1. TITLE PAGE

A Double-Blind, Controlled by Conventional BCG, Dose-escalation Phase I Study, to Evaluate Safety, Tolerability and Immunogenicity of a *Mycobacterium bovis* BCG (Bacillus Calmette-Guérin) Vaccine, 1331 Danish Strain, Live Attenuated and Recombinant for the Expression of Human Respiratory Syncytial Virus Nucleoprotein (N) in Healthy Males Within 18 and 50 Years of Age

Final Integrated Clinical/Statistical Report

Trial Number code:	1) Public Health Institute of Chile Registry (Nº 4060). 2) Clinicaltrials.gov identifier: NCT03213405.
Development Phase:	Phase I
Indication Studied:	Respiratory Syncytial Virus Infections
Product:	rBCG-N-hRSV 001
Form/Route:	Intradermal
Sponsor:	Pontificia Universidad Católica de Chile
Principal Investigator:	Alexis M. Kalergis, PhD
Clinical/Medical Monitor:	Katia Abarca, MD
Laboratory Monitor:	Susan Bueno, PhD
Biostatistician:	Jaime Cerda, MD
Pharmacovigilance (Safety Narratives):	Jose Vicente Gonzalez, PhD
Clinical Trial Initiation Date:	June 27 2017
Clinical Trial Completion Date:	January 8 2018
Date of the report:	January 8 2018
Version Number:	0.2

This study was performed in compliance with Good Clinical Practice

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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE: Adverse Events

ARTIs: Acute Respiratory Tract Infections

BCG: Bacillus Calmette-Guérin

BCG-WT: Nonrecombinant, wild type Bacillus Calmette-Guérin

CFU: Colony Forming Units

IC: Informed Consent DSMB: Data and Safety Monitoring Board

FI-rRSV: Formalin-inactivated vaccine

ID: Identification Number

HRP: Horseradish Peroxidase

hRSV: Human Respiratory Syncytial Virus

IFN-γ: Interferon Gamma

IL-2: Interleukin 2

NA: Not Applicable

N-RSV: Respiratory Syncytial Virus Nucleoprotein

PPD: purified protein derivative of Mycobacterium tuberculosis

rBCG-N-hRSV: recombinant Mycobacterium bovis BCG vaccine expressing the nucleoprotein of hRSV

Th: T helper cells

TNF-α: Tumor necrosis factor alpha

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6. ETHICS

6.1. Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

The first signed informed consent was provided to the Institutional Ethics Committee on June 19th, 2017. The trial was approved by both, the Institutional Ethical Committee of the Pontificia Universidad Católica de Chile (document number 15-216) and the Chilean Public Health Institute (Instituto de Salud Pública de Chile, document number EC819077/16).

6.2. Ethical Conduct of the Study

The trial (clinicaltrials.gov NCT03213405) was conducted in Santiago of Chile, in a single center (Clinical Research Center of Pontificia Universidad Católica de Chile (CICUC)). The protocol was conducted according to the current Tripartite Guidelines of Good Clinical Practice, Declaration of Helsinki (17) and local regulations (Instituto de Salud Pública). Written informed consent was obtained from each participant prior to study entry. A Data Safety Monitoring Board (DSMB) evaluated safety data for each dose cohort after all subjects of the group reached day 30 of follow up to determine whether the dose escalation could continue.

6.3. Subject Information and Consent

The Informed Consent (IC) document version 3.0 dated March 10th of 2017 was used. During the screening visit, the study was explained to each individual and each subject signed the consent form in duplicate. One copy was provided to the subject and the other copy was archived in the subject file for this study. The identity of each participant was confirmed and documented using a unique, study-specific identification number (ID) which was archived in the study file.

All the volunteers signed the IC approved by the Institutional Ethic Committee of the Facultad de Medicina of the Pontificia Universidad Católica de Chile, before starting the first screening visit.

7. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

7.1. Administrative Structure at the Clinical Sites

Lead Site

Principal Investigator:	Alexis M. Kalergis, PhD
Clinic Manager:	Katia Abarca, MD
Laboratory Manager:	Susan Bueno, PhD
Study Coordinator:	Carolina Iturriaga, RN
Laboratory Supervisor:	Susan Bueno, PhD and Alexis M. Kalergis, PhD

7.2. Administrative Structure for the Trial

Principal Investigator:	Alexis M. Kalergis, PhD
Scientific Lead:	Alexis M. Kalergis, PhD
Medical Monitor:	Katia Abarca, MD
Laboratory Supervisor	Susan Bueno, PhD
Clinical Project Manager:	Carolina Iturriaga, RN
Biostatistician:	Jaime Cerda, MD, Pontificia Universidad Católica de Chile.
Pharmacovigilance (Safety Narratives):	-Jose Vicente Gonzalez, PhD
Report Author:	Alexis M. Kalergis, PhD
Statistical and Data Coordinating Center:	Pontificia Universidad Católica de Chile
Clinical Monitoring:	SMOLAM LTDA

8. INTRODUCTION

The human respiratory syncytial virus (hRSV) is of great public health significance causing acute respiratory tract infections (ARTIs) in children worldwide (1). hRSV can cause mild manifestations such as rhinorrhea, cough and congestion, to severe manifestations such as alveolitis, bronchiolitis and pneumonia (2). Importantly, worldwide hRSV infections are responsible for more than 3 million hospitalizations and more than 33 million ARTI episodes each year among children up to five years (1).

No licensed vaccine is currently available to prevent hRSV infection. The only current hRSV treatment is a humanized monoclonal antibody that targets the F protein of the virus. This approach is only used as a prophylactic treatment, mainly for high-risk infants to prevent the most severe symptoms of hRSV infection (4). An early hRSV vaccine attempt utilized a formalin-inactivated vaccine (FI-hRSV) in the 1960s (5). Unfortunately, the administration of this vaccine caused hospitalization in up to 80% of vaccinated children, triggering an exacerbation of the disease upon exposure to natural infection (6, 7). Therefore, there is a need to develop a safe and effective hRSV vaccine that induces a protective immunological response, but without enhancing pulmonary disease after hRSV infection. It has been shown that in children with acute hRSV bronchiolitis a predominantly T helper (Th)-2 cell biased response occurs and may be responsible for the pathologic outcomes (8). Further, a reduction in the frequency of γδ T cells producing IFN-γ has also been observed in samples from children presenting hRSV disease (9). These previous studies suggest that immunologic protection against hRSV involves a type 1-biased immune response (including CD4+ Th1 cells producing IFN-γ, TNF-α and IL-2), whereas enhanced hRSV disease is associated with a type 2-biased immune response (including CD4+ Th2 cells producing IL-4, IL-5 and IL-13). Therefore, a current view is that optimal hRSV vaccines should induce potent $CD4^+$ Th1 cell responses, and not $CD4^+$ Th2 cell responses. According to the 2017 report from Program for Appropriate Technology in Health (PATH, www.path.org), multiple hRSV vaccine candidates are in clinical evaluation including live-attenuated, particle-based and adenovirus-vectored approaches (10).

A vaccine candidate consisting on a recombinant *Mycobacterium bovis* (BCG) that expresses the nucleoprotein (N) of hRSV (rBCG-N-hRSV) has been developed by the team of Dr. Alexis Kalergis at the Pontificia Universidad Católica de Chile (11). BCG has been historically

used to prevent tuberculous meningitis and miliary TB disease and has been applied more than 4 billon times since its introduction in most countries around the world (12). In addition, BCG induces strong Th1, and not Th2 immune responses in both, animal models and in humans, and therefore is hypothesized to be an ideal vector for a vaccine directed against hRSV infection (13). Importantly, immunization with rBCG-N-hRSV in mice prevented lung associated damage from hRSV infection, decreased inflammatory cell infiltrations and induced an early recruitment of $CD4^+$ and $CD8^+$ T cells to the lungs (11, 14, 15). In addition, rBCG-N-hRSV generated an effective neutralizing antibody response in RSV-infected mice (16).

9. STUDY OBJECTIVES

The primary objective of this study was to characterize the safety and tolerability of escalating doses of the rBCG-N-hRSV vaccine, including doses of $5x10^3$, $5x10^4$ and $1x10^5$ CFU in healthy adult males 18 to 50 years of age.

The secondary objectives included characterization of the immune responses induced against the hRSV-N and against mycobacterial antigens with escalating doses of the rBCG-N-hRSV vaccine.

10. INVESTIGATIONAL PLAN

10.1. Overall Study Design and Plan Description

This was a phase I, double blind trial to evaluate the safety, tolerability and immunogenicity of an investigational recombinant BCG vaccine expressing hRSV-N compared to a control, nonrecombinant wild type BCG vaccine (conventional BCG) within each cohort, performed in healthy adult males 18 to 50 years of age.

After a full clinical and laboratory evaluation to exclude those with underlying diseases, immunodeficiency and latent tuberculosis infection per inclusion and exclusion criteria, the participants were enrolled into three cohorts. Within each cohort, the participants were randomly and in a blinded-manner assigned to receive the tested vaccine (rBCG-N-hRSV) or the control vaccine (conventional BCG).

Each cohort was vaccinated according to their assigned groups followed by a period of 6 months of follow-up. Safety data was evaluated by a Data and Safety Monitoring Board (DSMB), that determined whether, according to previously defined parameters, the escalation to the next cohort was possible, or whether the study needed to be halted due to safety concerns. Blood, saliva and urine samples were obtained pre-vaccination and on days 14, 30 and 180 post-vaccination, and (peripheral blood mononuclear cells) PBMCs were purified from the blood for cellular immune assays and serum isolated for humoral immune assays. The study design can be seen in Table I.

Table I: Study design

Cohort	Number of vaccinated	Safety analysis by CIMD	Follow up	Study completion
A	n=8 6 rBCG-N-hRSV 5x10^3 2 BCG 2x10^5	Day 30	Until day 180	n=8 per group TOTAL VACCINATED THAT COMPLETED THE STUDY=24
B	n=8 6 rBCG-N-hRSV 5x10^4 2 BCG 2x10^5			

C	n=8 6 rBCG-N-hRSV 1x10^5 2 BCG 2x10^5			

Samples were taken from all enrolled subjects at different time-points for the following purposes:

Day 0: Venous blood for basal immunogenicity assays (cellular and humoral, 26 ml total).

Day 7: Venous blood (16 ml) for laboratory adverse events study. Venous blood (4 ml), urine (10 ml) and saliva (>1 ml) for BCG excretion studies.

Day 14: Venous blood (16 ml) for laboratory adverse events study. Venous blood immunogenicity assays (cellular and humoral, 26 ml total). Venous blood (4 ml), urine (10 ml) and saliva (>1ml) for BCG excretion studies.

Day 30: Venous blood (16 ml) for laboratory adverse events study. Venous blood immunogenicity assays (cellular and humoral, 26 ml total). Venous blood (4 ml), urine (10 ml) and saliva (>1ml) for BCG excretion studies.

Day 60: Venous blood (16 ml) for laboratory adverse events study. Venous blood immunogenicity assays (cellular and humoral, 26 ml total). Venous blood (4 ml), urine (10 ml) and saliva (>1ml) for BCG excretion studies.

Day 120: Venous blood (16 ml) for laboratory adverse events study. Venous blood immunogenicity assays (cellular and humoral, 26 ml total). Venous blood (4 ml), urine (10 ml) and saliva (>1ml) for BCG excretion studies.

Day 180: Venous blood (16 ml) for laboratory adverse events study. Venous blood immunogenicity assays (cellular and humoral, 26 ml total). Venous blood (4 ml), urine (10 ml) and saliva (>1ml) for BCG excretion studies.

10.2. Rationale for Study Design

Because this was a first-in-human phase I trial to study a novel recombinant BCG vaccine designed to protect against both, hRSV and *Mycobacterium tuberculosis* infections, a careful dose escalation trial was designed with safety monitoring between escalation groups. The specific doses were selected based on the standard dose of BCG utilized in Chile for infant vaccination to protect against TB. The first group received a recombinant RSV-BCG vaccine dose that was equivalent to $1/100^{th}$ of the standard dose of non-recombinant BCG licensed for use in infants in Chile. The second group received a recombinant RSV-BCG vaccine dose that was equivalent to $1/10^{th}$ of the standard dose of non-recombinant BCG licensed for use in infants in Chile. The third group received a recombinant RSV-BCG vaccine dose that was equivalent to a full dose of non-recombinant BCG licensed for use in infants in Chile. The novel recombinant hRSV-BCG vaccine

could provide the advantage of inducing protective immunity against both, hRSV and TB infection and disease. If shown to be safe and effective, this one recombinant vaccine could replace standard BCG vaccination currently given to protect against TB. The reason to perform a double blind study was to assure that the study would not be biased. It is worth mentioning that, due that BCG vaccination is mandatory in Chile, all enrolled subjects were BCG-positive.

10.3. Selection of Study Population

10.3.1. Inclusion Criteria

The inclusion criteria were as follows:

- Chilean male between 18 and 50 years old.
- Evidence of voluntary participation through documentation of informed consent.
- Good health, according to the medical history, physical examination and normal laboratory test.
- A history of vaccination with BCG once or twice during the participant's life. In this population, the vaccine will work as a boost for BCG.

10.3.2. Exclusion Criteria

The exclusion criteria were as follows:

- Symptoms or diagnosis suggesting any type of systemic disease including renal, liver, cardiovascular or pulmonary impairment, immunodeficiency, autoimmune diseases, malignancies, psychiatric or other conditions that could interfere with the interpretation of the results or compromise the health of the participants.
- Body mass index lower than 19 and higher than 30 kg/m2 and/or weight under 50 kg.

- Not being able to attend all the study visits (face-to-face and telephone contacts) or follow the specified instructions (fasting, avoidance of intense physical exercise during the 24 hours preceding the study visits and 72 hours post-vaccination).
- Signs of latent or active infection with *Mycobacterium tuberculosis*: QuantiFERON-TB positive test or Chest X-ray suggesting Tuberculosis (TB).
- Positive screening for the human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAG) and hepatitis C virus (HCV).
- Evidence of primary or secondary immunodeficiency, determined by history, physical test and levels of serum immunoglobulins and lymphocytes sub-populations at the screening.
- Use of immunosuppressing drugs during the last 6 months prior to, or during the study.
- Use of inhaled corticosteroids for bronchial hyper-reactivity during the last year.
- History of close contact exposure to patients with Tuberculosis or other mycobacterial infections, even if under treatment.
- History of substance abuse (drugs or alcohol), according to DMS IV (See footnote*).
- Occurrence of any serious adverse events associated with previous BCG vaccination.
- History of severe allergic reactions or anaphylaxis to vaccines.
- History of severe infections (use of IV antibiotics, latent TB, herpes zoster) six months previous to screening.
- Refusal of condom use during sexual contact or abstinence from sexual activity during the study (See footnote**).
- Administration of immunoglobulins or blood-derived products six months previous to participation in the study or planned use of these products during the study.
- Eczema at the vaccination site (deltoid zone).
- Antecedents of keloid scar.

- Being vaccinated with BCG during the last 10 years.
- History of being vaccinated with BCG three or more times or the presence of three BCG scars.
- Receipt of other investigational products 30 days previous to the study.
- Administration of any vaccine 8 weeks prior to recruitment.
- Administration of any other vaccine during the first 30 days after vaccination with the rBCG-hRSV.
- Acute illness symptoms and/or feverish symptoms at the time, or during the last seven days prior to enrollment (fever defined as an oral or axillary temperature of >38°C).

(*) Substance abuse (drugs or alcohol): Maladaptive pattern of substance abuse that leads to a clinically significant mental or physical deterioration during the previous twelve months. Clinically significant deterioration would include evidence of any of the following: inability to complete personal and/or professional obligations; use of drugs or alcohol in dangerous situations, such as driving a vehicle; and legal problems related to drug or alcohol use.

(**) Given the remote possibility of negative effects produced by the vaccination on sperm, only volunteers that are not planning on conceiving a child during the study duration were enrolled. During each visit, abstinence or the use of effective contraceptive device will be confirmed.

10.3.3. Removal of Subjects from Therapy or Assessment

18 subjects were not enrolled in the study because they presented one or more exclusion parameters, including: Gilbert Syndrome, hepatitis B and latent *Mycobacterium tuberculosis* infection, HIV infection, three (3) BCG scars and screening tests out of the normal range. All enrolled subjects completed the trial. This was due to good safety results. Subjects were not enrolled due to non-compatible clinical or laboratory screening results before enrollment for the trial. These data are in section 10.7.1 below.

10.4. Vaccinations/Treatments

10.4.1. Vaccinations/Treatments Administered

Two vaccines were administrated during this study. Two volunteers per cohort were vaccinated with conventional BCG full dose ($2x10^5$ CFU). Six volunteers per cohort were vaccinated with escalating doses of rBCG-N-hRSV (cohort A $5x10^3$ CFU, cohort B $5x10^4$ CFU, and cohort C $1x10^5$ CFU). These vaccines were administered as an intradermal injection at study entry.

10.4.2. Identity of Investigational Product(s)

The study vaccine consisted of a novel, live attenuated, recombinant *Mycobacterium bovis* BCG (Bacillus Calmette-Guérin), Danish strain 1331, expressing the nucleoprotein (N) from the human respiratory syncytial virus (hRSV serogroup A2, strain 13018-8, obtained from the Institute of Public Health of Chile (11)), called rBCG-N-hRSV. The vaccine was designed at the Pontificia Universidad Católica de Chile and manufactured under cGMP conditions at IDT Biologika (former AERAS TB Vaccine Foundation)(USA).

10.4.3. Method of Assigning Subjects to Study Groups

This phase I study was performed as a double blind, randomized trial. The study was organized in three groups, each including 8 subjects (total number of subjects was 24). Each group was created using the random.org software and the random-sequence-generator command for 8 numbers (1 to 8). The first 6 numbers were assigned to the vaccine under study and the last 2 numbers to the control vaccine.

10.4.4. Selection of Doses in the Study

The doses were selected according to the publications by Cautivo, K.M. *et al* and by Céspedes, P.C. *et al*. (14,15), which describe that 1x10^8 CFU and 3x10^5 CFU were used respectively to immunize mice, showing safety and efficacy in mice in both studies. Further, the current recommended dose for BCG was also considered as part of the dose selection (https://www.who.int/immunization_standards/vaccine_quality/118_bcg/en/). Because this was a first-in-human phase I trial to study a novel recombinant BCG vaccine designed to protect against

both, hRSV and *Mycobacterium tuberculosis* infections, a careful dose escalation trial was designed with safety monitoring between escalation groups. The dose escalation in the clinical trial began with $1/100^{th}$ of the standard full dose licensed for infant BCG vaccination in Chile, then proceeded to $1/10^{th}$ of the standard full dose licensed for infant BCG vaccination in Chile, and then proceeded to the standard full dose licensed for infant BCG vaccination in Chile.

10.4.5. Selection and Timing of Dose for Each Subject

This study followed a careful dose escalation strategy, with pauses by the DSMB to review the data after all subjects in each cohort had been evaluated for at least 30 days post-vaccination and before proceeding to the following escalation dose. In cohorts A, B and C the doses of rBCG-N-hRSV were $5x10^3$ CFU, $5x10^4$ CFU and $1x10^5$ CFU, respectively. The BCG-WT dose for all control subjects was the same, which was the standard full dose ($2x10^5$ CFU) licensed for use in infants in Chile.

10.4.6. Blinding

This study was a double blinded study in which both, the participants and personnel were blinded to all the groups in the study.

10.4.7. Prior and Concomitant Therapy

NA

10.4.8. Treatment Compliance

N/A

10.5. Efficacy/Immunogenicity and Safety Variables

10.5.1. Safety Measurements Assessed and Flow Chart

To assess the safety of the vaccine, a series of clinical tests to assess possible adverse events was performed. These tests can be seen in Table II. Adverse events (severe, local, general) were recorded through day 180 and laboratory tests were performed at days 1, 2, 3, 7, 14, 30, 60, 120 and 180 post-vaccination.

Table II: Safety and Efficacy/Immunogenicity evaluation.

Safety test		
Clinical	Local adverse events	Pain, sensitivity (tenderness to touch) erythema, scab, induration, abscess and axillary lymphadenopathy
	General adverse events	Fever, tachycardia, hypo/hypertension, headache, fatigue, myalgia, nausea/vomiting and diarrhea
Laboratory	Hematological	Blood count (hemoglobin, leukocytes, neutrophils, lymphocytes and platelets count)
	Biochemical	Transaminases, bilirubin, cholesterol, creatine, ureic nitrogen, plasmatic electrolytes, coagulation test, creatine phosphokinase and urine analyses

10.5.2. Appropriateness of Measurements

The above safety measurements were conducted to identify clinical symptoms or laboratory parameters that were uniquely related to the administration of the experimental rBCG-N-hRSV vaccine. Unusual local systemic clinical reactions were documented, and laboratory evidence for renal, liver, hematologic disease adverse events were recorded.

10.5.3. Primary Efficacy/Immunogenicity Endpoints

NA

10.5.4. Primary Safety Endpoints

The primary safety endpoints of the study were the following:

- Evaluation of reactogenicity (Local and systemics AE)
- Evaluation of laboratory AE
- Serious AE (SAE)
- Evaluation of the presence of the BCG vaccine (wild-type and recombinant) in body fluids (blood, urine and saliva were cultured).

10.5.5. Secondary Efficacy/Immunogenicity and Safety Endpoints

The secondary efficacy/immunogenicity and safety endpoints were the following:

- Evaluation of the humoral and cellular immune responses against *M. bovis* BCG.
- Evaluation of the humoral and cellular immune responses against hRSV.

10.5.6. Drug Concentration Measurements

NA

10.6. Data Quality Assurance

10.6.1. Data Collection and Management

For the clinical and laboratory data collection, a handwritten and electronic Case Report File (CRF) was used for each visit. In addition, the local BCG lesion sites were photographed to document the local reactogenicity responses (pictures of the vaccine area were taken).

To look for evidence of disseminated and/or persistent BCG infection vaccinated donors provided samples of blood, urine and saliva.

For the cellular immunogenicity assays 20 ml of venous blood were collected in heparinized tubes (BD Vacutainer, New Jersey, USA), obtained from volunteers at day 0, 14, 30, 60, 120 and 180 post-vaccination. The venous blood was purified by gradient centrifugation with Leukocyte Separation Medium (LSM, Corning, Virginia, USA) for 30 minutes at 20°C/300g. Cells were collected, washed twice with 1X PBS (Gibco, New York, USA), counted in a Neubauer chamber and then frozen with DMSO in liquid nitrogen. All samples were stored in a -150°C Ultrafreezer until the assays were performed.

For the humoral immunogenicity assays, 6 ml of venous blood were collected in non-heparinized tubes (BD Vacutainer, New Jersey, USA), acquired from volunteers at day 0, 14, 30, 60, 120 and 180 days post-vaccination. The venous blood was incubated vertically at room temperature for at least 30 minutes, then serum obtained by centrifugation for 15 minutes at room temperature in an Eppendorf centrifuge with a horizontal rotor at 1,500 g. 1.8 ml of serum were collected, aliquoted in 6 vials and frozen at -80°C (Glacier^{TM} -86°C Ultra low Freezer) until the assays were performed.

Assays to detect disseminated/persistent infection with the BCG vaccines included PCR and conventional culture, the cellular immunogenicity assays were assessed by ELISPOT and flow cytometry and the humoral immunogenicity assays were evaluated using indirect ELISA assays. These results were reported on specific study report forms

10.6.1.1. Data Recording Methods

The Source Documents used for documenting the clinical data were the institutional clinical records at PUCC hospital and clinical evaluating unit and for the volunteers. In each study visit the anamnesis-clinical record/history for each subject, physical exam and all the study procedures as described above were collected on the CRF to properly inform the clinician about the individual health history.

For the laboratory data, an electronic report issued by the clinical laboratory at PUCC hospital was generated.

10.6.1.2. Subject Identifiers

Each sample was identified with the number of each subject (i.e. the samples from RSV01 were identified as RSV01)

10.6.2. Monitoring, Auditing, and Archiving

Once the healthy volunteers met the inclusion and exclusion criteria, the subjects received a single dose of the vaccine intradermally in the deltoid area. They were observed in the study clinic for the next 3 hours. Participants were evaluated at days 1, 2, 3, 7, 14, 30, 60, 120 and 180 after vaccination. Follow-up phone calls were performed at days 4, 21, 45, 90 and 150 after vaccination.

10.6.3. Database Lock

The staff of the clinical team entered information from each participant into an electronic CRF using a software called FMED (generated by the company "Brain Up"), which automatically organizes the data into a single coded excel file.

10.7. Statistical Methods Planned in the Protocol and Determination of Sample Size

10.7.1. Sample Size

A total of 42 healthy males between ages 18 and 50 years of age were screened, and 24 were enrolled and vaccinated with 8 participants in each cohort. Table III shows the number and age of participants that were screened and vaccinated.

Table III: Subjects receiving investigational product.

Subject number	Age	Received vaccine number	Subject number	Age	Received vaccine number
RSV01	31	CL01	RSV22	20	NA
RSV02	32	CL02	RSV23	25	NA
RSV03	22	CL03	RSV24	22	CL12
RSV04	22	NA	RSV25	44	CL13
RSV05	21	CL04	RSV26	25	CL14
RSV06	35	NA	RSV27	22	CL15
RSV07	36	CL05	RSV28	25	NA
RSV08	26	NA	RSV29	19	NA
RSV09	22	NA	RSV30	24	CL16
RSV10	25	CL06	RSV31	33	NA
RSV11	27	NA	RSV32	21	CL17
RSV12	24	NA	RSV33	21	CL18
RSV13	20	CL07	RSV34	21	CL19
RSV14	34	CL08	RSV35	20	NA
RSV15	24	NA	RSV36	25	CL20
RSV16	24	CL09	RSV37	29	NA
RSV17	20	CL10	RSV38	19	CL21
RSV18	28	CL11	RSV39	27	NA
RSV19	48	NA	RSV40	21	CL22
RSV20	25	NA	RSV41	21	CL23
RSV21	21	NA	RSV42	20	CL24

*NA: non applicable; CL-number: refers to the vaccine code received

10.7.2. Statistical Analysis Plan

This was a phase I clinical trial to evaluate safety and was not statistically powered. For the clinical data obtained the Student´s *t*-test was used. For immunogenicity assays, statistical significance was assessed using One-way ANOVA with a posteriori Tukey test or Two-way ANOVA test with a posteriori Tukey test.

11. STUDY SUBJECTS

11.1. Disposition of Subjects

Once inclusion criteria were met, volunteers were enrolled into three cohorts. Each cohort included 6 volunteers vaccinated with escalating doses of rBCG-N-hRSV ($5x10^3$ CFU; $5x10^4$ CFU; $1x10^5$ CFU) and 2 volunteers vaccinated with the standard BCG (BCG-WT) (full dose of $2x10^5$ CFU). Figure 1 shows the clinical study flow diagram.

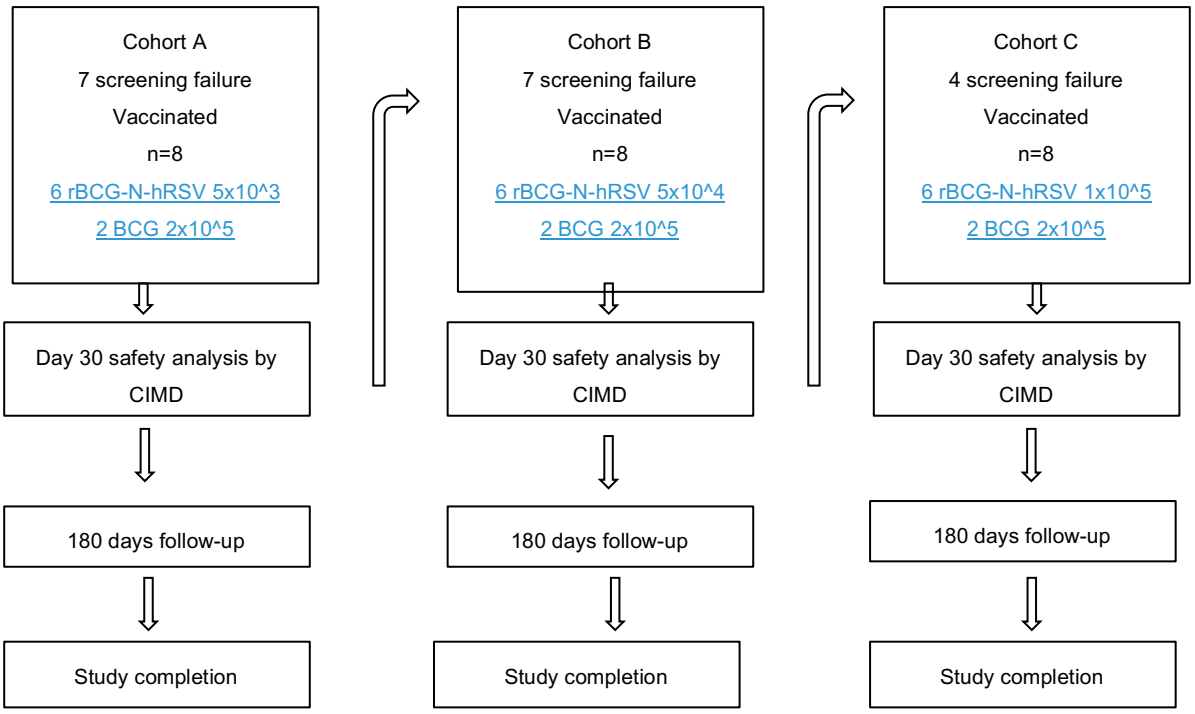

Figure 1: Clinical study flow diagram. The phase 1 study was a double blind dose ranging study. Each cohort included 6 volunteers vaccinated with escalating doses of rBCG-N-hRSV (5×10^3 CFU; 5×10^4 CFU; 1×10^5 CFU) and 2 volunteers vaccinated with the standard BCG (BCG-WT) (2×10^5 CFU). Furthermore, the DSMB evaluated safety data of each cohort after the first 30 days of follow up and decided if escalation could continue.

Table IV show the disposition of subjects according to the cohort in which they were (from all the subjects including the ones that were excluded from the study).

Table IV: Cohort by subject's number.

Cohort	Subject number	Cohort	Subject number
A	RSV01	B	RSV22
	RSV02		RSV23
	RSV03		RSV24
	RSV04		RSV25
	RSV05		RSV26
	RSV06		RSV27
	RSV07		RSV28
	RSV08		RSV29
	RSV09		RSV30
	RSV10	C	RSV31
	RSV11		RSV32
	RSV12		RSV33
	RSV13		RSV34
	RSV14		RSV35
	RSV15		RSV36
B	RSV16		RSV37
	RSV17		RSV38
	RSV18		RSV39
	RSV19		RSV40
	RSV20		RSV41
	RSV21		RSV42

11.1.1. Demographic Data by Study Group

The Table V show the demographic data of subjects according to study group (from all subjects including the ones that were excluded from the study).

Table V: Demographic data by study group.

Study group	Age range	Sex/Gender
Cohort A	20-36	Male
Cohort B	20-44	
Cohort C	19-25	

11.1.2. Summary of Prior and Concurrent Medical Conditions

NA

11.1.3. Study Visit Schedule

The Table VI show the study visit schedule for the participants.

Table VI. Study visit Schedule

Name/number of visit	Screening Day -3 to -10	Visit 1 Day 0	Visit 2 Day 1 (+1)	Visit 3 Day 2 (+1)	Visita 4 Día 3 (+1)	Call Day 4	Visita 5 Day 7 (±2)	Visit 6 Day 14 (±3)	Call Day 21	Visit 7 Day 30 (±5)	Call Day 45	Visit 8 Day 60 (±7)	Call Day 90	Visit 9 Day 120 (±7)	Call Day 150	Visit 10 Day 180 (±7)
Description of the visit	Screening	Vaccination	Follow up Visit	Follow up Visit	Follow up Visit	Telephonic contact	Follow up Visit	Follow up Visit	Telephonic contact	Follow up Visit	Telephonic contact	Follow up Visit	Telephonic contact	Follow up Visit	Telephonic contact	Final visit
Informed Consent	x															
Medical History	x															
Physical exam	x	x	x	x	x		x	x		x		x		x		x
Vital Signs	x	x	x	x	x		x	x		x		x		x		x
Verification of inclusion/exclusion criteria	x	x														
Designation of study #	x															
Eligibility tests	x															
Verification of Inclusion criteria		x														
Randomization		x														
Samples for immunogenicity tests		x						x		x		x		x		x
Vaccine administration		x														
Observation for 3 h		x														
Daily Chart deliver		x					x	x		x		x		x		
Safety contact						x			x		x		x		x	
Daily chart revision			x	x	x		x	x		x		x		x		x
Evaluation of papule			x	x	x		x	x		x		x		x		x
Safety Tests			x	x	x		x	x		x		x		x		x
Transmisibility tests							x			x						x
AE, SAEs						x	x	x	x	x	x	x	x	x	x	x

11.1.4. Vital Signs Grading

The vital signs were graded from 1 to 4.

Table VII: Vital signs grading.

Vital signs	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potential life risk (Grade 4)
Fever (°C) (oral or axillary)	38.0-38.4	38.5-38.9	39.0-40.0	>40.0
Tachycardia – beats per minute	101-115	116-130	>130	Emergency visit or hospitalization due to arrhythmia

Bradycardia – beats per minute	50-54	45-49	< 45	Emergency visit or hospitalization due to bradyarrhythmia
Hypertension (systolic) – mmHg	141-150	151-155	>155	Emergency visit or hospitalization due to malignant hypertension
Hypertension (diastolic) - mmHg	91-95	96-100	>100	Emergency visit or hospitalization due to malignant hypertension
Hypotension (systolic) – mmHg	85-89	80-84	< 80	Emergency visit or hospitalization due to shock
Respiratory frequency – breaths per minute	17-20	21-25	>25	Intubation

11.2. Protocol Deviations

Table VIII shows the protocol deviations for each subject, all of which took place during the eligibility exams. The deviations were reported to the institutional ethics committee and to the Data and Safety Monitoring Board (DSMB).

The DSMB analyzed these deviations and requested additional information on the lymphocytic subpopulations. Upon review, the DSMB concluded that the protocol deviations did not have any impact on the safety of the subjects and recommended that the study continue.

Table VIII: Protocol deviation by each subject

Subject	Deviation	Corrective action
RSV01	Albumin at baseline (eligibility tests) out of the range indicated in amendment 2 (5.1 mg/dl, value indicated is 3.5-5.0)	All study personnel were trained to rigorously adhere

RSV01	Cholesterol at baseline (eligibility tests) out of the range indicated in amendment 2, 200 mg/dl (the amendment 2 indicated, by mistake, the normal value is <200, being ≤200 correct)	to the values of the laboratory
RSV01	Missing values for CD16 or CD56/19 in the lymphocytic populations at baseline (eligibility tests)	The laboratory was trained to report these values of the study subjects
RSV02	Missing values for CD16 or CD56/19 in the lymphocytic populations at baseline (eligibility tests)	
RSV03	Missing values for CD16 or CD56/19 in the lymphocytic populations at baseline (eligibility tests)	
RSV05	Missing values for CD16 or CD56/19 in the lymphocytic populations at baseline (eligibility tests)	
RSV07	Missing values for CD16 or CD56/19 in the lymphocytic populations at baseline (eligibility tests)	
RSV25	From day 9, the subject did not register appropriately the measurements for erythema and induration, but all of these were less than 25 mm	The subject and study personnel were retrained to ensure these measurements were performed until day 30
RSV27	In Visit 6 (day 14 post-vaccination) the PT and PTT were not measured.	Study personnel were retrained on the correct tubes to be used for these measurements
RSV 36	Visit 7, 1 day out of the window period	The subject was further educated as to the importance of following study procedures

12. EFFICACY/IMMUNOGENICITY EVALUATION

12.1. Analysis Populations

The population analyzed were healthy male adults, between 18 and 50 years of age.

12.2. Demographics and Other Baseline Characteristics

The participants were healthy Chilean males 18 to 50 years old, who were vaccinated with BCG once or twice during their life, prior to study participation. The information was recording by an objective evaluation of the BCG vaccination scar or scars in each subject. It is not possible to determine which BCG strain the participant received previous to this study, because the Chilean Government obtain different vaccines from different sources (Statens Serum Institut or Serum Institute of India)

12.2.1. Prior and Concurrent Medical Conditions

The subjects were healthy and tested negative for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAG) and hepatitis C virus (HCV), and had no evidence of primary or secondary immunodeficiency.

12.2.2. Prior and Concomitant Medications

The subjects had to meet the inclusion and exclusion criteria prior to enrolling in the trial. Prior to the study, the subjects were not allowed to use inhaled corticosteroids or immunosuppressors, had not received treatment for tuberculosis or other mycobacteria, had not used illegal drug substances and had not been administered immunoglobulins or blood-derived products.

12.3. Measurements of Treatment Compliance

Since the treatment is an immunization with a single dose of either, control BCG vaccine provided by the Ministry of Health in Chile (Serum Institute of India, Bacillus Calmette Guerin Moscow strain 361- I) or rBCG-N-hRSV, no measurements of treatment compliance were required.

12.4. Efficacy/Immunogenicity Results and Tabulations of Individual Subject Data

12.4.1. Methodology and Primary Statistical Analysis of Efficacy/ Immunogenicity Data

The immune responses were measured as follows: Peripheral blood mononuclear cells (PBMC) and serum samples from twenty four subjects were collected on visits 1 (day 0), 6 (day 14), 7 (day 30) and 10 (day 180) post-vaccination and stored. The 24 subjects were divided in three groups of 8 according to the dose of rBCG-N-hRSV used: Cohort A ($5x10^3$ CFU), cohort B ($5x10^4$ CFU) and cohort C ($1x10^5$ CFU). To evaluate the cellular response, the cells obtained from peripheral blood were thawed, counted and stimulated *in vitro* with PPD and N-RSV antigens to measure the antigen-specific immune response. Total cells that secreted IL-2 and/or IFN-γ were measured by ELISPOT and cellular subpopulations of $CD4^+$ / $CD8^+$ producers of $IL\text{-}2^+$ IFN-γ were measured by flow cytometry. To evaluate the humoral response, sera were thawed and incubated in pre-activated ELISA plates with PPD and N-RSV antigens. Afterwards, they were incubated

with human anti-IgG secondary antibody conjugated to horseradish peroxidase (HRP). The specific immunoglobulins against PPD and N-RSV were quantified using a standard curve with the humanized anti-F antibody (Palivizumab). The results were obtained based on the absorbance of the product generated by the anti-IgG HRP antibody and TMB substrate (3,3′,5,5′-Tetramethylbenzidine) in a spectrophotometer.

All statistical analyses for the immunogenicity assays were performed using GraphPad Prism version 7.0 Software. Statistical significance was assessed using One-way ANOVA with a *posteriori* Tukey test, or two-way ANOVA test with a *posteriori* Tukey test.

12.4.1.1. Handling of Dropouts or Missing Data

Data for some time points for ELISPOT evaluation in cohort A was missing, as described in table V.

12.4.2. Tabulation of Individual Response Data

Table IX: Immunogenicity Individual Response

	IFN-y and IL-2 SFC/million cells against PPD						IFN-y and IL-2 SFC/million cells against hRSV N protein					
	BCG-WT 2x10^5											
	VRS01	**VRS 13**	**VRS18**	**VRS24**	**VRS34**	**VRS38**	**VRS01**	**VRS 13**	**VRS18**	**VRS24**	**VRS34**	**VRS38**
0 dpi	0	23.3	110	10	60	123.3	0	0	13.3	0	0	0
14 dpi	23.3		103.3	3.3	63.3	196.7	0	*	*	0	0	6.7
30 dpi	120	73.3	140	3.3	86.7	120	10	3.3	0	0	0	3.3
60 dpi	86.7	130	126.7	33.3	73.3	110	3.3	3.3	0	0	3.3	0
120 dpi	70	96.7	256.7	46.7	6.7	113.3	10	0	6.7	0	0	10
180 dpi	53.3	6.7	160	93.3	0	56.7	3.3	0	3.3	3.3	3.3	0
	COHORT A											
	VRS02	**VRS03**	**VRS05**	**VRS07**	**VRS10**	**VRS14**	**VRS02**	**VRS03**	**VRS05**	**VRS07**	**VRS10**	**VRS14**
0 dpi	*	36.7	90	20	70	266.7	*	3.3	46.7	0	0	16.7
14 dpi	*	*	*	36.7		200	*	*	*	3.3	*	13.3
30 dpi	*	150	33.3	110	263.3	126.7	*	0	16.7	3.3	0	6.7
60 dpi	56.7	50	10	33.3	156.7	66.7	0	0	3.3	10	0	3.3
120 dpi	6.7	146.7	40	83.3	83.3	143.3	0	10	20	0	0	0
180 dpi	23.3	70	13.3	46.7	16.7	43.3	0	0	13.3	6.7	0	0
	COHORT B											
	VRS16	**VRS27**	**VRS17**	**VRS25**	**VRS26**	**VRS30**	**VRS16**	**VRS27**	**VRS17**	**VRS25**	**VRS26**	**VRS30**
0 dpi	33.3	0	90	20	46.7	10	10	0	6.7	0	6.7	10
14 dpi	106.7	253.3	236.7	13.3	63.3	46.7	6.7	0	3.3	0	0	3.3
30 dpi	106.7	306.7	300	60	136.7	46.7	6.7	0	3.3	3.3	23.3	6.7
60 dpi	180	413.3	216.7	146.7	106.7	20	6.7	16.7	3.3	3.3	10	3.3

120 dpi	93.3	176.7	143.3	6.7	90	13.3	10	13.3	0	0	3.3	0
180 dpi	100	100	113.3	73.3	50	13.3	0	0	0	3.3	10	0
	COHORT C											
	VRS32	**VRS33**	**VRS36**	**VRS40**	**VRS41**	**VRS42**	**VRS32**	**VRS33**	**VRS36**	**VRS40**	**VRS41**	**VRS42**
0 dpi	6.7	43.3	110	46.7	10	440	0	6.7	23.3	46.7	10	0
14 dpi	66.7	276.7	180	153.3	26.7	543.3	0	0	56.7	46.7	10	6.7
30 dpi	103.3	126.7	166.7	106.7	13.3	340	6.7	3.3	66.7	33.3	16.7	10
60 dpi	50	46.7	20	70	16.7	223.3	3.3	3.3	3.3	46.7	6.7	3.3
120 dpi	16.7	36.7	383.3	103.3	0	76.7	0	3.3	0	46.7	10	23.3
180 dpi	36.7	73.3	280	63.3	0	116.7	6.7	13.3	3.3	36.7	13.3	23.3

*Missing data

dpi: Days post-immunization.

12.4.3. Efficacy/Immunogenicity Conclusions

Cellular immunogenicity measurements showed that 14 days after vaccination all volunteers increased cellular production of IFN-γ and IL-2 upon *in vitro* stimulation with PPD antigen by ELISPOT (Figure 2). The cellular response against the RSV N protein was increased 30 days after vaccination, indicating the induction of a specific immune response against antigens included in the vaccine.

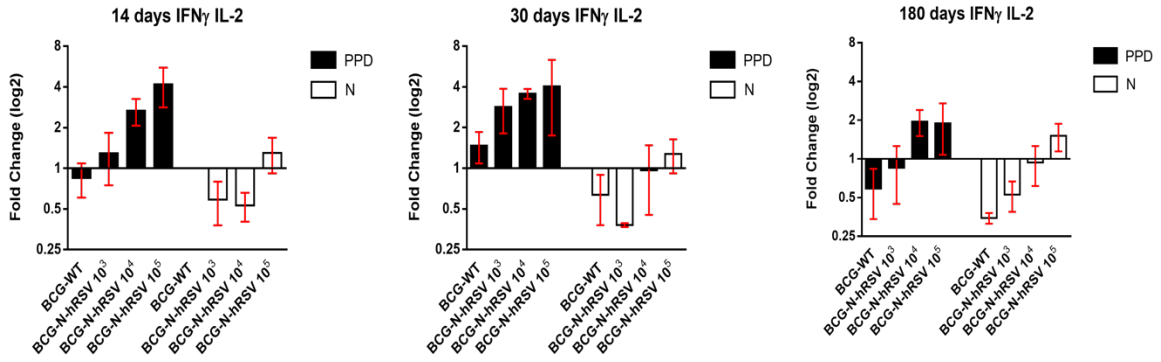

Figure 2: Measurement of the specific cellular response by ELISPOT against the PPD antigens (in black) and N protein (in white) of the human respiratory syncytial virus. The results are expressed as the fold change (log2) with respect to visit 1 (day 0) for IFN-g and IL-2 secretory cells at times 14, 30 and 180 days after vaccination for the three doses of rBCG-N-hRSV (5x10^3 CFU, 5x10^4 CFU, 1x10^5 CFU) and for BCG-WT (2x10^5 CFU).

Furthermore, the amount of specific IgG response against PPD and N in the serum increased 60 days post-vaccination (Figure 3). In summary, rBCG-N-hRSV showed a good safety profile in healthy adults and induced specific cellular and humoral immune responses.

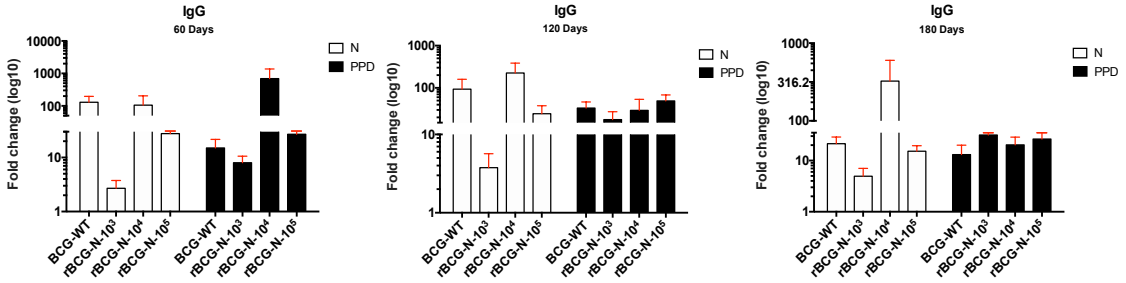

Figure 3: Measurement of the specific humoral immune response by indirect ELISA assay against the N protein (in white) and PPD antigens (in black) of the human respiratory syncytial virus. The result is expressed in fold change (log10) with respect to visit 1 (day 0) in the detection of specific IgG at times 60, 120 and 180 days after vaccination for the three doses of rBCG- N-hRSV (5x10^3 CFU, 5x10^4 CFU, 1x10^5 CFU) and for BCG-WT (2x10^5 CFU).

13. SAFETY EVALUATION

13.1. Extent of Exposure

From the total of 24 participants, there were 524 adverse events.

13.2. Adverse Events (AEs)

13.2.1. Brief Summary of Adverse Events

Overall, 524 adverse events were registered for the 24 participants: 244 local adverse events (46.6%), 157 general adverse events (30.0%) and 123 laboratory adverse events (23.5%). Importantly, no participants were discontinued due to an AE. The most frequent local solicited adverse events were abscess, scabbing and tenderness at the BCG injection sites, occurring in all participants. The most common solicited adverse events were headache, fatigue, diarrhea and myalgia. As for the laboratory adverse events (as defined by a significant deviation from normal ranges for laboratory tests), 56.9% were classified as not related to vaccine and 43.1% as possibly

related to vaccine because no definitive etiology was found. The most common laboratory adverse event was decreased hemoglobin (see Table XII).

13.2.2. Display of Adverse Events

A severe laboratory adverse event (SAE) G4 was presented during the study of cohort C. This event relates to subject RSV34 that on day 14 (December 06 2017), while being asymptomatic, presented a rise in CPK values (20.488 U/L). The subject did intense exercise at the gym on December 03th, 2017 for 1.5 hour, resulting in fatigue at the end of his exercise and myalgias for the next few days. This was accompanied by a grade 3 rise in SGOT (276 U/L). On December 11, 2017 the subject was found to have a CPK of 3.827 U/L and SGOT of 186 U/L. On visit day 30 (December 21, 2017), both values had normalized (CPK 134 U/L and SGOT 18 U/L). The SAE from this study are shown in Table VI. This event was considered to be unrelated to the study vaccine, by the investigator as well as the sponsor's security delegate, Dr. Fernando Altermatt. The SAE was reported to the institutional ethics committee (CEC-MedCUC) and to the sponsor's security delegate, who notified the Institute for Public Health of Chile (Instituto de Salud Pública de Chile).

Table X: SAE from the three cohorts, at January 8 2018, completion of day 30 post vaccination Cohort C

Cohort	SAEs	SAE type	Relation with the vaccine	Final Disposition
A	0	None	None	None
B	0	None	None	None
C	1	Grade 4 rise of CPK	Not related	Resolved
Total	1	Laboratory abnormality	Not related	All resolved

Clinical adverse events (CAE) were presented at day 30 and are shown in Table XI. A rise of local AEs was observed in cohort B as compared to cohort A, and in cohort C as compared to cohort B, being significant only for the difference between cohort A and C (p=0.04 test U Mann Whitney). As for the total AEs, there were no significant differences between cohorts.

Table XI: Clinical Adverse Events Cohorts A, B and C, at day 30 at January 8 2018, completion of day 30 post vaccination Cohort C

Event	Cohort A	Cohort B	Cohort C	Total
Solicited local AE	51	70	83	204
Non solicited local AE	8	6	8	22
Subtotal local AE	59	76	91	226
Solicited general AE	21	19	28	68
Non solicited general AE	15	2	11	28
Subtotal general AE	36	21	39	96
Total AE	95	97	130	322

Clinical adverse events (CAE) identified by January 8th 2018, which is completion of day 30 post vaccination of Cohort C, are shown in table XII.

Table XII: Clinical adverse events for Cohorts A, B and C at the day of the inform (January 8th 2018) , completion of day 30 post vaccination Cohort C.

Event	Cohort A Day 150-180	Cohort B Day 60	Cohort C Day 30	Total
Solicited local AE	57	72	83	212
Non solicited local AE	11	6	8	25
Subtotal local AE	68	78	91	237
Solicited general AE	22	20	28	70
Non solicited general AE	38	6	11	55
Subtotal general AE	60	26	39	125
Total AE	128	104	130	258

13.2.2.1. Solicited AEs

Clinical solicited adverse events were followed through day 30 post-vaccination. Local solicited AE included pain, sensitivity, erythema, scab, induration, abscess and axillary lymphadenopathy. General solicited AE included fever, tachycardia, hypo/hypertension, headache, fatigue, myalgia, nausea/vomiting and diarrhea. Local solicited grade 3 AE were identified only in cohort C, and included 2 grade 3 reactions (1 pain and 1 sensitivity) at the vaccination site. Both events were resolved.

Table XIII: Solicited general adverse events grade 3. The number of low, moderate and severe events per cohort and per type of event is shown in the Table. The vital risk events are not included in this Table.

Event	Cohort A			Cohort B			Cohort C		
	low	moderate	severe	low	moderate	severe	low	moderate	severe
Headache	3	0	0	0	0	0	9	2	0
Fatigue	2	0	0	3	0	0	4	1	0
Nausea/vomiting	7	2	0	5	1	0	4	0	0
Diarrhea	6	0	0	4	0	0	5	0	0
Myalgia	1	0	0	6	0	0	3	0	0
Fever	0	0	0	0	0	0	0	0	0
TOTAL	19	2	0	18	1	0	25	3	0

13.2.2.2. Unsolicited AEs

Clinical unsolicited adverse events were recorded through day 30. The episodes of high blood pressure and tachycardia did not occur in the period immediately after vaccination, but at the beginning of subsequent visits. In Cohort A, these measurements were not repeated by the staff. In Cohort B, these measurements were repeated and the values were repeatedly high.

Table XIV: Number of Non-Solicited Clinical Adverse events.

Event	Cohorts A (5x10^3)	Cohorts A (5x10^4)	Cohorts A (1x10^5)	Control BCG WT (2x10^5)	TOTAL
Viral upper respiratory infection	4	4	7	3	18
Headache	1	2	0	14	17
Other events respiratory tract	7	0	3	1	11
Diarrhea/gastroenteritis	1	0	4	0	5
Toothache	3	0	0	0	3
Ecchymosis injection site	1	0	1	0	2
Bruise on hand	1	0	1	0	2
Contusion of hand/wrist	0	0	1	1	2
Cellulitis tight	0	1	0	1	2
Muscular contraction back	0	1	0	1	2
Abdominal pain	0	0	0	1	1
Arterial hypertension	0	0	1	0	1
Foot injury due to beat	0	0	0	1	1
General malaise	0	0	1	0	1
Urethritis	0	0	1	0	1
Urticaria	0	0	1	0	1
Sclap ache	0	0	1	0	1
Retro ocular ache	1	0	0	0	1

Fever	1	0	0	0	1
Epistaxis	0	0	0	1	1
Nausea	0	0	1	0	1
Ansiety	0	0	1	0	1
Insomnia	0	0	1	0	1
Myalgia	0	0	1	0	1
Leg pain	0	0	0	1	1
Scratch in vaccination site	1	0	0	0	1
TOTAL	**20**	**6**	**25**	**25**	**76**

13.2.3. Analysis of Adverse Events

There were more solicited local grade 2 and grade 3 clinical AEs (severe and moderate) in Cohort B and C compared to Cohort A ($p = 0.012$ and $p = 0.001$, respectively), but there were no significant differences between Cohort B and Cohort C ($p = 0.362$): Cohort A (3/51 = 5.9%), Cohort B (16/70 = 22.9%), Cohort C (25/83 = 30.1%). There were no significant differences in the solicited general AEs between cohorts, and therefore there was no association with increasing doses of the study vaccine. There were no significant differences in unsolicited clinical AEs between the groups.

The listing of local adverse events by subjects, can be seen in Table XXV (annex).

The listing of general adverse events by subjects, can be seen in Table XXVI (annex).

13.3. Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

13.3.1. Listing of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

No deaths occurred in any study subject during the trial observation period.

Two Serious Adverse Events were registered during the study.

13.3.1.1. Deaths

No deaths were occurred in this study.

13.3.1.2. Serious Adverse Events

The listing of serious adverse events, can be seen in Table XV.

Table XV: Serious adverse events.

Subject	Age	Diagnosis	Vaccination Date	Start Date (days post-vaccination)	Resolution Date (days post-vaccination)	Severity Criterion	Vaccine	Assigned Cause	Related to vaccination
RSV34	22	Increase in CPK	21-11-17	17	31	Lab AE G4	Control	Intense exercises the day before	No
RSV42	20	Precordial pain secondary to Supraventricular Tachycardia	04-12-17	51	53	Hospitalization	$5x10^5$	Previous pre-excitation syndrome	No

13.3.1.3. Other Significant Adverse Events

NA

13.3.2. Narratives of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

There were no deaths.

RSV34:

One SAE laboratory grade 4 AE occurred in subject RSV34 enrolled in cohort C, who was vaccinated on day November 21st, 2017 and on day 14 (December 06th, 2017 17 days after vaccination) presented to the clinic and was found to have an asymptomatic grade 4 increase in CPK (20,488 U/L). The subject had engaged in intense exercise at a gym on December 03, 2017 for 1.5 hours, and experienced marked fatigue at the end of the exercise and myalgia for the next few days. This was associated with a grade 3 increase in SGOT (276 U/L). At follow up on

December 11, 2017, the subject was found to have decreased levels of CPK (3,827 U/L) and SGOT (186 U/L). At his next scheduled visit on day 30 post-vaccination (December 21, 2017) both values had normalized (CPK of 134 U/L and SGOT of 18 U/L). The events were considered not to be related to the study vaccine by both, the investigator and the security delegate sponsor, Dr. Fernando Altermatt. The SAE was reported to the institutional ethic committee (CEC-MedUC) and the security delegate sponsor notified the Instituto de Salud Pública de Chile (ISP). The event was not related to the vaccination.

RSV42:

A second subject was hospitalized on January 25th, 2018 (51 days post vaccination) when he presented precordial pain beginning the night before. At the hospital, his EKG was essentially normal (only abnormality was a delta wave compatible with pre-excitation, which was a previous condition identified in the patient). However, he was found to have elevated cardiac enzymes. Echocardiogram findings were normal. The physicians determined that the precordial pain was most likely secondary to a supra-ventricular tachycardia due to a pre-existing pre-excitation pathway that had been diagnosed when the subject was an infant. The final diagnosis for this SAE was pre-cordial pain secondary to a supra-ventricular tachycardia due to a pre-existing pre-excitation syndrome. The event was resolved the day of his medical release (January 26, 2018, day 53 post-vaccination). The event was not related to the vaccination.

13.3.3. Analysis and Discussion of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

According to the narrative, the Serious Adverse Events detected were not related to immunization. No deaths were reported in this study.

13.4. Clinical Laboratory Evaluation

13.4.1. Individual Laboratory Measurements and Abnormal Laboratory Values

Laboratory adverse events (LAE) are presented in table XVI. No significant differences were observed comparing the 3 cohorts.

Table XVI: Laboratory adverse events from cohort A, B and C at day January 8th, 2018(30 days after Cohort C vaccination)

	Cohort A		Cohort B		Cohort C	
Event	Total	Grade 1/2/3	Total	Grade 1/2/3	Total	Grade 1/2/3
Decrease of Hb	7*	5/1/1	5**	5/0/0	8	7/1/0
Increase in CPK	6	3/2/1	2	2/0/0	4	2/2/0
Leukopenia	5#	5/0/0	1	1/0/0	0	NA
Increase in cholesterol	2	2/0/0	1	1/0/0	0	NA
Proteinuria[$]	2	0/2/0	1	1/0/0	1	1/0/0
Leukocytosis	1	1/0/0	0	NA	0	NA
Neutropenia	1	0/1/0	0	NA	0	NA
Increased SGOT or SGPT	1	1/0/0	1	1/0/0	1	0/0/1
Hypoproteinemia	1	1/0/0	0	NA	0	NA
Hyperglycemia[&]	1	1/0/0	0	NA	0	NA
Hypophosphatemia	1	1/0/0	1	1/0/0	1	1/0/0
Increase in prothrombin	1	1/0/0	0	NA	0	NA
Pyuria	0	NA	1	1/0/0	2	1/1/0
Eosinophilia	0	NA	1	1/0/0	1	1/0/0
Hematuria	0	NA	0	NA	1	0/1/0
Increased LDH	0	NA	0	NA	1	1/0/0
Hypokalemia	0	NA	0	NA	1	1/0/0
Increase alkaline phosphatases	0	NA	0	NA	1	1/0/0
Total	29	22/5/2	14	14/0/0	22	16/5/1

*7 episodes in 6 subjects, **5 episodes in 4 subjects. Two recovered and presented again.

#5 episodes in 4 subjects, one recovered and presented again.

[$]Proteinuria +- is considered mild and +, moderate

[&]Patient was not fasting

There was no relation of frequency and intensity of some laboratory AE with the type of vaccine received.

13.4.2. Evaluation of Each Laboratory Parameter

Hematological and biochemical parameters were measured at days 7, 14, 30, 60, 120 and 180 post-vaccination.

13.4.2.1. Laboratory Values over Time

All grade 3 events reported decreased over time.

13.4.2.2. Individual Subject Changes

Subject RSV01 presented 3 grade 3 events and only 2 of them returned to normal values. Subject RSV14 presented 1 grade 3 event and at day 30 was back to normal. Subject RSV25 presented 1 grade 3 events and at day 60 it continued as a grade 3. It normalized at visit 10 (day 180 post vaccination). Finally, subject RSV34 presented 2 events which at day 30 were back to normal.

Table XVII: Grade 3 laboratory adverse events and follow-up

N	Cohort	Event (Subject)	Association with the vaccine	Visit when event presented	Evolution over time	Clinical Manifestation	Observations
1	A	Hb decreased (RSV01)	Likely. Alternative cause: blood samples	V5 (Day 7)	Basal: 17.4 Day 07: 15.9 (G1) Day 14: 15.1 (G3) Day 30: 15.2 (G3) Day 60: 16.7 (G1)	None	Initial Hb was above the upper limit (17.4) because of potential dehydration at enrollment. The participant did not have anemia.
2	A	CPK increased (RSV14)	Likely. Alternative cause: exercise in	V5 (Day 7)	Day 7: 972 (G3) Day 14: 168 (N) Day 30: 126 (N)	None	Limit values established by PUCC were twice those established by the USA and France. Taking

			previous days				this information into consideration, the AE corresponds to Grade 2.
3	A	Hematuria (RSV01)	Likely. Alternative cause: micro lithiasis	V8 (Day 60)	Day 60: 170 GR (G3) Day 62: 14 GR (G1) Day 120: 4 GR (N)	None	Family history of lithiasis. Culture negative.
4	A	Hypernatremia	Likely. Alternative cause: dehydration by fasting	V9 (Day 120)	Day 60: 150 mEq/L (G3) Day 62: 143 mEq/L (N)	None	Normal repeated fasting
5	B	Hypophosphatemia (RSV25)	Likely. Alternative cause: Low ingestion of phosphorus	V8 (Day 60)	Day 60: 1.8 mEq/L (G3)	None	At day 7 shows Grade 1, normalized at day 14.
6	C	CPK increased (RSV34)	Unrelated. Alternative cause: extreme exercise	V6 (Day 14)	Day 14:20.488 U/L (G4) Day 19: 3.827 U/L (G3) Day 30: 134 U/L (N)	None	Normal at day 30 (V7)
7	C	SGTO increased (RSV34)	Unrelated. Alternative cause: exercise in previous days	V6 (Day 14)	Day 14: 276 U/L (G3) Day 19: 186 U/L (G2) Day 30: 18 U/L (N)	None	Normal at day 30 (V7)

13.4.2.3. Displays of Laboratory Results

13.4.2.4. Chemistry Results

The biochemistry results from the 3 laboratory Cohorts, can be seen in Table XVIII.

Table XVIII: Biochemistry results from all laboratory cohorts. The total number of non-solicited clinical adverse events is shown per cohort ("Total" column). Also, the number of subjects that were categorized under a specific grade (1-low/2-moderate/3-severe) is shown in the Grades column.

Event	Cohort A		Cohort B		Cohort C	
	Total	Grades 1/2/3	Total	Grades 1/2/3	Total	Grades 1/2/3
Hb decreased	7*	5/1/1	6**	6/0/0	8	7/1/0
CPK increased	6	3/2/1	2	2/0/0	4	2/2/0
Alkaline phosphatases	0	NA	0	NA	1	1/0/0
TOTAL	**13**	**8/3/2**	**8**	**8/0/0**	**13**	**10/3/0**

*7 episodes in 6 subjects, one recovered and presented again

**6 episodes in 5 subjects, one recovered and presented again.

13.4.2.5. Hematology Results

The hematology results from the 3 laboratory Cohorts, can be seen in Table XIX.

Table XIX: Hematology results from all laboratory cohorts. The total number of non-solicited clinical adverse events is shown per cohort ("Total" column). Also, the number of subjects that were categorized under a specific grade (1-low/2-moderate/3-severe) is shown in the Grades column.

Event	Cohort A		Cohort B		Cohort C	
	Total	Grades 1/2/3	Total	Grades 1/2/3	Total	Grades 1/2/3
Leukopenia	5#	5/0/0	1	1/0/0	0	NA
Cholesterol increased	2	2/0/0	1	1/0/0	0	NA

Leukocytosis	1	1/0/0	0	NA	0	NA
Neutropenia	1	0/1/0	0	NA	0	NA
SGOT or SGPT increased	1	1/0/0	1	1/0/0	1	0/0/1
Hypoproteinemia	1	1/0/0	0	NA	0	NA
Hyperglycemia [&]	1	1/0/0	0	NA	0	NA
Hypophosphatemia	1	1/0/0	1	1/0/0	1	1/0/0
Prothrombin time increased	1	1/0/0	0	NA	0	NA
Leucocituria	0	NA	1	1/0/0	2	1/1/0
Eosinophilia	0	NA	1	1/0/0	1	1/0/0
LDH increase	0	NA	0	NA	1	1/0/0
Hypokalemia	0	NA	0	NA	1	1/0/0
TOTAL	**14**	**13/1/0**	**6**	**6/0/0**	**7**	**5/1/1**

[#] 5 episodes in 4 subjects, one recovered and presented again

The hematology results from the 3 clinical Cohorts, can be seen in Table XX.

Table XX: Hematology results from all 3 clinical cohorts. The total number of non-solicited clinical adverse events is shown per cohort ("Total" column). Also, the number of subjects that were categorized under a specific grade (1-low/2-moderate) is shown in the Grades column.

Event	**Cohort A**		**Cohort B**		**Cohort C**	
	Total	**Grades**	**Total**	**Grades**	**Total**	**Grades**
Viral upper respiratory infection*	5	5/0	1	1/0	2	2/0
Other events respiratory system and ORL	3	0/3	0	NA	1	1/0
Lipothymia due to blood sampling	1	0/1	0	NA	0	NA

TOTAL	**9**	**5/4**	**1**	**1/0**	**3**	**3/0**

13.4.2.6. Urinalysis Results

The urinalysis results from the 3 laboratory Cohorts, can be seen in Table XXI.

Table XXI: Urinalysis results from all laboratory cohorts. The total number of non-solicited clinical adverse events is shown per cohort ("Total" column). Also, the number of subjects that were categorized under a specific grade (1-low/2-moderate/3-severe) is shown in the Grades column.

Event	Cohort A		Cohort B		Cohort C	
	Total	Grades 1/2/3	Total	Grades 1/2/3	Total	Grades 1/2/3
Proteinuria[$]	2	0/2/0	1	1/0/0	1	1/0/0
Hematuria	0	NA	0	NA	1	0/1/0
TOTAL	**2**	**0/2/0**	**1**	**1/0/0**	**2**	**1/1/0**

The urinalysis results from the 3 clinical Cohorts, can be seen in Table XXII.

Table XXII: Urinalysis results from all clinical cohorts. The total number of non-solicited clinical adverse events is shown per cohort ("Total" column). Also, the number of subjects that were categorized under a specific grade (1-low/2-moderate) is shown in the Grades column.

Event	Cohort A		Cohort B		Cohort C	
	Total	Grades	Total	Grades	Total	Grades
Urethritis	0	NA	0	NA	1	1/0
TOTAL	**0**	**NA**	**0**	**NA**	**1**	**1/0**

13.5. Vital Signs, Physical Exam Findings, and Other Observations Related to Safety

13.5.1. Vital Signs Grading

The vital signs from the 3 clinical Cohorts, can be seen in Table XXIII.

Table XXIII: Vital signs from all clinical cohorts. The total number of non-solicited clinical adverse events is shown per cohort ("Total" column). Also, the number of subjects that were categorized under a specific grade (1-low/2-moderate) is shown in the Grades column.

Event	Cohort A		Cohort B		Cohort C	
	Total	Grades	Total	Grades	Total	Grades
Arterial hypertension	2	2/0	1	1/0	0	NA
Tachycardia	1	1/0	0	NA	0	NA
Systolic hypotension	0	NA	0	NA	2	1/1
TOTAL	**3**	**3/0**	**1**	**1/0**	**2**	**1/1**

13.5.2. Abnormal Vital Signs

The abnormal vital signs can be seen in table XXIV.

Table XXIV: Abnormal vital signs.

Subject N°	Cohort	Vaccine Type*	Vaccine Dose	AE N°** **	Diagnosis	AD Type ***	Vaccination day	AE Starts (day post vaccination)	AE Ends(day post vaccination)
RSV03	Cohort A	1	$5x10^3$	22	Tachycardia	3	1	1	1
RSV05	Cohort A	1	$5x10^3$	2	Hypertension	3	2	2	2
RSV07	Cohort A	1	$5x10^3$	6	Hypotension	3	7	7	7
RSV07	Cohort A	1	$5x10^3$	12	Tachycardia	3	2	2	2
RSV14	Cohort A	1	$5x10^3$	12	Hypertension	3	2	2	2
RSV30	Cohort B	1	$5x\ 10^4$	5	Hypertension	3	2	2	2
RSv38	Cohort C	2	$5x\ 10^5$	1	Hypotension	3	0	0	0
RSV42	Cohort C	1	$5x\ 10^5$	9	Hypotension	3	1	1	1

* rBCG-N-hRSV (1) or WT-BCG (2).

***AE number* indicates the relative total AE numbers registered up to the point of that AE.

*** local solicited AE (1), local non-solicited AE (2), general solicited AE (3), general non-solicited AE (4), laboratory registered AE (5).

13.6. Concomitant Medications

The use of concomitant medications was recorded. The concomitant medications used were associated with general adverse events (eg-upper respiratory infections) and general discomfort. No subject used any forbidden medications (corticosteroids, other live attenuated vaccines) throughout the protocol period.

13.7. Pregnancies (if applicable)

NA

13.8. Safety Conclusions

Clinical results indicated that both vaccines, rBCG-N-hRSV and BCG-WT, were safe and well tolerated. A higher reactogenicity in terms of abscess and scab formation at the vaccination sites was noted with dose escalation of the vaccine study, but none of these reactions were unexpected in the context of normal reactogenicity related to licensed intradermal BCG vaccines.

14. DISCUSSIONS AND OVERALL CONCLUSION

The rBCG-N-hRSV vaccine has shown to be safe, well tolerated and immunogenic in healthy male adult volunteers. In terms of safety and tolerability, no related SAE were reported through the 180 days of follow-up post-vaccination. A higher reactogenicity was observed with the dose escalation of the vaccine study in terms of time of appearance and severity of abscess and scabbing. Other local events were not increased in association with dose escalations of the study vaccine.

In terms of immunogenicity, rBCG-N-hRSV elicited antigen-specific IgG and cellular immune responses against PPD and N-hRSV. Therefore, the rBCG-N-hRSV is a promising vaccine to prevent hRSV infection/disease as well as tuberculosis infection/disease in children and the elderly.

HRSV may cause severe cases of pneumonia and bronchiolitis in young children and the elderly (2). Unfortunately, the only licensed treatment to date for use in preventing severe hRSV disease is the monoclonal antibody Palivizumab, mainly indicated for high-risk infants (4). However, such treatment is costly and requires repeated doses to be effective (19). Further, although high numbers of prototype vaccines against hRSV infection are under development, few of them are on clinical trials (10). In the current study, we present the results of a Phase I clinical trial of a recombinant BCG that expresses the nucleoprotein of hRSV. BCG is a safe and immunogenic vaccine, being a suitable vector for hRSV vaccine (12, 13). Because our vaccine was designed using BCG as the vector, as well as to provide Th1 cell-inducing adjuvant properties, we evaluated the cellular immune responses of participants against mycobacterial PPD antigens. As shown in the cellular immunogenicity assays (Figures 2 to 4), before vaccination all participants displayed a modest frequency of cells that secreted IFN-γ and IL-2 in response to PPD stimulation. These baseline modest levels of immune response were likely due to the fact that all enrolled participants had been vaccinated in childhood with BCG. Therefore, we expected specific "recall" immune responses after *in vitro* cell stimulation with PPD (20). Once participants were vaccinated with the study vaccines (independently of the vaccine used), all demonstrated a sustained increase in IFN-γ and IL-2 secretion, starting from 14th day post-vaccination and persisting at least until day 30 post-vaccination. We also found that the number of Spot Forming Cells by ELISpot, and the frequency by flow cytometry of CD4+ and CD8+ T cells secreting IFN-γ, IL-2 and TNF-α

after PPD stimulation, increased as higher doses of the rBCG-N-hRSV vaccine were tested. These results indicate that the rBCG-N-hRSV vaccine can induce relevant antigen-specific T cell responses protective against TB, and suggest that these TB-specific responses are dose-dependent.

In contrast to the conventional BCG vaccine, this phase I study was the first time that the rBCG-N-hRSV was tested in healthy volunteers, and hRSV-specific immune responses were measured to determine the cellular and humoral immune responses directed against the N-hRSV protein. Prior to vaccination, we measured the baseline immune response to N protein and found that cells from all participants responded to N protein *in vitro* by secreting IFN-γ, IL-2 and/or TNF-α (Figures 3, 4, and Suppl. Figure 1). These baseline N-RSV-specific responses are likely due to previous hRSV exposures (3). Similarly, increased anti-F IgG antibody responses were found in all subjects enrolled into Cohort A, also suggesting that those subjects had been previously exposed to hRSV. It is known that after hRSV infection, cellular and humoral immune responses can be increased against hRSV antigens, such as the N protein (21). However, these immune responses appear to be ineffective, as recurrent infections can occur (22). We previously described that low single doses of BCG-N-hRSV vaccine ($3x10^5$ CFUs) were enough to induce Th1 immune responses in mice that protected animals against hRSV challenge (15). This antiviral immune response was characterized by the secretion of high levels of IFN-γ and IL-17 from T cells after *in vitro* stimulation with hRSV antigens. In accordance with preclinical data, we found that all participants given BCG-N-hRSV vaccines increased the numbers of Spot Forming Cells and the frequencies of $CD4^+$ and $CD8^+$ T cells producing IFN-γ after hRSV nucleoprotein antigen *in vitro* stimulation. These levels increased from 14^{th} day post vaccination and remained high at least until day 60, and in some cases even until day 180 post-vaccination. As seen with PPD measurements, the hRSV-specific immune responses increased with dose escalation. Polyfunctional T cell responses (producing combinations of both IFN-γ and IL-2) were more pronounced at day 30 post-vaccination.

All available data to date suggest that protective hRSV immune responses must include strong CD4+ Th1 responses, and these Th1 responses are not associated with RSV disease exacerbation. This latter point is important since the first FI-hRSV vaccine failed to prevent hRSV infection, and even worse vaccinated children had an increased risk of severe disease after hRSV infection (7). As described above, we have previously observed in our clinical work that rBCG-N-hRSV is immunogenic without causing immune enhancement disease in mice (11, 15). Further, in

the present phase I clinical study, we did not find any related severe adverse events in response to the rBCG-N-hRSV in healthy adult donors. All subjects had a follow-up for 180 days, during which they could have been exposed to hRSV infection, and importantly, no severe disease was found in any subject.

15. TABLES, FIGURES, AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT

Table XXV: Listing of local adverse events by subjects.

***Vaccine type* : rBCG-N-hRSV (1), WT-BCG (2).**

****AE type:* local solicited AE (1), local non-solicited AE (2), general solicited AE (3), general AE (4), laboratory registered AE (5).**

Subject Number	Cohort	Vaccine Type*	Diagnosis	AE type**	Day post Vaccine	AE Start	Total AE Duration
RSV01	Cohort A	2	Vaccine site sensitivity	1	27-06-2017	27-06-2017	9
RSV01	Cohort A	2	Pain vaccination site	1	28-06-2017	28-06-2017	1
RSV01	Cohort A	2	Erythema vaccination site	1	29-06-2017	29-06-2017	1
RSV01	Cohort A	2	Vaccination site abscess	1	18-07-2017	18-07-2017	65
RSV01	Cohort A	2	Vaccination site crust	1	18-07-2017	18-07-2017	123
RSV02	Cohort A	1	Vaccine site sensitivity	1	28-06-2017	28-06-2017	38
RSV02	Cohort A	1	Erythema vaccination site	1	01-07-2017	01-07-2017	2
RSV02	Cohort A	1	Induration vaccination site	1	30-06-2017	30-06-2017	1
RSV02	Cohort A	1	Pain vaccination site	1	07-07-2017	07-07-2017	5
RSV02	Cohort A	1	Vaccination site abscess	1	11-07-2017	11-07-2017	2
RSV02	Cohort A	1	Vaccination site crust	1	11-07-2017	11-07-2017	67
RSV03	Cohort A	1	Pruritus vaccination site	2	30-06-2017	30-06-2017	7
RSV03	Cohort A	1	Flaking vaccination site	2	02-07-2017	02-07-2017	25
RSV03	Cohort A	1	Vaccine site sensitivity	1	28-06-2017	28-06-2017	74
RSV03	Cohort A	1	Pain vaccination site	1	29-06-2017	29-06-2017	3
RSV03	Cohort A	1	Vaccination site crust	1	06-08-2017	06-08-2017	40
RSV03	Cohort A	1	Vaccination site abscess	1	27-07-2017	27-07-2017	10
RSV05	Cohort A	1	Erythema vaccination site	1	06-07-2017	06-07-2017	2
RSV05	Cohort A	1	Vaccine site sensitivity	1	05-07-2017	05-07-2017	10
RSV05	Cohort A	1	Pain vaccination site	1	07-07-2017	07-07-2017	5
RSV05	Cohort A	1	Vaccination site abscess	1	22-07-2017	22-07-2017	3
RSV05	Cohort A	1	Vaccination site crust	1	25-07-2017	25-07-2017	33
RSV07	Cohort A	1	Pain vaccination site	1	13-07-2017	13-07-2017	10
RSV07	Cohort A	1	Vaccine site sensitivity	1	16-07-2017	16-07-2017	11
RSV07	Cohort A	1	Pruritus vaccination site	2	13-07-2017	13-07-2017	15
RSV07	Cohort A	1	Vaccination site abscess	1	18-07-2017	18-07-2017	7
RSV07	Cohort A	1	Vaccination site crust	1	23-07-2017	23-07-2017	74
RSV10	Cohort A	1	Tiredness in vaccinated arm	2	10-07-2017	10-07-2017	1
RSV10	Cohort A	1	Vaccine site sensitivity	1	10-07-2017	10-07-2017	17
RSV10	Cohort A	1	Pruritus vaccination site	2	12-07-2017	12-07-2017	12
RSV10	Cohort A	1	Erythema vaccination site	1	12-07-2017	12-07-2017	2

RSV10	Cohort A	1	Pain vaccination site	1	12-07-2017	12-07-2017	15
RSV10	Cohort A	1	Vaccination site abscess	1	20-07-2017	20-07-2017	7
RSV10	Cohort A	1	Vaccination site crust	1	20-07-2017	20-07-2017	131
RSV10	Cohort A	1	Induration vaccination site	1	11-07-2017	11-07-2017	1
RSV13	Cohort A	2	Pruritus vaccination site	2	18-07-2017	18-07-2017	6
RSV13	Cohort A	2	Vaccine site sensitivity	1	18-07-2017	18-07-2017	2
RSV13	Cohort A	2	Erythema vaccination site	1	18-07-2017	18-07-2017	3
RSV13	Cohort A	2	Vaccination site abscess	1	27-07-2017	27-07-2017	15
RSV13	Cohort A	2	Vaccination site crust	1	27-07-2017	27-07-2017	137
RSV13	Cohort A	2	Pain vaccination site	1	24-07-2017	24-07-2017	3
RSV14	Cohort A	1	Pain vaccination site	1	19-07-2017	19-07-2017	17
RSV14	Cohort A	1	Vaccine site sensitivity	1	19-07-2017	19-07-2017	28
RSV14	Cohort A	1	Vaccination site abscess	1	02-08-2017	02-08-2017	1
RSV14	Cohort A	1	Vaccination site crust	1	03-08-2017	03-08-2017	11
RSV14	Cohort A	1	Pruritus vaccination site	2	22-07-2017	22-07-2017	5
RSV14	Cohort A	1	Flaking vaccination site	2	16-08-2017	16-08-2017	8
RSV16	Cohort B	1	Vaccine site sensitivity	1	02-10-2017	02-10-2017	11
RSV16	Cohort B	1	Induration vaccination site	1	03-10-2017	03-10-2017	20
RSV16	Cohort B	1	Pruritus vaccination site	2	06-10-2017	06-10-2017	1
RSV16	Cohort B	1	Left axillary lymphadenopathy	1	06-10-2017	06-10-2017	3
RSV16	Cohort B	1	Vaccination site crust	1	14-10-2017	14-10-2017	170
RSV16	Cohort B	1	Vaccination site abscess	1	15-10-2017	15-10-2017	4
RSV17	Cohort B	1	Erythema vaccination site	1	03-10-2017	03-10-2017	4
RSV17	Cohort B	1	Vaccine site sensitivity	1	03-10-2017	03-10-2017	13
RSV17	Cohort B	1	Induration vaccination site	1	03-10-2017	03-10-2017	4
RSV17	Cohort B	1	Pain vaccination site	1	03-10-2017	03-10-2017	13
RSV17	Cohort B	1	Vaccination site abscess	1	12-10-2017	12-10-2017	75
RSV17	Cohort B	1	Vaccination site crust	1	13-10-2017	13-10-2017	92
RSV18	Cohort B	2	Vaccine site sensitivity	1	04-10-2017	04-10-2017	13
RSV18	Cohort B	2	Erythema vaccination site	1	04-10-2017	04-10-2017	4
RSV18	Cohort B	2	Induration vaccination site	1	05-10-2017	05-10-2017	9
RSV18	Cohort B	2	Pain vaccination site	1	10-10-2017	10-10-2017	3
RSV18	Cohort B	2	Vaccination site abscess	1	09-10-2017	09-10-2017	7
RSV18	Cohort B	2	Vaccination site crust	1	14-10-2017	14-10-2017	142
RSV24	Cohort B	2	Pain vaccination site	1	03-10-2017	03-10-2017	12
RSV24	Cohort B	2	Vaccine site sensitivity	1	03-10-2017	03-10-2017	15
RSV24	Cohort B	2	Erythema vaccination site	1	04-10-2017	04-10-2017	7
RSV24	Cohort B	2	Induration vaccination site	1	04-10-2017	04-10-2017	6
RSV24	Cohort B	2	Vaccination site abscess	1	14-10-2017	14-10-2017	13
RSV24	Cohort B	2	Vaccination site crust	1	18-10-2017	18-10-2017	34
RSV25	Cohort B	1	Pain vaccination site	1	05-10-2017	05-10-2017	1
RSV25	Cohort B	1	Vaccine site sensitivity	1	05-10-2017	05-10-2017	1

RSV25	Cohort B	1	Erythema vaccination site	1	06-10-2017	06-10-2017	8
RSV25	Cohort B	1	Vaccination site abscess	1	06-10-2017	06-10-2017	6
RSV25	Cohort B	1	Induration vaccination site	1	07-10-2017	07-10-2017	37
RSV25	Cohort B	1	Vaccination site crust	1	08-10-2017	08-10-2017	51
RSV26	Cohort B	1	Pain vaccination site	1	04-10-2017	04-10-2017	8
RSV26	Cohort B	1	Vaccine site sensitivity	1	04-10-2017	04-10-2017	13
RSV26	Cohort B	1	Erythema vaccination site	1	05-10-2017	05-10-2017	16
RSV26	Cohort B	1	Vaccination site abscess	1	11-10-2017	11-10-2017	5
RSV26	Cohort B	1	Ulcer vaccination site	2	17-10-2017	17-10-2017	2
RSV26	Cohort B	1	Vaccination site crust	1	15-10-2017	15-10-2017	91
RSV27	Cohort B	1	Induration vaccination site	1	18-10-2017	18-10-2017	11
RSV27	Cohort B	1	Erythema vaccination site	1	05-10-2017	05-10-2017	15
RSV27	Cohort B	1	Pain vaccination site	1	04-10-2017	04-10-2017	14
RSV27	Cohort B	1	Vaccine site sensitivity	1	04-10-2017	04-10-2017	11
RSV27	Cohort B	1	Pruritus vaccination site	2	09-10-2017	09-10-2017	2
RSV27	Cohort B	1	Vaccination site abscess	1	12-10-2017	12-10-2017	7
RSV27	Cohort B	1	Vaccination site crust	1	18-10-2017	18-10-2017	143
RSV30	Cohort B	1	Vaccine site sensitivity	1	10-10-2017	10-10-2017	10
RSV30	Cohort B	1	Pruritus vaccination site	2	11-10-2017	11-10-2017	7
RSV30	Cohort B	1	Left axillary pain	2	10-10-2017	10-10-2017	1
RSV30	Cohort B	1	Vaccination site crust	1	21-10-2017	21-10-2017	19
RSV30	Cohort B	1	Pain vaccination site	1	18-10-2017	18-10-2017	5
RSV30	Cohort B	1	Vaccination site abscess	1	19-10-2017	19-10-2017	3
RSV32	Cohort C	1	Pain vaccination site	1	21-11-2017	21-11-2017	15
RSV32	Cohort C	1	Vaccine site sensitivity	1	22-11-2017	22-11-2017	18
RSV32	Cohort C	1	Erythema vaccination site	1	22-11-2017	22-11-2017	12
RSV32	Cohort C	1	Vaccination site abscess	1	27-11-2017	27-11-2017	110
RSV32	Cohort C	1	Induration vaccination site	1	23-11-2017	23-11-2017	32
RSV32	Cohort C	1	Vaccination site crust	1	27-11-2017	27-11-2017	202
RSV33	Cohort C	1	Pain vaccination site	1	21-11-2017	21-11-2017	10
RSV33	Cohort C	1	Vaccine site sensitivity	1	21-11-2017	21-11-2017	10
RSV33	Cohort C	1	Erythema vaccination site	1	23-11-2017	23-11-2017	4
RSV33	Cohort C	1	Vaccination site abscess	1	26-11-2017	26-11-2017	5
RSV33	Cohort C	1	Vaccination site crust	1	28-11-2017	28-11-2017	67
RSV33	Cohort C	1	Induration vaccination site	1	28-11-2017	28-11-2017	1
RSV34	Cohort C	2	Pain vaccination site	1	21-11-2017	21-11-2017	18
RSV34	Cohort C	2	Vaccine site sensitivity	1	22-11-2017	22-11-2017	5
RSV34	Cohort C	2	Erythema vaccination site	1	22-11-2017	22-11-2017	3
RSV34	Cohort C	2	Induration vaccination site	1	23-11-2017	23-11-2017	1
RSV34	Cohort C	2	Pruritus vaccination site	2	24-11-2017	24-11-2017	17
RSV34	Cohort C	2	Vaccination site abscess	1	04-12-2017	04-12-2017	63
RSV34	Cohort C	2	Vaccination site crust	1	20-02-2018	20-02-2018	63

RSV36	Cohort C	1	Vaccine site sensitivity	1	27-11-2017	27-11-2017	55
RSV36	Cohort C	1	Erythema vaccination site	1	28-11-2017	28-11-2017	8
RSV36	Cohort C	1	Pain vaccination site	1	28-11-2017	28-11-2017	11
RSV36	Cohort C	1	Vaccination site abscess	1	01-12-2017	01-12-2017	5
RSV36	Cohort C	1	Vaccination site crust	1	04-12-2017	04-12-2017	44
RSV36	Cohort C	1	Ulcer vaccination site	2	15-12-2017	15-12-2017	14
RSV38	Cohort C	2	Vaccine site sensitivity	1	27-11-2017	27-11-2017	38
RSV38	Cohort C	2	Pain vaccination site	1	27-11-2017	27-11-2017	21
RSV38	Cohort C	2	Erythema vaccination site	1	28-11-2017	28-11-2017	2
RSV38	Cohort C	2	Pruritus vaccination site	2	29-11-2017	29-11-2017	7
RSV38	Cohort C	2	Vaccination site abscess	1	05-12-2017	05-12-2017	6
RSV38	Cohort C	2	Vaccination site crust	1	08-12-2017	08-12-2017	36
RSV38	Cohort C	2	Ulcer vaccination site	2	27-12-2017	27-12-2017	10
RSV40	Cohort C	1	Vaccine site sensitivity	1	28-11-2017	28-11-2017	19
RSV40	Cohort C	1	Pain vaccination site	1	04-12-2017	04-12-2017	11
RSV40	Cohort C	1	Erythema vaccination site	1	04-12-2017	04-12-2017	5
RSV40	Cohort C	1	Induration vaccination site	1	06-12-2017	06-12-2017	1
RSV40	Cohort C	1	Vaccination site abscess	1	04-12-2017	04-12-2017	28
RSV40	Cohort C	1	Vaccination site crust	1	05-12-2017	05-12-2017	27
RSV40	Cohort C	1	Ulcer vaccination site	2	01-01-2018	01-01-2018	15
RSV41	Cohort C	1	Vaccine site sensitivity	1	28-11-2017	28-11-2017	15
RSV41	Cohort C	1	Pain vaccination site	1	29-11-2017	29-11-2017	7
RSV41	Cohort C	1	Vaccination site abscess	1	30-11-2017	30-11-2017	8
RSV41	Cohort C	1	Induration vaccination site	1	01-12-2017	01-12-2017	1
RSV41	Cohort C	1	Vaccination site crust	1	03-12-2017	03-12-2017	185
RSV41	Cohort C	1	Erythema vaccination site	1	06-12-2017	06-12-2017	1
RSV42	Cohort C	1	Vaccine site sensitivity	1	04-12-2017	04-12-2017	14
RSV42	Cohort C	1	Pain vaccination site	1	05-12-2017	05-12-2017	6
RSV42	Cohort C	1	Erythema vaccination site	1	05-12-2017	05-12-2017	6
RSV42	Cohort C	1	Vaccination site abscess	1	06-12-2017	06-12-2017	7
RSV42	Cohort C	1	left axillary pain	1	07-12-2017	07-12-2017	7
RSV42	Cohort C	1	Vaccination site crust	1	11-12-2017	11-12-2017	103

Table XXVI: Listing of general adverse events by subjects.

***Vaccine type* : rBCG-N-hRSV (1), WT-BCG (2).**

****AE type:* local solicited AE (1), local non-solicited AE (2), general solicited AE (3), general AE (4), laboratory registered AE (5).**

Subject N°	Cohort	Vaccine Type*	AE N°	Diagnosis	AE Type	Day post Vaccine	AE Start	AE End
RSV01	Cohort A	2	1	Hypophosphatemia	5	8	05-07-2017	13-07-2017

RSV01	Cohort A	2	2	Hyperglycemia	5	8	05-07-2017	13-07-2017
RSV01	Cohort A	2	3	Sickness	3	13	10-07-2017	10-07-2017
RSV01	Cohort A	2	4	Left wrist contusion	4	9	06-07-2017	22-09-2017
RSV01	Cohort A	2	5	Vaccine site sensitivity	1	0	27-06-2017	29-06-2017
RSV01	Cohort A	2	6	Pain vaccination site	1	1	28-06-2017	28-06-2017
RSV01	Cohort A	2	7	Erythema vaccination site	1	2	29-06-2017	29-06-2017
RSV01	Cohort A	2	8	Decreased hemoglobin	5	8	05-07-2017	Continues
RSV01	Cohort A	2	9	Vaccination site abscess	1	21	18-07-2017	20-09-2017
RSV01	Cohort A	2	10	Proteinuria	5	30	27-07-2017	21-08-2017
RSV01	Cohort A	2	11	Leukocytosis	5	30	27-07-2017	21-08-2017
RSV01	Cohort A	2	12	Vaccine site sensitivity	1	17	14-07-2017	17-07-2017
RSV01	Cohort A	2	13	Abdominal pain	4	13	10-07-2017	10-07-2017
RSV01	Cohort A	2	14	Vaccination site crust	1	21	18-07-2017	17-11-2017
RSV01	Cohort A	2	15	Vaccine site sensitivity	1	23	20-07-2017	21-07-2017
RSV01	Cohort A	2	16	Hematuria	5	55	21-08-2017	24-10-2017
RSV01	Cohort A	2	17	Proteinuria	5	57	23-08-2017	24-10-2017
RSV01	Cohort A	2	18	Diarrhea	3	12	09-07-2017	09-07-2017
RSV01	Cohort A	2	19	Headache	3	12	09-07-2017	09-07-2017
RSV01	Cohort A	2	20	Hypernatremia	5	119	24-10-2017	26-10-2017
RSV02	Cohort A	1	1	Leukopenia	5	6	04-07-2017	11-07-2017
RSV02	Cohort A	1	2	Neutropenia	5	6	04-07-2017	11-07-2017
RSV02	Cohort A	1	3	Increase in CPK	5	6	04-07-2017	11-07-2017
RSV02	Cohort A	1	4	Vaccine site sensitivity	1	0	28-06-2017	04-08-2017
RSV02	Cohort A	1	5	Erythema vaccination site	1	3	01-07-2017	01-07-2017
RSV02	Cohort A	1	6	Induration vaccination site	1	2	30-06-2017	30-06-2017
RSV02	Cohort A	1	7	Pain vaccination site	1	9	07-07-2017	11-07-2017
RSV02	Cohort A	1	8	Decrease hemoglobin	5	13	11-07-2017	24-07-2017
RSV02	Cohort A	1	9	Vaccination site abscess	1	13	11-07-2017	11-07-2017
RSV02	Cohort A	1	10	Diarrhea	3	13	11-07-2017	11-07-2017
RSV02	Cohort A	1	11	Diarrhea	3	15	13-07-2017	13-07-2017
RSV02	Cohort A	1	12	Erythema vaccination site	1	6	04-07-2017	04-07-2017
RSV02	Cohort A	1	13	Leukopenia	5	26	24-07-2017	Continues
RSV02	Cohort A	1	14	Vaccination site crust	1	13	11-07-2017	15-09-2017

RSV02	Cohort A	1	15	Lymphopenia	5	55	22-08-2017	25-10-2017
RSV02	Cohort A	1	16	Diarrhea	3	11	09-07-2017	09-07-2017
RSV02	Cohort A	1	17	Vaccination site crust	1	17	15-07-2017	15-07-2017
RSV02	Cohort A	1	18	Increase in CPK	5	119	25-10-2017	18-12-2017
RSV02	Cohort A	1	19	Hyperglycemia	5	173	18-12-2017	26-12-2017
RSV02	Cohort A	1	20	Decreased hemoglobin	5	173	18-12-2017	Continues
RSV03	Cohort A	1	1	Pruritus vaccination site	2	3	30-06-2017	06-07-2017
RSV03	Cohort A	1	2	Flaking vaccination site	2	5	02-07-2017	26-07-2017
RSV03	Cohort A	1	3	Common cold	4	11	08-07-2017	24-07-2017
RSV03	Cohort A	1	4	Increase in CPK	5	7	04-07-2017	10-07-2017
RSV03	Cohort A	1	5	Hypoproteinemia	5	7	04-07-2017	10-07-2017
RSV03	Cohort A	1	6	Vaccine site sensitivity	1	1	28-06-2017	03-07-2017
RSV03	Cohort A	1	7	Pain vaccination site	1	2	29-06-2017	30-06-2017
RSV03	Cohort A	1	8	Decrease hemoglobin	5	7	04-07-2017	10-07-2017
RSV03	Cohort A	1	9	Fatigue	3	22	19-07-2017	19-07-2017
RSV03	Cohort A	1	10	Fatigue	3	24	21-07-2017	23-07-2017
RSV03	Cohort A	1	11	Headache	3	21	18-07-2017	19-07-2017
RSV03	Cohort A	1	12	Headache	3	24	21-07-2017	23-07-2017
RSV03	Cohort A	1	13	Myalgia	3	25	22-07-2017	23-07-2017
RSV03	Cohort A	1	14	Vaccine site sensitivity	1	10	07-07-2017	09-07-2017
RSV03	Cohort A	1	15	Vaccine site sensitivity	1	14	11-07-2017	16-07-2017
RSV03	Cohort A	1	16	Vaccine site sensitivity	1	21	18-07-2017	14-09-2017
RSV03	Cohort A	1	17	Decrease hemoglobin	5	34	31-07-2017	31-08-2017
RSV03	Cohort A	1	18	Leukopenia	5	34	31-07-2017	27-12-2017
RSV03	Cohort A	1	19	Vaccination site crust	1	40	06-08-2017	14-09-2017
RSV03	Cohort A	1	20	Vaccination site abscess	1	30	27-07-2017	05-08-2017
RSV03	Cohort A	1	21	Pain vaccination site	1	25	22-07-2017	22-07-2017
RSV03	Cohort A	1	22	Tachycardia	3	1	28-06-2017	28-06-2017
RSV03	Cohort A	1	23	Headache	4	148	22-11-2017	22-11-2017
RSV05	Cohort A	1	1	Puncture site ecchymosis	4	1	05-07-2017	10-07-2017
RSV05	Cohort A	1	2	Hypertension	3	2	06-07-2017	06-07-2017
RSV05	Cohort A	1	3	Erythema vaccination site	1	2	06-07-2017	07-07-2017
RSV05	Cohort A	1	4	Vaccine site sensitivity	1	1	05-07-2017	08-07-2017

RSV05	Cohort A	1	5	Pain vaccination site	1	3	07-07-2017	07-07-2017
RSV05	Cohort A	1	6	Decreased hemoglobin	5	8	12-07-2017	19-07-2017
RSV05	Cohort A	1	7	Headache	3	8	12-07-2017	13-07-2017
RSV05	Cohort A	1	8	Bilateral Otalgia	4	8	12-07-2017	14-07-2017
RSV05	Cohort A	1	9	Retro ocular left pain	4	8	12-07-2017	13-07-2017
RSV05	Cohort A	1	10	Fatigue	3	8	12-07-2017	12-07-2017
RSV05	Cohort A	1	11	Increase in CPK	5	15	19-07-2017	07-08-2017
RSV05	Cohort A	1	12	Tonsillitis	4	14	18-07-2017	02-08-2017
RSV05	Cohort A	1	13	Pain vaccination site	1	16	20-07-2017	23-07-2017
RSV05	Cohort A	1	14	Vaccine site sensitivity	1	16	20-07-2017	25-07-2017
RSV05	Cohort A	1	15	Vaccination site abscess	1	18	22-07-2017	24-07-2017
RSV05	Cohort A	1	16	Headache	3	18	22-07-2017	23-07-2017
RSV05	Cohort A	1	17	Headache	3	23	27-07-2017	28-07-2017
RSV05	Cohort A	1	18	Fatigue	3	18	22-07-2017	23-07-2017
RSV05	Cohort A	1	19	Fatigue	3	23	27-07-2017	28-07-2017
RSV05	Cohort A	1	20	Vaccination site crust	1	21	25-07-2017	26-08-2017
RSV05	Cohort A	1	21	Sickness	3	8	12-07-2017	12-07-2017
RSV05	Cohort A	1	22	Common cold	4	65	07-09-2017	10-09-2017
RSV05	Cohort A	1	23	Decrease haemoglobin	5	113	25-10-2017	Continues
RSV05	Cohort A	1	24	Increase in CPK	5	113	25-10-2017	29-12-2017
RSV05	Cohort A	1	25	Acute gastroenteritis	4	174	25-12-2017	01-01-2018
RSV07	Cohort A	1	1	Common cold	4	0	10-07-2017	12-07-2017
RSV07	Cohort A	1	2	Headache	3	0	10-07-2017	10-07-2017
RSV07	Cohort A	1	3	Pain vaccination site	1	3	13-07-2017	14-07-2017
RSV07	Cohort A	1	4	Headache	3	3	13-07-2017	13-07-2017
RSV07	Cohort A	1	5	Vaccine site sensitivity	1	6	16-07-2017	26-07-2017
RSV07	Cohort A	1	6	Hypotension	3	7	17-07-2017	17-07-2017
RSV07	Cohort A	1	7	Proteinuria	5	7	17-07-2017	26-07-2017
RSV07	Cohort A	1	8	Increase in CPK	5	7	17-07-2017	26-07-2017
RSV07	Cohort A	1	10	Pruritus vaccination site	2	3	13-07-2017	26-07-2017
RSV07	Cohort A	1	11	Hypercholesterolemia	5	16	26-07-2017	10-08-2017
RSV07	Cohort A	1	12	Tachycardia	3	2	12-07-2017	12-07-2017
RSV07	Cohort A	1	9	Cough	4	6	16-07-2017	22-07-2017

RSV07	Cohort A	1	13	Pain vaccination site	1	6	16-07-2017	22-07-2017
RSV07	Cohort A	1	14	Fatigue	3	8	18-07-2017	18-07-2017
RSV07	Cohort A	1	15	Vaccination site abscess	1	8	18-07-2017	22-07-2017
RSV07	Cohort A	1	16	Vaccination site crust	1	13	23-07-2017	04-10-2017
RSV07	Cohort A	1	17	Decreased haemoglobin	5	31	10-08-2017	08-09-2017
RSV07	Cohort A	1	18	Vaccination site abscess	1	40	19-08-2017	19-08-2017
RSV07	Cohort A	1	19	Pain vaccination site	1	40	19-08-2017	19-08-2017
RSV07	Cohort A	1	20	Wisdom tooth pain	4	38	17-08-2017	18-08-2017
RSV07	Cohort A	1	21	Pruritus vaccination site	2	3	13-07-2017	13-07-2017
RSV07	Cohort A	1	22	Wisdom tooth pain	4	42	21-08-2017	23-08-2017
RSV07	Cohort A	1	23	Wisdom tooth pain	4	54	02-09-2017	06-09-2017
RSV07	Cohort A	1	24	Scratch in crust area	4	48	27-08-2017	27-08-2017
RSV07	Cohort A	1	25	Vaccination site crust	1	48	27-08-2017	27-08-2017
RSV07	Cohort A	1	26	Hypercholesterolemia	5	60	08-09-2017	08-01-2018
RSV07	Cohort A	1	27	Headache	3	9	19-07-2017	20-07-2017
RSV07	Cohort A	1	28	Decreased hemoglobin	5	120	07-11-2017	Continues
RSV07	Cohort A	1	29	Pyuria	5	120	07-11-2017	08-01-2018
RSV07	Cohort A	1	30	Increased TTPA	5	120	07-11-2017	08-01-2018
RSV10	Cohort A	1	1	Tiredness in vaccinated arm (left)	2	0	10-07-2017	10-07-2017
RSV10	Cohort A	1	2	Vaccine site sensitivity	1	0	10-07-2017	10-07-2017
RSV10	Cohort A	1	3	Pruritus vaccination site	2	2	12-07-2017	23-07-2017
RSV10	Cohort A	1	4	Vaccine site sensitivity	1	1	11-07-2017	27-07-2017
RSV10	Cohort A	1	5	Erythema vaccination site	1	2	12-07-2017	13-07-2017
RSV10	Cohort A	1	6	Pain vaccination site	1	2	12-07-2017	15-07-2017
RSV10	Cohort A	1	7	Sickness	3	0	10-07-2017	10-07-2017
RSV10	Cohort A	1	8	Vaccination site abscess	1	10	20-07-2017	24-07-2017
RSV10	Cohort A	1	9	Decreased haemoglobin	5	14	24-07-2017	07-08-2017
RSV10	Cohort A	1	10	Increase in CPK	5	14	24-07-2017	07-08-2017
RSV10	Cohort A	1	11	Vaccination site crust	1	10	20-07-2017	27-11-2017
RSV10	Cohort A	1	12	Pain vaccination site	1	7	17-07-2017	27-07-2017
RSV10	Cohort A	1	13	Induration vaccination site	1	1	11-07-2017	11-07-2017
RSV10	Cohort A	1	14	Acute rhinopharyngousitis	4	36	15-08-2017	25-08-2017

RSV10	Cohort A	1	15	Fever	4	36	15-08-2017	16-08-2017
RSV10	Cohort A	1	16	Vaccination site abscess	1	73	21-09-2017	22-09-2017
RSV10	Cohort A	1	17	Acute pharyngitis	4	117	04-11-2017	23-11-2017
RSV10	Cohort A	1	18	Hypoglycemia	5	120	07-11-2017	06-01-2018
RSV10	Cohort A	1	19	Leukocytosis	5	120	07-11-2017	06-01-2018
RSV10	Cohort A	1	20	Decreased hemoglobin	5	180	06-01-2018	Continues
RSV13	Cohort A	2	1	Pruritus vaccination site	2	1	18-07-2017	23-07-2017
RSV13	Cohort A	2	2	Vaccine site sensitivity	1	1	18-07-2017	19-07-2017
RSV13	Cohort A	2	3	Erythema vaccination site	1	1	18-07-2017	20-07-2017
RSV13	Cohort A	2	4	Leukopenia	5	7	24-07-2017	08-09-2017
RSV13	Cohort A	2	5	Vaccination site abscess	1	10	27-07-2017	10-08-2017
RSV13	Cohort A	2	6	Headache	3	8	25-07-2017	25-07-2017
RSV13	Cohort A	2	7	Vaccination site crust	1	10	27-07-2017	07-09-2017
RSV13	Cohort A	2	8	Headache	3	13	30-07-2017	30-07-2017
RSV13	Cohort A	2	9	Odynophagia	4	24	10-08-2017	10-08-2017
RSV13	Cohort A	2	10	Pain vaccination site	1	7	24-07-2017	26-07-2017
RSV13	Cohort A	2	11	Headache	4	38	24-08-2017	24-08-2017
RSV13	Cohort A	2	12	Headache	4	40	26-08-2017	26-08-2017
RSV13	Cohort A	2	13	Common cold	4	45	31-08-2017	15-09-2017
RSV13	Cohort A	2	14	Epistaxis	4	49	04-09-2017	11-09-2017
RSV13	Cohort A	2	15	Vaccination site crust	1	55	10-09-2017	20-09-2017
RSV13	Cohort A	2	16	Vaccination site crust	1	68	23-09-2017	18-11-2017
RSV13	Cohort A	2	17	Leg pain	4	58	13-09-2017	15-09-2017
RSV13	Cohort A	2	18	Headache	4	75	30-09-2017	30-09-2017
RSV13	Cohort A	2	19	Headache	4	81	06-10-2017	06-10-2017
RSV13	Cohort A	2	20	Headache	4	116	10-11-2017	10-11-2017
RSV13	Cohort A	2	21	Leukopenia	5	120	14-11-2017	Continues
RSV13	Cohort A	2	22	Vaccination site crust	1	124	18-11-2017	26-11-2017
RSV13	Cohort A	2	23	Vaccination site crust	1	132	26-11-2017	12-12-2017
RSV13	Cohort A	2	24	Headache	4	130	24-11-2017	24-11-2017
RSV13	Cohort A	2	25	Headache	4	137	01-12-2017	01-12-2017
RSV13	Cohort A	2	26	Headache	4	143	07-12-2017	07-12-2017
RSV13	Cohort A	2	27	Headache	4	166	30-12-2017	30-12-2017

RSV13	Cohort A	2	28	Hypophosphatemia	5	175	08-01-2018	Continues
RSV14	Cohort A	1	1	Pain vaccination site	1	1	19-07-2017	04-08-2017
RSV14	Cohort A	1	2	Vaccine site sensitivity	1	1	19-07-2017	04-08-2017
RSV14	Cohort A	1	4	Increase in CPK	5	8	26-07-2017	02-08-2017
RSV14	Cohort A	1	5	Increase in SGOT	5	8	26-07-2017	02-08-2017
RSV14	Cohort A	1	6	Leukopenia	5	8	26-07-2017	02-08-2017
RSV14	Cohort A	1	7	Hypercholesterolemia	5	15	02-08-2017	16-08-2017
RSV14	Cohort A	1	8	Bronchitis	4	16	03-08-2017	12-08-2017
RSV14	Cohort A	1	9	Vaccination site abscess	1	15	02-08-2017	02-08-2017
RSV14	Cohort A	1	10	Vaccination site crust	1	16	03-08-2017	13-08-2017
RSV14	Cohort A	1	3	Pruritus vaccination site	2	4	22-07-2017	26-07-2017
RSV14	Cohort A	1	11	Increase TTPA	5	29	16-08-2017	13-09-2017
RSV14	Cohort A	1	12	Hypertension	3	2	20-07-2017	20-07-2017
RSV14	Cohort A	1	13	Vaccine site sensitivity	1	4	22-07-2017	01-08-2017
RSV14	Cohort A	1	14	Common cold	4	38	25-08-2017	01-09-2017
RSV14	Cohort A	1	15	Bronchitis	4	46	02-09-2017	15-09-2017
RSV14	Cohort A	1	16	Flaking vaccination site	2	29	16-08-2017	23-08-2017
RSV14	Cohort A	1	17	Leukopenia	5	57	13-09-2017	14-11-2017
RSV14	Cohort A	1	18	Neutropenia	5	57	13-09-2017	14-11-2017
RSV14	Cohort A	1	19	Leukopenia	5	181	15-01-2018	Continues
RSV14	Cohort A	1	20	Neutropenia	5	181	15-01-2018	Continues
RSV16	Cohort B	1	1	Vaccine site sensitivity	1	0	02-10-2017	05-10-2017
RSV16	Cohort B	1	2	Induration vaccination site	1	1	03-10-2017	22-10-2017
RSV16	Cohort B	1	3	Pruritus vaccination site	2	4	06-10-2017	06-10-2017
RSV16	Cohort B	1	4	Left axillary lymphadenopathy	1	4	06-10-2017	06-10-2017
RSV16	Cohort B	1	5	Left axillary lymphadenopathy	1	7	09-10-2017	09-10-2017
RSV16	Cohort B	1	6	Decreased haemoglobin	5	8	10-10-2017	Continues
RSV16	Cohort B	1	7	Vaccine site sensitivity	1	12	14-10-2017	20-10-2017
RSV16	Cohort B	1	8	Vaccination site crust	1	12	14-10-2017	01-04-2018
RSV16	Cohort B	1	9	Vaccination site abscess	1	13	15-10-2017	15-10-2017
RSV16	Cohort B	1	10	Vaccination site abscess	1	16	18-10-2017	18-10-2017
RSV16	Cohort B	1	11	Vaccination site abscess	1	18	20-10-2017	20-10-2017

RSV16	Cohort B	1	12	Vaccination site abscess	1	24	26-10-2017	26-10-2017
RSV16	Cohort B	1	13	Increase in SGPT	5	29	31-10-2017	11-12-2017
RSV16	Cohort B	1	14	Left axillary lymphadenopathy	1	25	27-10-2017	27-10-2017
RSV16	Cohort B	1	15	Common cold	4	108	18-01-2018	20-01-2018
RSV16	Cohort B	1	16	Increase in SGPT	5	182	02-04-2018	Continues
RSV17	Cohort B	1	1	Erythema vaccination site	1	1	03-10-2017	04-10-2017
RSV17	Cohort B	1	2	Vaccine site sensitivity	1	1	03-10-2017	15-10-2017
RSV17	Cohort B	1	3	Induration vaccination site	1	1	03-10-2017	06-10-2017
RSV17	Cohort B	1	4	Pain vaccination site	1	1	03-10-2017	15-10-2017
RSV17	Cohort B	1	5	Fatigue	3	1	03-10-2017	03-10-2017
RSV17	Cohort B	1	6	Erythema vaccination site	1	5	07-10-2017	08-10-2017
RSV17	Cohort B	1	7	Decrease haemoglobin	5	8	10-10-2017	16-10-2017
RSV17	Cohort B	1	8	Increase in CPK	5	8	10-10-2017	16-10-2017
RSV17	Cohort B	1	9	Vaccination site abscess	1	10	12-10-2017	13-10-2017
RSV17	Cohort B	1	10	Vaccination site crust	1	11	13-10-2017	20-10-2017
RSV17	Cohort B	1	11	Vaccination site abscess	1	14	16-10-2017	29-10-2017
RSV17	Cohort B	1	12	Decrease haemoglobin	5	28	30-10-2017	04-12-2017
RSV17	Cohort B	1	13	Leukopenia	5	28	30-10-2017	04-12-2017
RSV17	Cohort B	1	14	Increase in CPK	5	28	30-10-2017	04-12-2017
RSV17	Cohort B	1	15	Vaccination site crust	1	49	20-11-2017	11-02-2018
RSV17	Cohort B	1	16	Vaccination site abscess	1	70	11-12-2017	07-02-2018
RSV17	Cohort B	1	17	Decreased haemoglobin	5	121	31-01-2018	Continues
RSV18	Cohort B	2	1	Vaccine site sensitivity	1	1	04-10-2017	11-10-2017
RSV18	Cohort B	2	2	Erythema vaccination site	1	1	04-10-2017	07-10-2017
RSV18	Cohort B	2	3	Induration vaccination site	1	2	05-10-2017	13-10-2017
RSV18	Cohort B	2	4	Pain vaccination site	1	7	10-10-2017	11-10-2017
RSV18	Cohort B	2	5	Vaccination site abscess	1	6	09-10-2017	15-10-2017
RSV18	Cohort B	2	6	Diarrhea	3	7	10-10-2017	11-10-2017
RSV18	Cohort B	2	7	Hypercholesterolemia	5	9	12-10-2017	Continues
RSV18	Cohort B	2	8	Diarrhea	3	10	13-10-2017	13-10-2017
RSV18	Cohort B	2	9	Diarrhea	3	13	16-10-2017	16-10-2017
RSV18	Cohort B	2	10	Vaccination site crust	1	11	14-10-2017	31-12-2017

RSV18	Cohort B	2	11	Pain vaccination site	1	10	13-10-2017	13-10-2017
RSV18	Cohort B	2	12	Vaccine site sensitivity	1	10	13-10-2017	19-10-2017
RSV18	Cohort B	2	13	Diarrhea	3	25	28-10-2017	28-10-2017
RSV18	Cohort B	2	14	Diarrhea	3	28	31-10-2017	31-10-2017
RSV18	Cohort B	2	15	Left thigh cellulitis	4	28	31-10-2017	15-11-2017
RSV18	Cohort B	2	16	Hyperglycemia	5	63	05-12-2017	18-01-2018
RSV18	Cohort B	2	17	Headache	4	90	01-01-2018	01-01-2018
RSV18	Cohort B	2	18	Decreased haemoglobin	5	107	18-01-2018	26-03-2018
RSV18	Cohort B	2	19	Increase in CPK	5	107	18-01-2018	Continues
RSV18	Cohort B	2	20	Vaccination site crust	1	107	18-01-2018	21-03-2018
RSV18	Cohort B	2	21	Headache	4	148	28-02-2018	28-02-2018
RSV24	Cohort B	2	1	Pain vaccination site	1	0	03-10-2017	06-10-2017
RSV24	Cohort B	2	2	Vaccine site sensitivity	1	0	03-10-2017	06-10-2017
RSV24	Cohort B	2	3	Headache	3	0	03-10-2017	03-10-2017
RSV24	Cohort B	2	4	Erythema vaccination site	1	1	04-10-2017	10-10-2017
RSV24	Cohort B	2	5	Induration vaccination site	1	1	04-10-2017	08-10-2017
RSV24	Cohort B	2	6	Pain vaccination site	1	5	08-10-2017	08-10-2017
RSV24	Cohort B	2	7	Vaccine site sensitivity	1	5	08-10-2017	18-10-2017
RSV24	Cohort B	2	8	Headache	3	10	13-10-2017	13-10-2017
RSV24	Cohort B	2	9	Vaccination site abscess	1	11	14-10-2017	23-10-2017
RSV24	Cohort B	2	10	Pain vaccination site	1	8	11-10-2017	17-10-2017
RSV24	Cohort B	2	11	Induration vaccination site	1	10	13-10-2017	13-10-2017
RSV24	Cohort B	2	12	Headache	3	19	22-10-2017	22-10-2017
RSV24	Cohort B	2	13	Headache	3	21	24-10-2017	24-10-2017
RSV24	Cohort B	2	14	Vaccination site crust	1	15	18-10-2017	20-11-2017
RSV24	Cohort B	2	15	Common cold	4	26	29-10-2017	31-10-2017
RSV24	Cohort B	2	16	Vaccination site abscess	1	22	25-10-2017	26-10-2017
RSV24	Cohort B	2	17	Vaccination site abscess	1	26	29-10-2017	29-10-2017
RSV24	Cohort B	2	18	Proteinuria	5	28	31-10-2017	29-11-2017
RSV24	Cohort B	2	19	Muscle contracture back	4	107	18-01-2018	23-01-2018
RSV25	Cohort B	1	1	Pain vaccination site	1	1	05-10-2017	05-10-2017
RSV25	Cohort B	1	2	Vaccine site sensitivity	1	1	05-10-2017	05-10-2017
RSV25	Cohort B	1	3	Erythema vaccination site	1	2	06-10-2017	12-10-2017

RSV25	Cohort B	1	4	Vaccination site abscess	1	2	06-10-2017	11-10-2017
RSV25	Cohort B	1	5	Induration vaccination site	1	3	07-10-2017	11-10-2017
RSV25	Cohort B	1	6	Vaccination site crust	1	4	08-10-2017	27-11-2017
RSV25	Cohort B	1	7	Decreased haemoglobin	5	7	11-10-2017	04-12-2017
RSV25	Cohort B	1	8	Hypophosphatemia	5	7	11-10-2017	31-10-2017
RSV25	Cohort B	1	9	Erythema vaccination site	1	14	18-10-2017	18-10-2017
RSV25	Cohort B	1	10	Induration vaccination site	1	14	18-10-2017	18-11-2017
RSV25	Cohort B	1	11	Hypophosphatemia	5	61	04-12-2017	02-04-2018
RSV25	Cohort B	1	12	Decreased haemoglobin	5	110	22-01-2018	Continues
RSV25	Cohort B	1	13	Increase in SGPT	5	110	22-01-2018	02-04-2018
RSV26	Cohort B	1	1	Pain vaccination site	1	0	04-10-2017	07-10-2017
RSV26	Cohort B	1	2	Vaccine site sensitivity	1	0	04-10-2017	08-10-2017
RSV26	Cohort B	1	3	Erythema vaccination site	1	1	05-10-2017	20-10-2017
RSV26	Cohort B	1	4	Vaccine site sensitivity	1	6	10-10-2017	17-10-2017
RSV26	Cohort B	1	5	Vaccination site abscess	1	7	11-10-2017	15-10-2017
RSV26	Cohort B	1	6	Decreased haemoglobin	5	7	11-10-2017	18-10-2017
RSV26	Cohort B	1	7	Fatigue	3	0	04-10-2017	04-10-2017
RSV26	Cohort B	1	8	Pain vaccination site	1	7	11-10-2017	13-10-2017
RSV26	Cohort B	1	9	Pain vaccination site	1	11	15-10-2017	15-10-2017
RSV26	Cohort B	1	10	Ulcer vaccination site	2	13	17-10-2017	18-10-2017
RSV26	Cohort B	1	11	Pyuria	5	14	18-10-2017	03-11-2017
RSV26	Cohort B	1	12	Vaccination site crust	1	11	15-10-2017	13-01-2018
RSV26	Cohort B	1	13	Eosinophilia	5	30	03-11-2017	05-12-2017
RSV26	Cohort B	1	14	Headache	4	56	29-11-2017	29-11-2017
RSV26	Cohort B	1	15	Common cold	4	67	10-12-2017	16-12-2017
RSV26	Cohort B	1	16	Hypercholesterolemia	5	114	26-01-2018	Continues
RSV26	Cohort B	1	17	Increase in SGPT	5	114	26-01-2018	Continues
RSV26	Cohort B	1	18	Pyuria	5	180	02-04-2018	Continues
RSV26	Cohort B	1	19	Increase in SGOT	5	180	02-04-2018	Continues
RSV27	Cohort B	1	1	Induration vaccination site	1	14	18-10-2017	20-10-2017
RSV27	Cohort B	1	2	Erythema vaccination site	1	1	05-10-2017	06-10-2017
RSV27	Cohort B	1	3	Induration vaccination site	1	1	05-10-2017	10-10-2017
RSV27	Cohort B	1	4	Pain vaccination site	1	0	04-10-2017	17-10-2017

RSV27	Cohort B	1	5	Vaccine site sensitivity	1	0	04-10-2017	14-10-2017
RSV27	Cohort B	1	6	Pruritus vaccination site	2	5	09-10-2017	10-10-2017
RSV27	Cohort B	1	7	Erythema vaccination site	1	5	09-10-2017	21-10-2017
RSV27	Cohort B	1	8	Vaccination site abscess	1	8	12-10-2017	18-10-2017
RSV27	Cohort B	1	9	Vaccination site crust	1	14	18-10-2017	09-03-2018
RSV27	Cohort B	1	10	Induration vaccination site	1	20	24-10-2017	25-10-2017
RSV27	Cohort B	1	11	Hyperglycemia	5	63	06-12-2017	26-01-2018
RSV27	Cohort B	1	12	Headache	4	113	25-01-2018	25-01-2018
RSV27	Cohort B	1	13	Decreased haemoglobin	5	114	26-01-2018	03-04-2018
RSV27	Cohort B	1	14	Proteinuria	5	181	03-04-2018	Continues
RSV30	Cohort B	1	1	Vaccine site sensitivity	1	0	10-10-2017	12-10-2017
RSV30	Cohort B	1	2	Headache	3	0	10-10-2017	18-10-2017
RSV30	Cohort B	1	3	Fatigue	3	1	11-10-2017	11-10-2017
RSV30	Cohort B	1	4	Pruritus vaccination site	2	1	11-10-2017	13-10-2017
RSV30	Cohort B	1	5	Hypertension	3	2	12-10-2017	12-10-2017
RSV30	Cohort B	1	6	Left axillary pain	2	0	10-10-2017	10-10-2017
RSV30	Cohort B	1	7	Vaccination site crust	1	11	21-10-2017	26-10-2017
RSV30	Cohort B	1	8	Pain vaccination site	1	8	18-10-2017	22-10-2017
RSV30	Cohort B	1	9	Vaccine site sensitivity	1	7	17-10-2017	23-10-2017
RSV30	Cohort B	1	10	Headache	3	10	20-10-2017	24-10-2017
RSV30	Cohort B	1	11	Myalgia	3	3	13-10-2017	13-10-2017
RSV30	Cohort B	1	12	Myalgia	3	7	17-10-2017	18-10-2017
RSV30	Cohort B	1	13	Myalgia	3	12	22-10-2017	22-10-2017
RSV30	Cohort B	1	14	Vaccination site abscess	1	9	19-10-2017	21-10-2017
RSV30	Cohort B	1	15	Myalgia	3	15	25-10-2017	25-10-2017
RSV30	Cohort B	1	16	Myalgia	3	17	27-10-2017	27-10-2017
RSV30	Cohort B	1	17	Myalgia	3	19	29-10-2017	29-10-2017
RSV30	Cohort B	1	18	Pruritus vaccination site	2	17	27-10-2017	30-10-2017
RSV30	Cohort B	1	19	Vaccination site crust	1	23	02-11-2017	14-11-2017
RSV30	Cohort B	1	20	Common cold	4	34	13-11-2017	18-11-2017
RSV30	Cohort B	1	21	Common cold	4	125	12-02-2018	18-02-2018
RSV30	Cohort B	1	22	Decreased haemoglobin	5	174	02-04-2018	Continues
RSV32	Cohort C	1	1	Pain vaccination site	1	0	21-11-2017	05-12-2017

RSV32	Cohort C	1	2	Vaccine site sensitivity	1	1	22-11-2017	06-12-2017
RSV32	Cohort C	1	3	Erythema vaccination site	1	1	22-11-2017	24-11-2017
RSV32	Cohort C	1	4	Headache	3	1	22-11-2017	25-11-2017
RSV32	Cohort C	1	5	Fatigue	3	1	22-11-2017	24-11-2017
RSV32	Cohort C	1	6	Pain vaccination site	4	1	22-11-2017	22-11-2017
RSV32	Cohort C	1	7	Myalgia	3	2	23-11-2017	24-11-2017
RSV32	Cohort C	1	8	Erythema vaccination site	1	5	26-11-2017	01-12-2017
RSV32	Cohort C	1	9	Vaccination site abscess	1	6	27-11-2017	27-11-2017
RSV32	Cohort C	1	10	Induration vaccination site	1	2	23-11-2017	24-11-2017
RSV32	Cohort C	1	11	Induration vaccination site	1	6	27-11-2017	28-11-2017
RSV32	Cohort C	1	12	Vaccination site crust	1	6	27-11-2017	30-11-2017
RSV32	Cohort C	1	13	Vaccination site abscess	1	9	30-11-2017	18-12-2017
RSV32	Cohort C	1	14	Erythema vaccination site	1	12	03-12-2017	03-12-2017
RSV32	Cohort C	1	15	Erythema vaccination site	1	14	05-12-2017	05-12-2017
RSV32	Cohort C	1	16	Induration vaccination site	1	9	30-11-2017	30-11-2017
RSV32	Cohort C	1	17	Induration vaccination site	1	12	03-12-2017	29-12-2017
RSV32	Cohort C	1	18	Vaccination site crust	1	11	02-12-2017	17-06-2018
RSV32	Cohort C	1	19	Vaccination site abscess	1	10	01-12-2017	05-12-2017
RSV32	Cohort C	1	20	Erythema vaccination site	1	19	10-12-2017	10-12-2017
RSV32	Cohort C	1	21	Vaccination site abscess	1	16	07-12-2017	16-12-2017
RSV32	Cohort C	1	22	Vaccine site sensitivity	1	20	11-12-2017	13-12-2017
RSV32	Cohort C	1	23	Vaccination site abscess	1	28	19-12-2017	03-03-2018
RSV32	Cohort C	1	24	Acute gastroenteritis	4	33	24-12-2017	26-12-2017
RSV32	Cohort C	1	25	Decreased haemoglobin	5	62	22-01-2018	20-03-2018
RSV32	Cohort C	1	26	Hypoglycemia	5	62	22-01-2018	20-03-2018
RSV32	Cohort C	1	27	Hypertension	4	62	22-01-2018	20-03-2018
RSV32	Cohort C	1	28	Common cold	4	149	19-04-2018	22-04-2018
RSV32	Cohort C	1	29	Common cold	4	167	07-05-2018	22-05-2018
RSV32	Cohort C	1	30	Hypoglycemia	5	174	14-05-2018	Continues
RSV32	Cohort C	1	31	Hyponatremia	5	174	14-05-2018	Continues
RSV33	Cohort C	1	1	Pain vaccination site	1	0	21-11-2017	22-11-2017
RSV33	Cohort C	1	2	Vaccine site sensitivity	1	0	21-11-2017	23-11-2017
RSV33	Cohort C	1	3	Fatigue	3	0	21-11-2017	21-11-2017

RSV33	Cohort C	1	4	Erythema vaccination site	1	2	23-11-2017	24-11-2017
RSV33	Cohort C	1	5	Puncture site ecchymosis	4	5	26-11-2017	03-12-2017
RSV33	Cohort C	1	6	Vaccine site sensitivity	1	5	26-11-2017	02-12-2017
RSV33	Cohort C	1	7	Headache	3	5	26-11-2017	29-11-2017
RSV33	Cohort C	1	8	Vaccination site abscess	1	5	26-11-2017	30-11-2017
RSV33	Cohort C	1	9	Vomiting	3	10	01-12-2017	01-12-2017
RSV33	Cohort C	1	10	Diarrhea	3	10	01-12-2017	01-12-2017
RSV33	Cohort C	1	11	Headache	3	10	01-12-2017	02-12-2017
RSV33	Cohort C	1	12	Vaccination site crust	1	7	28-11-2017	04-12-2017
RSV33	Cohort C	1	13	Vaccination site crust	1	15	06-12-2017	30-12-2017
RSV33	Cohort C	1	14	Pain vaccination site	1	3	24-11-2017	24-11-2017
RSV33	Cohort C	1	15	Pain vaccination site	1	6	27-11-2017	02-12-2017
RSV33	Cohort C	1	16	Pain vaccination site	1	14	05-12-2017	05-12-2017
RSV33	Cohort C	1	17	Hypokalemia	5	15	06-12-2017	20-12-2017
RSV33	Cohort C	1	18	Erythema vaccination site	1	7	28-11-2017	28-11-2017
RSV33	Cohort C	1	19	Erythema vaccination site	1	9	30-11-2017	30-11-2017
RSV33	Cohort C	1	20	Induration vaccination site	1	7	28-11-2017	28-11-2017
RSV33	Cohort C	1	21	Decreased hemoglobin	5	29	20-12-2017	24-01-2018
RSV33	Cohort C	1	22	Increase in CPK	5	29	20-12-2017	24-01-2018
RSV33	Cohort C	1	23	Vaccination site crust	1	42	02-01-2018	05-02-2018
RSV33	Cohort C	1	24	Pyuria	5	119	20-03-2018	18-05-2018
RSV33	Cohort C	1	25	Common cold	4	153	23-04-2018	07-05-2018
RSV33	Cohort C	1	26	Common cold	4	170	10-05-2018	25-05-2018
RSV34	Cohort C	2	1	Pain vaccination site	1	0	21-11-2017	02-12-2017
RSV34	Cohort C	2	2	Vaccine site sensitivity	1	1	22-11-2017	26-11-2017
RSV34	Cohort C	2	3	Erythema vaccination site	1	1	22-11-2017	24-11-2017
RSV34	Cohort C	2	4	Induration vaccination site	1	2	23-11-2017	23-11-2017
RSV34	Cohort C	2	5	Pruritus vaccination site	2	3	24-11-2017	26-11-2017
RSV34	Cohort C	2	6	Headache	3	6	27-11-2017	04-12-2017
RSV34	Cohort C	2	7	Decreased hemoglobin	5	7	28-11-2017	06-12-2017
RSV34	Cohort C	2	8	Pruritus vaccination site	2	13	04-12-2017	05-12-2017
RSV34	Cohort C	2	9	Proteinuria	5	15	06-12-2017	21-12-2017
RSV34	Cohort C	2	10	Increase in SGOT	5	15	06-12-2017	21-12-2017

RSV34	Cohort C	2	12	Fatigue	3	12	03-12-2017	03-12-2017
RSV34	Cohort C	2	13	Myalgia	3	13	04-12-2017	07-12-2017
RSV34	Cohort C	2	14	Sickness	3	19	10-12-2017	13-12-2017
RSV34	Cohort C	2	15	Headache	3	15	06-12-2017	08-12-2017
RSV34	Cohort C	2	16	Vaccination site abscess	1	13	04-12-2017	04-12-2017
RSV34	Cohort C	2	17	Vaccination site abscess	1	30	21-12-2017	20-02-2018
RSV34	Cohort C	2	18	Hypophosphatemia	5	30	21-12-2017	18-01-2018
RSV34	Cohort C	2	19	Decreased hemoglobin	5	30	21-12-2017	18-01-2018
RSV34	Cohort C	2	20	Eosinophilia	5	30	21-12-2017	18-01-2018
RSV34	Cohort C	2	21	Hyperbilirubinemia	5	58	18-01-2018	20-03-2018
RSV34	Cohort C	2	22	Hypoglycemia	5	58	18-01-2018	20-03-2018
RSV34	Cohort C	2	23	Pain vaccination site	1	86	15-02-2018	20-02-2018
RSV34	Cohort C	2	24	Pruritus vaccination site	2	86	15-02-2018	26-02-2018
RSV34	Cohort C	2	25	Vaccination site crust	1	91	20-02-2018	23-04-2018
RSV34	Cohort C	2	26	Headache	4	98	27-02-2018	27-02-2018
RSV34	Cohort C	2	27	Eosinophilia	5	119	20-03-2018	23-05-2018
RSV34	Cohort C	2	28	Thrombocytopenia	5	119	20-03-2018	23-05-2018
RSV34	Cohort C	2	29	increase in CPK	5	15	06-12-2017	21-12-2017
RSV36	Cohort C	1	1	Vaccine site sensitivity	1	0	27-11-2017	20-01-2018
RSV36	Cohort C	1	2	Headache	3	0	27-11-2017	27-11-2017
RSV36	Cohort C	1	3	Erythema vaccination site	1	1	28-11-2017	05-12-2017
RSV36	Cohort C	1	4	Pain vaccination site	1	1	28-11-2017	08-12-2017
RSV36	Cohort C	1	5	Vaccination site abscess	1	4	01-12-2017	05-12-2017
RSV36	Cohort C	1	6	Fatigue	3	4	01-12-2017	01-12-2017
RSV36	Cohort C	1	7	Vaccination site crust	1	7	04-12-2017	14-12-2017
RSV36	Cohort C	1	8	Decreased haemoglobin	5	8	05-12-2017	02-01-2018
RSV36	Cohort C	1	9	Increase in CPK	5	8	05-12-2017	11-12-2017
RSV36	Cohort C	1	10	Ulcer vaccination site	2	18	15-12-2017	28-12-2017
RSV36	Cohort C	1	11	Urethritis	4	35	01-01-2018	01-01-2018
RSV36	Cohort C	1	12	Increase in CPK	5	36	02-01-2018	25-01-2018
RSV36	Cohort C	1	13	Vaccination site crust	1	32	29-12-2017	30-01-2018
RSV36	Cohort C	1	14	Pyuria	5	59	25-01-2018	27-03-2018
RSV36	Cohort C	1	15	Decreased haemoglobin	5	59	25-01-2018	Continues

RSV36	Cohort C	1	16	Increase in SGOT	5	59	25-01-2018	27-03-2018
RSV36	Cohort C	1	17	Increase in SGPT	5	59	25-01-2018	27-03-2018
RSV36	Cohort C	1	18	Hypokalemia	5	120	27-03-2018	28-05-2018
RSV38	Cohort C	2	1	Hypotension	3	0	27-11-2017	27-11-2017
RSV38	Cohort C	2	2	Vaccine site sensitivity	1	0	27-11-2017	01-12-2017
RSV38	Cohort C	2	3	Pain vaccination site	1	0	27-11-2017	30-11-2017
RSV38	Cohort C	2	4	Erythema vaccination site	1	1	28-11-2017	29-11-2017
RSV38	Cohort C	2	5	Pruritus vaccination site	2	2	29-11-2017	02-12-2017
RSV38	Cohort C	2	6	Vaccine site sensitivity	1	6	03-12-2017	04-01-2018
RSV38	Cohort C	2	7	Traumatic wound, left foot	4	5	02-12-2017	09-01-2018
RSV38	Cohort C	2	8	Decreased haemoglobin	5	8	05-12-2017	11-12-2017
RSV38	Cohort C	2	9	Increase in alkaline phosphatases	5	8	05-12-2017	Continues
RSV38	Cohort C	2	10	Pain vaccination site	1	8	05-12-2017	21-12-2017
RSV38	Cohort C	2	11	Pruritus vaccination site	2	9	06-12-2017	08-12-2017
RSV38	Cohort C	2	12	Common cold	4	11	08-12-2017	22-12-2017
RSV38	Cohort C	2	13	Vaccination site abscess	1	8	05-12-2017	07-12-2017
RSV38	Cohort C	2	14	Vaccination site crust	1	11	08-12-2017	26-12-2017
RSV38	Cohort C	2	15	Vaccination site abscess	1	12	09-12-2017	10-12-2017
RSV38	Cohort C	2	16	Vaccination site abscess	1	17	14-12-2017	14-12-2017
RSV38	Cohort C	2	17	Headache	3	18	15-12-2017	15-12-2017
RSV38	Cohort C	2	18	Fatigue	3	18	15-12-2017	15-12-2017
RSV38	Cohort C	2	19	Ulcer vaccination site	2	30	27-12-2017	05-01-2018
RSV38	Cohort C	2	20	Headache	3	26	23-12-2017	23-12-2017
RSV38	Cohort C	2	21	Diarrhea	3	25	22-12-2017	22-12-2017
RSV38	Cohort C	2	22	Vaccination site crust	1	39	05-01-2018	21-01-2018
RSV38	Cohort C	2	23	Headache	3	16	13-12-2017	13-12-2017
RSV38	Cohort C	2	24	Headache	3	23	20-12-2017	20-12-2017
RSV38	Cohort C	2	25	Headache	4	161	07-05-2018	07-05-2018
RSV38	Cohort C	2	26	Headache	4	182	28-05-2018	28-05-2018
RSV40	Cohort C	1	1	Vaccine site sensitivity	1	0	28-11-2017	16-12-2017
RSV40	Cohort C	1	2	Pain vaccination site	1	6	04-12-2017	08-12-2017
RSV40	Cohort C	1	3	Erythema vaccination site	1	6	04-12-2017	07-12-2017

RSV40	Cohort C	1	4	Induration vaccination site	1	8	06-12-2017	06-12-2017
RSV40	Cohort C	1	5	Vaccination site abscess	1	6	04-12-2017	31-12-2017
RSV40	Cohort C	1	6	Vaccination site crust	1	7	05-12-2017	31-12-2017
RSV40	Cohort C	1	7	Increase in CPK	5	8	06-12-2017	09-12-2017
RSV40	Cohort C	1	8	Decreased haemoglobin	5	11	09-12-2017	30-01-2018
RSV40	Cohort C	1	9	Pain vaccination site	1	14	12-12-2017	17-12-2017
RSV40	Cohort C	1	10	Tonsillitis	4	15	13-12-2017	16-12-2017
RSV40	Cohort C	1	11	Contusion right hand	4	18	16-12-2017	18-12-2017
RSV40	Cohort C	1	13	Erythema vaccination site	1	26	24-12-2017	24-12-2017
RSV40	Cohort C	1	14	Ulcer vaccination site	2	34	01-01-2018	15-01-2018
RSV40	Cohort C	1	15	Malaise	3	12	10-12-2017	10-12-2017
RSV40	Cohort C	1	16	Diarrhea	3	29	27-12-2017	27-12-2017
RSV40	Cohort C	1	17	Diarrhea	4	31	29-12-2017	30-12-2017
RSV40	Cohort C	1	18	Headache	3	12	10-12-2017	10-12-2017
RSV40	Cohort C	1	19	Myalgia	3	28	26-12-2017	27-12-2017
RSV40	Cohort C	1	20	Diarrhea	4	35	02-01-2018	02-01-2018
RSV40	Cohort C	1	21	Sickness	4	32	30-12-2017	30-12-2017
RSV40	Cohort C	1	22	Common cold	4	29	27-12-2017	15-01-2018
RSV40	Cohort C	1	23	Increase in CPK	5	36	03-01-2018	30-01-2018
RSV40	Cohort C	1	24	Diarrhea	4	65	01-02-2018	08-02-2018
RSV40	Cohort C	1	26	Anxiety	4	93	01-03-2018	14-04-2018
RSV40	Cohort C	1	27	Insomnia	4	169	16-05-2018	16-05-2018
RSV41	Cohort C	1	1	Vaccine site sensitivity	1	0	28-11-2017	09-12-2017
RSV41	Cohort C	1	2	Pain vaccination site	1	1	29-11-2017	30-11-2017
RSV41	Cohort C	1	3	Vaccination site abscess	1	2	30-11-2017	02-12-2017
RSV41	Cohort C	1	4	Induration vaccination site	1	3	01-12-2017	01-12-2017
RSV41	Cohort C	1	5	Vaccination site abscess	1	6	04-12-2017	05-12-2017
RSV41	Cohort C	1	6	Pain vaccination site	1	7	05-12-2017	07-12-2017
RSV41	Cohort C	1	7	Vaccination site crust	1	5	03-12-2017	03-12-2017
RSV41	Cohort C	1	8	Decreased haemoglobin	5	8	06-12-2017	Continues
RSV41	Cohort C	1	9	Erythema vaccination site	1	8	06-12-2017	06-12-2017
RSV41	Cohort C	1	10	Vaccination site crust	1	8	06-12-2017	22-12-2017
RSV41	Cohort C	1	11	Urticaria	4	12	10-12-2017	10-12-2017

RSV41	Cohort C	1	12	Headache	3	20	18-12-2017	19-12-2017
RSV41	Cohort C	1	13	Vaccination site abscess	1	20	18-12-2017	20-12-2017
RSV41	Cohort C	1	14	Vaccination site crust	1	26	24-12-2017	08-02-2018
RSV41	Cohort C	1	15	Vaccine site sensitivity	1	25	23-12-2017	25-12-2017
RSV41	Cohort C	1	16	Pain vaccination site	1	25	23-12-2017	24-12-2017
RSV41	Cohort C	1	17	Common cold	4	45	12-01-2018	29-01-2018
RSV41	Cohort C	1	18	Myalgia	4	49	16-01-2018	18-01-2018
RSV41	Cohort C	1	19	Increase in SGOT	5	56	23-01-2018	02-04-2018
RSV41	Cohort C	1	20	Increase in CPK	5	56	23-01-2018	02-04-2018
RSV41	Cohort C	1	21	Tonsillitis	4	62	29-01-2018	08-02-2018
RSV41	Cohort C	1	22	Common cold	4	72	08-02-2018	07-03-2018
RSV41	Cohort C	1	23	Vaccination site crust	1	75	11-02-2018	10-06-2018
RSV41	Cohort C	1	24	Hyperglycemia	5	125	02-04-2018	28-05-2018
RSV41	Cohort C	1	25	Hypernatremia	5	125	02-04-2018	28-05-2018
RSV41	Cohort C	1	26	Bronchitis	4	150	27-04-2018	12-05-2018
RSV42	Cohort C	1	1	Vaccine site sensitivity	1	0	04-12-2017	17-12-2017
RSV42	Cohort C	1	2	Pain vaccination site	1	1	05-12-2017	10-12-2017
RSV42	Cohort C	1	3	Erythema vaccination site	1	1	05-12-2017	06-12-2017
RSV42	Cohort C	1	4	Vaccination site abscess	1	2	06-12-2017	11-12-2017
RSV42	Cohort C	1	5	General discomfort	4	1	05-12-2017	06-12-2017
RSV42	Cohort C	1	6	Left axillary lymphadenopathy	1	3	07-12-2017	13-12-2017
RSV42	Cohort C	1	7	Headache	3	2	06-12-2017	06-12-2017
RSV42	Cohort C	1	8	Erythema vaccination site	1	5	09-12-2017	12-12-2017
RSV42	Cohort C	1	9	Hypotension	3	1	05-12-2017	05-12-2017
RSV42	Cohort C	1	10	Pyuria	5	7	11-12-2017	18-12-2017
RSV42	Cohort C	1	11	Vaccination site abscess	1	11	15-12-2017	15-12-2017
RSV42	Cohort C	1	12	Vaccination site crust	1	7	11-12-2017	23-03-2018
RSV42	Cohort C	1	13	Pyuria	5	25	29-12-2017	03-01-2018
RSV42	Cohort C	1	14	Hematuria	5	25	29-12-2017	03-01-2018
RSV42	Cohort C	1	15	Decreased hemoglobin	5	25	29-12-2017	05-04-2018
RSV42	Cohort C	1	16	Proteinuria	5	30	03-01-2018	07-02-2018
RSV42	Cohort C	1	17	Precordial pain secondary to supraventricular tachycardia	4	51	24-01-2018	26-01-2018

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