Sponsored by:
Aeras

In Collaboration with:
The National Institute of Allergy and Infectious Diseases (NIAID)
And
The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)

Pharmaceutical Support Provided by:
Sanofi Pasteur
And
Statens Serum Institut

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Version 2.0
FINAL
07/25/13
FOREWORD

IMPAACT P1113/Aeras C-015-404 is a collaborative study sponsored by Aeras in conjunction with the National Institute of Allergy and Infectious Diseases (NIAID) and the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD). The study is also supported by Sanofi Pasteur and Statens Serum Institut (SSI), the pharmaceutical companies providing the active vaccine and placebo.

- Aeras is a non-profit product development organization dedicated to the development of effective tuberculosis (TB) vaccines and other biopharmaceuticals to prevent TB across all age groups in an affordable and sustainable manner. Aeras is the sponsor of the study and is responsible for the following:
  a. Development and distribution of the Clinical Investigator’s Brochure
  b. Regulatory compliance
  c. Central randomization
  d. Case report form development and data management, in conjunction with the designated CRO
  e. Clinical research site (CRS) monitoring
  f. Serious adverse event reporting
  g. Statistical support for protocol development and data analysis

- Sanofi Pasteur is the vaccines division of the Sanofi Group. Sanofi Pasteur is responsible for the following:
  a. Supply of the H4 antigen for the active vaccine
  b. Supply of the placebo
  c. Package, label and manage supply of the study vaccine

- Statens Serum Institut (SSI) is a state-owned enterprise under the Danish Ministry of Health and Prevention. It operates as a market-oriented production and service enterprise with the mission to prevent and control infectious diseases, biological threats and congenital disorders. SSI is responsible for supplying the IC31 adjuvant.

- NIAID and NICHD are collaborating partners with Aeras in this study and are responsible for the following:
  a. Project management and protocol team support*
  b. Protocol development*
  c. CRS initiation visits
  d. CRS management
  e. Study Monitoring Committee (SMC) appointment and support*
  f. Central Immunology Laboratory support†
  g. Fiscal support for CRS and HIV Vaccine Trials Network (HVTN) Central Immunology Laboratory costs will be funded through NIAID
FOREWORD (cont.)

The Statistical and Data Analysis Center (SDAC) will not conduct any data analysis for this study at this time.

Specimen tracking will be through the Laboratory Data Management System (LDMS) of the IMPAACT Data Management Center (DMC).

Each CRS will submit their Local Ethics Committee (EC) approvals and all required regulatory documents directly to Aeras. They will not be submitted to the Division of AIDS (DAIDS) Protocol Registration Office (PRO). Aeras will issue the authorization for a CRS to begin participation in the study*.

* Through IMPAACT and the Operations Center.
† Through HVTN
All questions concerning this protocol should be sent via e-mail to impaact.teamp1113@fstrf.org. Remember to include the subject’s PID when applicable. Questions concerning medical and safety events and management should be sent via email to the P1113 Core Team (impaact.p1113core@fstrf.org). The appropriate team member will respond to questions via e-mail with a "cc" to impaact.teamp1113@fstrf.org or impaact.p1113core@fstrf.org, as applicable. A response should generally be received within 24 hours (Monday - Friday).

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A list of the sites participating in the study may be found on the IMPAACT P1113 protocol-specific web page (PSWP) tab on the IMPAACT website (https://impaactgroup.org/). Enter the Member/MIS area using your individual username and password. Search for the study number (P1113). From the protocol (P1113) web page you will have the option to click the PSWP tab.
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VI DAIDS SAMPLE INFORMED CONSENT TEMPLATE
### GLOSSARY

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>ACTG</td>
<td>AIDS Clinical Trials Group</td>
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<tr>
<td>AE/EAE</td>
<td>Adverse Event / Expedited Adverse Event</td>
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<tr>
<td>AG</td>
<td>Antigen</td>
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<tr>
<td>AIDS</td>
<td>Acquired Immunodeficiency Syndrome</td>
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<tr>
<td>ALT</td>
<td>Amino Alanine Transferase</td>
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<tr>
<td>AST</td>
<td>Aspartate Amino Transferase</td>
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<td>BCG</td>
<td>Bacille Calmette-Guerin</td>
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<td>BUN</td>
<td>Blood Urea Nitrogen</td>
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<tr>
<td>BW</td>
<td>Body Weight</td>
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<tr>
<td>CBC</td>
<td>Complete Blood Count</td>
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<tr>
<td>CD4 / CD8</td>
<td>Cluster of Differentiation 4 / Cluster of Differentiation 8</td>
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<tr>
<td>CHUV</td>
<td>Centre d’Immunothérapie et de Vaccinologie</td>
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<tr>
<td>CI</td>
<td>Confidence Intervals</td>
</tr>
<tr>
<td>CMI</td>
<td>Cell-Mediated Immunity</td>
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<tr>
<td>CPK</td>
<td>Creatine Phosphokinase</td>
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<tr>
<td>COG</td>
<td>Collaboration Oversight Group</td>
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<tr>
<td>CRF</td>
<td>Case Report Form</td>
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<tr>
<td>CRS</td>
<td>Clinical Research Site</td>
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<td>DAIDS</td>
<td>Division of AIDS, NIAID</td>
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<tr>
<td>DMC</td>
<td>Data Management Center</td>
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<tr>
<td>DNA</td>
<td>Deoxyribonucleic acid</td>
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<tr>
<td>EC</td>
<td>Ethics Committee</td>
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<tr>
<td>ELISA</td>
<td>Enzyme-linked Immunosorbent Assay</td>
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<td>ELISPOT</td>
<td>Enzyme-linked Immunosorbent Spot</td>
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<tr>
<td>EPI</td>
<td>Expanded Program on Immunization</td>
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<tr>
<td>ESAT</td>
<td>Early Secretory Antigenic Target</td>
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<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
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<tr>
<td>GLP</td>
<td>Good Laboratory Practice</td>
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<tr>
<td>GM</td>
<td>Geometric Mean</td>
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<tr>
<td>GMM</td>
<td>Global Medical Monitor</td>
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<tr>
<td>HHS</td>
<td>Health and Human Services</td>
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<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
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<tr>
<td>HSR</td>
<td>Hypersensitivity Reaction</td>
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<tr>
<td>HVTN</td>
<td>HIV Vaccine Trials Network</td>
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<tr>
<td>IB</td>
<td>Investigator’s Brochure</td>
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<tr>
<td>IC</td>
<td>Intracardiac</td>
</tr>
<tr>
<td>ICF</td>
<td>Informed Consent Form</td>
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<tr>
<td>ICH</td>
<td>International Conference on Harmonization</td>
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<tr>
<td>ICS</td>
<td>Intracellular Cytokine Staining</td>
</tr>
<tr>
<td>IL</td>
<td>Interleukin</td>
</tr>
<tr>
<td>IM</td>
<td>Intramuscular Injection</td>
</tr>
<tr>
<td>IMPAACT/PACTG</td>
<td>International Maternal Pediatric Adolescent AIDS Clinical Trials Group (previously the Pediatric AIDS Clinical Trials Group – PACTG)</td>
</tr>
<tr>
<td>INF</td>
<td>Interferon</td>
</tr>
<tr>
<td>IP</td>
<td>Investigational Product</td>
</tr>
<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
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### Glossary (cont.)

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tbody>
<tr>
<td>IVRS / IWRS</td>
<td>Interactive Voice Response System / Web Response System</td>
</tr>
<tr>
<td>LAR</td>
<td>Legally Authorized Representative</td>
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<tr>
<td>LFT</td>
<td>Liver Function Test</td>
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<tr>
<td>LPC</td>
<td>Laboratory Processing Chart</td>
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<tr>
<td>LUMC</td>
<td>Leiden University Medical Center</td>
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<tr>
<td>MCC</td>
<td>Medicines Control Council (of South Africa)</td>
</tr>
<tr>
<td>MOP</td>
<td>Manual of Operations</td>
</tr>
<tr>
<td>M.t.b. / Mtb</td>
<td>Mycobacterium tuberculosis</td>
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<tr>
<td>NIAID</td>
<td>National Institute of Allergy and Infectious Diseases</td>
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<tr>
<td>NICHD</td>
<td>National Institute of Child Health and Human Development</td>
</tr>
<tr>
<td>NIH</td>
<td>National Institutes of Health</td>
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<tr>
<td>OHRP</td>
<td>Office for Human Research Protections</td>
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<tr>
<td>PBMC</td>
<td>Peripheral Blood Mononuclear Cell</td>
</tr>
<tr>
<td>PCR</td>
<td>Polymerase Chain Reaction</td>
</tr>
<tr>
<td>PDMC</td>
<td>Protocol Development and Monitoring Committee</td>
</tr>
<tr>
<td>PI</td>
<td>Principal Investigator</td>
</tr>
<tr>
<td>PPD</td>
<td>Purified Protein Derivative</td>
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<tr>
<td>PSWP</td>
<td>Protocol-Specific Web Page</td>
</tr>
<tr>
<td>QFT-GIT</td>
<td>QuantiFERON TB Gold In-Tube</td>
</tr>
<tr>
<td>RBC</td>
<td>Red Blood Cells</td>
</tr>
<tr>
<td>RNA</td>
<td>Ribonucleic Acid</td>
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<tr>
<td>TBS</td>
<td>Tris Buffered Saline</td>
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<tr>
<td>TEAE</td>
<td>Treatment Emergent Adverse Events</td>
</tr>
<tr>
<td>TH-1 / TH-2</td>
<td>T Helper Cell Type 1 / T Helper Cell Type 2</td>
</tr>
<tr>
<td>TNF</td>
<td>Tumor Necrosis Factor</td>
</tr>
<tr>
<td>SADR</td>
<td>Suspected Adverse Drug Reaction</td>
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<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
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<tr>
<td>SAP</td>
<td>Statistical Analysis Plan</td>
</tr>
<tr>
<td>SATVI</td>
<td>South African Tuberculosis Vaccine Initiative</td>
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<tr>
<td>SCID</td>
<td>Severe Combined Immunodeficiency</td>
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<tr>
<td>SDAC</td>
<td>Statistical and Data Analysis Center</td>
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<tr>
<td>SIP</td>
<td>Site Implementation Plan</td>
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<td>SMC</td>
<td>Study Monitoring Committee</td>
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<td>SSI</td>
<td>Statens Serum Institut</td>
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<td>SUSAR</td>
<td>Suspected Unexpected Serious Adverse Reaction</td>
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<tr>
<td>TB</td>
<td>Tuberculosis</td>
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<tr>
<td>TST</td>
<td>Tuberculin Skin Test</td>
</tr>
<tr>
<td>ULN</td>
<td>Upper Limit of Normal</td>
</tr>
<tr>
<td>US</td>
<td>United States</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
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SUMMARY OF CHANGES


All changes in this version appear in boldface type. Editorial changes, corrections of typographical errors, and other changes required to update information that do not affect regulatory issues or patient consent may also be included.

The major changes in Version 2.0 are related to the inclusion of immunogenicity criteria and scheduled review of the immunogenicity data from select cohorts, which will inform the decision to open the younger age cohorts to enrollment. This will prevent opening the younger age cohorts to the risk of receiving a novel vaccine where there is insufficient data to warrant continuation of the study. A new cohort, Cohort 3B, has been added. This cohort will be used to evaluate the safety and immunogenicity response to 2 doses of AERAS-404 with dose of 15µg H4/500 nmol IC31. An observed difference of at least 30% in immunogenicity response rate between the AERAS-404 group and placebo group must be achieved in Cohort 3B for the study to proceed with enrollment into Cohort 4. A new secondary objective – “To assess the immunogenicity of a 2-dose AERAS-404 regimen in HIV-uninfected, HIV-unexposed, BCG-primed infants” – was also added.

The prior Cohort 4 (in Version 1.0) has been deleted and the regimen of 3 doses of AERAS-404 with dose of 5µg H4/500 nmol IC31 is not moving forward. The succeeding cohorts were renumbered (i.e. Cohort 5 is now Cohort 4, Cohort 6 is now Cohort 5, etc.). If the enrollment proceeds to Cohorts 4 and 5, the immunogenicity response rate in both these cohorts will be evaluated. An observed difference of at least 50% in immunogenicity response rate between the AERAS-404 group and placebo group in either Cohort 4 or Cohort 5 must be achieved to proceed with enrollment into Cohort 6.

Refer to the detailed list of changes below for the specific changes made in the sections of the protocol.

Detailed list of changes:

1. The Foreword has been updated to include clarification that CRF development and data management will be in conjunction with a designated CRO, clarification of the role of HVTN and the IMPAACT DMC, and information on the CRS funding source was removed.

2. The team roster has been updated.
3. The glossary has been updated.

4. A Core Team email address has been added for notification of the Protocol Core Team of medical and safety events and management. The following sections have been revised to include this change: team roster, Section 6.11, Section 6.4 and Section 7.1.

5. The following cohorts have been added:
   - Cohort 3A with treatment regimen of 2 doses of 5µg H4/500 nmol IC31 (AERAS-404) or Placebo administered at Study Day 0 (≥ 168 to ≤ 189 days of age) and Study Day 28, a sample size of N = 11 AERAS-404 and N = 3 Placebo, and receiving 2 doses of AERAS-404 with dose of 5µg H4/500 nmol IC31.
   - Cohort 3B with treatment regimen of 2 doses of 15µg H4/500 nmol IC31 (AERAS-404) or Placebo administered at Study Day 0 (≥ 168 to ≤ 189 days of age) and Study Day 28, a sample size of N = 39 AERAS-404 and N = 6 Placebo, and receiving 2 doses of AERAS-404 with dose of 15µg H4/500 nmol IC31.

The following sections have been revised to include these changes: Schema, Section 1.2, Section 1.21, Section 1.22, Section 3.0, Section 4.111, Section 5.12, Section 5.13 (Table 15), Section 5.2 (Table 16), Section 6.2, Section 8.1, Section 8.3, Section 8.4, Section 8.52, Section 8.621, Section 8.622, and Appendix I-B.

6. The following cohorts have been removed:
   - Cohort 3 with treatment regimen of 2 doses of 5µg H4/500 nmol IC31 (AERAS-404) or Placebo administered at ≥ 126 to ≤ 140 days of age and ≥ 147 to ≤ 161 days of age and a sample size of N = 11 AERAS-404 and N = 3 Placebo.
   - Cohort 4 with treatment regimen of 3 doses of 5µg H4/500 nmol IC31 (AERAS-404) or Placebo administered at ≥ 84 to ≤ 98 days of age, ≥ 119 to ≤ 133 days of age and ≥ 175 to ≤ 189 days of age and a sample size of N = 29 AERAS-404 and N = 6 Placebo.

All succeeding cohorts have been renumbered, i.e., Cohort 5 is now Cohort 4, Cohort 6 is now Cohort 5 and Cohort 7 is now Cohort 6.

The following sections have been revised to include these changes: Schema, Section 1.21, Section 1.22, Section 3.0, Section 4.111, Section 5.0, Section 5.12, Section 5.13 (Table 15), Section 5.2 (Table 16), Section 6.2, Section 6.3, Section 6.5, Section 6.9, Section 8.1, Section 8.221, Section 8.3, Section 8.4, Section 8.52, Section 8.54, Section 8.61, Section 8.621, Section 8.622, Appendix I-B, Appendix I-C and Appendix I-D.
7. The Schema has been revised to include changes in the Sample Size, Table 1 and Treatment Duration with the addition of Cohorts 3A and 3B and the removal of Cohorts 3 and 4, as described in numbers 4 and 5 above. The safety and immunogenicity response rate criteria for opening Cohort 4 and subsequent cohorts, and the safety and immunogenicity response rate criteria for opening Cohort 6, have also been included.

8. The age range for the second and third study vaccine doses for Cohorts 4, 5 and 6 have been removed and replaced with the Study Visit Day when the doses should be administered. The doses after Entry (i.e., Dose 1) for Cohorts 4 and 5 are now at Study Day 42 for Dose 2 and Study Day 98 for Dose 3, while for Cohort 6 Dose 2 is at Study Day 28 and Dose 3 is at Study Day 210. The age range for Dose 1 has been retained as these correspond with an eligibility criterion; however “Study Day 0” has been added for this dosing time point throughout the protocol. For clarity and consistency, the time points for study vaccine dosing have also been relabeled as Study Day throughout the protocol.

The following sections have been revised to include these changes: Schema, Section 1.22, Section 3.0, Section 5.13 (Table 15), Section 8.1, and Appendices I-A through I-D.

Table 1 in the Schema has also been revised to clarify the reference to Appendices I-B to I-D for subsequent study vaccine dosing windows and to add a footnote to explain the simultaneous study vaccine and EPI vaccine dosing in Cohort 6.

9. The Schema and Section 2.2 have been revised to add a new secondary objective to assess the immunogenicity of a 2-dose AERAS-404 regimen.

10. Section 1.14, Summary of Immunogenicity Profile of AERAS-404 sub-section, has been updated to include clarification of the responses seen to the different strengths of AERAS-404 in the C-006-404 study. A new figure has also been added as Figure 5.

Subsequent to the addition of the new figure, all succeeding figures have been renumbered and references to the figures updated.

11. Section 1.2 has been revised to include the rationale for adding early assessment of immune responses for the decision whether enrollment will proceed with the next cohort/s.

12. Section 1.21 has been revised to clarify the H4 antigen doses that will be tested for Cohorts 1 through 5 and to include the explanation of why a 3-dose regimen using the vaccine dose with 5 µg H4 will not be evaluated.
13. Section 1.22 has been revised to include clarification that Cohort 3A will provide safety data, Cohort 3B will provide safety and immunogenicity data, continued enrollment to Cohort 4 and succeeding cohorts will depend on safety and immunogenicity data meeting defined criteria in Section 8.53, and enrollment to Cohort 6 will depend on safety and immunogenicity data meeting defined criteria in Sections 8.222 and 8.54.

14. Section 3.0 has been revised to include the reason for adding Cohort 3B, the description of the safety and immune response evaluation and the criteria that need to be achieved in Cohort 3B for moving forward to Cohort 4, and the description of the safety and immune response evaluation and the criteria that need to be achieved in Cohorts 4 or 5 for moving forward to open Cohort 6. The process for determining the specific functional markers that will be used to evaluate the response rate before the immunologic data are reviewed has also been added.

15. Section 4.111 has been reformatted for clarity.

16. Section 4.112 has been revised to include the new Cohort 6 and to include the operational signs ≥ and ≤ to the eligibility age range at entry.

17. Section 4.14 has been revised to apply to Cohorts 4, 5 and 6 only.

18. Section 4.31 has been revised to include the use of topical traditional medicines at the site of injection within 7 days before or after study vaccine administration is not recommended.

19. Section 5.0 has been revised to include clarification on the source of the EPI vaccines and the preferred setting for the administration of the EPI vaccines.

20. Section 5.12 has been revised to include clarification that only the Vaccine Request Form corresponding to a specific dosing visit is to be submitted to the pharmacist and that the succeeding dose information in a subject’s treatment regimen will be from the IVRS/IWRS. The detailed procedures for preparing the investigational product and the control product, including Table 15, have been transferred to the Manual of Procedures (MOP); brief descriptions of the procedures and references to the MOP for the detailed instructions for study vaccine preparation have been added. Clarifications for and reference to the MOP for the preparation and labeling of the syringe and the documentation instructions have also been added.

Subsequent to the removal of Table 15, the succeeding tables have been renumbered, and the references to the corresponding tables have been updated, in Sections 5.13, Section 5.2, and Section 8.4.
21. Section 5.13 has been revised to remove the instruction regarding where the EPI vaccines and study vaccine will be injected in Cohorts 4 to 7 and instructions on where these vaccines will be injected for Cohort 6 has been added. Table 15 has also been revised to include the study day of vaccination for all cohorts, the visit window for Dose 2 and Dose 3, and additional vaccination guidelines as applicable for the cohorts receiving more than 1 dose, and replace the age range for study vaccine doses after Dose 1 with the Study Day when the vaccine should be administered.

22. Section 5.3 has been revised to include clarification that the H4 antigen will be shipped directly to the CRS from Sanofi Pasteur in Toronto, Canada. The details of the procedures and instructions for study vaccine shipment, shipment receipt, study vaccine storage, communication for study vaccine-related issues, and requesting additional study vaccine in case of expected or potential shortage were transferred to the MOP; references to the MOP were added to guide the sites on where to find the procedures and instructions. Clarifications for the individual responsible for product management at the site, who the CRS PI or authorized designee should contact in case of accidental thawing or disruption of the cold chain, the individual responsible to verify the site’s product accountability records, who will direct the disposal or return of unused or wasted study vaccine, and only when disposal can occur have also been added.

23. Section 5.4 has been revised to include the Aeras IP manager to the list of unblinded study personnel and to remove the study injection administrator as this role is no longer required since a syringe overlay will be used.

24. Section 5.5 has been revised to include the new unblinding procedure that will be used.

25. Section 6.2 has been revised to change Figure 11 to only show management of Cohorts 1 through 3B and to add Figure 12 to outline the management of Cohorts 4 through 6. The explanation of the evaluation of safety and immunogenicity data from Cohort 3B for the decision to open Cohort 4 and subsequent cohorts, the clarification of the evaluation of safety data from Cohort 4 for moving forward to Cohort 5, the clarification of the evaluation of safety and immunogenicity data for the decision to open and the study vaccine dose for Cohort 6, and the method that will be used to inform the CRS of the selected dose for Cohort 6 have also been added.

26. Section 6.10 has been revised to include clarification that refusal of further treatment and/or follow-up evaluations would result in the subject being withdrawn from the study.
27. Section 7.1 has been updated to change the time period for submitting SAE reports to the PPD World Wide Safety Center to “48 hours (two business days)” so it is consistent with Appendix IV.

28. Section 7.23 has been revised to include clinical stabilization of the SAE as one of the end points for SAE follow-up for an SAE that is ongoing at the time of the final study visit.

29. Section 8.1 has been revised to add a reference for the immunogenicity response criteria to the requirements for proceeding with Cohort 6 and the explanation of how the placebo subjects in all cohorts will be used in the analysis.

30. Section 8.222 has been revised to include the evaluation of the immune response in Cohort 3B for the decision to open Cohort 4 and subsequent cohorts, the evaluation of the immune response in Cohort 4 and Cohort 5 for the decision to open Cohort 6, and how the specific functional markers used to evaluate the response rate will be determined before the immunologic data are reviewed.

31. Section 8.3 has been revised to include the ratio of AERAS-404 to placebo subjects for Cohort 3B and update the ratio of AERAS-404 to placebo subjects for Cohorts 4 and 5.

32. Section 8.4 has been revised to include clarification and updates to the minimum number of evaluable subjects required, the estimated drop-out rate, and the target number of evaluable subjects for each cohort for the immunogenicity analysis. Clarification of the selection of the sample sizes for the planned descriptive analyses of safety and immunogenicity, and the sample size for evaluating safety for study vaccine dose escalation and subject age de-escalation, have also been added. Explanations for the sample size for Cohort 3B, the larger sample size for Cohorts 4 and 5, and new Tables 17 and 18 for estimating probability of achieving immunogenicity criterion in Cohorts 3B and 4/5 have also been added. The adverse event rate calculation for a sample size of 25 and 30 have been removed and calculation for a sample size of 11, 35 and 39 have been added to Table 19, the title of Table 19 has been updated, and a sentence referencing the calculations and probabilities in this table has been added in the “Anticipated Accrual Duration” sub-section. The previous Table 19 (“Sample Size and Adverse Event Rate for Cohorts 1 to 6, Based on Number of Evaluable Subjects”) has been removed, Table 20 has been updated to clarify that it presents the “True Adverse Event Rate” for a sample size of 35 in each group in Cohort 6, and Table 21 has been updated so it reflects 95% Confidence Intervals for a sample size of 35.
33. Section 8.511 has been updated to clarify that the blinded summaries of safety data will be prepared by the statistician with the Aeras designated CRO data management team.

34. Section 8.512 has been revised to clarify that the SMC may recommend, and not will recommend, to stop further enrollment and study vaccine administration if the listed events occur.

35. Section 8.52 has been revised to add the cohort escalation procedure for moving from Cohort 3B to Cohorts 4 and 5, and to update Table 22. The percentage chance of failing safety guidelines and not failing safety guidelines in paragraphs 7 and 8, and the true rates of ≥ Grade 3 (except fever) or life-threatening event at least possibly related to study vaccine, death or anaphylactic reaction and ≥ Grade 3 fever at least possibly related to study vaccine in paragraph 8, have also been updated.

36. Section 8.53, Cohort opening – Cohort 4, has been added.

37. Section 8.54 title has been revised and the presentation of the data that will be reviewed for the decision to open Cohort 6 and the dose for Cohort 6 in the first paragraph has also been reformatted and updated for clarity. The immune response rate criterion that must be achieved to proceed with Cohort 6 and clarification for the basis for dose selection have also been added; the section referenced for the post-vaccination positive response and how dose selection will be done if there is more than one AERAS-404 dose remaining after review of safety and immunogenicity data have been updated; and system organ class has been removed from the summaries that will be provided for safety analyses.

The section number for this section has also been changed with the addition of Section 8.53. The following sections have been revised to include this change: Section 3.0, Section 6.6, Section 6.7, Section 8.1, Section 8.223 and Section 8.512.

38. Section 8.61 has been revised to clarify that subjects who received at least one dose of study vaccine will be included in the primary safety analyses while subjects who have 7 days of post-dose safety data to each dose of study vaccine will be included in the secondary safety analyses. Clarifications of the safety analyses that will be done for the secondary objectives, the data that will be included in the safety analyses for subjects who withdraw due to safety considerations, and the evaluation of safety endpoints have also been added. Inclusion of adverse events relative to EPI vaccines in the summaries of safety has also been clarified.
39. Section 8.621 has been updated to clarify that only subjects who have data through 28 days after completing the third dose will be included in the per-protocol analysis.

40. Section 8.622 has been revised to change the laboratory that will perform the flow cytometry, ICS assay and update the name and location information for the laboratory that will perform the multiplex antibody binding assay in the 2nd paragraph and Table 23. Table 23 has also been revised to correct the sample type for the immune binding antibody assay to plasma, replace Cohort 3 with Cohorts 3A and 3B in the 6th column header, replace Cohorts 4, 5 & 6 with Cohorts 4 and 5 in the 7th column header, replace Cohort 7 with Cohort 6 in the last column header, and update the time points for the collection of the samples for flow cytometry, ICS and antibody titers assays to replace Study Day 280 with Study Day 182 for Cohorts 3A and 3B. The definition of positive responses and the analyses for the new secondary objective have also been added. The format of how post-vaccination responders will be presented has also been added.

41. Section 12.0 has been updated.

42. Appendix I-A, Schedule of Evaluations and Footnotes for Cohorts 1 and 2, has been revised to add that the Study Day 98 visit may be done after the subject receives the 9-month EPI vaccines in footnote 3, include clarification that subjects will be observed at the CRS for at least 60 minutes for the immediate post vaccination monitoring in footnote 12, and correct the table referenced in footnote 19 to Table 23.

43. Appendix I-B schedule of evaluations and footnotes have been revised to now apply to Cohorts 3A and 3B. The visit window for Study Day 42 has been changed to ± 7 days, Study Day 84 has been removed, and Study Days 154, 238, 329 and 420 has been changed to Study Days 98, 182, 273 and 364. A statement that Study Day 98 may be done after the subject receives the 9-month EPI vaccines has been added to footnote 3, a reference to Table 16 for the dose and Table 15 for the dosing schedule and additional guidelines for Cohorts 3A and 3B has been included in footnote 10, clarification that subjects will be observed at the CRS for at least 60 minutes for the immediate post vaccination monitoring has been made in footnote 12, and the table referenced in footnote 19 has been corrected to Table 23.

44. Appendix I-C, Schedule of Evaluations and Footnotes for Cohorts 4 and 5, has been revised to change the window for Study Days 14, 56 and 112 to ± 7 days in the schedule of evaluations, include a rule that study entry and the first study vaccination must occur at least 10 days before EPI vaccine doses at 14 weeks of age in footnote 2, add a statement that Study Day 98 may be
done after the subject receives that 9-month EPI vaccines to footnote 3, include a reference to Table 16 for the dose and Table 15 for the dosing schedule and additional guidelines for Cohorts 4 and 5 in footnote 11, clarify that EPI vaccines at 14 weeks of age must be given at least 10 days after the study vaccine dose at entry (1st bullet) and remove the instruction regarding where the EPI vaccines and study vaccine will be given (2nd bullet) in footnote 12, clarify that subjects will be observed at the CRS for at least 60 minutes for the immediate post vaccination monitoring in footnote 13, and correct the table referenced in footnote 20 to Table 23.

45. Appendix I-D, Schedule of Evaluations and Footnotes for Cohort 6, has been revised to change the window of Study Days 14, 42 and 224 to $+7$ days in the schedule of evaluations, include a reference to Table 16 for the dose and Table 15 for the dosing schedule and additional guidelines for Cohort 6 in footnote 11, clarify how the EPI vaccines and study vaccine should be injected in footnote 12, clarify that subjects will be observed at the CRS for at least 60 minutes for the immediate post vaccination monitoring in footnote 13, and correct the table referenced in footnote 20 to Table 23.

46. Appendix IV, Serious Adverse Event (SAE) Reporting Process, diagram has been updated for clarity of the reporting process with the use of EDC and remove the determination of preliminary reportability from the role of the Global Medical Monitor.

47. Appendix V, Suspected Unexpected Serious Adverse Reaction (SUSAR) Reporting Process, diagram has been updated for clarity of the reporting process, and specify the national regulatory authority for the participating sites and replace the EMA with the participating Study Investigators as part of the recipients of the Blinded CIOMS.

48. Appendix VI has been revised as follows:

- The protocol title in the first page has been corrected to be consistent with the title of the protocol document.

- “Why is this study being done” section has been revised to move the “measurement of the immune response your baby develops after receiving AERAS-404” before “finding the best dose schedule for AERAS-404” to be consistent with the list of secondary objectives for the study.

- “What does my baby have to do if he/she is in this study” section has been revised to add Study Groups 3A and 3B, remove Study Groups 3 and 4, renumber Study Groups 5, 6 and 7 as Study Groups 4, 5 and 6, include an explanation of the safety and immune response reviews that will be done for the decision to open Study Group 4, update the probability of
receiving study vaccine in Study Groups 4 and 5, include an explanation of the safety and immune response reviews that will be done for the decision to open Study Group 6, and clarify the basis for the dose for Study Group 6.

- “Entry visit (Study Day 0)” section has been revised to remove Table 1 and replace with a reference to the tables of tests for each study group in bullet 7, add a statement explaining to parent/caregiver that axillary temperature will be taken in bullet 9, and change Study Group 7 to Study Group 6 in bullets 9 and 10.

- “Study visits” section has been revised to clarify that the baby will be on study until he/she is about 18 months of age in bullet 1, and to add a statement explaining to parent/caregiver that axillary temperature will be taken and change Study Group 7 to Study Group 6 in bullet 5. The table of tests for Study Group 3 has also been revised for Cohorts 3A and 3B, and the amount of blood to be collected at Study Day 28 has been corrected to 6.5 mL. The items under the table have also been revised to update the following time points: routine pediatric vaccines given at 9 and 18 months of age to Study Days 98 and 364, HIV test to Study Day 182, the last time point for the special immunology tests to Study Day 182 and the interaction with other vaccines to Study Day 182. The title of the last two tables of tests has been updated so they are labeled for Study Groups 4 and 5 and Study Group 6, respectively. The first paragraph under the table for Study Groups 4 and 5 has been updated to remove the last sentence about the location where the routine pediatric vaccines will be injected. The first paragraph under the table for Study Group 6 has been updated to include the explanation of how the EPI vaccines will be injected for this group. The explanation of the total amount of blood that will be collected at the visits, in the fourth paragraph in bullet 2, has been clarified to be no more than 11 mL or about 2 teaspoons.

- “Other information” section has been updated to add a statement about shipment and/or storage of samples outside the country where they were collected.

- “How many participants will take part in this study” section has been revised to update the sample size to 229.

- “Why the study doctor may take my baby off this study early” has been revised to include “Ethics Committee (EC)” as one of the organizations that may stop the study and to have the definition of an IRB also applicable for an “EC”.

- “What happens if my baby is injured” section has been revised to clarify that the sponsor has taken out insurance in the event of a study-related injury to the participant and the guidelines for compensation.
“What do I do if I have questions or problems” has been revised to include a 24-hour telephone number that the participant’s parent or guardian can call for any questions about the study or research-related injury and to add the address for the South African Medicines Control Council (MCC) in case the doctor or Ethics Committee did not provide answers to the satisfaction of the participant’s parent or guardian.
PHASE I/II, SAFETY AND IMMUNOGENICITY STUDY OF A RECOMBINANT PROTEIN TUBERCULOSIS VACCINE (AERAS-404) IN BCG-PRIMED INFANTS

DESIGN: Phase I/II, randomized, double-blind, placebo-controlled, safety, immunogenicity and dose-range finding study of AERAS-404 Tuberculosis (TB) vaccine* administered intramuscularly in BCG-primed infants.

* The AERAS-404 vaccine is also known as H4:IC31.

SAMPLE SIZE: 229 subjects

POPULATION: Human Immunodeficiency Virus (HIV)-uninfected, HIV-unexposed, BCG-primed infants, ≥ 64 days to ≤ 196 days of age

ENROLLMENT: Subjects will be enrolled into the study and into a cohort in sequence. The first subjects will be enrolled in Cohort 1. Once enrollment in a Cohort has been completed and safety established, the next Cohort will open to enrollment.

Cohort 4 will open contingent on the safety data and the immunogenicity response in Cohort 3B. If there are no safety concerns identified, and an observed difference in immune response rate between AERAS-404 and placebo of at least 30% is achieved in Cohort 3B, enrollment into Cohort 4 and subsequent cohorts will be opened.

Cohort 6 will open contingent on the safety data from Cohorts 1 through 5 and immunogenicity data from Cohorts 4 and 5. There must be no safety concerns identified in Cohorts 1 through 5, and an observed difference of at least 50% in immune response rate between the AERAS-404 treatment group in Cohort 4 OR Cohort 5 and the pooled placebo group (Cohort 4 and Cohort 5 pooled placebo subjects) must be achieved, to proceed with Cohort 6. Clinical Research Sites will be notified of the dose selected for Cohort 6 via a memorandum.

Subjects in each cohort will be randomized to receive AERAS-404 or Placebo as shown in Table 1.
### Table 1. Treatment Regimen and Allocation by Cohort

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Day of Vaccination†§</th>
<th># of Doses</th>
<th>Treatment Regimen (AERAS-404 dose/Placebo)</th>
<th>Number of subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Study Day 0 (≥ 168 to ≤ 196 days of age)</td>
<td>1</td>
<td>5 μg H4/100 nmol IC31</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Placebo</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>Study Day 0 (≥ 168 to ≤ 196 days of age)</td>
<td>1</td>
<td>5 μg H4/500 nmol IC31</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Placebo</td>
<td>3</td>
</tr>
<tr>
<td>3A</td>
<td>Study Day 0 (≥ 168 to ≤ 189 days of age), Study Day 28</td>
<td>2</td>
<td>5 μg H4/500 nmol IC31</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Placebo</td>
<td>3</td>
</tr>
<tr>
<td>3B</td>
<td>Study Day 0 (≥ 168 to ≤ 189 days of age), Study Day 28</td>
<td>2</td>
<td>15 μg H4/500 nmol IC31</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Placebo</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>Study Day 0 (≥ 84 to ≤ 98 days of age), Study Day 42, Study Day 98</td>
<td>3</td>
<td>15 μg H4/500 nmol IC31</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Placebo</td>
<td>6</td>
</tr>
<tr>
<td>5</td>
<td>Study Day 0 (≥ 84 to ≤ 98 days of age), Study Day 42, Study Day 98</td>
<td>3</td>
<td>50 μg H4/500 nmol IC31</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Placebo</td>
<td>6</td>
</tr>
<tr>
<td>6</td>
<td>Study Day 0 (≥ 64 to ≤ 83 days of age), Study Day 28, Study Day 210</td>
<td>3</td>
<td>Pending*</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Placebo</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td></td>
<td></td>
<td>229</td>
</tr>
</tbody>
</table>

† Expanded Program on Immunization (EPI) vaccine schedule for South Africa: 6 weeks, 10 weeks, 14 weeks and 9 months of age. See Appendix II for the EPI vaccines and dose schedule.
‡ Refer to Appendices I-B to I-D for the subsequent study vaccine dosing windows in Cohorts 3A to 6.
§ Study vaccine doses for Cohort 6 will be administered coincident with EPI vaccine doses at 10 weeks, 14 weeks and 9 months of age.
* Dose for Cohort 6 will be one of the doses studied in Cohorts 4 and 5 (15 μg H4/500 nmol IC31 or 50 μg H4/500 nmol IC31, respectively) based on unblinded safety and immunogenicity data for Cohorts 4 and 5 (see Section 8.54).

**REGIMEN:** AERAS-404 or placebo

AERAS-404 is an investigational vaccine manufactured by Sanofi Pasteur (SP) and Statens Serum Institut (SSI). AERAS-404 has two components: the H4 antigen and the IC31 adjuvant. The reconstitution of the vaccine components, H4 antigen (manufactured at SP) and IC31 adjuvant (supplied by SSI), will take place at the CRS prior to injection.

**TREATMENT DURATION:**

Cohorts 1 and 2 will receive 1 dose of AERAS-404/placebo at study entry (Study Day 0).

**Cohorts 3A and 3B** will receive 2 doses of AERAS-404/placebo at study entry (Study Day 0) and Study Day 28.
Cohorts 4 and 5 will receive 3 doses of AERAS-404/placebo at study entry (Study Day 0), Study Day 42 and Study Day 98.

Cohort 6 will receive 3 doses of AERAS-404/placebo at study entry (Study Day 0), Study Day 28 and Study Day 210, concomitant with EPI vaccines.

STUDY DURATION:
Due to the different ages at entry, subjects will be on study from 364 to 476 days. All subjects will be on study until between 490 and 602 days of age, depending on the study cohort.

OBJECTIVES:
Primary:
To investigate the safety of AERAS-404 in HIV-uninfected, HIV-unexposed, BCG-primed infants.

Secondary:
1. To investigate the safety of a 3-dose AERAS-404 regimen in HIV-uninfected, HIV-unexposed, BCG-primed infants.


5. To explore interactions between AERAS-404 and EPI vaccines.
1.0 INTRODUCTION

1.1 Background

Tuberculosis (TB), a highly contagious infectious disease, is a significant cause of mortality in the developing world [1,2]. The World Health Organization (WHO) reports that over 250,000 children develop TB disease and 100,000 die from the disease each year [3]. The annual risk of TB for children in developing countries is reported to be as high as 2 to 3%, such that approximately 40% may be infected by 15 years of age [4]. In general, the younger the child with TB infection is, the greater the risk of progression to disease. In addition, TB-related mortality is highest in infants following primary infection [5].

The primary medical intervention currently used to prevent TB disease in infants and children is administration of Bacille Calmette-Guerin (BCG) vaccine. Although effective chemotherapy is available, inadequate diagnosis and treatment result in continued morbidity and death. BCG vaccine has been shown to decrease the incidence of disseminated or miliary TB disease in infants but unfortunately does not prevent TB infection or TB diseases such as intrathoracic TB, the most common form of pediatric TB.

For unknown reasons, a BCG revaccination or “booster” does not provide significant additional protection [6]. A more effective booster vaccine that enhances the efficacy of BCG during infancy is clearly needed. The AERAS-404 vaccine containing recombinant TB antigens is being developed as a booster vaccine following BCG to augment the immune response to Mycobacterium tuberculosis (Mtb) in BCG vaccinated infants. In conclusion, children who live in areas with a high TB burden are at high risk of exposure to Mtb very early in life. We postulate that administration of a novel protective vaccine in infants will provide protection early in life, as opposed to administration in older children, and may prevent TB infection and disease in this high risk fragile population.

1.11 Description of AERAS-404 Vaccine

AERAS-404 (HyVac4) is an investigational vaccine, originally developed by SSI (Copenhagen, Denmark) and currently in further development jointly by SSI, Sanofi Pasteur and Aeras. AERAS-404 has two active components: the H4 antigen and the IC31® adjuvant. The term HyVac4 refers to the H4 antigen and IC31 adjuvant in various dose combinations used by SSI in non-clinical development. The term AERAS-404 refers to the H4 antigen and IC31 adjuvant in various dose combinations used in clinical development sponsored by
Aeras (Rockville, Maryland USA). The initial formulation of AERAS-404 is a field-reconstituted vaccine with H4 antigen and IC31 adjuvant supplied in different vials. The components are dissolved in a sterile aqueous buffer containing tris-hydroxymethylaminomethane (Tris) and sodium chloride (NaCl).

**H4 Antigen**

The H4 antigen is a fusion protein created from two *Mtb* antigens: antigen 85B (Ag85B) and TB10.4. Ag85B is also referred to as α-antigen and is a 30-kDa mycolyl transferase protein [7,8]. Ag85B has been previously demonstrated in the guinea pig tuberculosis test system to induce a substantial protective immunity against aerosol challenge with the highly virulent Erdman strain of *Mtb* [7]. TB10.4 is one of three members of the very similar ESAT-6 group of proteins found in *Mtb* culture supernatants. TB10.4 induces the largest and broadest immune responses in T cells isolated from tuberculosis subjects compared to BCG-vaccinated donors and unvaccinated donors [9,10]. Immunization of mice with a fusion protein of TB10.4 and Ag85B induced a significant additive protective efficacy against subsequent aerosol challenge with *Mtb* [11-13,13]. The H4 antigen used in AERAS-404 has been evaluated in mice at 0.5, 5.0 and 15 mcg, in guinea pigs at 20 mcg and in rabbits at 150 mcg in combination with IC31 adjuvant.

**IC31 Adjuvant**

The IC31 adjuvant is a proprietary adjuvant of Intercell AG (Intercell, Vienna, Austria). IC31 is a combination of a leucine-rich peptide, named KLK, and a synthetic oligonucleotide, named ODN1a. KLK enhances the uptake of antigens into the antigen-presenting cell and increases the immune response to peptide antigens. ODN1a is a synthetic bacterial deoxyribonucleic acid (DNA) analogue that resembles a CpG pattern that will direct the adaptive immune response toward a T helper cell type-1 (Th-1) pattern with production of interferon-γ (IFN-γ) and interleukin-12 (IL-12). The amount of adjuvant given may affect the immune response. Mice have received 200 nmol KLK and 8 nmol ODN1a in 0.2 ml subcutaneously. The optimal molar ratio of KLK to ODN1a in mice is 25:1 [14]. This same molar ratio is used in all formulations of AERAS-404 tested in clinical studies. For simplicity and clarity hereafter, amounts and concentrations of IC31 adjuvant will be expressed as molar equivalents of KLK.
SSI has developed several related recombinant protein plus adjuvant candidates, beginning with Hybrid 1 (H1) [15]. At the onset of development efforts, IC31 was the most readily available adjuvant that provided induction of the immune profile thought to be most relevant for protection against *Mtb*. While other adjuvants are available, less clinical experience with those adjuvants has led to IC31 as the preferred adjuvant for clinical development.

1.12 Non-clinical Toxicology Studies

Multiple toxicology studies have been evaluated in a variety of animal models (Table 2) showing a good toxicity profile.

Table 2. Summary of Non-clinical toxicology studies performed with HyVac4.

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Vaccine/Adjuvant Administered</th>
<th>Dose</th>
<th>Species</th>
<th>Route of Administration</th>
<th>Study Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Repeat dose</td>
<td>HyVac4</td>
<td>H4:150mcg IC31:500nmol</td>
<td>NZW rabbits</td>
<td>IM</td>
<td>63014 (LAB Scantox)</td>
</tr>
<tr>
<td>Acute toxicity</td>
<td>IC31</td>
<td>3335nmol/kg body weight (bw)</td>
<td>CD1 mice</td>
<td>SC</td>
<td>17386/03 (LPT Hamburg)</td>
</tr>
<tr>
<td>Acute toxicity</td>
<td>IC31</td>
<td>3335nmol/kg bw</td>
<td>CD1 mice</td>
<td>IM</td>
<td>17387/03 (LPT Hamburg)</td>
</tr>
<tr>
<td>Repeat dose</td>
<td>IC31</td>
<td>up to 750nmol/kg bw</td>
<td>CD1 mice</td>
<td>SC</td>
<td>17388/03 (LPT Hamburg)</td>
</tr>
<tr>
<td>Repeat dose</td>
<td>IC31</td>
<td>up to 750nmol/kg bw</td>
<td>CD1 mice</td>
<td>IM</td>
<td>17389/03 (LPT Hamburg)</td>
</tr>
<tr>
<td>Local tolerance</td>
<td>IC31</td>
<td>500nmol</td>
<td>Himalayan rabbits</td>
<td>SC</td>
<td>17391/03 (LPT Hamburg)</td>
</tr>
<tr>
<td>Local tolerance</td>
<td>IC31</td>
<td>500nmol</td>
<td>Himalayan rabbits</td>
<td>IM</td>
<td>17392/03 (LPT Hamburg)</td>
</tr>
</tbody>
</table>

The repeated dose toxicity study (Study 63014, Repeated intramuscular [3 times] toxicity study in rabbits of Ag85-TB10.4) was performed to assess the acute and chronic toxicity of HyVac4 administered to rabbits with and without a BCG priming vaccination approximately 70 days before exposure to the first dose of HyVac4 (Table 2).
Three intramuscular doses of 150mcg/500 nmol HyVac4 were administered on Days 1, 15 and 29. Standard Good Laboratory Practice (GLP) measurements and observations included the following: mortality, clinical observations, food consumption, body temperature, ophthalmology, local tolerance (Days 1, 15 and 29), clinical pathology (after each dosing), necropsy and microscopic examination (3-6 and 13-14 days post final dose), and serology (Pre BCG and 1-3 days post each dose and prior to necropsy).

Three intramuscular (IM) injections of HyVac4 resulted in local reaction and minor fluctuations in white blood cell populations consistent with injection of a vaccine in both BCG pre-vaccinated and BCG non-vaccinated animals. Administration of HyVac4 was not associated with overt signs of toxicity and did not demonstrate mortality, adverse clinical signs, effects on body weight or food consumption, body temperature, ophthalmology, or clinical pathology.

Additional details of toxicology studies in mouse and rabbits are available in the product Investigator’s Brochure (IB).

1.13 Non-clinical Immunology and Animal Challenge Studies with HyVac4

The H4 antigen used in AERAS-404 has been evaluated in mice at 0.5, 5.0 and 15 mcg and in guinea pigs at 20 mcg in combination with IC31 adjuvant. HyVac4 is immunogenic in mice and induced a significant additive protective efficacy against subsequent aerosol challenge with \textit{Mtb} compared to BCG alone [11,13]. Administration of 20 mcg of H4 antigen after BCG prime has been shown to protect guinea pigs from aerosol challenge with \textit{Mtb} compared to BCG alone [12].

Additional details regarding the nonclinical experience with HyVac4 can be found in the current version of the IB.

1.14 Clinical Experience with AERAS-404

AERAS-404 has been studied in 198 adults who were enrolled in 4 Phase I studies as shown on the table below (Table 3). Three studies are completed. The C-013-404 database has been locked and data analyses are ongoing. Subjects in the three completed studies received a 2 dose regimen of the vaccine or placebo at the doses indicated in Table 3 with an interval of at least 8 weeks between doses.
Table 3. Studies of AERAS-404 performed to date

<table>
<thead>
<tr>
<th>Study Number</th>
<th>Population/Location</th>
<th>Treatment regimen H4(μg)/IC31(nmol)</th>
<th>Number of doses/ Dosing schedule</th>
<th>Number dosed with H4 (with or without IC31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-005-404</td>
<td>18-45y / Sweden</td>
<td>0,50,150 / 0,100,500</td>
<td>1 or 2 / SD 0, 56</td>
<td>56</td>
</tr>
<tr>
<td>C-006-404</td>
<td>18-45y / Finland</td>
<td>0,5,15,50,150 / 0,100,500</td>
<td>2 / SD 0, 56</td>
<td>50</td>
</tr>
<tr>
<td>C-011-404</td>
<td>18-45y / South Africa</td>
<td>0,5,15,50,150 / 0,500</td>
<td>2 / SD 0, 56</td>
<td>32</td>
</tr>
<tr>
<td>C-013-404</td>
<td>18-45y / Switzerland</td>
<td>0,50 / 0,500</td>
<td>3 / SD 0, 56, 231 or 2 / SD 56, 231</td>
<td>60</td>
</tr>
</tbody>
</table>

Protocol C-005-404 (A Phase I Randomized Placebo-Controlled, Double-Blind Study to Evaluate Safety and Immunogenicity of AERAS-404 Administered as Different Amounts of Antigen and Adjuvant Combinations in HIV-Negative BCG-Vaccinated Adults Without Evidence of Tuberculosis Infection) began in November 2007 to evaluate the safety and immunogenicity of AERAS-404 administered in a one- or two-dose series at H4 doses up to 150 mcg without adjuvant and up to 50 mcg with an IC31 dose of 100 nmol or 500 nmol. This study was conducted in 64 HIV-negative, BCG-vaccinated Swedish adults with a negative QuantiFERON-TB Gold In-Tube (QFT-GIT) test and a negative tuberculin skin test (TST). In this study, AERAS-404 was shown to induce post-vaccination hypersensitivity reactions (HSR) at the sites of recently administered TST (pre-study enrollment). These reactions are further discussed in the Summary of Overall Safety Profile of AERAS-404 section below. For this reason, the TST was removed as a study procedure from C-005-404 and subsequent protocols.

Protocol C-011-404 (A Phase I Randomized Placebo-Controlled, Double-Blind Study to Evaluate Safety and Immunogenicity of AERAS-404 When Administered as a Single Adjuvant Amount with Different Antigen Amounts in HIV-Negative BCG-Vaccinated Adults Without Evidence of Tuberculosis Infection) began in December 2008 to evaluate the safety and immunogenicity of AERAS-404 administered in a two-dose series at H4 doses up to 150 mcg with an IC31 dose of 500 nmol to 40 HIV-negative, BCG-vaccinated South African adults with a negative QFT-GIT test. All three studies have been completed; no related serious adverse events have been identified.

Protocol C-013-404 (A Phase I Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Safety and Immunogenicity of BCG and AERAS-404 Administered as a Prime-Boost Regimen to HIV-Negative, TB-Negative, BCG-Naïve Adults) began in December 2010 to evaluate the safety and immunogenicity of AERAS-404 (H4 50 mcg: IC31 500 nmol) or placebo in 70 healthy BCG-naive Swiss adults primed with BCG. Using EPI-vaccine simulated intervals, volunteers received AERAS-404 vaccine at 14 weeks and 9 months or 6 weeks, 14 weeks and 9 months after BCG vaccination. This study was also designed to assess potential safety interactions between BCG and AERAS-404 with specific attention to the BCG vaccination site. No vaccine-related serious adverse events have been identified.

Summary of the Overall Safety Profile of AERAS-404

The overall safety summary profile of AERAS-404 includes data from the four completed Phase I studies of AERAS-404 for which data analysis is complete: C-005-404, C-006-404, C-011-404 and C-013-404. These studies represent a combined population of 234 healthy, BCG-vaccinated, TB-negative, HIV-negative adults, of whom 198 received at least one dose of AERAS-404 and 36 received placebo.

Table 4 presents the number and percentage of subjects in all four Phase I studies of AERAS-404 experiencing adverse events related to AERAS-404 for events occurring in ≥ 5% of subjects.
### Table 4. Adverse Events in the AERAS-404 arm in Adults with Event Rate of ≥ 5% and Number of Subjects for Each Event

<table>
<thead>
<tr>
<th>Related Adverse Event&lt;sup&gt;a&lt;/sup&gt;</th>
<th>AERAS-404 (N=198)&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>MedDRA Preferred Term&lt;sup&gt;b&lt;/sup&gt;</td>
<td>n&lt;sup&gt;d&lt;/sup&gt; (%)</td>
</tr>
<tr>
<td>Injection site pain</td>
<td>109 (55.1)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>95 (48.0)</td>
</tr>
<tr>
<td>Headache</td>
<td>82 (41.4)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>76 (38.4)</td>
</tr>
<tr>
<td>Injection site swelling</td>
<td>39 (19.7)</td>
</tr>
<tr>
<td>Injection site erythema</td>
<td>37 (18.7)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>28 (14.1)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>25 (12.6)</td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td>18 (9.1)</td>
</tr>
<tr>
<td>Application site hypersensitivity&lt;sup&gt;e&lt;/sup&gt;</td>
<td>14 (7.1)</td>
</tr>
<tr>
<td>Chills</td>
<td>13 (6.6)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>12 (6.1)</td>
</tr>
<tr>
<td>Protein urine</td>
<td>12 (6.1)</td>
</tr>
<tr>
<td>Red blood cells urine</td>
<td>12 (6.1)</td>
</tr>
<tr>
<td>Haemoglobin decreased</td>
<td>11 (5.6)</td>
</tr>
<tr>
<td>Nausea</td>
<td>10 (5.1)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Adverse event data through the end of the study for C-005-404, C-006-404, C-011-404, and C-013-404; includes adverse events that occurred on or after the first dose of AERAS-404

<sup>b</sup> For the purpose of summarizing cumulative data across multiple studies, adverse events were coded using the same version of MedDRA, which may differ from the version of MedDRA that was used to code adverse events in an individual study.

<sup>c</sup> N is number of subjects who received at least 1 dose of AERAS-404 (HyVac4)

<sup>d</sup> n is number of subjects with at least 1 related adverse event for the preferred term in question

<sup>e</sup> Application site hypersensitivity refers to reactions at the tuberculin skin test application site

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**Hypersensitivity Reactions post TST**

The fourteen subjects with application site HSR noted above were observed in Study C-005-404 only. This study was conducted among remotely BCG-vaccinated adults (i.e. received BCG in childhood), and included administration of TST as a required screening procedure, with an exclusion criterion of a TST result of 10+ mm. A total of 26 subjects (19 in Study Group 1 and 7 in Study Group 2) received a screening TST before Study Day 0 vaccination. Of these 26 subjects, 21 received AERAS-404, of whom 14 (66.7%) experienced a post-vaccination TST site HSR, characterized by warmth, erythema and induration, with onset from several hours to two days after Study Day 0 vaccination, and duration from one to 28 days, typically resolving without treatment. Two of the 14 subjects also experienced pruritus at the TST site.
The study was temporarily paused and the study protocol was amended to remove the screening TST and to exclude subjects who had received a TST less than 90 days before Study Day 0, in order to eliminate this risk for further volunteers. One of the 26 subjects received a screening TST before the study pause, and was then enrolled after the study resumed, and received 150/0 (mcgH4/nmol IC31) on Study Day 0 (more than 90 days after the TST). This subject experienced no TST reaction.

**Local BCG Reactions**

Local BCG injection site reactions are well documented adverse events in subjects who receive BCG Vaccine. An induration appears at the site of the BCG injection which is followed by a local lesion (redness and swelling) that may ulcerate some weeks later. Aeras reviewed reports of BCG site redness, swelling, ulceration, and drainage in subjects who received BCG Vaccine followed by AERAS-404 or placebo in study C-013-404. All study participants received BCG Vaccine at Study Day -42, before receiving AERAS-404 or placebo at Study Days 0, 56, and 231.

BCG injection site reactions (pain, redness, swelling, warmth, ulceration, drainage) and axillary lymphadenopathy were assessed post-vaccination at Study Days -42, -14, 0, 7, 28, 56, 63, 84, 231, 238, and 259. Injection site findings at each visit time point after each vaccination are summarized in Figures 1 to 4.

Some of the local reactions of redness and swelling occurred immediately after BCG vaccination at Study Day -42. Redness was the most common local BCG injection site reaction with all 70 subjects (100%) experiencing redness after BCG vaccination. Redness persisted in the majority of the subjects throughout the study, with at least 60% of subjects in each group having redness at the final study assessment (Figure 1).
Swelling was the second most common local BCG injection site reaction. The number of subjects with swelling steadily declined through the course of the study with comparable proportions of subjects in each of the three treatment regimens having swelling at each time point (Figure 2). None of the redness or swelling at the BCG injection site met protocol-specified toxicity grading scale criteria for a severe (Grade 3 or higher) adverse event.
BCG injection site ulceration occurred after BCG vaccination in both placebo and AERAS-404 recipients. There was a decrease in the number of subjects with BCG site ulceration in all groups. There is no dose-related increase in frequency of BCG site ulceration after receiving AERAS-404 (Figure 3).

![Figure 3. Frequencies of Ulceration at BCG site of injection-Study C-013-404](image)

BCG site drainage also follows the same pattern as BCG site ulceration (Figure 4).

![Figure 4. Frequencies of Drainage at BCG site of injection-Study C-013-404](image)
The following conclusions were made:

- Local BCG Vaccine reactions are expected, according to the package insert.
- There was similar distribution of the BCG local reactions in subjects who received AERAS-404 and placebo.
- No dose response of BCG site reactions was noted in subjects who received 2 doses or 3 doses of AERAS-404.
- No evidence of acute worsening of BCG site reactions after AERAS-404 administrations.

A more complete description of post-vaccination TST site reactions and the most recently available information on all AERAS-404 clinical trials can be found in the most recent version of the IB for AERAS-404.

**Summary of Proteinuria from AERAS-404 Phase I Studies**

Proteinuria adverse events (including MedDRA Preferred Terms of proteinuria, protein urine and protein urine present) were reported in four Phase I studies of AERAS-404: C-005-404, C-006-404, C-011-404, and C-013-404. These studies represent a combined population of 234 healthy, BCG-vaccinated, TB-negative, HIV-negative adults, of whom 198 received at least one dose of AERAS-404 and 36 received placebo.

All reported AEs of protein in urine in the four studies were detected by visual interpretation of urine dipstick analyses performed according to the study protocols and graded according to the protocol-specified toxicity tables (Table 5).

<table>
<thead>
<tr>
<th>Urine</th>
<th>Mild (Grade 1)</th>
<th>Moderate (Grade 2)</th>
<th>Severe (Grade 3)</th>
<th>Potentially Life Threatening (Grade 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein</td>
<td>Trace</td>
<td>1+</td>
<td>2+</td>
<td>Hospitalization or dialysis</td>
</tr>
</tbody>
</table>

The number of subjects from each study who experienced protein in urine of any grade is summarized in Table 6. Of 198 subjects receiving at least one dose of AERAS-404, 44 (22.2%) experienced an AE of protein in urine. Among 36 subjects receiving placebo, 9 (25.0%) experienced protein in urine.
Table 6. Number (percentage) of subjects with AE of protein in urine of any grade from AERAS-404 Phase I Studies by study and treatment assignment

<table>
<thead>
<tr>
<th>Study #</th>
<th>Treatment Assignment</th>
<th>Placebo</th>
<th>AERAS-404</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1/8 (12.5%)</td>
<td>3/56 (5.4%)</td>
</tr>
<tr>
<td>C-005-404</td>
<td></td>
<td>2/10 (20.0%)</td>
<td>11/50 (22.0%)</td>
</tr>
<tr>
<td>C-006-404</td>
<td></td>
<td>3/8 (37.5%)</td>
<td>15/32 (46.9)</td>
</tr>
<tr>
<td>C-011-404</td>
<td></td>
<td>3/10 (30.0%)</td>
<td>15/60 (25.0%)</td>
</tr>
<tr>
<td>C-013-404*</td>
<td></td>
<td>9/36 (25.0%)</td>
<td>44/198 (22.2%)</td>
</tr>
</tbody>
</table>

*From preliminary data

The number of subjects from each study who experienced protein in urine of grade 2 or greater is summarized in Table 7. Of 198 subjects receiving at least one dose of AERAS-404, 18 (9.1%) experienced protein in urine of grade 2 or greater. Among 36 subjects receiving placebo, 3 (8.3%) experienced protein in urine of grade 2 or greater. The highest frequency of AEs of protein in urine was observed in Study C-011-404, conducted in South Africa, in which protein in urine at baseline was noted for 25% of subjects.

Table 7. Number (percentage) of subjects with protein in urine of grade 2 or greater from AERAS-404 Phase I Studies by study and treatment assignment

<table>
<thead>
<tr>
<th>Study #</th>
<th>Treatment Assignment</th>
<th>Placebo</th>
<th>AERAS-404</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0/8 (0%)</td>
<td>3/56 (5.4%)</td>
</tr>
<tr>
<td>C-005-404</td>
<td></td>
<td>2/10 (20.0%)</td>
<td>3/50 (6.0%)</td>
</tr>
<tr>
<td>C-006-404</td>
<td></td>
<td>1/8 (12.5%)</td>
<td>10/32 (31.3%)</td>
</tr>
<tr>
<td>C-011-404</td>
<td></td>
<td>0/10 (0%)</td>
<td>2/60 (3.3%)</td>
</tr>
<tr>
<td>C-013-404*</td>
<td></td>
<td>3/36 (8.3%)</td>
<td>18/198 (9.1%)</td>
</tr>
</tbody>
</table>

*From preliminary data

Among subjects receiving at least one dose of AERAS-404, 7 (3.5%) experienced AEs of protein in urine of grade 3 or greater. No subjects receiving placebo experienced AEs of protein in urine of grade 3 or higher. Of the 7 AEs of protein in urine of grade 3 or higher, 3 were judged by the study PIs to be related to study vaccine. All cases of protein in urine, including the seven with grade 3 severity, were asymptomatic and transient requiring no medical intervention. The proteinuria did not appear to be dose level related or adversely impacted with subsequent vaccination. No AEs of protein in urine had other associated clinical signs, symptoms, or lab tests indicative of renal disease.
The following conclusions were made:

- The frequencies of protein in the urine in the placebo and AERAS-404 recipients were comparable (25.0% vs. 22.2%, respectively), and there is no clear dose response to AERAS-404.

- 23 (10%) of study participants from AERAS-404 studies had protein in urine present at the baseline (2 subjects with grade 3, 5 subjects with grade 2 and 16 subjects with grade 1 protein in urine).

- The protein in urine was reported based on visual interpretation of the colorimetric tests (dip stick), which is sensitive but not specific. No further analyses were done to determine type of the protein (e.g., albumin, myoglobin).

- The cases of protein in urine were transitory, self-limited and improved without any treatment.

- There is no evidence of clinical manifestations of glomerulonephritis, nephrotic or nephritic syndromes, or cystitis in any of the subjects with protein in urine in the above-mentioned studies.

In summary, AERAS-404 was associated with a comparable frequency and severity of clinically non-significant proteinuria versus placebo. Although all Grade 3 events occurred in vaccine recipients, they were all self-limited and did not reoccur after repeat vaccination. The risk of urine contamination resulting in inaccurate data that will not contribute to safety assessment is very high in this age group. In addition the procedure will be burdensome to the participants. These concerns and the lack of toxicity in adult populations led the team to the decision not to do urinalysis in this study.

**Summary of Hematuria from AERAS-404 Phase I Studies**

Hematuria adverse events (including MedDRA Preferred Terms of hematuria and red blood cells urine) were reported in four Phase I studies of AERAS-404: C-005-404, C-006-404, C-011-404, and C-013-404. These studies represent a combined population of 234 healthy, BCG-vaccinated, TB-negative, HIV-negative adults, of whom 198 received at least one dose of AERAS-404 and 36 received placebo.

All reports AEs of red blood cells (RBCs) in urine in the four studies were detected by visual interpretation of urine dipstick analyses.
performed according to the study protocols and graded according to the protocol-specified toxicity tables (Table 8).

Table 8. Toxicity table for Urinalysis

<table>
<thead>
<tr>
<th>Urine</th>
<th>Mild (Grade 1)</th>
<th>Moderate (Grade 2)</th>
<th>Severe (Grade 3)</th>
<th>Potentially Life Threatening (Grade 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>Trace</td>
<td>1+</td>
<td>2+</td>
<td>Hospitalization or packed red blood cells (PRBC) transfusion</td>
</tr>
</tbody>
</table>

The number of subjects from each study who experienced RBCs in urine of any grade is summarized in Table 9. Of 198 subjects receiving at least one dose of AERAS-404, 48 (24.2%) experienced RBCs in their urine. Among 36 subjects receiving placebo, 8 (22.2%) experienced RBCs in urine.

Table 9. Number (percentage) of subjects with RBCs in urine of any grade from AERAS-404 Phase I Studies by study and treatment assignment

<table>
<thead>
<tr>
<th>Study #</th>
<th>Treatment Assignment</th>
<th>Placebo</th>
<th>AERAS-404</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-005-404</td>
<td>0/8 (0%)</td>
<td>11/56 (19.6%)</td>
<td></td>
</tr>
<tr>
<td>C-006-404</td>
<td>0/10 (0%)</td>
<td>0/50 (0%)</td>
<td></td>
</tr>
<tr>
<td>C-011-404</td>
<td>3/8 (37.5%)</td>
<td>16/32 (50.0%)</td>
<td></td>
</tr>
<tr>
<td>C-013-404*</td>
<td>5/10 (50.0%)</td>
<td>21/60 (35.0%)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>8/36 (22.2%)</td>
<td>48/198 (24.2%)</td>
<td></td>
</tr>
</tbody>
</table>

*From preliminary data

The number of subjects from each study who experienced RBCs in their urine of grade 3 or greater is summarized in Table 10. Of 198 subjects receiving any dose of AERAS-404, 10 (5.1%) experienced RBCs in urine of grade 3 or greater. Among 36 subjects receiving placebo, 3 (8.3%) experienced RBCs in their urine of grade 3 or greater.

Table 10. Number (percentage) of subjects with RBCs in urine of grade 3 or greater from AERAS-404 Phase I Studies by study and treatment assignment

<table>
<thead>
<tr>
<th>Study #</th>
<th>Treatment Assignment</th>
<th>Placebo</th>
<th>AERAS-404</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-005-404</td>
<td>0/8 (0%)</td>
<td>0/56 (0%)</td>
<td></td>
</tr>
<tr>
<td>C-006-404</td>
<td>0/10 (0%)</td>
<td>0/50 (0%)</td>
<td></td>
</tr>
<tr>
<td>C-011-404</td>
<td>0/8 (0%)</td>
<td>2/32 (6.3%)</td>
<td></td>
</tr>
<tr>
<td>C-013-404*</td>
<td>3/10 (30.0%)</td>
<td>8/60 (13.3%)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>3/36 (8.3%)</td>
<td>10/198 (5.1%)</td>
<td></td>
</tr>
</tbody>
</table>

*From preliminary data
All the 13 subjects experiencing RBCs in their urine of grade 3 or greater are female, of which, 12 subjects were menstruating at the time of assessments, and the AEs of RBCs in urine were judged to be unrelated to the study vaccine. No abnormalities for serum creatinine or blood urea nitrogen (BUN) or urine glucose were noted among these 13 female subjects. No AEs of RBCs in urine had other associated clinical signs and symptoms indicative of renal disease.

In summary, clinically non-significant RBC in urine occurred with comparable frequency and severity in vaccine and placebo recipients and could be explained by menses.

**Summary of Immunogenicity Profile of AERAS-404**

Immunogenicity of AERAS-404 has been assessed through measurement of IFN-γ release in enzyme-linked immunosorbent spot (ELISpot) assays and intracellular cytokine staining (ICS) of peripheral blood mononuclear cells (Table 11).

<table>
<thead>
<tr>
<th>Clinical Study</th>
<th>IFNγ ELISPOT</th>
<th>PBMC ICS</th>
<th>Whole Blood ICS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LUMC</td>
<td>CHUV</td>
<td>Aeras</td>
</tr>
<tr>
<td>C-005-404</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>C-006-404</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>C-011-404</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>C-013-404</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

Among participants in study C-006-404, increases in ELISpot responses were seen among all groups receiving AERAS-404, which peaked at Day 84. Responses were strongest among participants receiving IC31 at 500 nmol with stronger responses in groups receiving 15 and 50 mcg H4 as compared to the group receiving 5 mcg H4 (see Figure 5 below). ICS was performed at Aeras to evaluate cellular responses elicited by vaccination. In this study, PBMCs were stimulated with two peptide pools, each representing the entire amino acid sequence of the mycobacterial antigen Ag85B, and TB10.4. Ag85B-specific cluster of differentiation 4 (CD4+) T-cell responses were noted among all treatment groups, peaking at 2 or 4 weeks after the second dose of AERAS-404. The highest magnitude of responses was noted among the 5, 15, and 50 mcg H4 dose groups. CD4+ responses were predominantly of bifunctional or polyfunctional
profile. By comparison, TB10.4-specific CD4+ responses were lower in frequency and of lower magnitude compared to Ag85B-induced CD4 responses.

Figure 5. IFN-γ ELISpot Medium-Subtracted Responses for H4 (10 µg) - All Vaccinated Subjects

Samples from participants in C-011-404 were evaluated, following stimulation with Ag85B. Responses were noted in each dose group by 7-color Aeras ICS, with the highest responses being noted in the 15/500 H4:IC31 group and were predominantly against the Ag85B peptide pool. Both ICS and ELISpot were performed at CHUV, and demonstrated a strong correlation of responses between the two assay methods [16]. In the 9-color CHUV ICS assay, 76% of study participants were recorded to be responders (defined as total CD4+ T-cell responses to any antigen increased ≥ 2-fold over baseline and the frequency of cytokine-secreting T cells was ≥ 0.03%). No new T-cell responses were noted among participants receiving the highest level of antigen, 150 mcg H4. The mean frequencies of Mtb-specific CD4 T-cell responses at baseline in the 5/500, 15/500, and 50/500 H4:IC31 groups were 0.017, 0.021 and 0.026, respectively. Following the first dose of H4:IC31, the percentage of Mtb-specific CD4 T-cells increased from baseline to 0.209% (mean; P<0.0001) in the 5/500 H4:IC31 group, 0.132% (mean; P=0.0002) in the 15/500 H4:IC31 group and 0.151% (mean; P<0.0001) in the 50/500 H4:IC31 group.
Following the second dose of study vaccine, *Mtb*-specific CD4 T-cell responses did not significantly change in the 5/500 and 50/500 H4:IC31 groups, whereas a significant increase of *Mtb*-specific CD4 T-cell responses was observed in the 15/500 H4:IC31 group (mean 0.237%) at D84/182 as compared to both baseline (P<0.0001) and D14/28 (P=0.0364) (Figure 6).

**Figure 6.** Frequency of total (GM-CSF, IFN-γ, IL-2, MIP1-β, TNF-α) *Mtb*-specific CD4 T-cells at baseline, Study Days 14/28 and D84/182, Study C-011-404 (Gr1: 5/500, Gr2: 15/500, Gr3: 50/500, Gr4: 150/500; including placebo)

The functional profile of *Mtb*-specific T-cell responses using polychromatic flow cytometry was assessed at CHUV. The panel used included a viability marker, CD3, CD4, and CD8 antibodies to determine the different T-cell lineages and interleukin-2 (IL-2), IFN-γ, tumor necrosis factor (TNF)-α, GM-CSF and MIP1-β antibodies in order to assess the cytokine functional profile. The functional composition of the responses at baseline, D14/28 and D84/182 was compared in each group (Figure 7). A significant difference was observed in the functional composition of the responses at D14/28 and D84/182 versus baseline in the 5/500, 15/500, and 50/500 H4:IC31 groups. At baseline, the functional profile was homogeneous between the four study groups. Of note, a significant difference was observed between the 5/500 H4:IC31 and the other groups at D14/28 and D84/182. Indeed, the responses were more polyfunctional in the 5/500 H4:IC31 group (i.e. mostly composed of cells endowed with ≥ 4 functions). Furthermore, polyfunctional responses were also greater in magnitude in the 15/500 H4:IC31 group as compared to the 50/500 and 150/500 H4:IC31 groups at D84/182 (P<0.04). Overall, AERAS-404 boost increased the polyfunctionality of the *Mtb*-specific CD4 T-cell responses in the 5/500 H4:IC31 group after the first vaccination and in the 15/500 H4:IC31 group after the second vaccination.
**Figure 7.** Functional profile of *Mtb*-specific CD4 T-cell responses in the 4 groups at each time-point, Study C-011-404

In Study C-013-404, a dosage of 50/500 H4:IC31 was selected before 15/500 H4:IC31 was found to be the optimal dose for adults. The immunogenicity was assessed by ICS assay using frozen peripheral blood mononuclear cells (PBMCs) at Aeras. BCG vaccination failed to induce noticeable AERAS-404 antigen-specific CD4 and CD8 T cells as assessed at 42 days post-vaccination in all subjects. In contrast, as measured by the ICS assay, two or three doses of AERAS-404 were able to boost recent BCG priming and induced Ag85B antigen-specific CD4 T cells above that seen with placebo control (**Figure 8**). These responses were primarily polyfunctional (IFN-γ, IL-2 and TNF-α) and bi-functional (IL-2 and TNF-α) (**Figure 9**). In subjects receiving 3 doses of AERAS-404, the magnitude of Ag85B-specific CD4 T cell responses on Study Day 259 (28 days after the third dose) was comparable to that seen on Study Day 84 (28 days...
after the second dose), and slightly higher than that seen on Study Day 259 in subjects receiving 2 doses. The three dose regimen was seen to slightly outperform the two dose regimen as measured by the magnitude of Ag85B-specific CD4 T-cell responses (Figure 10).

Figure 8. Total CD4+ response to Antigen 85B, Study C-013-404

Figure 9. Functional CD4 T-cell response to Antigen 85B, Study C-013-404
Clinical Experience with IC31-adjuvanted Vaccines Related to AERAS-404

Hybrid-1 (H1) vaccine studies

The Hybrid-1 (H1) vaccine, a vaccine closely related to AERAS-404, consists of the HYB-01 fusion protein of the Mtb antigens Early Secretory Antigenic Target (ESAT)-6 and antigen 85B in combination with IC31, the same adjuvant used in AERAS-404. Three Phase I clinical trials have been completed by Statens Serum Institut: THYB-01, THYB-02, and THYB-03. These studies represent a combined population of 95 healthy, HIV (-) adults, of whom 80 received any dose of HYB-01. Table 12 shows the dose matrix of the 3 studies. All three studies were open label and non-randomized.

Table 12. Dose matrix of Studies THYB-01, THYB-02, and THYB-03

<table>
<thead>
<tr>
<th>Trial #</th>
<th>50 µg Antigen alone</th>
<th>50 µg Antigen 100 nmol IC31</th>
<th>50 µg Antigen 500 nmol IC31</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>THYB-01</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>36</td>
</tr>
<tr>
<td>THYB-02</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>THYB-03</td>
<td>12</td>
<td></td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Total</td>
<td>24</td>
<td>12</td>
<td>59</td>
<td>95</td>
</tr>
</tbody>
</table>
THYB-01

In a Phase I-A trial at LUMC, Protocol THYB-01 (A Safety and Immunogenicity Trial With an Adjuvanted Tuberculosis [TB] Subunit Vaccine), 36 mycobacterially-naïve male volunteers received at day 0 and 2 months the following dosage: group 1: 50 µg Ag, group 2: 50 µg Ag + 100 nmol IC31 and group 3: 50 µg Ag + 500 nmol IC31 [17]. The main safety findings are as follows:

No serious adverse events (SAEs) occurred.

A total of 18 (50%) of the subjects experienced any grade local vaccine related adverse reactions including transient itching, stiffness, bruising or soreness at the injection site on 1 day after vaccination. All local AEs were mild in severity and local symptoms had disappeared by 48 hours post administration of the vaccine. Mild systemic AEs of an influenza-like illness, fatigue, pyrexia, headache, nasopharyngitis and cough were observed in higher frequencies in the adjuvanted vaccination groups compared to the un-adjuvanted vaccination group.

Six (17%) subjects experienced moderate to severe AEs of increased creatine phosphokinase (CPK). The moderate to severe rises in CPK values were not temporally related to the administration of the vaccine, rather caused by excessive physical exercise like running a marathon or half-marathon. The rises in CPK values were transient as 5 out of 6 subjects had normal CPK values on subsequent and/or last follow up visits.

THYB-02

In a Phase I-B trial at LUMC, Protocol THYB-02 (A Safety and Immunogenicity Trial With an Adjuvanted Tuberculosis [TB] Subunit Vaccine in Purified Protein Derivative [PPD] Positive Volunteers), 10 BCG vaccinated volunteers and 10 Latent TB volunteers (Infection group) received at day 0 and 2 months 50 µg Ag + 500 nmol IC31 [18]. The main safety findings are as follows:

No SAEs were reported.

Seventeen subjects (85%) experienced local or regional adverse reactions including stiffness, soreness/pain, erythema, swelling and nodule at the injection site. Injection site movement impairment and injection site pain were the most frequently reported local reactions. Most local reactions were classified as grade I to II with one injection site pain classified as grade III. All subjects with local reaction
experienced full recovery within a maximum of 4 days. Systemic adverse events include fatigue, malaise and feeling cold were mild except for one individual where fatigue and malaise were classified as moderate (Table 13). Extensive follow-up of blood and urine parameters did not reveal abnormalities with respect to changes from baseline that could be related to the vaccine.

Table 13. Local and Systemic Adverse Events of Study THYB-02

<table>
<thead>
<tr>
<th>Vaccination</th>
<th>Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BCG vaccinated</td>
</tr>
<tr>
<td></td>
<td>I</td>
</tr>
<tr>
<td>Any local adverse event (n/N)</td>
<td>5/10a</td>
</tr>
<tr>
<td>Stiffness</td>
<td>2</td>
</tr>
<tr>
<td>Soreness and/or pain at injection site</td>
<td>4</td>
</tr>
<tr>
<td>Erythema and/or swelling</td>
<td>1</td>
</tr>
<tr>
<td>Nodule at injection site</td>
<td>-</td>
</tr>
<tr>
<td>Any systemic adverse event (n/N)</td>
<td>2/10a</td>
</tr>
<tr>
<td>Fever</td>
<td>1</td>
</tr>
<tr>
<td>Tired and/or malaise</td>
<td>2</td>
</tr>
</tbody>
</table>

a Number of subjects affected in each group/number of subjects in group.

b Reactions in same individual, temperature once elevated.

**THYB-03**

In a Phase I-C trial, Protocol THYB-03 (A Safety and Immunogenicity Trial With an Adjuvanted TB Subunit Vaccine [Ag85B-ESAT-6 + IC31]) at Armauer Hansen Research Institut in Addis Ababa, Ethiopia, 12 TB naïve volunteers (group 1) received at day 0 and 2 months 50 µg Ag, 12 TB naïve volunteers (group 2), 3 BCG vaccinated volunteers (group 3) and 12 latent TB volunteers (group 4) received at day 0 and 2 months 50 µg Ag + 500 nmol IC31 [19].

Preliminary safety analysis of the THYB-03 found 305 AEs reported in 39 volunteers. One hundred fifty mild systemic AEs were judged by the principal investigator (PI) to be possibly, probably or definitely vaccine related. There were two Serious Adverse Events in otherwise clinically stable participants which resolved in less than 72 hours’ time:

1. Participant Number 29 had a possible vaccine related serious adverse advent (Aspartate Amino Transferase [AST]/Amino Alanine Transferase [ALT] increase, with fever, chills,
generalized body weakness and erythema at previous purified protein derivative (PPD) injection site 12 hours post vaccination).

2. Participant Number 39 had a possible vaccine related serious adverse event (increase in CPK to 10545, 24 hours post 1st vaccination and 11025 IU/L 48 hours post 1st vaccination). This subject participated in weight lifting, which might explain the increase in CPK.

The two participants were withdrawn. The following were also withdrawn because of safety concerns:

1. Participant Number 5 was withdrawn because of progressively increasing eosinophilia (possible vaccine related mild adverse event). The participant was clinically stable.

2. Participant Number 6 was withdrawn because of erythema/itching at his previous PPD injection site (probable vaccine related mild adverse event). The participant was clinically stable.

3. Participant Number 30 was withdrawn since he was enrolled in error. He was included with an eosinophil count of 14% which is more than the 0 to 7% stated in the protocol.

Based on the experience obtained from the three Phase I clinical trials the following local injection site and systemic reactions may be expected in this study:

- Stiffness, bruising and pain at the site of injection
- Pharyngitis and nasopharyngitis
- Influenza like symptoms, fatigue, fever and cough
- Headache

IC31 in a Flu Vaccine Study

IC31 was used in a single-center, double-blind, randomized, controlled, parallel-group Phase I Flu Subunit Vaccine study. The study enrolled 72 healthy male and female adult subjects of ≥ 18 to ≤ 50 years of age (females without childbearing potential or with negative pregnancy test). The subjects were randomized into 3 study groups. All groups received seasonal trivalent influenza vaccine. Study group 1 did not receive IC31, study group 2 received low dose IC31 (0.1 mL IC31, 100 nmol KLK, 4 nmol ODN1a) and study group 3 received high dose IC31 (0.5mL IC31, 500 nmol KLK, 20 nmol
ODN1a). There was no difference in safety or adverse events across the 3 treatment groups. Forty subjects (55%) experienced an adverse event (AE), of which 12 were classified as severe adverse events. There were no serious adverse events (SAE) and there were no deaths.

In summary, analysis of the data shows a favorable safety and local tolerability profile for IC31 up to 500 nmol.

1.16 Risk of a child acquiring HIV infection during the trial

The HIV incidence rate among women in South Africa is estimated at between 3 and 5% depending on the region and the age group. If the child is breastfeeding and the mother does not take any prophylaxis because she is not aware of her status the risk of HIV transmission to the baby is 14% in the first 6 weeks of life and increases to 20% by 6 months of life [20]. Children to be enrolled in this study must be born to a mother who is HIV negative. Given the possibility of continuous exposure and to further reduce the risk of enrolling an HIV exposed or infected child we will require an HIV Enzyme-linked Immunosorbent Assay (ELISA) and a DNA polymerase chain reaction (PCR) for all children at screening. We will further monitor infants at 12 months of age with an HIV ELISA.

1.2 Rationale

AERAS-404 is currently intended to be deployed as a booster vaccine following BCG, to augment immune response to \textit{Mtb} during infancy. It may be more protective than BCG alone if given in infancy following BCG immunization at birth. This protection is highly desirable in children living in areas with high TB disease burden.

The proposed safety and immunogenicity study is the first study in which the AERAS-404 vaccine will be administered to infants. In addition, this study will evaluate the appropriate dose and schedule in infants aged 10 weeks to 9 months. The doses of antigen to be used in this study are the same as those evaluated in adults. A lower dose of the adjuvant (100 nmol) will be evaluated in the first study Cohort receiving vaccine prior to evaluation of the higher dose of the adjuvant used in adults (500 nmol) because this is the first time this vaccine is being studied in infants.

A single dose of MVA85A/AERAS-485, a modified Vaccinia Ankara virus expressing the immunodominant \textit{M.tuberculosis} antigen 85A, designed to boost BCG-induced immune responses, while well tolerated, did not show any protection against TB disease or infection in young infants [21].
Immunogenicity data on this vaccine in this age group was ten times lower than that seen in adults [21]. Recent data on AERAS-402, a replication deficient adenovirus vaccine expressing Ag85A, Ag85B, and TB10.4, also found low immune response in infants administered 2 doses of vaccine [22]. Though it is unknown what level of immune response or which specific characteristics of the immune response is needed to protect against TB, data from these studies nevertheless suggests TB vaccines in infants may be less immunogenic than in adults. In light of the new data, P1113/C-015-404 has been amended to include early assessments of immune responses to decide whether enrollment will proceed with the next cohort/s (Section 3.0). This stepwise approach increases protection of children by minimizing the number of volunteers exposed to the experimental vaccine in the event the immune response is low.

1.21 Rationale for vaccine dosage and frequency

Human data indicate that higher concentrations of IC31 (500 nmol) were more immunogenic than lower concentrations (100 nmol) when administered at all levels of H4 antigen (5, 15, 50 μg) (Aeras study protocols: C-005-404 and C-006-404). There has been no appreciable difference in toxicity profile between high and lower concentrations of IC31 in human studies. However, as this adjuvant has not been tested in infants, the initial cohort in this study will receive a low concentration of IC31. If there are no safety concerns all subsequent Cohorts will receive the higher concentration of IC31 (500 nmol).

Both animal (data available in the IB) and human studies also showed that H4 antigen at high dose (150 μg in the human studies) was less immunogenic and polyfunctional than lower doses. Furthermore in adults the 15 μg dose significantly boosted polyfunctional CD4 T cell response following the second dose compared to the 5 μg dose (Study C-011-404). Overall the 15 μg H4/500 nmol IC31 and 50 μg H4/500 nmol IC331 doses outperformed the 5 μg H4/500 nmol IC31 dose. In this study, antigen doses to be tested will include 5 μg (Cohorts 1, 2 and 3A), 15 μg (Cohorts 3B and 4), and 50 μg (Cohort 5). Furthermore, recognizing that infants often need more antigen to develop an immune response, this study will test a 3-dose regimen using the vaccine doses that overall were associated with the most robust immune response in adults.

Regarding number of doses, data from C-013-404 indicates that the three dose regimen resulted in higher responses than the two dose regimen, as measured by the magnitude of Ag85B-specific CD 4 T cell responses.
In summary, based on the preclinical animal data, the safety and immune profile of H4 in adults, and the uncertainties of predicting likely immune response in infants, this study will focus on the immunogenicity of three doses of H4 at 15 μg and 50 μg combined with IC31 500 nmol (Cohorts 4 and 5) and safety in an escalating dose and de-escalating age approach.

A protocol amendment will be required if the IC31 500 nmol dose is not tolerated and dose de-escalation will be needed.

1.22 Rationale for choosing the age time points in Cohorts 4 and 5 for assessing safety of 3-dose vaccine schedule

Administration of TB vaccine as early as 10 weeks of age may have the advantage of conferring earlier protection against TB for those living in a high endemic area for TB whose risk of TB acquisition is greatest. Cohorts 1 and 2 will receive the AERAS-404 vaccine at ≥168 to ≤196 days of age (Study Day 0), a time point with an interval of 12 weeks after EPI vaccinations. After safety is established, the vaccine will be administered to younger infants and closer to EPI vaccinations.

Co-administration with EPI vaccines in infants is crucial in areas where TB is endemic as it maximizes vaccine administration at time points where children are already receiving medical care, and possibly provides early needed protection against TB; hence, this study will explore potential interaction between AERAS-404 and the recommended EPI vaccines for infants at 10 weeks and 14 weeks and 9 months of age (ages for EPI vaccination) in Cohort 6. Safety of a single dose regimen will be first assessed at ≥168 to ≤196 days of age (Study Day 0) as it does not coincide with EPI vaccines administration, in order to assess vaccine safety without potential EPI vaccine interactions (Cohorts 1 and 2). Cohort 3A will provide crucial safety and immunogenicity data on a 2-dose, 4-week interval regimen with doses administered at ≥168 to ≤189 days of age (Study Day 0) and Study Day 28, while Cohort 3B will provide safety and immunogenicity data on a 2-dose, 4-week interval regimen with a higher AERAS-404 dose and with doses administered at ≥168 to ≤189 days of age (Study Day 0) and Study Day 28. Continued enrollment in the succeeding cohorts will depend on the safety and immunogenicity data meeting the criteria for opening Cohort 4 defined in Section 8.53. In Cohorts 4 and 5, a 3-dose regimen will be evaluated. In these cohorts, the study vaccine will be administered 2
to 4 weeks following the scheduled EPI vaccinations at ≥ 84 to ≤ 98 days of age (Study Day 0) and Study Day 42 (EPI is given at 10 and 14 weeks of age), and a third dose at Study Day 98 (prior to receipt of the 9 month EPI vaccine). If the data from the safety and immunogenicity reviews are deemed acceptable as defined in Sections 8.222 and 8.54, the study vaccine will then be co-administered with the EPI vaccines at ≥ 64 to ≤ 83 days of age (Study Day 0), Study Day 28 and Study Day 210 (Cohort 6).

1.23 Rationale for immunologic assays

The lack of understanding of host defense mechanism against TB infection and the lack of immune correlates of protection to TB vaccines are hampering the development of novel TB vaccines. There is an urgent need for clear immunological markers to predict and evaluate the immunogenicity and efficacy of vaccines and to optimize vaccine regimens. In that regard, the following immunologic assays are proposed:

Flow Cytometry, Intracellular Cytokine Staining (ICS) Assay

Immunity to TB depends critically on the generation of effective CD4 (+) T-cell responses. Sterile immunity has not been achieved through vaccination, although early T-cell responses are effective in controlling steady-state infection in the lungs. It is generally assumed that CD4 T cells making IFN-γ are required for protective immunity; however, this assumption is based largely on correlative data. The termination of bacterial growth correlates with detection of IFN-γ-producing CD4 T cells [23-26]. In addition, loss of CD4 T cells has been shown to result in increased tuberculosis-related mortality [27]. Various CD4 T cell effector subtypes have been identified, including those making only IL-2 or IFN-γ, as well as multifunctional cells expressing IL-2, IFN-γ, and TNF-α. The presence of these multifunctional cells has been associated with protection against some pathogens [28]. Furthermore, multifunctional cells have been found at high frequency in tuberculosis patients [29] as well as in people in high incidence areas [30] and in vaccinated infants [31]. More recently, other subsets of functional T cells, such as those producing IL-17 and IL-22, have been identified. These cells have been detected in both mice and humans exposed to tuberculosis [32]. The protective role of these subsets in tuberculosis is not yet known, however, they have been more definitively linked to protection against other pathogens including *Klebsiella pneumoniae* [33] and *Candida albicans* [34]. The flow cytometry panel proposed for this study will assess many of the markers implicated in CD4 mediated protection against
TB including IFN-γ, IL-2, TNF-α, IL-17 and IL-22. In addition this assay will provide the data needed to evaluate the induction of multifunctional cells by the study product. While a role for CD8+ T cells in protection against TB has not been clearly defined, the flow cytometric assay to be employed for this study will allow us to assess the induction of vaccine specific CD8+ T cells.

**Multiplex Binding Antibody Assay**

It is generally accepted that cell-mediated immunity (CMI) plays a pivotal role in controlling *Mtb* infection, whereas antibody responses are believed to have a limited role. However, a number of recent findings have spurred renewed interest in the potential role of the humoral response in protection against *Mtb*. Studies in Mexican-Amerindian ethnic groups indicated that IgG anti-Ag85 antibodies have beneficial effects in the clinical outcome of pulmonary tuberculosis [35]. Furthermore, recent studies demonstrate that passive serum therapy with human polyspecific IgG protects mice from *Mtb* infection [36]. Recent findings have also demonstrated that intranasal inoculation of human IgA specific to the mycobacterial α-crystallin antigen significantly reduces the infection with the H37Rv *Mtb* strain in CD89 transgenic mice [37]. Finally, it is well established that the profile of cytokine expression by T cells contributes to Ig class switching and, therefore, knowledge of Ig isotypes and subclasses can provide valuable information on the underlying characteristics of the immune response. We, therefore, propose to assess the level and character of binding antibodies induced by the vaccine products used in this study. A multiplex platform will be used that allows the simultaneous assessment of multiple Ig isotypes to multiple antigens.

**Exploratory Ribonucleic Acid (RNA) Analysis**

The innate immune system is at the interface between the vaccine antigen and the host’s adaptive immune response. Studying molecular signatures that are induced rapidly after vaccination will identify causal elements of the adaptive immune response, which may be ultimately used as biomarkers or surrogate endpoints in predicting protective immune responses. Such prediction may enable rapid evaluation of the efficacy or immunogenicity of untested vaccines in the general population or the identification of unresponsive individuals to vaccination. Furthermore, the predictive signatures may uncover new correlates of protection and further decipher the biological mechanisms by which such molecular signatures modulate vaccine-induced immunity and protection.
Biomarkers can be determined at different levels, for example, at the cellular-, protein-, or transcript level. Clinical studies using human transcriptome analysis have been performed in the context of systems biology and have tried to tie the signature immediately following vaccination (the “innate” immune profile) to either a known adaptive immunologic profile (e.g., T-cell subsets producing specific cytokines) or to a protective immune function or to protection itself. Gene signatures in humans have been recently identified to predict immune responses to yellow fever vaccine. Querec et al. identified early gene signatures in humans vaccinated with yellow fever vaccine YF-17D that predicted adaptive CD8+ T-cell immune responses with up to 90% accuracy and neutralizing antibody responses with up to 100% accuracy [38]. These data highlight the utility of a systems biology approach in predicting vaccine efficacy. A later mRNA signature may also be correlated with protection, and may be consistent with an adaptive T-cell response.

A secondary objective of this study is to evaluate the mRNA expression from whole blood samples. While some have observed the most gene expression changes 1 day post-vaccination for non-replicating viral vectors, this study will be evaluating mRNA expression 3-days after the third study vaccine dose in Cohorts 4 to 6 in order to identify early gene signatures that can inform on immune responses.

2.0 STUDY OBJECTIVES

2.1 Primary Objective

To investigate the safety of AERAS-404 in HIV-uninfected, HIV-unexposed, BCG-primed infants.

2.2 Secondary Objectives

2.21 To investigate the safety of a 3-dose AERAS-404 regimen in HIV-uninfected, HIV-unexposed, BCG-primed infants.

2.22 **To assess the immunogenicity of a 2-dose AERAS-404 regimen in HIV-uninfected, HIV-unexposed, BCG-primed infants.**

2.23 To assess the immunogenicity of 3-dose AERAS-404 regimen in HIV-uninfected, HIV-unexposed, BCG-primed infants.

2.25 To explore interactions between AERAS-404 and EPI vaccines.

3.0 STUDY DESIGN

This is a Phase I/II, randomized, double-blind, placebo-controlled, safety, immunogenicity and dose-range finding study in HIV-uninfected, HIV-unexposed, BCG-primed infants. The study vaccine AERAS-404 or placebo will be administered without concomitant EPI vaccines (Cohorts 1 to 5, N = 159 subjects) and with concomitant EPI vaccines (Cohort 6, N = 70 subjects, see Table 1). Study vaccine or placebo will be administered as a single dose (injection) at Study Day 0 (≥ 168 to ≤ 196 days of age, Cohorts 1 and 2), a 2-dose schedule at Study Day 0 (≥ 168 to ≤ 189 days of age) and Study Day 28 (Cohorts 3A and 3B) or a 3-dose schedule at Study Day 0 (≥ 84 to ≤ 98 days of age), Study Day 42 and Study Day 98 (Cohorts 4 and 5).

Refer to Table 1 in the Schema for the treatment regimen and allocation by study cohort. A cohort will enroll once safety in the previous cohort has been established (see Cohort Management, Section 6.2). A protocol amendment will be required if the IC31 500 nmol dose is not tolerated and dose de-escalation will be needed.

A new cohort, 3B, has been added to Version 2.0 to test both safety and immunogenicity. An observed difference of at least 30% in immune response rate in the AERAS-404 treatment group compared to the immune response rate in the placebo group is a condition for opening the next cohort for enrollment. Cohort 3B PBMC samples obtained 14 days (+ 7 days) following the second vaccination will be assayed by intracellular cytokine staining (ICS). The immune response to vaccine will be determined using validated, statistical positivity criteria comparing responses in peptide stimulated wells to unstimulated wells. A response may be positive for Ag85B and/or TB10.4, expressing at least one functional marker by either CD4 or CD8 T cells such as IL-2, IFNγ or TNFα. Cohort 4 will open contingent on the safety data, the immunogenicity response in Cohort 3B, and approval to proceed from the Collaboration Oversight Group (COG; see Section 8.54 for the description of the COG). If there are no safety concerns identified, and a difference in immune response rates between AERAS-404 and placebo of at least 30% is achieved in Cohort 3B, enrollment into Cohort 4 and subsequent cohorts will be opened. If the difference in immunogenicity response rate is not achieved, enrollment will be terminated.
If enrollment proceeds to Cohorts 4 and 5, PBMC samples obtained 14 days (+7 days) following the third vaccination will be assayed by intracellular cytokine staining (ICS). The immune response to the vaccine will be determined using statistical positivity criteria comparing responses in peptide stimulated wells to unstimulated wells. A response may be positive for Ag85B and/or TB10.4, defined as expression of two or more functional markers such as IL-2, IFNγ or TNFα by CD4 T cells. Cohort 6 will open contingent on the immune response in Cohort 4 or Cohort 5 after the third dose of AERAS-404. An acceptable safety profile and an observed difference of at least 50% in immune response rate between the AERAS-404 treatment group in Cohort 4 or Cohort 5 and pooled (Cohort 4 and Cohort 5) placebo group must be achieved to proceed with Cohort 6.

Specific validated functional markers, with established cut-off, used in determining response rate in Cohorts 3B, 4 and 5 will be prespecified and agreed upon by the COG prior to analysis. Prior to the review of the immunologic data, the COG will have the opportunity to assess if the criteria used to determine the response rate are still valid or may need modification based on new or relevant information from ongoing studies. This will give the COG the flexibility to consider the best information available at the time the immunologic data are reviewed.

Subjects in Cohort 6 will receive the study vaccine or placebo at Study Day 0 (≥ 64 to ≤ 83 days of age), Study Day 28 (≥ 91 to ≤ 105 days of age) and Study Day 210 (≥ 273 to ≤ 287 days of age). The vaccine dose selected for Cohort 6 will be based on unblinded safety (criteria specified in Section 8.52) and immunogenicity data from Cohorts 4 and 5 through Study Day 126. This data will be evaluated by the protocol team and the IMPAACT Study Monitoring Committee (SMC; see Section 8.512) and will be reviewed and endorsed by the COG (see Section 8.54 for the description of the COG). Cohort 6 will receive the vaccine or placebo concurrent with the EPI schedule. Clinical Research Sites will be notified of the dose selected for Cohort 6 via a memorandum.

Refer to Section 5.0 for guidance on EPI vaccine administration and contingency plan in the event of in-country EPI program shortage.

Due to the different ages at entry, subjects will be on study from 364 to 476 days. All subjects will be followed on study until between 490 and 602 days of age, depending on the study cohort.

Sites should refer to Appendices I-A to I-D for a complete description of clinical and laboratory evaluations to be performed.
4.0 SELECTION AND ENROLLMENT OF SUBJECTS

4.1 Inclusion Criteria

4.1.11 Age at time of entry:

4.1.11.1 Cohorts 1 to 5

- **Cohorts 1 and 2:** ≥ 168 to ≤ 196 days
- **Cohorts 3A and 3B:** ≥ 168 to ≤ 189 days
- **Cohorts 4 and 5:** ≥ 84 to ≤ 98 days (≥ 2 weeks after receipt of EPI vaccine doses at 10 weeks of age)

4.1.12 Cohort 6

- coincident with EPI vaccine doses at 10 weeks of age (≥ 64 to ≤ 83 days of age)

4.1.2 Source documentation of birth weight ≥ 2.5 kg.

4.1.3 Documented BCG vaccination within 72 hours of birth.

4.1.4 Documented receipt of all age-appropriate EPI vaccines, except Rotavirus, for Cohorts 4 to 6 (see Appendix II).

4.1.5 Source documentation of a negative HIV status in the mother, from any time during pregnancy with this child through randomization.

4.1.6 Documentation of infant HIV negative exposure or infection status with negative HIV ELISA and HIV DNA PCR tests.

4.1.7 Parent or legal guardian able and willing to provide signed informed consent.

4.1.8 Participant/parent/legal guardian able to attend all scheduled visits and to comply with all trial procedures.

4.2 Exclusion Criteria

4.2.1 History of TB exposure in household or non-household contact.

4.2.2 History/Evidence of TB disease or infection.

4.2.3 Quantiferon positive.
4.24 Prior TST test.

4.25 Any one of Anemia, Neutropenia, Thrombocytopenia, SGPT (ALT), SGOT (AST) or Creatinine \( \geq \) Grade 2 (see Appendix III).

4.26 Receipt of a live vaccine within 28 days prior to randomization.

4.27 Receipt or planned receipt of any investigational vaccine.

4.28 Known or suspected congenital immunodeficiency.

4.29 Receipt of immunosuppressive therapy or long-term systemic corticosteroid therapy (prednisone or equivalent for more than 2 consecutive weeks within the past 3 months).

4.210 Known or suspected autoimmune disease

4.211 Hypersensitivity to any of the vaccine components, or history of a life-threatening reaction to a vaccine containing any of the same substances as the vaccine used in the trial.

4.212 Participation in another clinical trial for an investigational product (IP).

4.213 Bleeding disorder or receipt of anticoagulants in the 3 weeks preceding randomization, contraindicating IM vaccination.

4.214 Chronic illness that, in the opinion of the investigator, is at a stage where it might interfere with trial conduct or completion.

4.215 Febrile illness (temperature \( \geq 100.4^\circ\text{F} \[\geq 38.0^\circ\text{C}\]) within 24 hours prior to randomization.

   *Note: A subject may enroll after recovery from febrile illness if the subject is still within the age window.*

4.216 Systemic antibiotic use within 48 hours prior to randomization.

4.3 **Concomitant Medication Guidelines**

The collection of information on concomitant medications used by subjects following vaccination will coincide with the collection period of adverse events. The collection period for concomitant medications associated with treatment of adverse events will be 4 weeks following each vaccination. The collection period of concomitant medications associated with the treatment of serious adverse events (SAE) will be from study entry up to the last study
visit. Any immunosuppressive medications, including corticosteroids, taken from study entry to the last study visit must be recorded.

Concomitant medication includes prescription and non-prescription drugs or other treatments and any vaccines other than the study vaccines. The names of medication, treatment start and stop dates (or ‘ongoing’ if the medication is still ongoing the last study visit), route of administration and indication must be recorded on the Concomitant Medications case report form (CRF). The indication recorded on the Concomitant Medications CRF must correspond to a medical term/diagnosis recorded on the adverse event (AE) CRF unless the indication is not an AE or a SAE, or to a pre-existing condition noted in the subject’s medical history, or as prophylaxis, e.g., dietary supplement.

4.31 Precautionary Medications

Systemic use of steroids of ≥ 1 mg/kg/day within 3 days prior to study vaccine administration is not allowed.

**Use of traditional topical medicines at the site of injection within 7 days prior to or after study vaccine administration is not recommended.**

TST is discouraged within 8 weeks prior to study vaccine administration. If TST is done within this time period, study vaccine administration will be discontinued.

Please contact the protocol team at impaact.teamp1113@fstrf.org if treatment with systemic steroids is necessary for clinical care.

4.32 Disallowed Medications

There are no disallowed medications in this study.

4.4 Enrollment Procedures

Prior to implementation of this study, each CRS must have the protocol document and the consent form approved by the local Institutional Review Board (IRB)/Ethics Committee (EC). A Site Implementation Plan (SIP) will be required from each CRS participating in the study. The plan must be submitted to the Protocol Team for review and approval before protocol registration can occur.

Each CRS must submit to Aeras all Essential Documents per the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines
and receive notification from Aeras of approval to begin enrollment before subjects can be enrolled in this study. Modifications made by the investigator to an informed consent form template that has been provided to the investigator by Aeras will be reviewed and approved by Aeras prior to being submitted to the IRB/EC.

Any documents or forms to be provided to the parent/legal guardian of the subject (e.g., information cards, form letters from the investigator), and all forms of study advertising (flyers, brochures, print advertisements, radio or television scripts, etc.) must be approved by Aeras prior to the CRS submitting them to the IRB/EC. Approval from the IRB/EC must be obtained prior to providing the documents or forms to the parent or legal guardian of the subject.

Written informed consent for study participation must be obtained before any study related procedures are performed. Subjects will be enrolled into a cohort based on the subject’s age at the time of study entry. Cohort 1 will be the first cohort opened to accrual. Cohorts 2 to 6 will open to accrual as described in Section 6.2.

Subjects will be randomized to receive AERAS-404 or placebo within a Cohort. Subjects will be considered randomized when a subject identification number is assigned; the day on which a subject is randomized is Study Entry. Randomization will be administered via a central Interactive Voice Response System/Web Response System (IVRS/IWRS). Instructions for the IVRS/IWRS will be provided in the Manual of Operations (MOP).

The CRS must notify the HIV Vaccine Trials Network (HVTN) Regulatory Affairs if institutional or local governmental requirements pose a conflict with or impose restrictions on the use of stored specimens for batch testing at the end of the study.

4.5 Co-enrollment Procedures

Co-enrollment in a study for an investigational product is not allowed. Contact the protocol team (impaact.teamp1113@fstrf.org) for all other studies.

5.0 STUDY TREATMENT

In this study, AERAS-404 is considered the study vaccine. All EPI vaccines, for example Rotavirus (RV), Diphtheria, Tetanus, acellular Pertussis-Inactivated Polio (DTaP-IPV)/Haemophilus influenza type B (Hib), Hepatitis B (HBV), Pneumococcal Conjugate (PCV) and Measles, are pediatric vaccines that are
routinely administered to all children as part of the EPI program in South Africa. In the event of in-country EPI program vaccine shortage, they may be purchased locally with study-related funds. However they are not to be considered as study-supplied study drugs. Sites should contact the protocol team (impaact.teamp1113@fstrf.org) if EPI vaccine shortage is anticipated.

For Cohorts 1 to 5, the EPI vaccines may be administered through the national EPI program. If the vaccines are not administered through the national program, they may be administered through the CRS clinic.

For Cohort 6, administration of the EPI vaccines by the CRS staff at the same time as the study vaccine is preferred. **The EPI vaccines may still be provided through the national program; however administration in the CRS clinic is preferred.**

5.1 Drug Regimens, Preparation and Administration

5.11 Drug Regimen

Investigational Product

AERAS-404 is an investigational vaccine manufactured by Sanofi Pasteur (Toronto, Canada) and Statens Serum Institut (SSI; Copenhagen, Denmark). AERAS-404 has two components: the H4 antigen and the IC31 adjuvant. The reconstitution of the vaccine components, H4 antigen (manufactured at Sanofi Pasteur) and IC31 adjuvant (supplied by SSI), will take place at the CRS.

To enable the CRS pharmacist reconstitution of the 4 dose combinations under evaluation, 3 strengths of H4 antigen and 2 strengths of IC31 adjuvant will be provided to the CRS.

*H4 antigen* is composed of a purified recombinant fusion protein. The H4 antigen is presented as a sterile, colorless, clear, or slightly yellow solution in single dose vials.

Each 1.0 mL of H4 antigen contains the following components:

- *Active ingredients:* (See Table 14.)
Table 14. Purified Recombinant H4 Protein

<table>
<thead>
<tr>
<th>H4 Antigen Vialled Amount</th>
<th>Vialled H4 Antigen Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 mcg</td>
<td>50 mcg/mL</td>
</tr>
<tr>
<td>75 mcg</td>
<td>150 mcg/mL</td>
</tr>
<tr>
<td>250 mcg</td>
<td>500 mcg/mL</td>
</tr>
</tbody>
</table>

- **Other ingredients:**
  H4 antigen is formulated in a buffer consisting of 10 mmol/L Tris-HCl, pH 8.3

The presentation is 0.20 mL/vial (label claim) with an actual fill volume of 0.50 mL ± 0.05 mL. The AERAS-404 antigen will be mixed further with adjuvant prior to injection (reconstitution).

IC31 adjuvant is composed of ODN1a and KLK peptide. When thawed, the liquid material appears as a translucent suspension presented in single dose vials.

The IC31 adjuvant vial contains 0.8 mL of translucent adjuvant solution with a targeted filling volume of 0.8 mL.

Each 0.8 mL dose of IC31 vaccine contains the following components:

IC31 adjuvant at either 200 nmol KLK + 8 nmol ODN1a or 1000 nmol KLK + 40 nmol ODN1a – solubilized in 10 mM Tris, pH 7.4, 168.75 mM sodium chloride

**Control Product (Placebo)**

The control product is a placebo (Tris buffered isotonic sodium chloride solution with no preservative).

Form: Solution for injection in single dose vials

Dose: 0.5 mL

Each control product is composed of Tris buffered saline (10 mM Tris, pH 7.4, 150 mM sodium chloride).

The fill volume for the control product is 0.72 mL (label claim 0.5 mL).

5.12 **Vaccine Preparation**

*NOTE: A maximum 2-hour time period is allowed between the time the study vaccine is reconstituted and vaccine administration.*
Preparation of each dose should be based on the treatment regimen assigned at the time of randomization (Study Day 0).

Preparation of the study vaccine for Dose 1 for Study Entry injection should not begin before the subject is in the clinic, is confirmed eligible, the parent/legal guardian agrees for the subject to receive the vaccine dose that day (i.e., preparation should not begin before the subject has been assigned a subject identification number), and a Vaccine Request Form for Study Day 0 is received by the CRS pharmacist.

The CRS pharmacist will be required to prepare the final vaccine mixture at the CRS prior to administration. Study vaccine will be prepared in a separate location using aseptic technique. Precautions should be taken to avoid contact of the study vaccine with broken skin, and disposable gloves and eye protection (safety goggles) should be worn. Reconstitution under a hood is not required.

For subjects randomized to AERAS-404, after thawing for at least 45 minutes, the AERAS-404 vaccine is reconstituted by adding 0.2 mL antigen solution to the 0.8 mL of adjuvant solution. To ensure proper combining of the antigen and adjuvant, the AERAS-404 vaccine must remain reconstituted in the vial for a minimum of 30 minutes prior to final extraction of 0.5 mL solution into a syringe.

For subjects randomized to control, 0.5 mL of the placebo control vaccine should be drawn into an identically-appearing syringe.

The CRS pharmacist will prepare and label the syringe as described in the MOP. To maintain blinding, a syringe overlay will be applied by the CRS pharmacist before the syringe is taken to the clinic. Further details on instructions for dose preparation, labeling and documentation are also provided in the MOP.

Requests for preparation for Dose 2 (Cohorts 3A to 6) and Dose 3 (Cohorts 4 to 6) will be made by the investigator in a similar fashion as for Dose 1 on Study Entry. The appropriate Vaccine Request Form for the corresponding study day visit for Dose 2 and Dose 3 must be sent to the CRS pharmacist prior to preparation of the study vaccine. The CRS pharmacist will prepare the appropriate study vaccine according to the treatment regimen indicated for that subject identification number for Dose 2 and Dose 3 (study week varies for Cohorts 3A to 6) according to the IVRS/IWRS.
Refer to the most recent version of the MOP for detailed instructions regarding study vaccine preparation.

5.13 Administration

Each dose is delivered by intramuscular (IM) injection into alternating thighs according to the Cohort study vaccination schedule. See Table 15 for the study vaccination days and windows for each dose in each cohort.

For Cohort 6, the EPI vaccines should be injected in the same thigh with a distance of at least 3 cm between the injection sites and the study vaccine injected in the opposite thigh.
<table>
<thead>
<tr>
<th>Cohort</th>
<th>Dose</th>
<th>Day of Vaccination (vaccination age or visit window)</th>
<th>Additional Vaccination Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5 μg H4/100 nmol IC31 Or Placebo</td>
<td>Study Day 0 ($\geq 168$ to $\leq 196$ days of age)</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>5 μg H4/500 nmol IC31 Or Placebo</td>
<td>Study Day 0 ($\geq 168$ to $\leq 196$ days of age)</td>
<td>None</td>
</tr>
<tr>
<td>3A</td>
<td>5 μg H4/500 nmol IC31 Or Placebo</td>
<td>Study Day 0 ($\geq 168$ to $\leq 189$ days of age)</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Study Day 28 ($\pm 7$ days)</td>
<td>None</td>
</tr>
<tr>
<td>3B</td>
<td>15 μg H4/500 nmol IC31 Or Placebo</td>
<td>Study Day 0 ($\geq 168$ to $\leq 189$ days of age)</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Study Day 28 ($\pm 7$ days)</td>
<td>None</td>
</tr>
</tbody>
</table>
| 4      | 15 μg H4/500 nmol IC31 Or Placebo | Study Day 0 ($\geq 84$ to $\leq 98$ days of age) | • Must occur $\geq 2$ weeks after receipt of EPI vaccine doses at 10 weeks of age  
• Must be at least 10 days before EPI vaccine doses at 14 weeks of age |
|        |      | Study Day 42 ($\pm 7$ days) | • Must be 28 days after receipt of EPI vaccine doses at 14 weeks of age |
|        |      | Study Day 98 ($\pm 7$ days) | None |
| 5      | 50 μg H4/500 nmol IC31 Or Placebo | Study Day 0 ($\geq 84$ to $\leq 98$ days of age) | • Must occur $\geq 2$ weeks after receipt of EPI vaccine doses at 10 weeks of age  
• Must be at least 10 days before EPI vaccine doses at 14 weeks of age |
|        |      | Study Day 42 ($\pm 7$ days) | • Must be 28 days after receipt of EPI vaccine doses at 14 weeks of age |
|        |      | Study Day 98 ($\pm 7$ days) | None |
| 6      | Pending (AERAS-404) Or Placebo | Study Day 0 ($\geq 64$ to $\leq 83$ days of age) | • Must occur coincident with EPI vaccine doses at 10 weeks of age |
|        |      | Study Day 28 ($\pm 7$ days) | • Must occur coincident with EPI vaccine doses at 14 weeks of age |
|        |      | Day 210 ($\pm 7$ days) | • Must occur coincident with EPI vaccine doses at 9 months of age |

* Refer to Appendices I-A to I-D for the detailed schedule of evaluations for each cohort.
5.2 Drug Formulation

The different AERAS-404 dose combinations and number of doses for each cohort are shown in Table 16.

Table 16. AERAS-404 formulation

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Dose Combination</th>
<th>Number of Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5 μg H4/100 nmol IC31</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>5 μg H4/500 nmol IC31</td>
<td>1</td>
</tr>
<tr>
<td>3A</td>
<td>5 μg H4/500 nmol IC31</td>
<td>2</td>
</tr>
<tr>
<td>3B</td>
<td>15 μg H4/500 nmol IC31</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>15 μg H4/500 nmol IC31</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>50 μg H4/500 nmol IC31</td>
<td>3</td>
</tr>
<tr>
<td>6</td>
<td>Pending†</td>
<td>3</td>
</tr>
</tbody>
</table>

* Dose for Cohort 6 will be one of the doses studied in Cohorts 4 and 5 (15 μg H4/500 nmol IC31 or 50 μg H4/500 nmol IC31 respectively) based on unblinded safety and immunogenicity data for Cohorts 4 and 5 (see Section 8.54).
† Clinical Research Sites will be notified of the selected dose of AERAS-404 as described in the Schema and Section 3.0.

Refer to Sections 1.21 and 3.0 for the plan if the IC31 500 nmol dose is not tolerated and dose de-escalation will be needed.

5.3 Drug Supply, Distribution and Pharmacy

Clinical Research Sites will be provided with adequate quantities of investigational (H4 antigen, IC31 adjuvant) and control (placebo control) products. The H4 antigen will be supplied as open label product in single-use, clear, 3 mL vials containing frozen product. The H4 antigen will be shipped directly to the CRS from Sanofi Pasteur in Toronto, Canada. The IC31 adjuvant will be supplied as open label product in a single-use, clear, 3 mL vials containing frozen product. The IC31 adjuvant will be shipped directly to the CRS from SSI in Copenhagen, Denmark. The placebo will be supplied as unit dose vials, under refrigeration storage, by Sanofi Pasteur. Refer to the MOP for the study vaccine shipment details and shipment receipt instructions.

The specifics of the syringe and needle that will be used for study vaccine administration are provided in the MOP.

The CRS PI will be responsible for product management and will designate the CRS pharmacist to assume this responsibility. At the CRS, products must be kept in a secure place with restricted access. Study vaccine should be
placed in a container clearly marked “For IMPAACT P1113 Study Only”. Vials should be stored in their original secondary packaging cartons in order to protect them from exposure to light. Vaccines will be stored in a freezer that can maintain consistent temperature of -15 °C or colder until time of use. Storage temperature must be monitored continuously and a log of the monitored temperature maintained for the entire time that the vaccine is at the CRS. The vaccine freezer must be equipped with a continuous temperature monitor (wheel or datalogger device) and should have an alarm in case the temperature exceeds specified ranges. Vaccine freezers should be equipped with back-up power systems.

In case of accidental thawing or disruption of the cold chain, study vaccine must not be administered and must be quarantined, and the CRS PI or authorized designee should contact the designated unblinded study monitor for further instructions.

The placebo will be stored at 2-8°C (refrigerator) and not frozen. Refrigerator temperature must be monitored with a continuous monitoring device and should have an alarm in case the temperature goes out of range. The refrigerator must be equipped with back-up power systems. Refer to the most recent version of the MOP for the detailed instructions regarding study vaccine storage and the communication instructions if any study vaccine related-issues (other than those already described) arise.

The CRS pharmacist will maintain records of product delivery to the CRS, product inventory at the CRS, the dose(s) given to each subject, and the disposal of unused doses. The necessary information on the product labels is to be entered into the source document and the CRF.

The designated unblinded study monitor will verify the trial site’s product accountability records against the record of administered doses in the CRFs and randomization documents. Refer to the MOP for the process to request additional study vaccine in case of expected or potential shortage.

Aeras will direct the disposal or return of unused or wasted study vaccine. Product accountability will be verified throughout the trial period. Any disposing of study vaccine conducted at the CRS will occur only after authorization has been provided by the Aeras IP Manager and must be documented in the study file.

5.4 Blinding of Study Personnel

Personnel at the CRS and at the sponsor organizations will be blinded to subject treatment assignments, with the exception of the CRS pharmacist (and
designee, if appointed), the Aeras IP manager and the study monitor(s). All unblinded persons must take care to not reveal individual subject treatment regimen assignments to any other member of the CRS team, including the immunologists. Unblinded study personnel must not participate in the evaluation of adverse events. A Delegation of Authority Log will be maintained by the CRS and will identify the individual(s) authorized to function as the CRS pharmacist. 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 unblinded persons) until notification from the sponsor or its designee that the study has been unblinded.

5.5 Unblinding for Clinical Emergencies

If there is an urgent clinical requirement to know a subject’s treatment assignment, the CRS Principal Investigator will request the urgent unblinding of a subject’s treatment (directly or via the unblinded pharmacist by following the “unblinding by site form call flow” process in the IVRS/IWRS). The designated protocol management team will be notified of the unblinding immediately via IVRS/IWRS system alert. It is recommended that the CRS investigator consult with the protocol core team (impaact.p1113core@fstrf.org) prior to unblinding of a subject. However, in urgent instances per the discretion of the CRS investigator, the site can proceed with the unblinding of a subject without prior consultation with the protocol team.

6.0 SUBJECT MANAGEMENT

6.1 Toxicity Management

The P1113 Pediatric Toxicity Table in Appendix III will be used for grading the severity of adverse events.

Management of adverse experiences will be according to the best clinical practice and the judgment of the CRS investigator. Alternate explanations for clinical and laboratory abnormalities must be sought. Laboratory normals will be the institutional values. Abnormal laboratory findings should be followed until resolution to \( \leq \) Grade 2. Abnormal clinical findings in subjects with serious adverse events or chronic conditions (e.g. epilepsy) should be followed until resolution or clinical stabilization of the condition.

The toxicity management guidelines are for events for which a relationship to study vaccine cannot be excluded. Clinical or laboratory AEs that are
definitely unrelated to study vaccine may not result in study vaccine interruption.

6.11 Protocol-specific ≥ Grade 3 laboratory events

Results from clinical laboratory tests obtained on the study must be reviewed by the CRS investigator (or a designee who is a medically qualified CRS team member) within three calendar days of receiving the results to determine if abnormalities exist. Post-vaccination laboratory values that represent increases in toxicity grade according to the toxicity table must be reported as adverse events. Only clinically significant abnormal laboratory values must be repeated promptly and followed until ≤ Grade 2. Every effort must be made to confirm all ≥ Grade 3 laboratory abnormalities within 72 hours. If a ≥ Grade 3 laboratory value is not repeated within the time limit, it will be managed as a ≥ Grade 3 abnormality. If the repeat value is ≤ Grade 2, it will be managed accordingly. Additional laboratory tests may be performed if the investigator deems them to be necessary to fully evaluate an adverse event. In the event that the investigator elects to order non-protocol-specified laboratory tests, the investigator must record the rationale for the tests and a determination of clinical significance of the result in the source documents. The CRS investigator must keep the protocol core team (impaaact.p1113core@fstrf.org) informed of adverse events of clinical significance.

Abnormal results and findings will be discussed with the parent or legal guardian, and will be managed according to the best clinical practice and the judgment of the CRS investigator. The protocol core team should be notified (impaaact.p1113core@fstrf.org) of the management plan if the abnormal result is clinically significant.

6.2 Cohort Management

Cohorts 1, 2 and 3A will have an enrollment rate of no more than 2 subjects per day per CRS.

There will be no daily enrollment cap for Cohorts 3B, 4, 5 and 6.
Figure 11. Management of Cohorts 1 through 3B

Note: The numbers in ○ correspond to the Cohort for clarity of the cohort management flow.
Figure 12. Management of Cohorts 4 through 6

Note: The numbers in ◆ correspond to the Cohort for clarity of the cohort management flow.
The study will start with enrollment into Cohort 1 (Figure 11). All clinical and laboratory safety data up to 7 days after the study vaccine dose for all subjects will be evaluated. If there are no safety concerns identified, enrollment into Cohort 2 will be opened. Evaluation of all clinical and laboratory safety data for Cohort 2 is similar to Cohort 1.

If there are no safety concerns in the data for Cohort 2, enrollment into Cohort 3A will be opened.

In Cohort 3A, all clinical and laboratory safety data up to 7 days after the second study vaccine dose for all subjects will be evaluated. If there are no safety concerns identified, enrollment into Cohort 3B will be opened.

In Cohort 3B, all clinical and laboratory safety data up to 7 days after the second study vaccine dose for all subjects will be evaluated. In addition, immunogenicity data after the second study vaccine dose in all subjects will be evaluated as described in Sections 3.0 and 8.53. If there are no safety concerns identified AND the immunogenicity response meets the criteria defined in Section 3.0, enrollment into Cohort 4 and subsequent Cohorts will be opened. However if the immunogenicity response does not meet the criteria, enrollment will be terminated.

Cohorts 4 and 5 will enroll in sequence, starting with Cohort 4 (Figure 12). All clinical and laboratory safety data up to 7 days after the second study vaccine dose in all subjects in Cohort 4 will be evaluated. If there are no safety concerns identified, enrollment into Cohort 5 will be opened.

After all subjects in Cohorts 4 and 5 have completed Study Day 126, cumulative safety data from Cohorts 1 through 5 and cumulative immunogenicity data from Cohorts 4 and 5 will be evaluated as described in Section 8.54. The cumulative safety and immunogenicity data will inform the decision to open, and the study vaccine dose for, Cohort 6.

If data from safety reviews of the first six cohorts are deemed acceptable by the SMC and the immunogenicity response in Cohort 4 or Cohort 5 meets the criteria defined in Section 3.0, and a dose is selected as described in Section 8.54, enrollment into Cohort 6 will open. The Clinical Research Sites will be notified of the selected dose via a memorandum from the P1113 Protocol Team.

6.3 Subject Diary and Daily Temperature Monitoring

The parent or legal guardian of subjects who receive study vaccine will receive, and be instructed in, the operation of a daily adverse event diary and a
digital thermometer to be used during the specified post-vaccination diary period after vaccine administration. The daily adverse event diary is a tool to help aid the PI and/or designee to engage in a conversation with the subject about any AEs that may have occurred in-between visits, including fever by means of axillary temperature monitoring.

The diary will be reviewed by the principal investigator (or designee) during the phone contact 3 days following most study vaccinations except after the third study vaccine dose in Cohorts 4 to 6 when the phone contact will be 7 days following study vaccination. The diary will be collected and reviewed by the principal investigator (or designee) during the study visit 7 days following most study vaccinations except after the third study vaccine dose in Cohorts 4 to 6. In these Cohorts, the study visit will be 3 days following study vaccination; the diary will be reviewed on that visit and then returned to the parent or legal guardian after review. The parent or legal guardian should be instructed to continue to use the diary up to 7 days post vaccination and to contact the study staff if any adverse events or fever occur. The diary will be collected during the next study visit after the 7 day post vaccination phone contact.

Clinical assessments of possible adverse events will be made based on the diary card information and subsequent discussion with the parent/legal guardian. Partial clinical assessments should be performed to evaluate possible adverse events if the parent/legal guardian does not bring the diary at the scheduled visit. Lost diaries will be reconstructed where possible on a new diary booklet by the parent or legal guardian from memory on the closest clinic visit and labeled as a reconstructed diary. The diary will be considered source documentation and adverse events obtained from the diary will be recorded and completely assessed on the Adverse Event CRF. Body temperatures below 38°C will not be considered fevers.

Any change to an observation or event recorded by the parent or legal guardian on the diary card (e.g., the severity level of an event is changed after interviewing the parent or guardian) based on the investigator’s evaluation of the event must be explained by notation in source documentation.

In circumstances where parent/legal guardian illiteracy is a factor, the CRS can choose to have a study staff member verbally administer the questions on the diary card to obtain this data.

### 6.4 Management of Vaccine Complications

- Subjects who experience a vaccine-related ≥ Grade 3 AE (except fever) or a vaccine-related SAE judged by the CRS investigator as possibly,
probably or definitely related to study vaccine will have study vaccine discontinued.

- Subjects who experience a Grade 2 vaccine-related event (possibly, probably or definitely as judged by the CRS investigator) will have the AE discussed with the protocol core team (impact.p1113core@fstrf.org) prior to revaccination.

- Subjects who experience a Grade 3 fever event may receive the next dose of vaccine after discussion with the protocol team (see Section 6.5).

All subjects who do not receive subsequent doses of study vaccine will be followed off treatment but on study for the remainder of the study.

6.5 Criteria for Postponing Vaccine Administration

- Subjects who present with fever (≥ 100.4°F, ≥ 38.0°C; axillary) at the time of planned study vaccine will have the vaccine held until they are afebrile ≥ 24 hours. They may receive study vaccine if they still fulfill the age criteria for the next dose. Subjects who are on antibiotics > 48 hours and afebrile may receive their next dose of vaccine.

- Subjects who have an unresolved ≥ Grade 3 anemia, neutropenia, thrombocytopenia, ALT, AST or creatinine that is not vaccine related may receive study vaccine once the toxicity is ≤ Grade 2 and if they still fulfill the age criteria.

- Subjects who have a severe illness that, in the CRS investigator’s opinion, is a contraindication to administering study vaccine because it could compromise the safety of the subject or an immune response to the vaccine, may receive study vaccine after discussion with the protocol team and if the subject is still within the age window.

- Subjects who receive a live vaccine within 28 days prior to the next study vaccine dose will have vaccine held. The subject may receive study vaccine if they still fulfill the age criteria after 28 days from the receipt of the live vaccine.

Refer to Section 6.9 for the management of a subject who does not receive the second study vaccine dose in Cohorts 4 to 6.
6.6 Rules for the Protocol Team to request an Study Monitoring Committee (SMC) review

These rules will govern the protocol team during review of blinded safety data at any time one of the listed events occur and will trigger the team to request a Study Monitoring Committee (SMC) review of (unblinded) safety data. Only the protocol team can request an SMC review.

- Death in any subject.
- An anaphylactic reaction to study vaccine in any subject.
- A life-threatening AE in any subject.
- An SAE related to study vaccine.
- The occurrence of a ≥ Grade 3 AE or laboratory abnormality, except fever (see below), that is possibly, probably or definitely related to study vaccine as judged by the CRS investigator.
- > 15% of subjects, assessed during the first 7 days post vaccination in an individual cohort or across cohorts, experiencing Grade 3 fever.
- A pattern of significant symptoms, physical findings or laboratory abnormalities (AEs) that, although individually minor, collectively represent a safety concern in the opinion of the protocol team.

The protocol team may decide to pause enrollment and study vaccine administration while awaiting SMC review. The SMC may recommend suspension or resumption of enrollment and study vaccine administration after review of (unblinded) safety data as described in Sections 6.7 and 8.512. However the COG (see Section 8.54 for the description of the COG) will make the final decision to suspend or resume study activities.

6.7 Pausing Rules for the Study by the Protocol Team

These rules will trigger the protocol team to pause further enrollment and study vaccine administration and request SMC review of (unblinded) safety data:

- Death in any subject that is judged by the CRS investigator as possibly, probably or definitely related to study vaccine.
- An anaphylactic reaction to study vaccine in any subject.
- A life-threatening AE in any subject that is judged by the CRS investigator as possibly, probably or definitely related to study vaccine.
• An SAE possibly, probably or definitely related to study vaccine as judged by the CRS investigator.

Section 8.512 describes the process if the SMC recommends suspension of enrollment and study vaccine administration and the recommendation is endorsed by the COG (see Section 8.54 for the description of the COG).

The SMC may recommend resumption of study vaccine administration if the study pause was for reasons less severe than those in the protocol-specified pausing rules (see Section 8.512 for the process). However the final decision to resume study activities will be made by the COG. The SMC may require changes to the protocol to ameliorate the safety concerns that pose a significant risk to protocol subjects. In the absence of protocol changes the SMC must follow the protocol-specified study stopping rules (see Section 8.512).

If a decision to resume study enrollment and study vaccine administration is made the COG will record their judgment in a memorandum to the protocol team, who will then forward the COG memorandum to the sponsor and clinical research sites. The CRS will be allowed to resume activities upon receipt of written notification from the protocol team.

6.8 Tuberculosis (TB) Case Evaluation

Subjects who develop TB will be evaluated according to standard of care. The CRS investigator will manage TB evaluation and care of the subjects after discussion with the protocol team.

6.9 Criteria for Treatment Discontinuation in an Individual Subject

• Treatment with systemic steroids of $>$ 1 mg/kg/day within 3 days prior to study vaccine administration
• Possibly, probably, or definitely related $\geq$ Grade 3 AE (except fever) or vaccine-related SAE
• Possibly, probably, or definitely related reaction, excluding fever, which in the opinion of the CRS investigator or the protocol team will compromise the safety of the subject.
• Grade 3 fever may or may not lead to treatment discontinuation and will be decided by the Protocol Team on a case-by-case basis.
• History of TB exposure or receipt of TB treatment at any time during the study.
• TST within 8 weeks prior to the next study vaccine dose.
• Allergic (systemic) reaction following previous study vaccine administration.

• A subject in Cohorts 4 to 6 who does not receive the second study vaccine dose (i.e. the subject should not receive the third study vaccine dose).

All subjects who discontinue the study vaccine will remain on study until up to 504 days (approximately 18 months) of age and complete the remaining study visits in the schedule of evaluations (Appendices I-A to I-D as appropriate) but will not receive additional study vaccine.

6.10 Criteria for Study Discontinuation for an Individual Subject

• The parent or legal guardian refuses further treatment and/or follow-up evaluations (withdraws from the study).

• The subject fails to comply with the study requirements so as to cause harm to him/herself or seriously interfere with the validity of the study results.

• The study is discontinued by Aeras, the IMPAACT network, the Office for Human Research Protections (OHRP), the National Institutes of Health (NIH), the local IRB or EC, other governmental agencies, or Sanofi Pasteur.

A subject who prematurely discontinues will have the Early Study Discontinuation visit as shown in the schedule of evaluations (Appendices I-A to I-D as appropriate).

7.0 EXPEDITED ADVERSE EVENT REPORTING

7.1 Expedited Adverse Event Reporting

The CRS will be provided with specific reporting procedures including the Serious Adverse Event Report CRF (SAER) and any supplemental reporting forms to be used. Serious adverse events will be reported on the SAER CRF using a recognized medical term or diagnosis that accurately reflects the event.

The SAE Report, containing a serious adverse event and the supplemental information, completed for that event must be faxed or emailed by the principal investigator or his/her designee to the PPD World Wide Safety Center within 48 hours (two business days) of the CRS becoming aware of the event (contact information below). The SAE Report should be completed
with all information known at the time and faxed or emailed even if all information concerning the event is not yet known.

The protocol core team should be notified immediately (impaaact.p1113core@fstrf.org) of fatal or life-threatening serious adverse events that the investigator suspects are possibly, probably or definitely related to the study vaccine upon the investigator’s awareness of the event. The protocol team will convene the SMC to review the (unblinded) safety data. The PPD World Wide Safety Center team will also notify the other participating clinical research sites of this SAE and will send all corresponding documentation of this SAE to the other sites for possible reporting to their local ethics committees and regulatory authorities. (See Appendices IV and V.)

Contact information for all safety personnel are contained in the Team Contact List which will be stored at the CRS in the Site Regulatory Binder and maintained by the study sponsor. The contact information for the PPD World Wide Safety Center is:

   Email: EMEAAAsiaSafetyCentral.SM@ppdi.com
   Fax: +44-1223-374-102
   Tel: +44-1223-374-950

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

- Protocol and site numbers, and name and contact number of the investigator
- Subject ID number (and date of birth, if available)
- Date subject received all study vaccines
- Serious adverse event(s) and date of event onset
- Current status of subject

Aeras has authorized the PPD World Wide Safety Center to execute its responsibilities for safety report submission to the appropriate regulatory authorities within specific time periods of being notified of the event (within 7 or 15 calendar days depending the character of the suspected unexpected serious adverse reaction [SUSAR, see Section 7.24]); therefore, it is important that the principal investigator submit additional information requested as soon as it becomes available.
7.11 Global Medical Monitor

The purpose of the Global Medical Monitor (GMM) is to authorize SUSAR (suspected unexpected serious adverse reaction) reporting to regulatory agencies without unblinding the sponsor, protocol team or the clinical research sites. Aeras retains a GMM through the contract research organization PPD, Inc., located in Cambridge, UK. The GMM reviews and unblinds all SUSAR reports and, if he or she deems it necessary may review and unblind selected SAE reports. The GMM may contact the CRS directly if additional information is needed for assessment of the SUSAR. For all SUSARS the GMM will make available to sponsor and the clinical research sites a completed blinded CIOMS II so that the sites and sponsor may remain blinded.

7.2 Reporting Requirements for this Study

Subjects will be monitored and safety data collected by way of clinical interviews, examinations, and reports of laboratory evaluations. Parents/legal guardians will be provided with a subject diary to facilitate collection of pre-specified local or systemic vaccine reactions that occur up to 7 days post vaccine administration (see Section 6.3). Time points and the specific data collected for each of these evaluations are described in Appendices I-A to I-D.

The collection periods for adverse events and adverse reactions are:

- Solicited adverse events: 28 days after each vaccination
- Unsolicited adverse events: Entire study period
- Serious adverse events: Entire study period

Through the 28-day period following each vaccination all adverse events and adverse reactions observed by the principal investigator (or designee) or reported by the subject's parent or legal guardian spontaneously or in response to a direct question, or recorded in the diary, will be medically evaluated and documented in terms of a medical diagnosis on the Adverse Event Case Report Form (CRF).

Through the entire study period all serious adverse events observed by the principal investigator (or designee) or reported by the parent or legal guardian of the subject spontaneously or in response to a question will be medically evaluated and documented on the appropriate Adverse Event CRF.
7.21 Adverse Event

An adverse event can be any unfavorable or unintended sign, symptom, disease, syndrome, abnormal laboratory finding, or concurrent illness that emerges or worsens relative to the subject’s pretreatment baseline, whether or not it is considered to be related to the medicinal product.

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

Any adverse change from the subject’s baseline condition (determined from screening evaluations conducted to confirm study eligibility) that occurs following the administration of the study vaccine 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 vaccine.

Adverse events will be reported on the Adverse Event CRF using a recognized medical term or diagnosis that accurately reflects the event. Adverse event evaluations will be reviewed by the principal investigator or by a designated medically qualified practitioner. Adverse event CRF pages are to be completed by members of the CRS team designated in writing by the principal investigator. The onset and resolution dates of the event and action taken in response to the event will be documented. All clinical adverse events, including solicited adverse events (see Section 7.211), must be followed until resolution; all laboratory events must be followed up to resolution to \( \leq \) Grade 2. The resolution date will be recorded on the CRF as the last date on which the subject experienced the adverse event. If an adverse event resolution date is uncertain the principal investigator should estimate the date based on medical judgment and interview of the subject’s family. Approximate dates of resolution from interviews may be taken as adverse event resolution dates.

Adverse events that are still present at the end of the trial should be recorded as ongoing. Information recorded on the CRF must be substantiated in the source documents. If an adverse event evolves into a condition that becomes “serious,” it will be designated as serious on the Adverse Event CRF and a Supplemental SAE Report (SAER) form will be completed.
7.211 Solicited Adverse Events and Injection Site Reactions

Solicited adverse events are events the subject's parent or legal guardian is specifically asked about. These adverse events are commonly observed soon after receipt of vaccines. For this study, solicited adverse events include: fever, vomiting, abnormal crying/irritability, drowsiness/lethargy and loss of appetite. Solicited adverse events of local injection site reactions (i.e., pain at injection site, redness at injection site, or swelling at injection site) will be considered causally related to study vaccine (adverse reaction).

The reporting period during which solicited adverse events will be asked of the subject's parent or legal guardian is the immediate 28-day period following each study vaccination. The solicited adverse event reporting period begins with the day of vaccination. Solicited adverse events will be entered on the Adverse Event CRF using protocol-specified terms.

Solicited adverse events that are local injection site reactions will be considered related to study vaccine and will be further assessed by the investigator for severity, possible additional etiologies, and whether the event meets criteria as a serious adverse event (see Section 7.3). Solicited adverse events that are systemic in nature will be assessed by the investigator for severity, causal relationship to the study vaccine, possible etiologies, and whether the event meets criteria as a serious adverse event (see Section 7.3). The protocol team will review all events during their scheduled safety review and will make an attribution assessment in addition to the assessment made by the CRS investigator to the AE in a blinded fashion.

If the event is ≥ Grade 3 and deemed related (possibly, probably and definitely) by either the CRS or the protocol team, it will be referred to the SMC for review.

Presence of ulceration and/or scarring at the site of injection and localized lymphadenopathy of the injection thigh(s) are considered to be adverse events that are causally related to the study vaccine and are of special interest. Site of injection ulceration (including presence of drainage) and lymphadenopathy in the groin region will be actively evaluated during each clinic visit through the end of the study. Site of
Injection assessment should include BCG site reactions (i.e. erythema or redness, induration or edema, and ulceration) due to the Koch phenomenon. These events will be recorded on the Adverse Event CRF.

In the event that the clinical presentation meets the definition of a serious adverse event, in addition to the Adverse Event CRF, a Supplemental SAE Report must be completed and the event reported per protocol instructions.

7.22 Adverse Reaction

An adverse reaction is an adverse event judged by the investigator to be possibly, probably and definitely related to the study vaccine (see Section 7.3).

7.23 Serious Adverse Event

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

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 vaccine, are not serious by this criterion. Hospitalization is defined as a hospital admission or 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).
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).

Serious adverse events will be assessed by the principal investigator for severity, causal relationship to the study vaccine, 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 or clinical stabilization of the condition. Information recorded on the CRF must be substantiated in the source documents.

7.24 Suspected Unexpected Serious Adverse Reaction (SUSAR)

When an adverse event is judged to be related to AERAS-404, and also is judged to be serious and unexpected (see Section 7.33), it is a SUSAR and is subject to expedited reporting.

7.25 Other Events Requiring Immediate Reporting

The investigator must report the following events by faxing the appropriate form to the protocol team and study monitors within 48 hours of becoming aware of the event:

- Withdrawal of consent during the study (Immediately Reportable Event Form).
- Emergency unblinding (Immediately Reportable Event Form).
- Protocol violation affecting the safety of a subject or involving the vaccination process (Immediately Reportable Event Form).
- Adverse event thought to be an allergic reaction to the study vaccine (Immediately Reportable Event Form, unless event meets SAE criteria).
- Any event that, in the opinion of the investigator, precludes further administration of the study vaccine (Immediately Reportable Event Form, unless meets SAE criteria).
• ≥ Grade 3 laboratory event that are possibly, probably and
definitely related to the study vaccine (Immediately Reportable
Event Form, unless meets SAE criteria).

7.3 Assessing Severity, Causal Relationship (Relatedness) and Expectedness

For all adverse events, the investigator (or designee, who is a healthcare
professional is someone the investigator deems qualified to review adverse
event information, to provide a medical evaluation of the event, and to classify
the event based upon medical judgment and the severity categories described
below) is responsible for assessing the severity of the event and the causal
relationship of the event to the study vaccine. The investigator or designee
will not have knowledge of whether the study vaccine or placebo was
administered (i.e., blinded).

7.31 Severity

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

The adverse event grades in the toxicity table do not correlate directly
with the classical severity grades of mild, moderate and severe. FOR
THE PURPOSES OF RECORDING EVENTS ON THE CRF, Grade
1 events will be considered mild in severity, Grade 2 events will be
considered moderate in severity, and both Grade 3 and 4 events will be
considered as severe. In the toxicity table certain local reactions such
as erythema (redness) and swelling 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 P1113 Pediatric Toxicity Table in
Appendix III, 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 subject.
• “Moderate” events generally have some impact on an individual’s normal activities and may require general symptomatic medical intervention by a healthcare professional or by the subject.

• “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.

7.32 Causal Relationship (Relatedness)

For assessing causality, a number of factors will be considered including: 1) the temporal relationship of the event to the administration of the study vaccine, 2) whether an alternative etiology has been identified, and 3) biological plausibility. The following guidelines will be used to assess the causal relationship of an adverse event to study vaccine:

• Not Related to study vaccine (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 subject’s study record).

• Unlikely Related to study vaccine (i.e., there is less than a reasonable possibility that the adverse event was caused by study vaccine).

• Possible relationship to study vaccine (i.e., there is a reasonable possibility that the adverse event was caused by study vaccine. There must be a plausible mechanism for the event to be related to study vaccine. The evidence is inadequate to accept or reject, or favors rejection of, a causal relationship; an association exists between the event and the study vaccine but there may also be an alternative etiology, such as characteristics of the subject’s clinical status or underlying condition).

• Probable relationship to study vaccine (i.e., it is likely that the adverse event was caused by administration of the study vaccine. The evidence favors acceptance of a causal
relationship; an association exists between the event and receipt of the study vaccine and there is a plausible mechanism for the event to be related to the study vaccine, and an alternative etiology is not apparent).

- **Definite** relationship to study vaccine (i.e., the study vaccine 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 vaccine and there is a plausible mechanism for the event to be related to the study vaccine, and causes other than the study vaccine have been ruled out).

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

### 7.33 Expectedness

Expected adverse events are adverse events consistent with the applicable product information provided in the investigator’s brochure for the study vaccine. The protocol team determines expectedness. If the assessment is that the serious adverse event is expected no further action is required. If the protocol team’s assessment is that the serious adverse event is unexpected, then the event may represent a SUSAR.

### 7.4 Expedited Adverse Event Reporting Period

Serious adverse events, which include SUSARs, are reported to the protocol team, the sponsor and to the PPD World Wide Safety Center for the entire study period. After the study ends, SUSARs are reported to the sponsor within 3 working days of when the protocol team or CRS becomes aware of them. Refer to Section 7.1 and Appendices IV and V for the reporting procedure.

The investigator will continue follow-up on clinical adverse events, including solicited adverse events, until the event has resolved, is otherwise satisfactorily explained, or the subject completes the study. Laboratory events should be followed up to resolution to ≤ Grade 2.

Follow-up for serious adverse events must continue until resolution and the outcome is reported to the protocol team, during the adverse event reporting period, or to the sponsor, 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.
If at any time after completion of the serious adverse event reporting period (the final study visit) the investigator becomes aware of a serious adverse event that is suspected by the investigator to be related to the study vaccine, the event must be reported to Aeras.

8.0 STATISTICAL CONSIDERATIONS

8.1 General Design Issues

This is a Phase I/II, randomized, double-blind, placebo-controlled, safety, immunogenicity and dose-finding study in HIV-uninfected, HIV-unexposed, BCG-primed infants aged $\geq 64$ to $\leq 196$ days with no history/evidence of TB disease or infection at time of enrollment. This will be the first study in which AERAS-404 will be administered to infants. This study will evaluate the appropriate dose and schedule for this population. The design will allow for evaluation of the safety of the 3-dose regimen with and without concomitant EPI vaccine administration and immunogenicity will be evaluated as a secondary objective.

Dose finding will begin with an evaluation of a lower dose of the IC31 adjuvant (100 nmol), before the higher dose of the adjuvant (500 nmol) is evaluated. Study vaccine or placebo will be administered in sequential cohorts demonstrating safety in a single dose (injection) at Study Day 0 ($\geq 168$ to $\leq 196$ days of age; Cohorts 1 and 2), followed by a 2-dose schedule at Study Day 0 ($\geq 168$ to $\leq 189$ days of age) and Study Day 28 (Cohorts 3A and 3B), and a 3-dose schedule at Study Day 0 ($\geq 84$ to $\leq 98$ days of age), Study Day 42 and Study Day 98 (Cohorts 4 and 5), each without concomitant EPI administration.

If data from safety reviews of the first six cohorts are deemed acceptable by the SMC and the immunogenicity response in Cohort 4 or Cohort 5 meets the criteria defined in Section 8.222, and the dose recommended by the protocol team based on unblinded data from Cohorts 4 and 5, with concurrence from the SMC, is endorsed by the COG (see Section 8.54 for a description of the COG), the study will continue with vaccine or placebo co-administered with EPI vaccines to infants Study Day 0 ($\geq 64$ to $\leq 83$ days of age), Study Day 28 and Study Day 210 in Cohort 6. Clinical Research Sites will be notified of the dose selected for Cohort 6 via a memorandum. Cohort 6 will be randomized to receive the study vaccine dose selected based on safety and immunogenicity criteria applied to data obtained in Cohort 4 and 5, or placebo control.
The placebo subjects in all cohorts will be used to measure background noise, which can then be compared to the relevant vaccine dose group to determine the strength of immunogenic response. In particular, the combined immunogenicity data from placebo subjects in Cohorts 1 through 3B (with combined size of potentially 15 evaluable subjects) will be compared with those from Cohort 3B vaccine subjects; the combined immunogenicity data from placebo subjects in Cohorts 4 and 5 (with combined size of potentially 12 evaluable subjects) will be compared to each of these cohorts’ vaccinated group. Finally, the vaccinated and placebo groups (with potentially 35 evaluable subjects in each group) within Cohort 6 will be compared.

All subjects will be followed until between 490 and 602 days of age, depending on the study cohort, to evaluate safety, clinical and immunological parameters.

8.2 Endpoint and Outcome Measures

8.21 Primary Endpoint (Safety)

The number and percentage of subjects with solicited and unsolicited AEs (including serious adverse events [SAEs], local and systemic reactions, and clinical laboratory values or vital sign values recorded as newly abnormal following study vaccination) recorded post-vaccination will be summarized to address the primary objective of the study.

8.22 Secondary Endpoints and Outcome Measures

8.221 Safety

The number and percentage of subjects who are enrolled into the three-dose regimen (Cohorts 4 to 6) with solicited and unsolicited AEs (including serious adverse events [SAEs], local and systemic reactions, and clinical laboratory values or vital sign values recorded as newly abnormal following study vaccination) recorded post-vaccination will be summarized to address the secondary safety objective of the study.

8.222 Immunogenicity

- T-cell response, as measured by ICS following stimulation with peptide pools spanning the vaccine antigens, will be used to assess immunogenicity. Flow cytometry will be used to examine vaccine-specific CD4+ and CD8+ T-cell
responses following stimulation of PBMCs with peptide pools, each representing the entire amino acid sequence of the mycobacterial antigens Ag85B, and TB10.4. ICS parameters will include cytokines such as IFN-γ, IL-2 and TNF-α, and may include other cytokines to identify T cells of specific functionality (such as IL-17, IL-22 and CD40L).

Cohort 3B PBMC samples obtained 14 days (+ 7 days) following the second vaccination will be assayed by ICS. The immune response to the vaccine will be determined using validated, statistical positivity criteria comparing responses in peptide stimulated wells to unstimulated wells. A response may be positive for Ag85B and/or TB10.4, expressing at least one functional marker by either CD4 or CD8 T cells such as IL-2, IFNγ or TNFα.

Cohorts 4 and 5 PBMC samples obtained 14 days (+ 7 days) following the third vaccination will be assayed by ICS. The immune response to the vaccine will be determined using statistical positivity criteria comparing responses in peptide stimulated wells to unstimulated wells. A response may be positive for Ag85B and/or TB10.4, defined as expression of two or more functional markers such as IL-2, IFNγ or TNFα by CD4 T cells.

Specific validated functional markers, with established cut-off, used in determining response rate in Cohorts 3B, 4 and 5 will be prespecified and agreed upon by the COG prior to analysis. Prior to the review of the immunologic data, the COG will have the opportunity to assess if the criteria used to determine the response rate are still valid or may need modification based on new or relevant information from ongoing studies. This will give the COG the flexibility to consider the best information available at the time the immunologic data are reviewed.

Additional cell surface markers, cytokines, or functional markers may also be analyzed.

- Antibody response to specific vaccine-specific antigens, as measured by an isotype-specific multiplex antibody assay, will also be used to assess immunogenicity.

- mRNA expression will be performed on cells collected at entry and post third study vaccine dose.
• Antibody concentration levels at 12 months of age for all Cohorts, and in addition at 28 days post second study vaccine dose (Study Day 56) for Cohort 6 will be presented. Summaries will include antibody titers to Tetanus toxoid vaccine (tetanus; given at 6, 10, 14 weeks of age), and Haemophilus influenza B conjugate vaccine (given at 6, 10, 14 weeks of age). Responses to other EPI vaccines may also be assessed.

8.223 Dose selection
Safety and immunogenicity analyses will be prepared in conjunction with the selection of the appropriate dose regimen (Section 8.54).

8.3 Randomization and Stratification
Subjects will be enrolled into the study and into a Cohort based on age at the time of enrollment and based on completion of screening evaluations. Within a cohort, subjects will be randomized in a 11:3 ratio (Cohorts 1 to 3A), a 13:2 ratio (Cohort 3B), a 5:1 ratio (Cohorts 4 and 5), and in a 1:1 ratio (Cohort 6) to receive AERAS-404 or placebo using a central IVRS/IWRS across clinical research sites. Cohorts 1, 2 and 3A will have an enrollment rate of no more than 2 subjects per day per CRS. There is no daily enrollment cap for Cohorts 3B, 4, 5 and 6.

Subjects will be considered randomized when a subject identification number is assigned; the day on which a subject is randomized is Study Entry.

8.4 Sample Size and Accrual
A total of 229 subjects for the safety analysis are planned to be enrolled in order to achieve a minimum total of 206 evaluable subjects based on an estimated cumulative drop-out rate of 10% through end of study. Similarly, the approximate target number of evaluable subjects with data available for the immunogenicity analysis will be 90% of each cohort, e.g. 10 evaluable subjects on active vaccine and 3 evaluable subjects on placebo for Cohorts 1 to 3A; 35 evaluable subjects on active vaccine and 5 evaluable placebo subjects in Cohort 3B; 27 evaluable subjects on active vaccine and 5 evaluable subjects on placebo for Cohorts 4 and 5; and 30 evaluable subjects each on active vaccine and placebo for Cohort 6 (see Table 1).
Sample sizes for each of the study cohorts and for the overall study are selected based on the planned descriptive analyses of safety and immunogenicity data rather than on formal statistical hypothesis testing.

The sample size per cohort in Cohorts 1 to 3A was chosen primarily for evaluating safety for study vaccine dose escalation and subject age de-escalation.

The sample size for Cohort 3B was selected as adequate for safety evaluation and to conduct a preliminary evaluation of statistical positivity criteria for immunogenicity as described in Section 8.54. Safety data will be evaluated and presented for all 229 subjects enrolled in the trial. The range for anticipated immunogenicity response rates in the AERAS-404 group for Cohort 3B were chosen based on previous AERAS-404 studies in adults with a nominal 5% response in the control group based on previous studies with false positives exhibited by placebo subjects. To maximize power, placebo controls will be pooled across Cohorts 1, 2, 3A, and 3B, for a control size of 15 subjects, of which N = 14 may be potentially evaluable due to drop-out considerations as mentioned above.

Given thirty-nine subjects in the AERAS-404 group and 15 subjects in the control group, of which approximately 90% (35 subjects in the AERAS-404 group and 14 subjects in the control group) will be evaluable for assessment of immunogenicity, there is a 74% probability of observing a > 30% difference in immune response rates between AERAS-404 and placebo groups (immunogenicity criterion to move forward to Cohort 4, see Section 8.53) if the true response rate in the AERAS-404 group is 40% and the true response rate in the control group is 5%. The probability is of course higher if the true response rate in the AERAS-404 group is higher than 40%. The estimated probability of observing a difference in proportions > 30% given specific true responses rates demonstrated by evaluable subjects in the AERAS-404 and placebo groups, respectively, are shown in Table 17.
Table 17: Estimated Probability of Achieving Immunogenicity Criterion in Cohort 3B Assuming 35 Evaluable Subjects in Vaccinated Group and 14 Evaluable Placebo Group Subjects

<table>
<thead>
<tr>
<th>True Immunogenicity Rate for Vaccinated Group (N=35)</th>
<th>True Immunogenicity Rate for Placebo Group (N=14)</th>
<th>Probability that Observed Difference in Proportions &gt; 30%</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.20</td>
<td>0.05</td>
<td>4%</td>
</tr>
<tr>
<td>0.25</td>
<td>0.05</td>
<td>14%</td>
</tr>
<tr>
<td>0.30</td>
<td>0.05</td>
<td>32%</td>
</tr>
<tr>
<td>0.35</td>
<td>0.05</td>
<td>55%</td>
</tr>
<tr>
<td>0.40</td>
<td>0.05</td>
<td>74%</td>
</tr>
<tr>
<td>0.45</td>
<td>0.05</td>
<td>87%</td>
</tr>
<tr>
<td>0.50</td>
<td>0.05</td>
<td>94%</td>
</tr>
<tr>
<td>0.55</td>
<td>0.05</td>
<td>97%</td>
</tr>
<tr>
<td>0.60</td>
<td>0.05</td>
<td>99%</td>
</tr>
</tbody>
</table>

Based on 5000 simulations using SAS

The larger sample size for Cohorts 4 and 5 was selected as adequate for expanded safety evaluation and dose selection. There is interest in obtaining more precise estimates of safety rates and immunogenicity parameters in the 3 dose cohorts to satisfy the secondary objective of this study, and the relative size of Cohort 4 and 5 (30 treated subjects, 6 placebos in each cohort) will permit this review. Additionally, placebo subjects will be pooled for Cohorts 4 and 5, allowing a maximum of 12 subjects for evaluation of immunogenicity.

Given thirty subjects in the AERAS-404 group in Cohort 4 or Cohort 5, and 12 (pooled Cohort 4 and 5) control subjects, and again assuming 90% of these subjects will be evaluable for the assessment of immunogenicity, there is a 71% probability of observing a > 50% difference in immune response rates between the AERAS-404 and placebo groups (immunogenicity criterion to move forward to Cohort 6, see Section 8.54) if the true response rate in the AERAS-404 group is 60% and the true response rate in the placebo group is 5%. The probability is of course higher if the true response rate in the AERAS-404 group is higher than 60%. The estimated probability of observing a difference in proportions > 50% given specific true responses rates demonstrated by evaluable subjects in the AERAS-404 and placebo groups, respectively, are shown in Table 18.
Table 18: Estimated Probability of Achieving Immunogenicity Criterion in Cohort 4/Cohort 5 Assuming 27 Evaluable Subjects in Vaccinated Group and 11 Evaluable Placebo Group Subjects

<table>
<thead>
<tr>
<th>True Immunogenicity Rate for Vaccinated Group (N=27)</th>
<th>True Immunogenicity Rate for Placebo Group (N=11)</th>
<th>Probability that Observed Difference in Proportions &gt; 50%</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.35</td>
<td>0.05</td>
<td>3%</td>
</tr>
<tr>
<td>0.40</td>
<td>0.05</td>
<td>9%</td>
</tr>
<tr>
<td>0.45</td>
<td>0.05</td>
<td>20%</td>
</tr>
<tr>
<td>0.50</td>
<td>0.05</td>
<td>35%</td>
</tr>
<tr>
<td>0.55</td>
<td>0.05</td>
<td>54%</td>
</tr>
<tr>
<td>0.60</td>
<td>0.05</td>
<td>71%</td>
</tr>
<tr>
<td>0.65</td>
<td>0.05</td>
<td>83%</td>
</tr>
<tr>
<td>0.70</td>
<td>0.05</td>
<td>92%</td>
</tr>
<tr>
<td>0.75</td>
<td>0.05</td>
<td>96%</td>
</tr>
<tr>
<td>0.80</td>
<td>0.05</td>
<td>99%</td>
</tr>
</tbody>
</table>

Based on 5000 simulations using SAS

**Anticipated Accrual Duration**

It is anticipated that it will take 1.5 years to recruit a total of 159 subjects into Cohorts 1 to 5. It is anticipated that it will take another 4 months to enroll Cohort 6. **Adverse event rate calculations and associated probabilities of observing at least one AE are shown in Table 19 for these cohorts, based on planned sample sizes.**
Table 19. Sample Size and Adverse Event Rate Calculation for Individual Cohorts

<table>
<thead>
<tr>
<th>Sample size</th>
<th>True rate (%)</th>
<th>Probability of observing at least one event (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>0.1</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>0.5</td>
<td>5.4</td>
</tr>
<tr>
<td></td>
<td>1.0</td>
<td>10.5</td>
</tr>
<tr>
<td></td>
<td>2.5</td>
<td>24.3</td>
</tr>
<tr>
<td></td>
<td>5.0</td>
<td>43.1</td>
</tr>
<tr>
<td></td>
<td>10.0</td>
<td>68.6</td>
</tr>
<tr>
<td></td>
<td>15.0</td>
<td>83.3</td>
</tr>
<tr>
<td></td>
<td>20.0</td>
<td>91.4</td>
</tr>
<tr>
<td>30</td>
<td>0.1</td>
<td>3.0</td>
</tr>
<tr>
<td></td>
<td>0.5</td>
<td>14.0</td>
</tr>
<tr>
<td></td>
<td>1.0</td>
<td>26.0</td>
</tr>
<tr>
<td></td>
<td>2.5</td>
<td>53.2</td>
</tr>
<tr>
<td></td>
<td>5.0</td>
<td>78.5</td>
</tr>
<tr>
<td></td>
<td>10.0</td>
<td>95.8</td>
</tr>
<tr>
<td></td>
<td>15.0</td>
<td>99.2</td>
</tr>
<tr>
<td>35</td>
<td>0.1</td>
<td>3.4</td>
</tr>
<tr>
<td></td>
<td>0.5</td>
<td>16.1</td>
</tr>
<tr>
<td></td>
<td>1.0</td>
<td>29.7</td>
</tr>
<tr>
<td></td>
<td>2.5</td>
<td>58.8</td>
</tr>
<tr>
<td></td>
<td>5.0</td>
<td>83.4</td>
</tr>
<tr>
<td></td>
<td>10.0</td>
<td>97.5</td>
</tr>
<tr>
<td></td>
<td>15.0</td>
<td>99.7</td>
</tr>
<tr>
<td>39</td>
<td>0.1</td>
<td>3.8%</td>
</tr>
<tr>
<td></td>
<td>0.5</td>
<td>17.8%</td>
</tr>
<tr>
<td></td>
<td>1.0</td>
<td>32.4%</td>
</tr>
<tr>
<td></td>
<td>2.5</td>
<td>62.7%</td>
</tr>
<tr>
<td></td>
<td>5.0</td>
<td>86.5%</td>
</tr>
<tr>
<td></td>
<td>10.0</td>
<td>98.4%</td>
</tr>
<tr>
<td></td>
<td>15.0</td>
<td>99.8%</td>
</tr>
<tr>
<td></td>
<td>15.0</td>
<td>99.7</td>
</tr>
</tbody>
</table>

Seventy subjects will be assigned to Cohort 6 and will be randomized to either AERAS-404 or placebo in a 1:1 ratio. While this study is not powered to detect differences in adverse event rates, Table 20 provides a review of the statistical power in Cohort 6.
### Table 20

<table>
<thead>
<tr>
<th>True Adverse Event Rate for Vaccinated Group (N=35)</th>
<th>True Adverse Event Rate for Placebo Group (N=35)</th>
<th>Power (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.10</td>
<td>0.05</td>
<td>3%</td>
</tr>
<tr>
<td>0.20</td>
<td>0.05</td>
<td>33%</td>
</tr>
<tr>
<td>0.30</td>
<td>0.05</td>
<td>74%</td>
</tr>
<tr>
<td>0.40</td>
<td>0.05</td>
<td>94%</td>
</tr>
<tr>
<td>0.50</td>
<td>0.05</td>
<td>99%</td>
</tr>
<tr>
<td>0.20</td>
<td>0.1</td>
<td>13%</td>
</tr>
<tr>
<td>0.30</td>
<td>0.1</td>
<td>46%</td>
</tr>
<tr>
<td>0.40</td>
<td>0.1</td>
<td>78%</td>
</tr>
<tr>
<td>0.50</td>
<td>0.1</td>
<td>95%</td>
</tr>
<tr>
<td>0.60</td>
<td>0.1</td>
<td>99.5%</td>
</tr>
<tr>
<td>0.20</td>
<td>0.15</td>
<td>5%</td>
</tr>
<tr>
<td>0.30</td>
<td>0.15</td>
<td>23%</td>
</tr>
<tr>
<td>0.40</td>
<td>0.15</td>
<td>56%</td>
</tr>
<tr>
<td>0.50</td>
<td>0.15</td>
<td>85%</td>
</tr>
<tr>
<td>0.60</td>
<td>0.15</td>
<td>97%</td>
</tr>
<tr>
<td>0.70</td>
<td>0.15</td>
<td>99.8%</td>
</tr>
</tbody>
</table>

Table 20 above shows there will be insufficient statistical power for a formal test of the difference in study arms with respect to safety in the absence of very large increase in adverse event rates in the vaccinated group compared to the placebo group. For example, we can only detect differences between the vaccinated versus the placebo group in Cohort 6 with 89% power if the true AE rate in the placebo group were 5% and the true adverse event rate in the vaccinated group were 40% (that is, a 35% difference in rates between the two groups). With insufficient power to detect smaller differences, a finding of no statistically significant difference would not provide acceptable evidence of no adverse vaccine effect.

Thus, the precision of the estimates of ≥ Grade 3 toxicity rates and ≥ Grade 3 adverse events judged to be possibly, probably or definitely due to the immunizations as bounded by 95% confidence intervals is presented in the Table 21.
Table 21: Exact 95% Confidence Intervals around Potential Proportions of Subjects Exhibiting ≥ Grade 3 Adverse Events

<table>
<thead>
<tr>
<th>N</th>
<th>Observed Rates</th>
<th>95% Confidence Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Lower</td>
</tr>
<tr>
<td>35</td>
<td>0% (0/35)</td>
<td>0%</td>
</tr>
<tr>
<td>3% (1/35)</td>
<td>0.1%</td>
<td>3%</td>
</tr>
<tr>
<td>11% (4/35)</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>20% (7/35)</td>
<td>8%</td>
<td>8%</td>
</tr>
<tr>
<td>40% (14/35)</td>
<td>24%</td>
<td>24%</td>
</tr>
</tbody>
</table>

8.5 Monitoring

8.5.1 Safety Monitoring

Safety will be monitored by the Protocol Team and a Study Monitoring Committee (SMC). The SMC is appointed by the IMPAACT Network for P1113 prior to study commencement.

8.5.11 Protocol Team

The protocol team will review and discuss blinded summaries of 7-day and cumulative safety data, as prepared by the statistician with the Aeras designated CRO data management team, on conference calls at least monthly. Conference calls will also be scheduled as needed in response to any adverse event that requires the immediate attention of the protocol team. Notification of team members will be by e-mail, phone or fax, depending on time differences. Data on accrual and all toxicities will be reviewed.

8.5.12 Study Monitoring Committee

The IMPAACT SMC will provide independent blinded and/or unblinded reviews to ensure subject safety. In accordance with IMPAACT and DAIDS procedures, this committee will be composed of the Network Principal Investigator (or designee), Network Vice-Chair (or designee), Laboratory Principal Investigator of the Network (or designee), two individuals from the Tuberculosis Scientific Committee, one Protocol Development and Monitoring Committee (PDMC) member and a statistician independent of the P1113 protocol team. Members of said SMC will have:
1. No financial interest in the study;
2. No planned authorship in publication of study results; and
3. No involvement in the conduct of the study.
While the SMC will review the data if a situation arises which requires independent review, ongoing review of toxicity data is the responsibility of the protocol team to protect subjects from undue risk. The triggers for the protocol team to request an SMC review are detailed in Sections 6.6 and 6.7, and the protocol stopping rules for the SMC below.

A scheduled SMC review will occur after Cohort 5 has completed the Study Day 126 visit to review clinical, laboratory and safety data before Cohort 6 is opened to enrollment.

**Protocol Stopping Rules for the SMC**

The SMC may recommend to stop further enrollment and study vaccine administration if any of the following occur:

- Death in any subject judged by the SMC to be related to study vaccine (definite, probable or possible).
- An anaphylactic reaction to study vaccine in any subject.
- A life-threatening adverse event in any subject judged by the SMC to be related (definite, probable or possible) to study vaccine.
- A pattern of significant symptoms, physical findings or laboratory abnormalities (AEs) that, although individually minor, collectively represent a safety concern and judged by the SMC to be related to study vaccine.

If the SMC is required by the protocol or chooses to recommend suspension of enrollment and study vaccine administration, the SMC shall immediately create a written memorandum to notify the COG (see Section 8.54 for the description of the COG) and the protocol team. However the final decision to suspend enrollment will be made by the COG after its review of the data. The protocol team will be notified of the decision of the COG by a written memorandum. The protocol team will then forward the memorandum to the sponsor and clinical research sites.

The protocol team and COG will also be informed in writing when the SMC recommends enrollment and study vaccine
administration can be resumed. However the COG will have the final decision to resume study activities. The process for informing the sponsor and the CRS will be as previously described (for suspension of enrollment and study vaccine administration).

The CRS investigator will be responsible for notifying the local IRB/EC in both situations.

8.52 Safety Guidelines for Cohort Escalation

Cohorts 1, 2, 3A and 3B Safety Data Review: Blinded safety data from the full cohort (7 days post study vaccine dose for Cohorts 1 and 2, 7 days post first and second study vaccine doses for Cohorts 3A and 3B) will be evaluated by the protocol team. If there are no safety concerns identified, the next cohort will be enrolled and vaccinated. **If there are no safety concerns identified, and the immunogenicity criterion in Section 8.53 is met, accrual will proceed to Cohorts 4 and 5.**

Cohorts 4 and 5 Safety Data Review: Blinded safety data from the full cohort (7 days post first and second study vaccine doses) will be evaluated by the protocol team. If there are no safety concerns identified, the next cohort will be enrolled and vaccinated. See Section 8.54 for guidelines for opening of Cohort 6.

Cohort 6 Safety Data Review: Blinded safety data from the full cohort (7 days post first, second and third study vaccine doses) will be evaluated by the protocol team.

Section 6.6 outlines the events that will trigger the team to request an SMC review. Enrollment and study vaccination may be paused, except as noted in Section 6.7, at the discretion of the protocol team pending the results of the SMC review. Otherwise, enrollment through the remainder of the Cohort will continue.

Given the small sample sizes in Cohorts 1 to 3A, the information available for preliminary safety decisions will be imperfect. Two types of sampling errors are possible:

a. In a group where the true rate of toxicity is too high to warrant increased exposure to the current starting dose of the medication, the sample data may pass the safety guidelines;
b. In a group where the true rate of toxicity is low enough that further exposure to the current starting dose is warranted, the sample data may fail the guidelines.

The extent to which the safety guidelines protect against the errors described above can be assessed by examining various hypothetical rates of "true toxicity" which could occur, if the study vaccine were used extensively among the subject population at the dose level and dosing frequency under question. The hypothetical situations presented in Table 22 range from conditions under which a given dose level and dosing frequency would cause a high incidence of severe and life threatening suspected adverse drug reactions (SADRs) to conditions under which severe SADRs would be relatively rare and would not be life threatening. For each of these hypothetical situations, we assume that a full cohort sample with 10 evaluable subjects is drawn from the subject population (those on active vaccine) and that the safety guidelines, summarized above, are followed.

Table 22: Probability of **Failing** Safety Guidelines for Each of Cohorts 1 to 3A with 11 Subjects on Active Study Vaccine, under Potential Rates of True Toxicity

<table>
<thead>
<tr>
<th>True Toxicity Rates</th>
<th>Probability of Failing Safety Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ Grade 3 fever possibly, probably or definitely related to study vaccine</td>
<td>≥ Grade 3 event (except fever) possibly, probably or definitely related to study vaccine, death, anaphylactic reaction to AERAS-404, or life-threatening adverse event</td>
</tr>
<tr>
<td>0.20</td>
<td>0.00</td>
</tr>
<tr>
<td>0.20</td>
<td>0.05</td>
</tr>
<tr>
<td>0.20</td>
<td>0.20</td>
</tr>
<tr>
<td>0.10</td>
<td>0.00</td>
</tr>
<tr>
<td>0.10</td>
<td>0.05</td>
</tr>
<tr>
<td>0.10</td>
<td>0.20</td>
</tr>
<tr>
<td>0.05</td>
<td>0.00</td>
</tr>
<tr>
<td>0.05</td>
<td>0.05</td>
</tr>
<tr>
<td>0.05</td>
<td>0.20</td>
</tr>
<tr>
<td>0.00</td>
<td>0.05</td>
</tr>
<tr>
<td>0.00</td>
<td>0.20</td>
</tr>
</tbody>
</table>

For example, Table 22 shows that there is a **83%** chance of failing the safety guidelines under conditions in which the true rate of ≥ Grade 3 event (except fever), a life-threatening event, death, or anaphylactic reaction at least possibly related to study vaccine is 5% and the true rate of ≥ Grade 3 fever at least possibly related to study vaccine is 20%.
Assuming that it would be undesirable to accrue additional subjects at a dose that had these true rates of adverse events, the 17% chance of NOT failing the safety guidelines would represent the probability of error. The table also shows that there is a 10% chance of failing, when the true rate of ≥ Grade 3 event (except fever) or life-threatening event at least possibly related to study vaccine, death or anaphylactic reaction to vaccine is 0% and the true rate of ≥ Grade 3 fever at least possibly related to study vaccine is 5%. Assuming that the potential benefits associated with exposing additional subjects to this dose of the drug would outweigh the risks associated with this relatively low rate of toxicity, failing the safety guidelines under these conditions would be an error.

8.53 Cohort opening – Cohort 4

Criteria for opening Cohort 4 after P1113 Protocol Team and COG review of unblinded data:

- No safety signal identified after review of all clinical and laboratory safety data up to 7 days post Dose 2 vaccination in Cohort 3B.

- An observed difference of at least 30% in immune response rate in the AERAS-404 treatment group compared to the immune response rate in the placebo group is a condition for opening the next cohort for enrollment after review of the immunogenicity data at 14 days (+ 7 days) post Dose 2 vaccination in Cohort 3B.

8.54 Cohort Opening and Dose selection – Cohort 6

Opening and dose selection for Cohort 6 will be based on:

- Review of all cumulative unblinded safety data through Day 126 (28 days post all study vaccine doses in Cohorts 1 through 5).

- Review of all cumulative unblinded immunogenicity data through Day 112 (14 days + 7 days post Dose 3 vaccination) for Cohorts 4 and 5.

- Achievement of an observed difference of at least 50% in immune response rate between the AERAS-404 treatment group in Cohort 4 OR Cohort 5 and the pooled (Cohort 4 and Cohort 5) placebo group to proceed with Cohort 6. Responder definitions may include any of the cumulative immunogenicity data through Day 112 for Cohorts 4 and 5.
Criteria for selection of the Cohort 6 dose will be prespecified in the statistical analysis plan (SAP) which will be finalized prior to unblinding for the dose selection process.

The cumulative data for the selected dose must meet the following criteria: (1) did not result in a pattern of SAEs and AEs that are judged to be possibly, probably, or definitely related to study vaccine and (2) resulted in the highest number of post-vaccination positive response as defined in Section 8.222. A stepwise procedure for dose selection based on prespecified safety and immunogenicity criteria will be performed, with the steps designed to be performed in the order specified so as to facilitate a review of safety and immunogenicity and eliminate dose levels. If, at the end of the process, more than one AERAS-404 dose level remains, the dose will be selected by the COG based on the available data.

Safety analyses in support of this stepwise algorithm will include summaries of number (percentage) of subjects with adverse events by preferred term, as well as by severity and by relationship to study vaccine; dose-safety curves and additional dose-safety and dose-response summaries will be presented for all subjects in the safety population. Immunogenicity analyses will include summaries of the number (percentage) of subjects meeting pre-specified responder criteria. Results of these analyses will enable the protocol team to perform dose selection for Cohort 6.

A recommendation for dose selection will be made by the protocol team, based on unblinded data grouped according to vaccine or placebo assignment, and will be provided to the SMC for review. The study team will not be informed of individual (per-subject) treatment assignments during the dose selection process. The dose recommended by the protocol team, with concurrence by the SMC, will be endorsed by the P1113/C-015-404 Collaboration Oversight Group (COG; composed of representatives from Aeras, Sanofi Pasteur, NIH, HVTN and IMPAACT members not involved with conducting the study but responsible for overseeing the collaborations and for making decisions on specific issues).

No changes to monitoring practices or clinical study procedures will be implemented following the review, and the study will continue following the review. Data summaries for this preliminary analysis
will be prepared by a statistician who is not the study statistician and who is not involved in study design, conduct, or analyses. Data identified for inclusion in the safety summaries will be cleaned prior to statistical analysis; all statistical analysis programs used for the study will be validated prior to presentation of results.

8.6 Analyses

8.6.1 Primary Objective

Safety: Evaluation of the safety profile of AERAS-404 will be performed using data from all subjects who received at least one dose of study vaccine.

Primary safety analyses will be performed based on all subjects who receive at least one dose of study vaccine, and additional (secondary) safety analyses will be performed based on subjects who have 7 days of post-(each) dose safety data completed. In support of the Secondary Objectives, safety analyses will be presented to evaluate post-vaccination safety data for subjects who have the course of prescribed vaccination regimen (2-dose or 3-dose) in a given Cohort, as described in Section 8.6.2.

Subjects who withdraw due to safety considerations will be included in safety analyses, with all available data included in relevant summaries and data listings.

Safety endpoints will be evaluated with, e.g., accompanying 95% confidence intervals (CI), to examine the proportion of adverse events by treatment group and cohort, as described below. The number (percentage) of subjects with any adverse event (including solicited, unsolicited, and serious adverse events) will be summarized by MedDRA system organ class and Preferred Term. Additional summaries will present the number (percentage) of subjects with any adverse events by severity and by relationship to study vaccine; parameters evaluable by the P1113 Pediatric Toxicity Table (Appendix III) will be summarized by severity corresponding to Toxicity Grade, as appropriate.

Additional summaries of solicited and unsolicited adverse events will present ≥ Grade 3 toxicity rates regardless of relatedness to study vaccine and accompanying 95% CIs by treatment group, for all subjects. Additional summaries of solicited and unsolicited adverse events will also be presented for all cohorts based on post-vaccination
intervals of interest (60 minutes, 7 days, 14 days, 28 days post vaccination, and overall) following each vaccination, and across all post-vaccination periods.

The number (percentage) of subjects with post-vaccination clinical laboratory values or vital sign values recorded as newly abnormal following study vaccination and meeting toxicity criteria (≥ Grade 1) as specified in the toxicity tables will be tabulated at each post-vaccination time point. Clinical, laboratory and vital sign abnormalities will also be reported as adverse events and will be included in the summary of adverse events.

Summaries of safety comparing solicited and unsolicited adverse events as recorded relative to the EPI vaccines will also be summarized by treatment group for subjects in Cohort 6. Additional summaries for Cohorts 1 through 5 will also be prepared. Separate summaries of solicited and unsolicited adverse events will be presented for these cohorts based on post-vaccination intervals of interest following each vaccination to evaluate pattern of prime and boost immune responses to study vaccine, and will be presented for all Cohorts by dose level.

Summaries for safety as described above (with the exception of the EPI evaluations) will also be presented for subjects in Cohorts 1 to 5, both at the selected dose and at additional doses as collected, as described above.

8.62 Secondary Objectives

8.621 Safety

Evaluation of the safety profile of three doses of AERAS-404 (per-protocol analysis) will be performed using data from Cohorts 4 and 5, and Cohort 6 at the selected dose, and will be summarized by treatment group. Only data from subjects who have data up to 28 days after they completed the third dose will be included in this presentation (per-protocol analysis). Analyses will include estimates of ≥ Grade 3 toxicity rates regardless of relatedness and accompanying 95% CIs by treatment group. Additional summaries of solicited and unsolicited adverse events will be presented for these cohorts based on post-vaccination intervals of interest following each vaccination, and across all post-vaccination periods. The number (percentage) of subjects with adverse events will be summarized by MedDRA system organ class and Preferred
Term. Additional summaries will present the number (percentage) of subjects with adverse events by severity and by relationship to study vaccine; parameters evaluable by the P1113 Pediatric Toxicity Table (Appendix III) will be summarized by severity corresponding to Toxicity Grade, as appropriate. The number (percentage) of subjects with post-vaccination clinical laboratory values or vital sign values recorded as newly abnormal following study vaccination and meeting toxicity criteria (Grade 1 and above) as specified in the toxicity table will be tabulated at each post-vaccination time point. Clinical, laboratory and vital sign abnormalities will also be reported as adverse events and will be included in the summary of adverse events.

8.622 Immunologic assays

A summary of immunologic assays to be performed on blood specimens is shown in Table 23.

The flow cytometry, ICS assay will be conducted at the Cape Town HVTN Immunology Laboratory in Cape Town, South Africa. The validated multiplex binding antibody assay is conducted at the Duke Human Vaccine Institute laboratory in Duke University in North Carolina, USA, which has extensive expertise and experience with this assay. Due to the complexity of this assay, it is not planned to be transferred to the new South African laboratory for this study.
Table 23. Summary of Immunology Laboratory Evaluations

<table>
<thead>
<tr>
<th>Sample type</th>
<th>Location</th>
<th>Assay</th>
<th>Purpose of Assay</th>
<th>Study Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBMC</td>
<td>HVTN Immunology Laboratory, Cape Town, South Africa</td>
<td>Flow cytometry, intracellular cytokine staining (ICS)†</td>
<td>Determine cellular immune response to study vaccine</td>
<td>Cohorts 1 &amp; 2: 0, 14, 182</td>
</tr>
<tr>
<td>Plasma</td>
<td>Duke University, North Carolina, USA</td>
<td>Multiplex binding antibody assay‡</td>
<td>Determine humoral immune response to study vaccine</td>
<td>0, 14, 182</td>
</tr>
<tr>
<td>Whole blood for RNA extraction</td>
<td>TBD (to be stored)</td>
<td>RNA analysis‡</td>
<td>To perform a multivariate analysis of the innate immune responses following study injection in order to identify early gene signatures that can predict immune responses</td>
<td>N/A</td>
</tr>
<tr>
<td>Serum</td>
<td>Sanofi-Pasteur, Pennsylvania USA</td>
<td>Antibody titers (ELISA)‡</td>
<td>Determine antibodies against EPI vaccines</td>
<td>182</td>
</tr>
</tbody>
</table>

† Primary assay
‡ Secondary assay

- Cellular assays

*Flow cytometry, intracellular cytokine staining (ICS)*

Flow cytometry will be used to examine vaccine-specific CD4+ and CD8+ T-cell responses following stimulation of PBMCs with peptide pools, each representing the entire amino acid sequence of the mycobacterial antigens Ag85B, and TB10.4.

Descriptive statistics will be used to summarize percentage of T-cell responses to each stimulation antigen by treatment group (study vaccine or placebo) at all available post-vaccination time points, and by cohort, for all evaluable subjects. Analyses will be presented by cytokine and antigen. Additional presentation of percentage T cell response for Cohort 6...
subjects by study vaccine or placebo will include summaries following each vaccination to evaluate pattern of prime and boost immune responses to study vaccine.

The number (percentage) of positive responses and accompanying 95% confidence intervals at 14 days post first, second, and third vaccinations will be presented by cohort, dose group, and treatment group, with positivity defined based on a validated methodology [39]. **Positive responses will be based on a validated, statistical positivity criteria approach in which responses in peptide stimulated wells are compared to responses to unstimulated wells.** Briefly, vaccine response at a given post-vaccination study day will be compared to response to the negative control using a one-sided Fisher's Exact test, with adjustment for multiple comparisons.

**The number (percentage) of post-vaccination responders will be presented by treatment regimen, for all vaccinated subjects who received at least 1 dose of study vaccine. The number (percentage) of post-vaccination responders will also be presented by treatment regimen, for subjects who received two doses of study vaccine in Cohorts 3A and 3B, and for all subjects who received three doses of study vaccine in Cohorts 4, 5, and 6.**

- **Antibody assays**

  **Multiplex binding antibody assay**

  Descriptive statistics will be used to summarize antibody concentration by treatment group and antigen **for all vaccinated subjects who received at least 1 dose of study vaccine, for subjects who received two doses of study vaccine in Cohorts 3A and 3B, and for all subjects who received three doses of study vaccine in Cohorts 4, 5, and 6.** Summaries will be presented by treatment group, cohort, and across cohorts as appropriate, for all evaluable subjects.
• Exploratory assay

RNA analysis

As an exploratory endpoint for examining mRNA gene expression signatures, mRNA expression will be performed. RNA will be isolated from whole blood. Signatures of gene expression changes after vaccination may be determined using computational systems biology tools.

Samples will be collected at entry and 3 days post the third study vaccine dose in Cohorts 4 to 6. Analysis will be done at the end of the study.

• Response to EPI vaccines

Seropositivity (as defined for each EPI vaccine) will be assessed by antibody levels measured for all Cohorts at 12 months of age, and in addition at 28 days post second study vaccine dose (Study Day 56) for Cohort 6. Summaries will include descriptive statistics for antibody titers to Tetanus toxoid vaccine (tetanus; given at 6, 10, 14 weeks of age), and Haemophilus influenza B conjugate vaccine (given at 6, 10, 14 weeks of age). Responses to other EPI vaccines including measles vaccine may also be assessed.

Summaries will be presented by treatment group, cohort, and across cohorts as appropriate, for all evaluable subjects.

Number (percentage) of seroconverters will be presented with 95% CIs to examine the difference in proportions between treatment groups. Summaries will be presented by time point, treatment group, cohort, and across cohorts as appropriate, for all evaluable subjects, at all available time points as described above.

Refer to the MOP for the assay methodology.
9.0 HUMAN SUBJECTS

9.1 Institutional Review Board/Ethics Committee and Informed Consent

The study will be conducted in compliance with country-specific laws and regulatory requirements. The conduct of the study will also adhere to the GCP principles laid out by the ICH and the Declaration of Helsinki.

This protocol, the informed consent document (Appendix VI), and any subsequent modifications must be reviewed and approved by the IRB or EC responsible for oversight of the study. Written informed consent must be obtained from the subject (or parents or legal guardians of subjects who cannot consent for themselves, such as those below the legal age). The informed consent will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the parent or legal guardian.

Each CRS which receives United States (US) Health and Human Services (HHS) funding and follows the ICH should have on record at the CRS a plan that detects and addresses any change in guardianship occurring in pediatric subjects and determines when a study subject must have a consent process which involves a legally authorized representative (LAR) other than a family member with guardianship. The plan will include how the CRS determines when a LAR is initially or no longer needed and how frequently the LAR resigns the consent. The plan should follow all IRB/EC, local, state, national and/or host country guidelines. Confirmation of such a plan at a CRS should be submitted with the regulatory documents.

9.2 Subject Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified only by a coded number to maintain subject confidentiality. All records will be kept in a secured area. All computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the Regulatory Authority, the Office for Human Research Protections (OHRP), the NIAID, the local IRB or Ethics Committee, Aeras or Sanofi Pasteur.

9.3 Study Discontinuation

The study may be discontinued at any time by the NIAID, the Regulatory Authority, the IRB or EC, Aeras, Sanofi Pasteur or other governmental agencies as part of their duties to ensure that research subjects are protected.
10.0 **PUBLICATION OF RESEARCH FINDINGS**

Publication of the results of this trial will be governed by IMPAACT and HVTN policies. Any presentation, abstract, or manuscript will be made available for review by the pharmaceutical sponsors prior to submission.

11.0 **BIOHAZARD CONTAINMENT**

As the transmission of HIV and other bloodborne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study, as currently recommended by the Centers for Disease Control and Prevention.

All infectious specimens will be sent using the ISS-1 SAF-T-PAK mandated by the International Air Transport Association Dangerous Goods Regulations-Packing Instruction 602. Refer to individual carrier guidelines (e.g., Federal Express or Airborne) for specific instructions.
12.0 REFERENCES

1. WHO. Tuberculosis (TB) and Poverty in SEAR. 2012. 
Ref Type: Online Source


Ref Type: Online Source


18. van Dissel JT, Soonawala D, Joosten SA, Prins C, Arend SM, Bang P *et al.*: Ag85B-ESAT-6 adjuvanted with IC31(R) promotes strong and long-lived Mycobacterium tuberculosis specific T cell responses in volunteers with previous BCG vaccination or tuberculosis infection. *Vaccine* 2011, 29: 2100-2109.


20. UNAIDS, WHO. South Africa Epidemiological Fact Sheet. UNAIDS and WHO. 2012. Ref Type: Abstract

   Ref Type: Online Source


## APPENDIX I-A

**Schedule of Evaluations for Cohorts 1 and 2**

<table>
<thead>
<tr>
<th>Study Visit</th>
<th>Screening</th>
<th>Entry(^2) (Day 0)</th>
<th>Day 3 (±1d)</th>
<th>Day 7 (±2d)</th>
<th>Day 14 (−3d and +4d)</th>
<th>Day 28 (±7d)</th>
<th>Day 56 (±7d)</th>
<th>Day 98(^3) (±7d)</th>
<th>Day 182 (±28d)</th>
<th>Day 273 (±42d)</th>
<th>Day 364 (±42d)</th>
<th>Last study visit</th>
<th>Early Study Discontinuation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CLINICAL EVALUATIONS</strong></td>
<td></td>
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</tr>
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<td>Informed Consent</td>
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<tr>
<td>Confirmation of BCG vaccination(^4)</td>
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<td>Physical(^6)</td>
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<td>X X X X X X X X X X X</td>
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<td>Counseling for HIV Status(^9)</td>
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<td>AERAS-404/placebo vaccination(^10)</td>
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<td>EPI vaccinations(^11)</td>
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<tr>
<td>Delayed post vaccination monitoring(^13)</td>
<td>X X(^{13a})</td>
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</tbody>
</table>

*Randomized to receive study vaccine/placebo at Study Day 0 (≥168 to ≤196 days of age).*
APPENDIX I-A
Schedule of Evaluations for Cohorts 1 and 2* (cont.)

<table>
<thead>
<tr>
<th>Study Visit</th>
<th>Screening</th>
<th>Entry (Day 0)</th>
<th>Day 3 (±1d)</th>
<th>Day 7 (±2d)</th>
<th>Day 14 (−3d and +4d)</th>
<th>Day 28 (±7d)</th>
<th>Day 56 (±7d)</th>
<th>Day 98 (±7d)</th>
<th>Day 182 (±28d)</th>
<th>Day 273 (±42d)</th>
<th>Day 364 (±56d)</th>
<th>Early Study Discontinuation</th>
</tr>
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<tr>
<td>LABORATORY EVALUATIONS</td>
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<tr>
<td>Hematology</td>
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<td>0.5 mL</td>
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<tr>
<td>Chemistries</td>
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<tr>
<td>HIV DNA PCR</td>
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<tr>
<td>Quantiferon</td>
<td>3 mL</td>
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<tr>
<td>Special immuno.</td>
<td>5 mL</td>
<td>5 mL</td>
<td>5 mL</td>
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<tr>
<td>EPI antibody titers</td>
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</tr>
<tr>
<td>TOTAL BLOOD VOLUMES‡</td>
<td>6.5 mL</td>
<td>5 mL</td>
<td>1.5 mL</td>
<td>5 mL</td>
<td>1.5 mL</td>
<td>11 mL</td>
<td>4.5 mL</td>
<td>1.5 – 9.5 mL</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

* Randomized to receive study vaccine/placebo at Study Day 0 (≥ 168 to ≤ 196 days of age).
‡ Blood drawing limits for research purposes: For pediatric patients, no more than 5 mL/kg may be drawn for research purposes in a single day, and no more than 9.5 mL/kg may be drawn over any eight-week period.

For insufficient blood draws, priorities are as follows:
1. Safety (Hematology, Chemistries)
2. Virology (HIV DNA PCR, HIV EIA)
3. Quantiferon
4. Special immuno.
5. EPI antibody titers
APPENDIX I-A

Footnotes for Cohorts 1 and 2

1. Screening evaluations must be completed within 30 days of Study Entry.
2. Study Entry window is ≥ 168 to ≤ 196 days of age.
3. Study Day 98 must not occur before the subject is 9 months of age. **The visit may be done after the subject has received the 9-month EPI vaccines.**
4. The child’s immunization card needs to be reviewed prior to entry. BCG vaccination at birth needs to be confirmed at screening or at entry visit ALL previous EPI immunizations and dates given need to be recorded in the participant’s source documents.
5. A complete history is required at Screening; a targeted history is sufficient at subsequent visits. Screening: record baseline signs/symptoms, diagnoses and medications; Subsequent visits: record new diagnoses, changes in signs/symptoms and new/changes in medications since the last visit.
6. Physical exam should include length/height, weight, head circumference, and vital signs (temperature, pulse and respiratory rate).
7. Adverse Events and Serious Adverse Events: collected beginning at entry and throughout the duration of the study; recorded at each study visit or at interim/unscheduled visits.
8. The child should be evaluated for TB through screening (i.e. family history and exposure to active case) and QuantiFERON testing. Refer to MOP.
9. All parents/legal guardians will be offered pre-test counseling before HIV testing and post-test counseling after HIV and will be explained the need to evaluate their child for HIV-1 infection. This will be done as part of the screening and entry procedures and at the study visit at about the time the participant is 12 months old. HIV testing will be done as per the Schedule of Evaluations.
10. The dose of AERAS-404 or placebo should be administered after completion of randomization procedures. Dose differs for Cohort 1 and Cohort 2. Please refer to the study treatment section (Section 5.0) for the dose for each cohort.
11. EPI vaccines will be given through the EPI program in South Africa. Refer to Appendix II for the routine pediatric vaccines based on the EPI schedule in South Africa. Refer to Section 5.0 for guidance on EPI vaccine administration and contingency plan in the event of in-country EPI program shortage.
12. Subjects will be observed at the CRS for at least 60 minutes after receiving study vaccine. Repeat vital signs prior to discharge.
13. Parents/legal guardians will be provided with a daily adverse event subject diary to facilitate collection of pre-specified local or systemic vaccine reactions that occur up to 7 days post vaccine administration. A digital thermometer will also be provided for daily (axillary) temperature monitoring. Refer to Section 6.3 (Subject Diary and Daily Temperature Monitoring). The parent/legal guardian should be instructed to contact the study staff if an adverse event or reaction or fever occurs within 7 days post vaccine administration.
   13a. Phone call: Evaluations at study day 3 will be completed via phone call.
   13b. Clinic visit: Evaluations at study day 7 will be completed via a clinic visit.
14. Hematology should include complete blood count (CBC) with differential and platelet count.
15. Chemistries should include SGPT (ALT), SGOT (AST) and Creatinine.
16. Must be performed at DAIDS VQA-certified laboratory.
17. Refer to the Laboratory Processing Chart (LPC) and MOP for collection and processing instructions. Sample at early discontinuation is not required if a sample was drawn within 30 days of the visit.
18. ICS and multiplex antibody binding assays. Sample at entry can be drawn anytime between screening and entry; it must be collected prior to vaccination at entry. Sample at early discontinuation is not required if a sample was drawn within 30 days of the visit.
19. Refer to Table 23 in Section 8.622 for the sample type and laboratory information, and to the LPC and MOP for collection, processing and shipment instructions.
APPENDIX I-B
Schedule of Evaluations for Cohorts 3A and 3B*

<table>
<thead>
<tr>
<th>Study Visit</th>
<th>Screening</th>
<th>Entry(^1) (Day 0)</th>
<th>Day 3 (± 1d)</th>
<th>Day 7 (± 2d)</th>
<th>Day 14 (± 2d)</th>
<th>Day 28 (+ 7d)</th>
<th>Day 31 (± 1d)</th>
<th>Day 35 (± 2d)</th>
<th>Day 42 (+7d)</th>
<th>Day 56 (± 7d)</th>
<th>Day 98 (± 7d)</th>
<th>Day 182 (± 28d)</th>
<th>Day 273 (± 42d)</th>
<th>Day 364 (± 42d)</th>
<th>Last study visit</th>
<th>Early Study Discontinuation</th>
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<tbody>
<tr>
<td>CLINICAL EVALUATIONS</td>
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<td>X</td>
<td>X</td>
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<tr>
<td>Confirmation of BCG vaccination(^4)</td>
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<td>TB assessment(^8)</td>
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<td>X</td>
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<tr>
<td>Counseling for HIV Status(^9)</td>
<td>X</td>
<td>X</td>
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<tr>
<td>AERAS-404/placebo vaccination(10)</td>
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<td>EPI vaccinations(11)</td>
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<tr>
<td>Immediate post vaccination monitoring(13)</td>
<td>X</td>
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<tr>
<td>Delayed post vaccination monitoring(13)</td>
<td>X</td>
<td>X(^{13a})</td>
<td>X(^{13b})</td>
<td>X</td>
<td>X(^{13a})</td>
<td>X</td>
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</table>

* Randomized to receive study vaccine/placebo at Study Day 0 (≥ 168 to ≤ 189 days of age) and Study Day 28.
## APPENDIX I-B

Schedule of Evaluations for **Cohorts 3A and 3B** (cont.)

<table>
<thead>
<tr>
<th>Study Visit</th>
<th>Screening</th>
<th>Entry(^2) (Day 0)</th>
<th>Day 3 ((± 1\text{d}))</th>
<th>Day 7 ((± 2\text{d}))</th>
<th>Day 14 ((± 2\text{d}))</th>
<th>Day 28 ((± 7\text{d}))</th>
<th>Day 31 ((± 1\text{d}))</th>
<th>Day 35 ((± 2\text{d}))</th>
<th>Day 42 ((± 7\text{d}))</th>
<th>Day 56 ((± 7\text{d}))</th>
<th>Day 98 ((± 7\text{d}))</th>
<th>Day 182 ((± 28\text{d}))</th>
<th>Day 273 ((± 42\text{d}))</th>
<th>Day 364 ((± 42\text{d}))</th>
<th>Last study visit</th>
<th>Early Study Discontinuation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LABORATORY EVALUATIONS</strong></td>
<td></td>
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<tr>
<td>Hematology(^{14})</td>
<td>0.5 mL</td>
<td>0.5 mL</td>
<td>0.5 mL</td>
<td>0.5 mL</td>
<td>0.5 mL</td>
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<tr>
<td>Chemistries(^{15})</td>
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<td>1 mL</td>
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<tr>
<td>HIV DNA PCR(^{16})</td>
<td>1 mL</td>
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<tr>
<td>HIV EIA</td>
<td>1 mL</td>
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<tr>
<td>QuantiFERON(^{17})</td>
<td>3 mL</td>
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<tr>
<td>Special immunology(^{18,19})</td>
<td>5 mL</td>
<td>5 mL</td>
<td>5 mL</td>
<td>5 mL</td>
<td>5 mL</td>
<td>5 mL</td>
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<tr>
<td>EPI antibody titers(^{19})</td>
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<tr>
<td><strong>TOTAL BLOOD VOLUMES(^2)</strong></td>
<td>6.5 mL</td>
<td>5 mL</td>
<td>1.5 mL</td>
<td>6.5 mL</td>
<td>1.5 mL</td>
<td>5 mL</td>
<td>1.5 mL</td>
<td>11 mL</td>
<td>4.5 mL</td>
<td>1.5 – 9.5 mL</td>
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</tbody>
</table>

\(^*\) Randomized to receive study vaccine/placebo at **Study Day 0 (≥ 168 to ≤ 189 days of age) and Study Day 28.**

\(^{\dagger}\) Blood drawing limits for research purposes: For pediatric patients, no more than 5 mL/kg may be drawn for research purposes in a single day, and no more than 9.5 mL/kg may be drawn over any eight-week period.

For insufficient blood draws, priorities are as follows:
1. Safety (Hematology, Chemistries)
2. Virology (HIV DNA PCR, HIV EIA)
3. QuantiFERON
4. Special immunology
5. EPI antibody titers
APPENDIX I-B

Footnotes for **Cohort 3A and 3B**

1. Screening evaluations must be completed within 30 days of Study Entry.
2. Study Entry window is \( \geq 168 \) to \( \leq 189 \) days of age.
3. Study **Day 98** must not occur before the subject is 9 months of age. **The visit may be done after the subject has received the 9-month EPI vaccines.**
4. The child’s immunization card needs to be reviewed prior to entry. BCG vaccination at birth needs to be confirmed at screening or at entry visit ALL previous EPI immunizations and dates given need to be recorded in the participant’s source documents.
5. A complete history is required at Screening; a targeted history is sufficient at subsequent visits. Screening: record baseline signs/symptoms, diagnoses and medications; Subsequent visits: record new diagnoses, changes in signs/symptoms and new/changes in medications since the last visit.
6. Physical exam should include length/height, weight, head circumference, and vital signs (temperature, pulse and respiratory rate).
7. **Adverse Events and Serious Adverse Events:** collected beginning at entry and throughout the duration of the study; recorded at each study visit or at interim/unscheduled visits.
8. The child should be evaluated for TB through screening (i.e. family history and exposure to active case) and QuantiFERON testing. Refer to MOP.
9. All parents/legal guardians will be offered pre-test counseling before HIV testing and post-test counseling after HIV and will be explained the need to evaluate their child for HIV-1 infection. This will be done as part of the screening and entry procedures and at the study visit at about the time the participant is 12 months old. HIV testing will be done as per the Schedule of Evaluations.
10. Dose 1 of AERAS-404 or placebo should be administered after completion of randomization procedures. Please refer to the study treatment section (Section 5.0) for the dose **(Table 16) and the dosing schedule and additional guidelines (Table 15) for Cohorts 3A and 3B.**
11. EPI vaccines will be given through the EPI program in South Africa. Refer to Appendix II for the routine pediatric vaccines based on the EPI schedule in South Africa. Refer to Section 5.0 for guidance on EPI vaccine administration and contingency plan in the event of in-country EPI program shortage.
12. Subjects will be observed at the CRS for at least 60 minutes after receiving study vaccine. Repeat vital signs prior to discharge.
13. Parents/legal guardians will be provided with a daily adverse event subject diary to facilitate collection of pre-specified local or systemic vaccine reactions that occur up to 7 days post vaccine administration. A digital thermometer will also be provided for daily (axillary) temperature monitoring. Refer to Section 6.3 (Subject Diary and Daily Temperature Monitoring). The parent/legal guardian should be instructed to contact the study staff if an adverse event or reaction or fever occurs within 7 days post vaccine administration.
   13a. Phone call: Evaluations at study day 3 and study day 31 will be completed via phone call.
   13b. Clinic visit: Evaluations at study day 7 and study day 35 will be completed via a clinic visit.
14. Hematology should include CBC with differential and platelet count.
15. Chemistries should include SGPT (ALT), SGOT (AST) and Creatinine.
16. Must be performed at DAIDS VQA-certified laboratory.
17. Refer to the LPC and MOP for collection and processing instructions. Sample at early discontinuation is not required if a sample was drawn within 30 days of the visit.
18. ICS and multiplex antibody binding assays. Samples at entry and study day 28 must be drawn prior to vaccination. Sample at entry can be drawn anytime between screening and entry. Sample at early discontinuation is not required if a sample was drawn within 30 days of the visit.
19. Sample at entry must be drawn prior to vaccination. Refer to Table 23 in Section 8.622 for the sample type and laboratory information, and to the LPC and MOP for collection, processing and shipment instructions.
APPENDIX I-C
Schedule of Evaluations for Cohorts 4 and 5 *

| Study Visit          | Screening 1 | Entry 2 (Day 0) | Day 3 (± 1d) | Day 7 (± 2d) | Day 14 (± 7d) | Day 28 (± 7d) | Day 42 (± 7d) | Day 45 (± 1d) | Day 56 (± 7d) | Day 59 (± 7d) | Day 66 (± 7d) | Day 70 (± 7d) | Day 77 (± 7d) | Day 84 (± 7d) | Day 98 (± 7d) | Day 101 (± 1d) | Day 105 (± 2d) | Day 112 (± 7d) | Day 126 (± 7d) | Day 196 (± 7d) | Day 280 (± 28d) | Day 371 (± 42d) | Day 462 (± 42d) | Last Study Visit | Early Study Discontinuation |
|---------------------|-------------|-----------------|-------------|-------------|--------------|--------------|--------------|--------------|--------------|--------------|----------------|--------------|----------------|--------------|--------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|
| CLINICAL EVALUATIONS |             |                 |             |             |              |              |              |              |              |              |                 |              |                |              |              |                |              |                |              |                |                |                |                |                |                |
| Informed Consent    | X           |                 |             |             |              |              |              |              |              |              |                 |              |                |              |              |                |              |                |              |                |                |                |                |                |                |
| Confirmation of BCG vaccination | X           |                 |             |             |              |              |              |              |              |              |                 |              |                |              |              |                |              |                |              |                |                |                |                |                |                |
| History 6,8         | X           | X               | X           | X           | X            | X            | X            | X            | X            | X            | X              | X            | X              | X            | X            | X              | X            | X              | X            | X              | X              | X              | X              | X              | X              |
| Physical 7,8        | X           | X               | X           | X           | X            | X            | X            | X            | X            | X            | X              | X            | X              | X            | X            | X              | X            | X              | X            | X              | X              | X              | X              | X              | X              |
| TB assessment 9     | X           | X               | X           | X           | X            | X            | X            | X            | X            | X            | X              | X            | X              | X            | X            | X              | X            | X              | X            | X              | X              | X              | X              | X              | X              |
| Counseling for HIV Status 10 | X           | X               |             |             |              |              |              |              |              |              |                 |              |                |              |              |                |              |                |              |                |              |                |                |                |                |                |
| AERAS-404/placebo vaccination 11 | Dose 1       |                 |             |             |              |              |              |              |              |              |                 |              |                |              |              |                |              |                |              |                |              |                |                |                |                |                |
| EPI vaccinations 12  | X           |                 |             |             |              |              |              |              |              |              |                 |              |                |              |              |                |              |                |              |                |              |                |                |                |                |                |
| Immediate post vaccination monitoring 13 | X           |                 |             |             |              |              |              |              |              |              |                 |              |                |              |              |                |              |                |              |                |              |                |                |                |                |                |
| Delayed post vaccination monitoring 14 | X           | X 14a          | X 14b       | X           | X 14a        | X 14b        | X            | X 14a        | X 14b        | X            | X 14a         | X 14b        | X              | X 14b        | X 14a        | X              |                 |                 |                 |                 |                 |                 |                 |                 |

Randomized to receive study vaccine/placebo at Study Day 0 (≥ 84 to ≤ 98 days of age), Study Day 42 and Study Day 98.
## APPENDIX I-C

Schedule of Evaluations for Cohorts 4 and 5* (cont.)

<table>
<thead>
<tr>
<th>Study Visit</th>
<th>Screening(^1)</th>
<th>Entry(^2) (Day 0)</th>
<th>Day 3 (± 1d)</th>
<th>Day 7 (± 2d)</th>
<th>Day 14 (± 7d)</th>
<th>Day 28 (± 7d)</th>
<th>Day 42 (± 20)</th>
<th>Day 45 (± 20)</th>
<th>Day 56 (± 70)</th>
<th>Day 70 (± 70)</th>
<th>Day 98 (± 70)</th>
<th>Day 101 (± 10)</th>
<th>Day 105 (± 20)</th>
<th>Day 112 (± 70)</th>
<th>Day 126 (± 70)</th>
<th>Day 196 (± 70)</th>
<th>Day 280 (± 28d)</th>
<th>Day 371 (± 42d)</th>
<th>Day 462 (± 42d)</th>
<th>Last study visit</th>
<th>Early Study Discontinuation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LABORATORY EVALUATIONS</strong></td>
<td>Hematology(^5)</td>
<td>0.5 mL</td>
<td>0.5 mL</td>
<td>0.5 mL</td>
<td>0.5 mL</td>
<td>0.5 mL</td>
<td>0.5 mL</td>
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<tr>
<td></td>
<td>Chemistries(^6)</td>
<td>1 mL</td>
<td>1 mL</td>
<td>1 mL</td>
<td>1 mL</td>
<td>1 mL</td>
<td>1 mL</td>
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<tr>
<td></td>
<td>HIV DNA PCR(^7)</td>
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<td></td>
<td>HIV EIA</td>
<td>1 mL</td>
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<tr>
<td></td>
<td>QuantIFERON(^8)</td>
<td>3 mL</td>
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<tr>
<td></td>
<td>Special immunology(^9,10)</td>
<td>5 mL</td>
<td>5 mL</td>
<td>5 mL</td>
<td>5 mL</td>
<td>5 mL</td>
<td>5 mL</td>
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<td></td>
<td>EPI antibody titers(^20)</td>
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<td>RNA analysis(^20)</td>
<td>2.5 mL</td>
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<tr>
<td><strong>TOTAL BLOOD VOLUMES(^\dagger)</strong></td>
<td>6.5 mL</td>
<td>7.5 mL</td>
<td>1.5 mL</td>
<td>1.5 mL</td>
<td>1.5 mL</td>
<td>1.5 mL</td>
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<td>1.5 mL</td>
<td>1.5 mL</td>
<td>1.5 mL</td>
<td>4 mL</td>
<td>5 mL</td>
<td>1.5 mL</td>
<td>11 mL</td>
<td>4.5 mL</td>
<td>1.5 – 9.5 mL</td>
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</tbody>
</table>

Randomized to receive study vaccine/placebo at **Study Day 0 (≥ 84 to ≤ 98 days of age), Study Day 42 and Study Day 98.**

Blood drawing limits for research purposes: For pediatric patients, no more than 5 mL/kg may be drawn for research purposes in a single day, and no more than 9.5 mL/kg may be drawn over any eight-week period. **Note: The blood drawing limits may be exceeded if a subject is < 4 kg. Contact the protocol team at [impaact.teamp1113@fstrf.org](mailto:impaact.teamp1113@fstrf.org) if blood limits may be exceeded and follow the blood draw priority list below.**

For insufficient blood draws, priorities are as follows:
1. Safety (Hematology, Chemistries)
2. Virology (HIV DNA PCR, HIV EIA)
3. QuantIFERON
4. Special immunology
5. RNA analysis
6. EPI antibody titers

---

\(^1\) Randomized to receive study vaccine/placebo at Study Day 0 (≥ 84 to ≤ 98 days of age), Study Day 42 and Study Day 98.

\(^\dagger\) Blood drawing limits for research purposes: For pediatric patients, no more than 5 mL/kg may be drawn for research purposes in a single day, and no more than 9.5 mL/kg may be drawn over any eight-week period. **Note: The blood drawing limits may be exceeded if a subject is < 4 kg. Contact the protocol team ([impaact.teamp1113@fstrf.org](mailto:impaact.teamp1113@fstrf.org)) if blood limits may be exceeded and follow the blood draw priority list below.**
APPENDIX I-C

Footnotes for Cohorts 4 and 5

1. Screening evaluations must be completed within 30 days of Study Entry.
2. Study Entry window is ≥ 84 to ≤ 98 days of age (≥ 2 weeks after receipt of EPI vaccine doses at 10 weeks of age and at least 10 days before EPI vaccine doses at 14 weeks of age).
3. Study day 42 must occur 28 days after EPI vaccine doses administered at 14 weeks of age.
4. Study day 196 must not occur before the subject is 9 months of age. The visit may be done after the subject has received the 9-month EPI vaccines.
5. The child’s immunization card needs to be reviewed prior to entry. BCG vaccination at birth needs to be confirmed at screening or at entry visit ALL previous EPI immunizations and dates given need to be recorded in the participant’s source documents.
6. A complete history is required at Screening; a targeted history is sufficient at subsequent visits. Screening: record baseline signs/symptoms, diagnoses and medications; Subsequent visits: record new diagnoses, changes in signs/symptoms and new/changes in medications since the last visit.
7. Physical exam should include length/height, weight, head circumference, and vital signs (temperature, pulse and respiratory rate).
8. Adverse Events and Serious Adverse Events: collected beginning at entry and throughout the duration of the study; recorded at each study visit or at interim/unscheduled visits.
9. The child should be evaluated for TB through screening (i.e. family history and exposure to active case) and QuantiFERON testing. Refer to MOP.
10. All parents/legal guardians will be offered pre-test counseling before HIV testing and post-test counseling after HIV and will be explained the need to evaluate their child for HIV-1 infection. This will be done as part of the screening and entry procedures and at the study visit at about the time the participant is 12 months old. HIV testing will be done as per the Schedule of Evaluations.
11. Dose 1 of AERAS-404 or placebo should be administered after completion of randomization procedures. Dose differs for Cohort 4 and Cohort 5. Please refer to the study treatment section (Section 5.0) for the dose (Table 16) and the dosing schedule and additional guidelines (Table 15) for Cohorts 4 and 5.
12. EPI vaccines will be given through the EPI program in South Africa. Refer to Appendix II for the routine pediatric vaccines based on the EPI schedule in South Africa. Refer to Section 5.0 for guidance on EPI vaccine administration and contingency plan in the event of in-country EPI program shortage.
13. Subjects will be observed at the CRS for at least 60 minutes after receiving study vaccine. Repeat vital signs prior to discharge.
14. Parents/legal guardians will be provided with a daily adverse event subject diary to facilitate collection of pre-specified local or systemic vaccine reactions that occur up to 7 days post vaccine administration. A digital thermometer will also be provided for daily (axillary) temperature monitoring. Refer to Section 6.3 (Subject Diary and Daily Temperature Monitoring). The parent/legal guardian should be instructed to contact the study staff if an adverse event or reaction or fever occurs within 7 days post vaccine administration.
14a. Phone call: Evaluations at study day 3, study day 45 and study day 105 will be completed via phone call.
14b. Clinic visit: Evaluations at study day 7, study day 49 and study day 101 will be completed via a clinic visit.
15. Hematology should include CBC with differential and platelet count.
16. Chemistries should include SGPT (ALT), SGOT (AST) and Creatinine.
17. Must be performed at DAIDS VQA-certified laboratory.
18. Refer to the LPC and MOP for collection and processing instructions. Sample at early discontinuation is not required if a sample was drawn within 30 days of the visit.
19. ICS and multiplex antibody binding assays. Sample at entry must be drawn prior to vaccination; it can be drawn anytime between screening and entry. Sample at early discontinuation is not required if a sample was drawn within 30 days of the visit.
20. Sample at entry must be drawn prior to vaccination. Refer to Table 23 in Section 8.622 for the sample type and laboratory information, and to the LPC and MOP for collection, processing and shipment instructions.
## APPENDIX I-D

Schedule of Evaluations for Cohort 6*

<table>
<thead>
<tr>
<th>Study Visit</th>
<th>Screening</th>
<th>Entry$^3$ (Day 0)</th>
<th>Day 3 (± 1d)</th>
<th>Day 7 (± 2d)</th>
<th>Day 14 (+7d)</th>
<th>Day 28$^4$ (± 7d)</th>
<th>Day 35 (± 2d)</th>
<th>Day 42 (+7d)</th>
<th>Day 56 (± 7d)</th>
<th>Day 112 (± 28d)</th>
<th>Day 210$^6$ (± 7d)</th>
<th>Day 217 (± 7d)</th>
<th>Day 224 (+7d)</th>
<th>Day 238 (± 7d)</th>
<th>Day 245 (± 28d)</th>
<th>Day 294 (± 28d)</th>
<th>Day 385 (± 28d)</th>
<th>Day 476 (± 42d)</th>
<th>Early Study Discontinuation</th>
</tr>
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<tr>
<td>Clinical Evaluations</td>
<td>Informed Consent</td>
<td>X</td>
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<tr>
<td></td>
<td>Confirmation of BCG vaccination$^5$</td>
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<td>(X)</td>
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<td>History$^5,^8$</td>
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<td>Counseling for HIV Status$^{10}$</td>
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<tr>
<td></td>
<td>AERAS-404/placebo vaccination$^{11}$</td>
<td>Dose 1</td>
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<td>Dose 2</td>
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<tr>
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<td></td>
<td>Immediate post vaccination monitoring$^{13}$</td>
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<td>X$^{14b}$</td>
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<td>X$^{14a}$</td>
<td>X$^{14b}$</td>
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<td>X$^{14b}$</td>
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</table>

*Randomized to receive study vaccine/placebo at Study Day 0 (≥ 64 to ≤ 83 days of age), Study Day 28 and Study Day 210.
APPENDIX I-D
Schedule of Evaluations for Cohort 6* (cont.)

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<td>TOTAL BLOOD VOLUMES3</td>
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</tbody>
</table>

* Randomized to receive study vaccine/placebo at Study Day 0 (≥ 64 to ≤ 83 days of age), Study Day 28 and Study Day 210.

‡ Blood drawing limits for research purposes: For pediatric patients, no more than 5 mL/kg may be drawn for research purposes in a single day, and no more than 9.5 mL/kg may be drawn over any eight-week period. Note: The blood drawing limits may be exceeded if a subject is < 4 kg. Contact the protocol team (impaaact.teamp1113@fstrf.org) if blood limits may be exceeded and follow the blood draw priority list below.

For insufficient blood draws, priorities are as follows:
1. Safety (Hematology, Chemistries)
2. Virology (HIV DNA PCR, HIV EIA)
3. Quantiferon
4. Special Immunology
5. RNA analysis
6. EPI antibody titers
APPENDIX I-D

Footnotes for Cohort 6

1. Screening evaluations must be completed within 30 days of Study Entry.
2. Study entry window is coincident with EPI vaccine doses at 10 weeks of age (≥ 64 to ≤ 83 days of age).
3. Study day 28 must occur coincident with EPI vaccine doses at 14 weeks of age.
4. Study day 210 must occur coincident with EPI vaccine doses at 9 months of age.
5. The child’s immunization card needs to be reviewed prior to entry. BCG vaccination at birth needs to be confirmed at screening or at entry visit ALL previous EPI immunizations and dates given need to be recorded in the participant’s source documents
6. A complete history is required at Screening; a targeted history is sufficient at subsequent visits. Screening: record baseline signs/symptoms, diagnoses and medications; Subsequent visits: record new diagnoses, changes in signs/symptoms and new/changes in medications since the last visit.
7. Physical exam should include length/height, weight, head circumference, and vital signs (temperature, pulse and respiratory rate).
8. Adverse Events and Serious Adverse Events: collected beginning at entry and throughout the duration of the study; recorded at each study visit or at interim/unscheduled visits.
9. The child should be evaluated for TB through screening (i.e. family history and exposure to active case) and QuantiFERON testing. Refer to MOP.
10. All parents/legal guardians will be offered pre- test counseling before HIV testing and post-test counseling after HIV and will be explained the need to evaluate their child for HIV-1 infection. This will be done as part of the screening and entry procedures and at the study visit at about the time the participant is 12 months old. HIV testing will be done as per the Schedule of Evaluations.
11. Dose of AERAS-404 or placebo should be administered after completion of randomization procedures. Please refer to the study treatment section (Section 5.0) for the dose (Table 16) and the dosing schedule and additional guidelines (Table 15) for Cohort 6.
12. EPI vaccines will be given through the EPI program in South Africa. Refer to Appendix II for the routine pediatric vaccines based on the EPI schedule in South Africa. Refer to Section 5.0 for guidance on EPI vaccine administration and contingency plan in the event of in-country EPI program shortage.
   • The EPI vaccines should be injected in the same thigh with a distance of at least 3 cm between the injection sites, and the study vaccine injected in the opposite thigh.
13. Subjects will be observed at the CRS for at least 60 minutes after receiving study vaccine. Repeat vital signs prior to discharge.
14. Parents/legal guardians will be provided with a daily adverse event subject diary to facilitate collection of pre-specified local or systemic vaccine reactions that occur up to 7 days post vaccine administration. A digital thermometer will also be provided for daily (axillary) temperature monitoring. Refer to Section 6.3 (Subject Diary and Daily Temperature Monitoring). The parent/legal guardian should be instructed to contact the study staff if an adverse event or reaction or fever occurs within 7 days post vaccine administration.
   14a. Phone call: Evaluations at study day 3, study day 31 and study day 217 will be completed via phone call
   14b. Clinic visit: Evaluations at study day 7, study day 35 and study day 213 will be completed via a clinic visit.
15. Hematology should include CBC with differential and platelet count.
16. Chemistries should include SGPT (ALT), SGOT (AST) and Creatinine.
17. Must be performed at DAIDS VQA-certified laboratory.
18. Refer to the LPC and MOP for collection and processing instructions. Sample at early discontinuation is not required if a sample was drawn within 30 days of the visit.
19. ICS and multiplex antibody binding assays. Sample at entry must be drawn prior to vaccination; it can be drawn anytime between screening and entry. Sample at early discontinuation is not required if a sample was drawn within 30 days of the visit.
20. Refer to Table 23 in Section 8.622 for the sample type and laboratory information, and to the LPC and MOP for collection, processing and shipment instructions.
APPENDIX II

EXPANDED PROGRAM ON IMMUNIZATION (EPI) VACCINE SCHEDULE FOR SOUTH AFRICA

<table>
<thead>
<tr>
<th>EPI Vaccine</th>
<th>Age of vaccination</th>
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<tbody>
<tr>
<td></td>
<td>Birth</td>
</tr>
<tr>
<td>BCG</td>
<td>X</td>
</tr>
<tr>
<td>OPV</td>
<td>X</td>
</tr>
<tr>
<td>IPV</td>
<td>Dose 1</td>
</tr>
<tr>
<td>DTaP</td>
<td>Dose 1</td>
</tr>
<tr>
<td>Hib</td>
<td>Dose 1</td>
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<tr>
<td>Hepatitis B</td>
<td>Dose 1</td>
</tr>
<tr>
<td>PCV</td>
<td>Dose 1</td>
</tr>
<tr>
<td>RV</td>
<td>Dose 1</td>
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<tr>
<td>Measles</td>
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</table>
# APPENDIX III

## P1113/C-015-404

### PEDIATRIC TOXICITY TABLE

<table>
<thead>
<tr>
<th>Local Site of Injection Symptoms</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection site pain (pain without touching)</td>
<td>Minimal or no limitation of use of limb</td>
<td>Limitation of use of limb OR greater than minimal interference with usual activities</td>
<td>Inability to perform usual activities</td>
<td>N/A</td>
</tr>
<tr>
<td>Tenderness (pain when area is touched)</td>
<td>Minimal or no limitation of use of limb</td>
<td>Limitation of use of limb OR greater than minimal interference with usual activities</td>
<td>Inability to perform usual activities</td>
<td>N/A</td>
</tr>
<tr>
<td>Erythema (Redness)*</td>
<td>Present, ≤ 1.0 cm in diameter</td>
<td>&gt; 1.0 cm to 2.5 cm in diameter</td>
<td>&gt;2.5 cm in diameter</td>
<td>Local or extensive exfoliative dermatitis</td>
</tr>
<tr>
<td>Induration or Edema</td>
<td>Present, ≤ 1.0 cm in diameter</td>
<td>&gt; 1.0 cm to 2.5 cm in diameter</td>
<td>&gt;2.5 cm in diameter</td>
<td>Local or extensive exfoliative dermatitis</td>
</tr>
<tr>
<td>Ulceration</td>
<td>N/A</td>
<td>Presence of ulcer</td>
<td>Necrosis (involving dermis and deeper tissue)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Systemic (General)</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased oral intake</td>
<td>Minimal decrease in oral intake</td>
<td>Below 50% of normal oral intake in 24 hr</td>
<td>No oral intake in 24 hr</td>
<td>N/A</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 episode in 24 hr; no interference with activity</td>
<td>2-3 episodes in 24 hr OR some interference with activity</td>
<td>&gt; 3 episodes in 24 hours OR prevents daily activity</td>
<td>N/A</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Unformed stool OR 1-3 more stools than baseline in 24 hr</td>
<td>Partially liquid stools OR 4-6 more stools than baseline in 24 hr</td>
<td>Completely liquid stools OR &gt;6 more stools than baseline in 24 hr</td>
<td>N/A</td>
</tr>
<tr>
<td>Irritability</td>
<td>Easily consolable; minimal or no interference with activity</td>
<td>Difficult to console; some interference with activity</td>
<td>Inconsolable; prevents daily activity</td>
<td>N/A</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Minimal or no interference with activity</td>
<td>Some interference with activity</td>
<td>Prevents daily activity</td>
<td>N/A</td>
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<tr>
<td>Lethargy</td>
<td>Minimal decrease in alertness; minimal interference with activity</td>
<td>Some interference with activity</td>
<td>Unable to achieve normal level of alertness; prevents daily activity</td>
<td>N/A</td>
</tr>
<tr>
<td>Illness or clinical adverse event</td>
<td>Minimal or no interference with activity</td>
<td>Some interference with activity not requiring medical intervention</td>
<td>Prevents daily activity and requires medical intervention</td>
<td>N/A</td>
</tr>
<tr>
<td>Vital Signs</td>
<td>Grade 1</td>
<td>Grade 2</td>
<td>Grade 3</td>
<td>Grade 4</td>
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</table>
| **Fever (Axillary)** | 38.0 – 38.4°C  
100.4 – 101.1°F | 38.5 - 40°C  
101.2 - 104°F | >40°C  
>104°F | N/A |
<p>| <strong>Tachycardia – beats per minute</strong> | 6 months | 181-200 | 201-220 | &gt;220 | N/A |
| | 6 months – 1 year | 171-190 | 191-210 | &gt;210 | N/A |
| | 1-2 years | 151-170 | 171-190 | &gt;190 | N/A |
| <strong>Bradycardia – beats per minute</strong> | 6 months | 96-105 | 91-95 | &lt;91 | N/A |
| | 6 months – 1 year | 91-100 | 81-90 | &lt;81 | N/A |
| | 1-2 years | 81-90 | 71-80 | &lt;71 | N/A |
| <strong>Hypertension (systolic) - mm Hg</strong> | Females ≤ 1 yr | Height &lt;25th percentile | 98-101 | &gt;101 | Clinical or laboratory evidence of end-organ damage |
| | Height 25th-75th percentile | 100-103 | &gt;103 | |
| | Height &gt;75th percentile | 103-106 | &gt;106 | |
| | Females 1 yr – 2 yr | Height &lt;25th percentile | 99-102 | &gt;102 | |
| | Height 25th-75th percentile | 102-104 | &gt;104 | |
| | Height &gt;75th percentile | 104-107 | &gt;107 | |
| | Males ≤ 1 yr | Height &lt;25th percentile | 95-98 | &gt;98 | |
| | Height 25th-75th percentile | 98-101 | &gt;101 | |
| | Height &gt;75th percentile | 102-105 | &gt;105 | |
| | Males 1 yr – 2 yr | Height &lt;25th percentile | 99-101 | &gt;101 | |
| | Height 25th-75th percentile | 102-105 | &gt;105 | |
| | Height &gt;75th percentile | 105-108 | &gt;108 | |
| <strong>Hypertension (diastolic) – mm Hg</strong> | Females ≤ 1 yr | Height &lt;25th percentile | 53-56 | &gt;56 | Clinical or laboratory evidence of end-organ damage |
| | Height 25th-75th percentile | 54-57 | &gt;57 | |
| | Height &gt;75th percentile | 56-59 | &gt;59 | |
| | Females 1 yr – 2 yr | Height &lt;25th percentile | 57-60 | &gt;60 | |
| | Height 25th-75th percentile | 58-61 | &gt;61 | |
| | Height &gt;75th percentile | 60-63 | &gt;63 | |
| | Males ≤ 1 yr | Height &lt;25th percentile | 51-54 | &gt;54 | |
| | Height 25th-75th percentile | 53-56 | &gt;56 | |
| | Height &gt;75th percentile | 55-58 | &gt;58 | |
| | Males 1 yr – 2 yr | Height &lt;25th percentile | 55-58 | &gt;58 | |
| | Height 25th-75th percentile | 57-60 | &gt;60 | |
| | Height &gt;75th percentile | 59-62 | &gt;62 | |</p>
<table>
<thead>
<tr>
<th>Hypotension/ Hypovolemia</th>
<th>N/A</th>
<th>Symptomatic, requiring oral fluid replacement</th>
<th>Symptomatic, requiring IV fluid replacement</th>
<th>N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tachypnea – breaths per minute</td>
<td>39-44</td>
<td>45-48</td>
<td>&gt;48</td>
<td>N/A</td>
</tr>
<tr>
<td>≤ 1 year</td>
<td>31-36</td>
<td>37-44</td>
<td>&gt;44</td>
<td>N/A</td>
</tr>
<tr>
<td>1 - 2 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory Distress/ Hypoxia</td>
<td></td>
<td>Wheezing, nasal flaring or retractions; minimal or no interference with activity</td>
<td>Some interference with activity or pulse oximetry &lt;95%</td>
<td>Prevents normal activity or pulse oximetry &lt;90%</td>
</tr>
</tbody>
</table>

### Serum/Plasma Chemistry

<table>
<thead>
<tr>
<th>Grade</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium – hyponatremia mEq/L or mmol/L:</td>
<td>132 – 134</td>
<td>130 – 131</td>
<td>&lt;130</td>
</tr>
<tr>
<td>Sodium – hypernatremia mEq/L or mmol/L:</td>
<td>145-146</td>
<td>147-148</td>
<td>&gt;148</td>
</tr>
<tr>
<td>Potassium – hyperkalemia mEq/L or mmol/L:</td>
<td>5.3 – 5.4</td>
<td>5.5 – 5.6</td>
<td>&gt;5.6</td>
</tr>
<tr>
<td>≤ 1 year:</td>
<td>5.1 – 5.2</td>
<td>5.3 – 5.4</td>
<td>&gt;5.4</td>
</tr>
<tr>
<td>1 - 2 years:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potassium – hypokalemia mEq/L or mmol/L:</td>
<td>3.5 – 3.6</td>
<td>3.3 – 3.4</td>
<td>3.1 – 3.2</td>
</tr>
<tr>
<td>Glucose – hypoglycemia mg/dL:</td>
<td>55-59</td>
<td>50-54</td>
<td>&lt;50</td>
</tr>
<tr>
<td>mmol/L:</td>
<td>3.0 – 3.2</td>
<td>2.8 – 2.9</td>
<td>&lt;2.8</td>
</tr>
<tr>
<td>Glucose – hyperglycemia Fasting - mg/dL:</td>
<td>101 – 110</td>
<td>111 – 125</td>
<td>&gt;125</td>
</tr>
<tr>
<td>mmol/L:</td>
<td>5.7 – 6.0</td>
<td>6.1 – 6.8</td>
<td>&gt;6.8</td>
</tr>
<tr>
<td>Random – mg/dL:</td>
<td>110 – 125</td>
<td>126 – 200</td>
<td>&gt;200</td>
</tr>
<tr>
<td>mmol/L:</td>
<td>6.1 – 6.8</td>
<td>6.9 – 11.0</td>
<td>&gt;11.0</td>
</tr>
<tr>
<td>Blood urea nitrogen (BUN) – increased mg/dL:</td>
<td>21 – 24</td>
<td>25 – 28</td>
<td>&gt;28</td>
</tr>
<tr>
<td>mmol/L:</td>
<td>7.5 – 8.9</td>
<td>9.0 – 10.0</td>
<td>&gt;10.0</td>
</tr>
<tr>
<td>Creatinine – increased mg/dL:</td>
<td>0.8 – 0.9</td>
<td>1.0 – 1.2</td>
<td>&gt;1.2</td>
</tr>
<tr>
<td>umol/L:</td>
<td>66 – 82</td>
<td>83 – 100</td>
<td>&gt;100</td>
</tr>
<tr>
<td>Calcium – hypocalcemia mg/dL:</td>
<td>8.0 – 8.4</td>
<td>7.5 – 7.9</td>
<td>&lt;7.5</td>
</tr>
<tr>
<td>mmol/L:</td>
<td>2.00 – 2.10</td>
<td>1.87 – 1.99</td>
<td>&lt;1.87</td>
</tr>
<tr>
<td>Calcium – hypercalcemia mg/dL:</td>
<td>11.1-11.3</td>
<td>11.4 – 11.6</td>
<td>&gt;11.6</td>
</tr>
<tr>
<td>mmol/L:</td>
<td>2.78 – 2.84</td>
<td>2.85 – 2.92</td>
<td>&gt;2.92</td>
</tr>
<tr>
<td>Magnesium – hypomagnesemia mg/dL:</td>
<td>1.3 – 1.5</td>
<td>1.1 – 1.2</td>
<td>&lt;1.1</td>
</tr>
<tr>
<td>mmol/L:</td>
<td>0.52 – 0.62</td>
<td>0.43 – 0.51</td>
<td>&lt;0.43</td>
</tr>
<tr>
<td>Phosphorus – hypophosphatemia mg/dL:</td>
<td>2.3 – 2.5</td>
<td>2.0 – 2.2</td>
<td>&lt;2.0</td>
</tr>
<tr>
<td>mmol/L:</td>
<td>0.73 – 0.80</td>
<td>0.63 – 0.72</td>
<td>&lt;0.63</td>
</tr>
<tr>
<td>Albumin – hypoalbuminemia</td>
<td>g/dL:</td>
<td>2.5 – 2.7</td>
<td>2.2 – 2.4</td>
</tr>
<tr>
<td>----------------------------</td>
<td>------</td>
<td>-----------</td>
<td>-----------</td>
</tr>
<tr>
<td></td>
<td>g/L:</td>
<td>25 – 27</td>
<td>22 – 24</td>
</tr>
<tr>
<td>Total protein – hypoproteinemia</td>
<td>g/dL:</td>
<td>4.4 – 4.6</td>
<td>4.1 – 4.3</td>
</tr>
<tr>
<td></td>
<td>g/L:</td>
<td>44 – 46</td>
<td>41 – 43</td>
</tr>
<tr>
<td>Alkaline phosphatase (ALP)</td>
<td>increased</td>
<td>1.1 – 2.0 x ULN**</td>
<td>2.1 – 3.0 x ULN</td>
</tr>
<tr>
<td>Liver Function Tests (LFT)</td>
<td>AST, ALT, GGT</td>
<td>increased</td>
<td>1.1 – 2.5 x ULN</td>
</tr>
<tr>
<td>Bilirubin (with any increase in LFT)</td>
<td>increased</td>
<td>1.1 – 1.25 x ULN</td>
<td>1.26 – 1.5 x ULN</td>
</tr>
<tr>
<td>Bilirubin (with normal LFT)</td>
<td>increased</td>
<td>1.1 – 1.5 x ULN</td>
<td>1.6 – 2.0 x ULN</td>
</tr>
<tr>
<td>Cholesterol – increased</td>
<td>mg/dL:</td>
<td>171 - 185</td>
<td>186 – 199</td>
</tr>
<tr>
<td></td>
<td>mmol/L:</td>
<td>5.1 – 5.5</td>
<td>5.6 – 6.0</td>
</tr>
<tr>
<td>Pancreatic enzymes</td>
<td>amylase, lipase</td>
<td>increased</td>
<td>1.1 – 1.5 x ULN</td>
</tr>
</tbody>
</table>

** ULN is the upper limit of the normal age-appropriate reference range.

<table>
<thead>
<tr>
<th>Hematology</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (36 days – 56 days) – g/dL:</td>
<td>8.5 – 9.4</td>
<td>7.0 – 8.4</td>
<td>&lt;6.00</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>85 – 94</td>
<td>70 – 84</td>
<td>&lt;60</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin (≥ 57 days=6 month) – g/dL:</td>
<td>9.0 – 9.4</td>
<td>8.5 – 8.9</td>
<td>&lt;8.5</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>90 – 94</td>
<td>85 – 89</td>
<td>&lt;85</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin (6 mo - 2yr) – g/dL:</td>
<td>10.0 – 10.4</td>
<td>9.5 – 9.9</td>
<td>&lt;9.5</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>100 – 104</td>
<td>95 - 99</td>
<td>&lt;95</td>
<td></td>
</tr>
<tr>
<td>WBC – increased cells/mm³</td>
<td>18,700 – 22,000</td>
<td>22,100 – 25,000</td>
<td>&gt;25,000</td>
<td>N/A</td>
</tr>
<tr>
<td>WBC – decreased cells/mm³</td>
<td>4,500 – 5,500</td>
<td>3,500 – 4,400</td>
<td>&lt;3,500</td>
<td>N/A</td>
</tr>
<tr>
<td>Lymphocytes - decreased cells/mm³</td>
<td>2,000-2,700</td>
<td>1,500-1,900</td>
<td>&lt;1,500</td>
<td>N/A</td>
</tr>
<tr>
<td>Neutrophils - decreased</td>
<td>Age (&gt; 7 days – 3 mo)</td>
<td>1,000 – 1,300</td>
<td>750 – 999</td>
<td>&lt; 500</td>
</tr>
<tr>
<td></td>
<td>cells/mm³:</td>
<td>750-990</td>
<td>500-740</td>
<td>&lt;500</td>
</tr>
<tr>
<td></td>
<td>(≥ 3 mo)</td>
<td>850 – 1,500</td>
<td>1,501 – 5,000</td>
<td>&gt;5,000</td>
</tr>
<tr>
<td>Eosinophils – increased cells/mm³</td>
<td>125,000 – 140,000</td>
<td>100,000 – 124,000</td>
<td>&lt;100,000</td>
<td>N/A</td>
</tr>
<tr>
<td>Platelets - decreased cells/mm³</td>
<td>125,000 – 140,000</td>
<td>100,000 – 124,000</td>
<td>&lt;100,000</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>1.1 – 1.2 x ULN**</td>
<td>1.3 – 1.4 x ULN</td>
<td>&gt;1.4 x ULN</td>
<td>N/A</td>
</tr>
<tr>
<td>-------------------------</td>
<td>------------------</td>
<td>-----------------</td>
<td>------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>Prothrombin Time (PT)/International normalized ratio (INR) – increased</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partial thromboplastin time (PTT) – increased</td>
<td>1.1 – 1.2 x ULN</td>
<td>1.3 – 1.4 x ULN</td>
<td>&gt;1.4 x ULN</td>
<td>N/A</td>
</tr>
<tr>
<td>Fibrinogen – increased</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mg/dL:</td>
<td>400 – 500</td>
<td>501 – 600</td>
<td>&gt;600</td>
<td>N/A</td>
</tr>
<tr>
<td>g/L:</td>
<td>4.00 – 5.00</td>
<td>5.01 – 6.00</td>
<td>&gt;6.00</td>
<td></td>
</tr>
<tr>
<td>Fibrinogen – decreased</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mg/dL:</td>
<td>150 - 170</td>
<td>125 – 149</td>
<td>&lt;125</td>
<td>N/A</td>
</tr>
<tr>
<td>g/L:</td>
<td>1.50 – 1.70</td>
<td>1.25 – 1.49</td>
<td>&lt;1.25</td>
<td></td>
</tr>
</tbody>
</table>

** “ULN” is the upper limit of the normal age-appropriate reference range.

<table>
<thead>
<tr>
<th>Urine</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein</td>
<td>Trace</td>
<td>1+</td>
<td>2+</td>
<td>N/A</td>
</tr>
<tr>
<td>Glucose</td>
<td>Trace</td>
<td>1+</td>
<td>2+</td>
<td>N/A</td>
</tr>
<tr>
<td>Blood (microscopic) – red blood cells per high power field (rbc/hpf)</td>
<td>6-10</td>
<td>11 – 50</td>
<td>&gt;50 and/or gross blood</td>
<td>N/A</td>
</tr>
</tbody>
</table>

For adverse events not specifically listed in the Toxicity Table, please refer to definitions of Grade 1, 2, 3, and 4 toxicity listed for 'Illness or clinical adverse event' in the table in this appendix for 'Systemic (General)' events.
APPENDIX IV

P1113/C-015-404

SERIOUS ADVERSE EVENT (SAE) REPORTING PROCESS

SAE reported at CRS

Site

Completes SAE

- CRS PI/designee determines causality & severity
- Enters SAE in EDC. In case SAE data cannot be entered in EDC, site should:
  - fax/email SAER to World Wide Safety Group (PPD PVG)
  - email SAER to Protocol Team (+ phone call if event is life-threatening or death)
- Notifies Local EC, as required

Protocol Team
- Receives SAE notification
- Performs medical assessment
- Determines expectedness
- Communicates with CRS PI, Global Medical Monitor, if applicable SMC

World Wide Safety Group (PPD)
- Safety Team
  - Receives SAE notification or email/fax
  - Processes SAE/SUSAR
  - Notifies sponsor and other parties
- Global Medical Monitor
  - Receives unblinded treatment assignment
- Unblinding Team
  - Manages unblinding information

Study Monitors

Aeras/Sanofi/NIH

48 HOURS

24 HOURS
APPENDIX V

P1113/C-015-404
SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTION (SUSAR) REPORTING PROCESS

AE reported at CRS

- CRS PI/Designee:
  - Assesses AE as Serious
  - Determines causality as Related
  - (Possible, Probable, Definite)

- Protocol Team assesses the SAE as unexpected

SUSAR

World-Wide Safety Group (PPD)

MCC
- Blinded CIOMS

Aeras/Sanofi/NIH
- Blinded CIOMS

Participating study investigators
- Blinded CIOMS

Study Monitors
- Blinded CIOMS
APPENDIX VI

DIVISION OF AIDS
INTERNATIONAL MATERNAL PEDIATRIC ADOLESCENT AIDS CLINICAL TRIALS GROUP (IMPAACT)

SAMPLE INFORMED CONSENT

For protocol:

PHASE I/II, SAFETY AND IMMUNOGENICITY STUDY OF A RECOMBINANT PROTEIN TUBERCULOSIS VACCINE (AERAS-404) IN BCG-PRIMED INFANTS

IMPAACT P1113 / Aeras C-015-404
Version 2.0

SHORT TITLE FOR THE STUDY: IMPAACT P1113 / Aeras C-015-404

INTRODUCTION

You are being asked to allow your baby to take part in this research study of an experimental vaccine against tuberculosis (TB). This study is sponsored by Aeras in partnership with the National Institutes of Health (NIH). Aeras is a non-profit organization that is dedicated to developing effective and affordable vaccines to prevent TB. The experimental vaccine is manufactured and provided by Sanofi Pasteur and Statens Serum Institut (SSI), which are pharmaceutical companies. The doctor in charge of this study at this site is: (insert name of Principal Investigator). Before you decide if you want to your baby to be a part of this study, we want you to know about the study.

This is a consent form. It gives you information about this study. The study staff will talk with you about this information. You are free to ask questions about this study at any time. If you agree to allow your baby to take part in this study, you will be asked to sign this consent form. You will get a copy to keep.

WHY IS THIS STUDY BEING DONE?

TB is an infection caused by a germ called *Mycobacterium tuberculosis*. TB is common in your country, with approximately _____ new cases per year (sites – add number of cases). TB can spread from one person to another and is a common cause of death especially in young children. There are many medicines that can treat and cure TB after it begins. These TB medicines may cost a lot of money and must be taken for a long time. In some people, TB medicines cause bad side effects even when TB is getting better. There is only one vaccine approved to keep TB from happening. In many
countries, including your country, this TB vaccine called BCG (Bacillus Calmette-Guérin) is given to most babies. BCG is made from a weakened strain of the TB germ so it does not usually make people sick. The BCG vaccine helps the body fight off the TB germ, but many people who get the BCG vaccine may still get TB and about 40% will be infected by 15 years of age. A better vaccine to prevent TB is needed. This research study is being done to help find a better TB vaccine.

The experimental TB vaccine in this study is called AERAS-404. It is experimental because it is not approved for use in any country and we are not sure how well it will work. AERAS-404 is a combination of TB proteins and substances to stimulate an immune response (the ability to fight disease). It is being studied to see if it is safe and if it will help BCG work better to prevent TB from infecting babies. Other studies in adults have been completed to test the safety of this vaccine. The vaccine has been found safe in the adult studies. This is the first study of this vaccine in children and babies.

In this study, babies who have received BCG and who also receive the AERAS-404 vaccine will be compared to babies who only got the BCG vaccine. This study is being done to test the AERAS-404 vaccine for safety and effectiveness when given to babies. Another purpose of the study is to measure the immune response your baby develops after receiving AERAS-404, and to find the best dose schedule for AERAS-404. There is a chance that your baby could still get TB as we are not sure yet if this vaccine will prevent TB. Another purpose of this study is to find out how this vaccine works with other vaccines babies normally get at their local clinics.

WHAT DOES MY BABY HAVE TO DO IF HE/SHE IS IN THIS STUDY?

If you allow your baby to be in this study, your baby will be randomized (by chance as by a flip of a coin) to receive AERAS-404 or a placebo vaccine by an injection in the upper thigh. A placebo is an inactive substance that is made to look like the actual vaccine being given so you cannot tell what your baby is receiving.

Your baby will be enrolled into one of 7 study groups based on your baby’s age at the time of entry into the study. The 7 study groups are:

- **Study Group 1**: 168 to 196 days of age
- **Study Group 2**: 168 to 196 days of age
- **Study Group 3A**: 168 to 189 days of age
- **Study Group 3B**: 168 to 189 days of age
- **Study Group 4**: 84 to 98 days of age
- **Study Group 5**: 84 to 98 days of age
- **Study Group 6**: 64 to 83 days of age

A different amount (dose) of AERAS-404 vaccine will be given to each group. The groups will enrol one after the other starting with Study Group 1. The next group will
open after enrolment in the previous group is completed and it is determined that it is safe to move to the next group. Study Group 1 will be given the lowest dose and the amounts will slowly increase up to Study Group 5.

Babies in Study Groups 1 and 2 will have about a 2 out of 3 chance of receiving AERAS-404 vaccine (not the placebo). They will be given 1 vaccination (injection). Study Group 1 will receive a lower dose of vaccine than Study Group 2.

Babies in Study Group 3A will have about a 2 out of 3 chance of receiving AERAS-404 vaccine (not the placebo). They will be given 2 vaccinations about 1 month apart. They will receive the same dose of vaccine as Study Group 2.

Babies in Study Group 3B will have about an 8 out of 9 chance of receiving AERAS-404 (not placebo). They will be given 2 injections about 1 month apart. They will receive a higher dose of vaccine than Study Group 3A.

After Study Group 3B has completed, the information from Study Group 3B will be reviewed to check that AERAS-404 is safe and to measure the immune response of the babies after receiving AERAS-404. If AERAS-404 vaccine is found to be safe in babies, and the immune response of Study Group 3B meets the level that we are looking for, the study will continue with the next study groups (i.e., Study Groups 4 and then 5). If AERAS-404 vaccine is found not to be safe or the immune response of Study Group 3B does not meet the level that we are looking for, the study will be stopped.

Babies in Study Groups 4 and 5 will have about a 5 out of 6 chance of receiving AERAS-404 vaccine (not the placebo). They will be given 3 vaccinations within about 3 months. Study Group 4 will receive a lower dose of vaccine (the same dose as Study Group 3B) than Study Group 5.

After Study Group 5 has completed, all the information from all the groups will be reviewed to check that the AERAS-404 vaccine is safe. The information from Study Groups 4 and 5 will also be reviewed to measure the immune response of the babies in these groups after receiving AERAS-404. The safest and best dose of the AERAS-404 vaccine will be chosen after all the information is reviewed. If the AERAS-404 vaccine is found to be safe in babies, and the immune response in Study Group 4 or 5 meet the level that we are looking for, the study will continue with Study Group 6. If the AERAS-404 vaccine is found not to be safe in babies or the immune response in both Study Group 4 and 5 does not meet the level that we are looking for, the study will be stopped.

Babies in Study Group 6 will have about an equal chance of receiving AERAS-404 vaccine or placebo. They will be given 3 vaccinations within about 6.5 months. The
The safest and best dose of AERAS-404 vaccine found after review of all the information from the previous groups will be the dose for babies that will receive AERAS-404 vaccine in Study Group 6.

Screening visit to see if your baby can be in this study:
If you decide you want your baby to be in this study, we will do some tests to see if your baby is able to enter the study. This visit will last about ________ (sites – add time based on local site processes).

- You will be asked to give the study staff a telephone number or a method to contact you during the study.
- The study staff will ask if you are willing for your baby to complete all scheduled study visits.
- The study staff will then ask you questions about your baby’s health.
- The study staff will take your baby’s measurement of height, weight and vital signs (temperature, pulse and respiratory rate), and the study doctor will examine your baby.
- You will be asked questions about whether you or your baby has/had TB or has been close to someone who has/had TB. If your baby has/had TB or has been exposed to someone who has/had TB, your baby will not be enrolled in the study. If your baby has had a Tuberculin Skin Test (TST, a test placed on the skin of your arm using a small needle that can help determine if a person has been exposed to TB) in the past, your baby will also not be enrolled in the study.
- Your baby’s health record will be checked to find the date your baby received his or her BCG vaccine and to check that your baby is up-to-date with all other vaccinations for his/her age.
- Study staff may contact your baby’s regular doctor (if you have one) to get your baby’s medical history, and to inform the doctor about this study.
- The study staff will ask for your permission to review your (the Mother) medical records to check your HIV status. If you had a positive HIV test at any time while pregnant with your baby, your baby will not be enrolled in this study. You and your baby will be referred for follow-up care from your regular doctor.
- Your baby will have blood tests to make sure that he/she is healthy.
- Your baby will also have blood test(s) for HIV. You will be given information on HIV/AIDS before your baby’s HIV test(s), and the study staff will meet with you to help you understand why the test(s) is/are being done, how it is/they are done and what the result(s) may mean for you and your baby. The study staff will meet with you again when the result(s) is/are ready. If the test(s) for HIV is/are positive, the result(s) will be provided to you and to your regular doctor, and your baby will be
referred for follow-up care from your regular doctor. Your baby will not be enrolled into the study. Mothers of babies whose HIV test(s) is/are positive will also be referred for follow-up care because they may be the source of their baby’s positive test(s).

- A blood test for TB will also be done. If this TB test is positive, your baby will not be enrolled in the study.

- The total amount of blood collected for this visit is 6.5 mL or a little over 1 teaspoon (*sites – add locally relevant description of blood volume*).

**Entry visit (Study Day 0)**

- If your baby is able to join the study, the study staff will ask you a few more health questions about your baby.

- You will be asked if your baby has recently been vaccinated with any other vaccines.

- Your baby will have 5 to 7.5 mL or 1 to 1½ teaspoon (*sites – add locally relevant description of blood volume*) of blood taken, depending on which study group your baby is in, before your baby is given the vaccine. The blood will be used to measure how your baby’s body identifies and defends itself against the TB germ after receiving AERAS-404 vaccine. You have an option to have this blood collected at the same time the blood for the screening visit is collected.

- Your baby will be assigned a study group depending on his/her age when he/she joins the study.

- Your baby will be randomly assigned to receive AERAS-404 or placebo vaccine within the study group. Neither you nor the study staff will know which injection your baby will get until later in the study.

- The study staff will take your baby’s measurement of height, weight and vital signs (temperature, pulse and respiratory rate), and the study doctor will examine your baby before the injection is given.

- Depending on the study group your baby is in, your baby will receive one to three injections with either AERAS-404 or placebo vaccine, at up to three different visits as shown in the tables of tests for each study group. At this visit, your baby will receive the first injection in the muscle in the upper leg.

- Your baby must remain in the clinic for at least 60 minutes after the injection to make sure he/she is well. His/her temperature, respiratory rate, and pulse rate will be taken after the injection, before he/she may leave the clinic. The study staff will call you 3 days after the injection to see how your baby is doing and you will be asked to come back to clinic 7 days after the injection to check for any possible side effects.

- You will be asked to keep a diary of side effects your baby has and take your baby’s temperature each day starting on the day of injection up to 7 days after the injection.
You will receive the diary and a digital thermometer before you leave the clinic, along with instructions on how to complete the diary and take the temperature of your baby daily. **You will take your baby’s axillary temperature, which is taking the temperature under the arm or in his/her armpit.** You will fill out the diary every day up to 6 days after the injection is given. The study staff will review the diary with you at the phone call or visit 3 days and 7 days after each injection. For most injections, the study staff will check on your baby 3 days after the injection by phone (you will be contacted by phone) and your baby will have a visit 7 days after the injection. If you baby is in Study Groups 4 to 6, your baby will have a clinic visit 3 days after the third injection and the study staff will check on your baby 7 days after the third injection by phone (you will be contacted by phone). You must contact the study doctor or staff if your baby has a side effect or fever during the 7 days after an injection. You have to bring the diary to the clinic at the next study visit after the injection is given.

- If your baby is enrolled in study group 6, your baby will receive the routine pediatric vaccines given at 10 weeks of age in your country. The vaccines may be given by the study doctor or study staff at the same time that your baby has the entry visit. The vaccines will be given in the opposite leg of the AERAS-404 or placebo vaccine vaccination.

- This visit will last about _______ (sites – add time based on local site processes).

**Study visits**

- After your baby has been given the first injection, you will be asked to bring him/her back to the clinic from nine to eighteen (18) times, depending on the study group your baby is in, until he/she is **about** 18 months of age.

- Depending on the study group your baby is in, the study visits your baby will have and the total blood to be collected after the first injection at Entry (Study Day 0) are shown below (sites – add locally relevant description of blood volume). Most visits will require your baby to be seen in the clinic but some visits will be done through a phone contact and those visits are noted in the tables below.
(Sites – encircle the table that is relevant to the subject being consented and cross out the tables that do not apply.)

### Study Groups 1 and 2
#### Tests done on Study Day 3 to Day 364

<table>
<thead>
<tr>
<th>Study Days</th>
<th>Physical Exam</th>
<th>Blood Taken</th>
<th>Safety Tests</th>
<th>TB Test</th>
<th>HIV Test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1.5 mL (about ½ teaspoon)</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>7</td>
<td>Yes</td>
<td>5 mL (about 1 teaspoon)</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>14</td>
<td>Yes</td>
<td>1.5 mL (about ½ teaspoon)</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>28</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>56, 98</td>
<td>Yes</td>
<td>11 mL (about 2 teaspoons)</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>182</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>273</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>364</td>
<td>Yes</td>
<td>4.5 mL (about 1 teaspoon)</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

- Your baby will receive the routine pediatric vaccines given at 9 and 18 months of age in your country at Study Days 98 and 364, respectively. Your baby may receive these vaccines through your baby’s regular doctor or through the study doctor.
- Your baby will have an HIV test at around the time your baby is 12 months of age (Study Day 182). Before the test is done, the study doctor or staff will discuss the test with you and possible results. The study doctor or staff will discuss the results of the test with you.
- Some of the blood taken at Study Day 14 and Day 182 will be used to measure how your baby’s body identifies and defends itself against the TB germ after receiving the AERAS-404 vaccine.
- Some of the blood taken at Study Day 182 will be used to find out how the AERAS-404 vaccine works with other vaccines babies normally get.
### Study Groups 3A and 3B
Tests done on Study Day 3 to Day 364

<table>
<thead>
<tr>
<th>Study Days</th>
<th>Physical Exam</th>
<th>AERAS-404 or placebo</th>
<th>Blood Taken</th>
<th>Safety Tests</th>
<th>TB Test</th>
<th>HIV Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>3, 31</td>
<td>Phone call</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7, 35</td>
<td>Yes</td>
<td>No</td>
<td>1.5 mL</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(about ½ teaspoon)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>28</td>
<td>Yes</td>
<td>Yes</td>
<td>6.5 mL</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(about 1½ teaspoon)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>42</td>
<td>Yes</td>
<td>No</td>
<td>5 mL</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(about 1 teaspoon)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>56</td>
<td>Yes</td>
<td>No</td>
<td>1.5 mL</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(about ½ teaspoon)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>98, 273</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>182</td>
<td>Yes</td>
<td>No</td>
<td>11 mL</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(about 2 teaspoons)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>364</td>
<td>Yes</td>
<td>No</td>
<td>4.5 mL</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(about 1 teaspoon)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Your baby will receive the routine pediatric vaccines given at 9 and 18 months of age in your country at Study Days 98 and 364, respectively. Your baby may receive these vaccines through your baby’s regular doctor or through the study doctor.

- Your baby will have an HIV test at around the time your baby is 12 months of age (Study Day 182). Before the test is done, the study doctor or staff will discuss the test with you and possible results. The study doctor or staff will discuss the results of the test with you.

- Some of the blood taken at Study Day 28, Day 42 and Day 182 will be used to measure how your baby’s body identifies and defends itself against the TB germ after receiving the AERAS-404 vaccine.

- Some of the blood taken at Study Day 182 will be used to find out how the AERAS-404 vaccine works with other vaccines babies normally get.
Study Groups 4 and 5
Tests done on Study Day 3 to Day 462

<table>
<thead>
<tr>
<th>Study Days</th>
<th>Physical Exam</th>
<th>AERAS-404 or placebo</th>
<th>Blood Taken</th>
<th>Safety Tests</th>
<th>TB Test</th>
<th>HIV Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>3, 45, 105</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7, 49</td>
<td>Yes</td>
<td>No</td>
<td>1.5 mL (about ½ teaspoon)</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>14, 56, 112</td>
<td>Yes</td>
<td>No</td>
<td>5 mL (about 1 teaspoon)</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>28</td>
<td>Yes</td>
<td>No</td>
<td>1.5 mL (about ½ teaspoon)</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>42, 98</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>70, 126</td>
<td>Yes</td>
<td>No</td>
<td>1.5 mL (about ½ teaspoon)</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>101</td>
<td>Yes</td>
<td>No</td>
<td>4 mL (about 1 teaspoon)</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>196, 371</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>280</td>
<td>Yes</td>
<td>No</td>
<td>11 mL (about 2 teaspoons)</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>462</td>
<td>Yes</td>
<td>No</td>
<td>4.5 mL (about 1 teaspoon)</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

- Your baby will receive the routine pediatric vaccines given at 14 weeks, 9 months and 18 months of age in your country at Study Days 14, 196 and 462, respectively. Your baby may receive these vaccines through your baby’s regular doctor or through the study doctor.

- Your baby will have an HIV test at around the time your baby is 12 months of age (Study Day 280). Before the test is done, the study doctor or staff will discuss the test with you and possible results. The study doctor or staff will discuss the results of the test with you.

- Some of the blood taken at Study Day 14, Day 56, Day 101, Day 112 and Day 280 will be used to measure how your baby’s body identifies and defends itself against the TB germ after receiving the AERAS-404 vaccine.

- Some of the blood taken at Study Day 280 will be used to find out how the AERAS-404 vaccine works with other vaccines babies normally get.
Study Group 6
Tests done on Study Day 3 to Day 476

<table>
<thead>
<tr>
<th>Study Days</th>
<th>Physical Exam</th>
<th>AERAS-404 or placebo</th>
<th>Blood Taken</th>
<th>Safety Tests</th>
<th>TB Test</th>
<th>HIV Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>3, 31, 217</td>
<td>Yes</td>
<td>No</td>
<td>1.5 mL (about ½ teaspoon)</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>7, 35</td>
<td>Yes</td>
<td>No</td>
<td>5 mL (about 1 teaspoon)</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>14, 42, 224, 385</td>
<td>Yes</td>
<td>No</td>
<td>1.5 mL (about ½ teaspoon)</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>28</td>
<td>Yes</td>
<td>Yes</td>
<td>2.5 mL (about ½ teaspoon)</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>56, 238</td>
<td>Yes</td>
<td>No</td>
<td>2.5 mL (about ½ teaspoon)</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>112</td>
<td>Yes</td>
<td>No</td>
<td>2 mL (about ½ teaspoon)</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>210</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>213</td>
<td>Yes</td>
<td>No</td>
<td>4 mL (about 1 teaspoon)</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>294</td>
<td>Yes</td>
<td>No</td>
<td>6 mL (about 1 teaspoon)</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>476</td>
<td>Yes</td>
<td>No</td>
<td>4.5 mL (about 1 teaspoon)</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

- Your baby will receive the routine pediatric vaccines given at 14 weeks, 9 months and 18 months of age in your country at Study Days 28, 210 and 476, respectively. Your baby may receive these vaccines through your baby’s regular doctor or through the study doctor. The vaccines will be given in 2 injections about 3 cm apart in the opposite leg of the AERAS-404 or placebo vaccine vaccination.

- Your baby will have an HIV test at around the time your baby is 12 months of age (Study Day 294). Before the test is done, the study doctor or staff will discuss the test with you and possible results. The study doctor or staff will discuss the results of the test with you.

- Some of the blood taken at Study Day 14, Day 42, Day 213, Day 224 and Day 294 will be used to measure how your baby’s body identifies and defends itself against the TB germ after receiving the AERAS-404 vaccine.

- Some of the blood taken at Study Days 56 and 294 will be used to find out how the AERAS-404 vaccine works with other vaccines babies normally get.
The safety tests that will be done are a CBC or complete blood count (which shows how many red and white blood cells there are) and blood chemistries (which checks how well the liver and kidneys are working).

The phone contact visit will take about 30 minutes. The visits when AERAS-404 or placebo vaccine injection is given will last about __________ (sites – add time based on local site processes). All other visits will last about ______ (sites – add time based on local site processes).

The total amount of blood collected is the most that will vary depending on country or site guidelines and what is needed for the tests that are being done, but will always be no more than 11 mL or about 2 teaspoons. If the study doctor is concerned about your baby’s health, he/she may ask your permission to do additional tests.

- At each of your baby’s clinic visits, you will be asked about any symptoms your baby may have had and any medications your baby has taken since the last visit. The injection site on the leg will be examined at each visit up to 28 days after the injection days. The study doctor or a study site team member will also briefly check your baby’s general health at each visit to see if there are any health problems. If you have any concerns about your baby’s health, the doctor will send your baby for appropriate medical care.

- Your baby must remain in the clinic for at least 60 minutes after receiving each AERAS-404 or placebo vaccine injection to make sure he/she is well. His/her temperature, respiratory rate, and pulse rate will be taken after the injection, before he/she may leave the clinic. The study staff will call you 3 days after the injection to see how your baby is doing and you will be asked to come back to clinic 7 days after the injection to check for any possible side effects.

- After each of your baby’s injection you will be asked to keep a diary of side effects your baby has and take your baby’s temperature each day starting on the day of injection up to 7 days after the injection. You will receive the diary and a digital thermometer before you leave the clinic, along with instructions on how to complete the diary and take the temperature of your baby daily. You will take your baby’s axillary temperature, which is taking the temperature under the arm or in his/her armpit. You will fill out the diary every day up to 6 days after each injection is given. The study staff will review the diary with you at the phone call or visit 3 days and 7 days after each injection. For most injections, the study staff will check on your baby 3 days after the injection by phone (you will be contacted by phone) and your baby will have a visit 7 days after the injection. If you baby is in Study Groups 4 to 6, your baby will have a clinic visit 3 days after the third injection and the study staff will check on your baby 7 days after the third injection by phone (you will be contacted by phone). You must contact the study doctor or staff if your baby has a side effect or fever during the 7 days after an injection. You have to bring the diary to the clinic at the next study visit after each injection.
• You may be asked to bring your baby into the clinic between the scheduled visits if the study doctor is concerned about your baby’s health.

• If your baby is treated for any illness by a doctor who is not the study doctor, the study doctor may ask for copies of the medical records for your baby’s care. You should tell a study site team member if your baby is sick or does not feel well. You should also tell a study site team member about changes in medications, or if your baby starts taking new medications. If at any point during the study we think that your baby might have TB, your baby will be referred for medical testing and care.

OTHER INFORMATION
Your baby’s blood samples will be tested to see how your baby’s body identifies and defends itself against the TB germ after receiving the AERAS-404 vaccine. Your baby’s blood samples might be shipped and/or stored outside of the country that they were collected. Your baby’s blood samples may be stored in the laboratory until the tests are done later in the study. The blood will only be used for tests for this study.

If the study doctor needs to know if your baby received AERAS-404 or placebo vaccine for a clinical emergency, the study pharmacist will provide this information to the study doctor.

The information collected in this study may be used for other IMPAACT-approved research.

HOW MANY PARTICIPANTS WILL TAKE PART IN THIS STUDY?
About 229 babies will take part in this study.

HOW LONG WILL MY BABY BE IN THIS STUDY?
You baby will be in this study until your baby is about 18 months of age.

WHY THE STUDY DOCTOR MAY STOP FURTHER VACCINATION FOR THE BABY
The study doctor may need to stop further vaccination of your baby with AERAS-404 or placebo vaccine if:

• Your baby receives steroids by mouth equal to your baby’s weight in kg, daily for any one of the 3 days before a scheduled AERAS-404 or placebo vaccine injection. Steroids are drugs that are often prescribed by a doctor to control swelling, redness and tenderness in the body.
• Your baby has a bad reaction that is related to the vaccine.
• Your baby has a bad reaction to the vaccine that the study doctor or protocol team feels will be harmful to your baby.
• Your baby has fever of more than 40°C/104°F and the protocol team decides that continuing to receive the vaccine will be harmful to your baby.
• Your baby is exposed to TB or receives anti-TB medications during the study.
• Your baby has an allergic reaction after receiving vaccine.
• Your baby has a Tuberculin Skin Test (TST; a test placed on the skin of the arm using a small needle that can help determine if a person has been exposed to tuberculosis) during the 8 weeks before a scheduled AERAS-404 or placebo vaccine injection.
• If your baby is in Study Groups 4 to 6 and your baby did not receive the second AERAS-404 or placebo vaccine injection.

If your baby must stop getting AERAS-404 or placebo vaccine before the study is over, the study doctor will discuss other options that may be of benefit to your baby. However your baby will still remain on study until your baby is about 18 months of age and complete the remaining study visits but will not receive additional study vaccine.

WHY THE STUDY DOCTOR MAY TAKE MY BABY OFF THIS STUDY EARLY

The study doctor may need to take your baby off the study early without your permission if:

• The study is stopped by the U.S. National Institutes of Health (NIH), Aeras, Sanofi Pasteur, U.S. Office for Human Research Protections (OHRP), a Regulatory Authority, or the site’s Institutional Review Board (IRB) or Ethics Committee (EC). An IRB/EC is a committee that watches over the safety and rights of research subjects.
• Your baby is not able to attend the study visits or you refuse to have your baby receive further vaccine or attend further study visits as required by the study.
• The study doctor feels continuing in the study will be harmful to your baby.

If your baby is taken off the study early, your baby will have an Early Study Discontinuation visit. The following will be done at the visit:

• The study staff will ask you questions about your baby’s health.
• The study staff will take your baby’s measurement of height, weight and vital signs (temperature, blood pressure, pulse and respiratory rate), and the study doctor will examine your baby.
• About 9.5 mL or 2 teaspoons of blood will be collected for safety, TB and immunogenicity tests. But if blood for the TB and immunogenicity tests were taken within 1 month before your baby is taken off study, blood will not be taken again for these tests. Then only about 1.5 mL or less than ½ teaspoon of blood will be collected.
WHAT ARE THE RISKS OF THE STUDY?

AERAS-404 vaccine is considered an “experimental” vaccine because it is only approved for use in research studies. The combination of TB proteins and substances in AERAS-404 vaccine have been tested and shown to be safe in animals such as mice, rabbits and guinea pigs, and to be safe in adults. AERAS-404 vaccine does not contain any TB germs. There is no danger of getting TB from an injection of AERAS-404 vaccine.

AERAS-404 vaccine was previously given to healthy BCG-vaccinated adult males and sterile females in a clinical trial in Sweden (Aeras C-005-404). Some participants in that study experienced redness and swelling on their skin where they had a TST in the past. One subject had blistering and scaling, which healed 2 weeks later without medical treatment. For this reason, your baby cannot enter this study if he/she had a TST in the past. While your baby is in the study, your baby cannot have a TST within 8 weeks before a scheduled vaccination with AERAS-404. You must inform the study staff if your baby has a TST at any time your baby is in the study. You must also inform your baby’s regular doctor (if he/she is not the study doctor) that your baby is in a study that advises against the use of TST. It may decrease the ability of your baby’s regular doctor to diagnose TB in your baby. In addition, children who receive the AERAS-404 vaccine may have a positive TB test in the future.

Your baby received BCG vaccine at birth and may experience some redness, swelling or ulcer at the site where injection was given. You may also have noticed some swollen glands in the armpit. These reactions may reappear at the time of the AERAS-404 injection or the size of existing redness and swelling may increase.

Expected side effects to AERAS-404 vaccine may include those commonly seen with other vaccine injections, such as tenderness, redness, warmth and swelling at the site of injection. Other possible side effects to AERAS-404 vaccine include fatigue (feeling tired), muscle aches, headache, joint pain, fever, chills, and nausea. These side effects usually start within a day after the injection. They are usually not severe, and go away on their own in a few days. Other less likely risks include allergic reactions that include skin rash, hives, itching, hoarseness or wheezing, difficulty breathing, fast heart beat and shock (or a condition caused by lack of flowing blood).

Studies evaluating this vaccine in adults showed a low level of red blood cells and protein in their urine. These findings were seen in both those who received the vaccine and those who received placebo. These findings disappeared without treatment and did not reappear after repeat vaccination. The majority of these findings were in women whose urines were tested during menstruation. We will not be testing your child's urine since the results are not of clinical concern and were not related to study vaccine.

Your baby will be observed by the study staff and doctor for 60 minutes after each injection, to watch for reactions that may happen soon after the injection. The study staff
will contact you by phone or will see your baby for a follow-up visit starting 3 to 7 days after each injection, to check for reactions that may occur later. Your baby will be followed by the study doctor for the entire time your baby is participating in the study to evaluate any side effects. There may be side effects and risks not known at this time; the researchers cannot predict with certainty about the side effects that may occur with this experimental vaccine. You should inform the study doctor right away if your baby has any side effects or problems during the study.

Receiving any injections of a liquid substance and having blood drawn may cause a brief painful or burning sensation at the site of the needle puncture.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

There is no medical or other advantage or benefit to you as a result of your baby taking part in the study. Your baby may or may not receive better protection against TB from being part of this study. However, people at risk for getting TB may benefit from the information that is learned in this study.

WHAT OTHER CHOICES DOES MY BABY HAVE BESIDES THIS STUDY?

You do not have to enroll your baby in this study. Your baby can still receive care without being in this study.

Please talk to your baby’s doctor about these and other choices available to your baby. Your baby’s doctor will explain the risks and benefits of these choices.

WHAT ABOUT PERSONAL INFORMATION?

Efforts will be made to keep your baby’s personal information secret, but this cannot be guaranteed. Your baby’s personal information may be disclosed if required by law. Any publication of the results from this study will not use your baby’s name or identify your baby personally.

Your baby’s records may be reviewed by the U.S. National Regulatory Authority, the U.S. Office of Human Research Protections (OHRP), (insert name of site) IRB, the U.S. National Institutes of Health (NIH), Aeras, Sanofi Pasteur, study staff, and study monitors.

WHAT ARE THE COSTS TO ME?

There is no cost to you for the study-related visits and procedures given to your baby. Taking part in this study may lead to added costs to you and your insurance company. In some cases it is possible that your insurance company will not pay for these costs because your baby is taking part in a research study. (Sites – modify per local guidelines.)
If your baby is suspected of having TB, your baby will have tests and receive treatment through the national TB program. Treatment for TB will not be provided in this study.

**WILL I RECEIVE ANY PAYMENT?**

You will not be paid for your baby to be in this study. You may be paid back for the cost of transportation, meals and other personal expenses for this study. *(Sites – modify per local guidelines.)*

**WHAT HAPPENS IF MY BABY IS INJURED?**

The sponsor has taken out insurance in the event of a study-related injury to your baby. This insurance follows the Association of the British Pharmaceutical Industry Guidelines. The guidelines recommend that the sponsor compensate you for any injury that is caused by the study vaccine or study procedures. You do not have to prove that the company is at fault.

Aeras will not pay to treat a medical condition or disease you had before joining this study or expenses for injury, treatment, or hospitalization you may require that are not the result of your participation in the study.

No other compensation, such as lost wages or other damages, will be available. You do not waive any of your legal rights by signing this consent form.

**WHAT ARE MY BABY’S RIGHTS AS A RESEARCH SUBJECT?**

Taking part in this study is completely voluntary. You may choose not to allow your baby to take part in this study or take your baby out of the study at any time. Your baby will be treated the same no matter what you decide.

We will tell you about new information from this or other studies that may affect your baby’s health, welfare or willingness to stay in this study. If you want the results of the study, let the study staff know.

**WHAT DO I DO IF I HAVE QUESTIONS OR PROBLEMS?**

For questions about this study or a research-related injury, contact:

- name of the investigator or other study staff
- telephone number of above

The 24-hour telephone number to call is <insert telephone numbers>.

For questions about your/your child’s/baby’s rights as a research subject, contact:

- name or title of person on the Institutional Review Board (IRB) or other organization appropriate for the site
• telephone number of above

If your doctor or the Ethics Committee did not provide you with answers to your satisfaction, you should write to the South African Medicines Control Council (MCC) at:

The Registrar
SA Medicines Control Council
Department of Health
Private Bag X828
Pretoria
0001
SIGNATURE PAGE

If you have read this consent form (or had it explained to you), all your questions have been answered and you agree for your baby to take part in this study, please sign your name below.

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<th>Participant’s Legal Guardian (print)</th>
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<th>Father’s Name</th>
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If you give permission for your baby to be tested for HIV when your baby is about 12 months of age, please sign your name below.

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If you, the participant’s Mother, allow the study staff to review your medical records and have your HIV status known by the study staff and the protocol team, please sign your name below.

________________________________________  ________________________________
Participant’s Mother (print)                     Mother’s Signature and Date