INFORMED CONSENT FORM

Name of the Study:	Double-blind, controlled by conventional BCG vaccine, dose-escalated 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 the Human Respiratory Syncytial Virus (hRSV) nucleoprotein (N) (rBCG-N-hRSV) in healthy adults within 18 and 50 years of age.
Protocol Acronym:	rBCG-N-hRSV Vaccine Protocol
Sponsoring Institution:	Pontificia Universidad Católica de Chile
Funding Source:	FONDEF; Millennium Institute in Immunology and Immunotherapy
Responsible Investigator:	Dra. Katia Abarca Phone 223546825
Department/UDA:	Departamento de Enfermedades Infecciosas e Inmunología Pediátrica Facultad de Medicina, Pontificia Universidad Católica de Chile
Research Sponsor:	Dr. Alexis Kalergis Phone 226862225
Department/UDA:	Departamento de Microbiología y Genética Molecular Facultad de Ciencias Biológicas, Pontificia Universidad Católica de Chile

---

The purpose of this information is to help you make the decision to participate -or not- in a medical study.

Take enough time to make up your mind, read this document carefully, and ask our doctor or study staff any questions you want.

This study is financed by FONDEF (Fondo de Fomento al Desarrollo Científico y Tecnológico) and by the Millennium Institute in Immunology and Immunotherapy, of the Pontificia Universidad Católica de Chile.

RESEARCH OBJECTIVES

Respiratory syncytial virus (RSV) is one of the main viruses that cause respiratory infections in the world. In our country, it occurs every year in the form of a winter epidemic outbreak lasting several months, mainly affecting children under 2 years of age, in whom it produces a pulmonary inflammation and bronchial obstruction condition. This causes a large number of medical consultations in emergency services, hospitalizations, and even deaths. In the long term, the infection is associated with recurrent obstructive bronchitis and bronchial asthma.

There are no vaccines yet available to prevent this serious infection. Currently, there is only one preventive injectable drug, indicated in children with a higher risk of becoming ill or dying from the infection (premature infants, with chronic lung disease or congenital heart disease).

The purpose of this study is to evaluate in healthy adults, for the first time, the safety, tolerability and the ability to induce an immune response of a vaccine against RSV developed in Chile, by researchers from the Pontificia Universidad Católica de Chile. Because this will be the first time this vaccine has been administered to people (phase I study), regulations require that it be done in healthy adults, so that it can later be applied to young children.

This vaccine is made using as a base the vaccine against tuberculosis called BCG, which is administered to all newborns in the country. This vaccine consists of a bacterium close to the tuberculosis bacillus, alive but attenuated, meaning it does not cause the disease. The information necessary to produce an RSV protein, which stimulates the production of defenses that can protect against infection caused by RSV, has been incorporated into this bacterium.

The vaccine under study has been tested in laboratory animals, in which it was shown to be capable of generating protective defenses against RSV infection. The development of this vaccine has already passed the phase known as "pre-clinical" and we are in a position to start studies in people. This vaccine was produced for use in humans in a vaccine manufacturing plant in the USA, using all the procedures required by the FDA (Food and Drug Administration of that country) for this type of product. This type of facilities and vaccine production complies with the standards known as "good manufacturing practices". This type of facility does not exist in our country.

You have been invited to participate in this study because you are a healthy Chilean adult male. The study will be carried out at the Center for Clinical Research of the Pontificia Universidad Católica de Chile (CICUC), Portugal 61, Santiago, and healthy males between 18 and 50 years old are invited to participate. The minimum number of people who will receive the vaccine will be 24; 18 of which will receive the vaccine under study, and 6 will receive the BCG vaccine commonly used in newborns in Chile (control group). That is, you will have a 2 out of 3 chance of receiving the study vaccine and a 1 out of 3 chance of receiving the control BCG vaccine. Assignment to one or the other group will be random (done by a computer, using a similar random mechanism). Neither you nor the researchers will know until the end of the study, who received one or the other vaccine (double-blind). The number of participants may need to be increased if the initial results with 24 people warrant it.

INVESTIGATION PROCEDURES

General Study Design:

Only men with normal health will enter the study, which will be confirmed after a medical evaluation and several laboratory tests, through which medical conditions that may involve a risk for their participation will be ruled out; and whoever has received between one and two doses of BCG vaccine previously.

Participants will be admitted in a staggered manner, in 3 groups, which will receive different doses of the vaccine under study. In the first group (Cohort A), 6 participants will receive a small dose of the vaccine under study (around 50,000 colony-forming units of the BCG component, equivalent to one-hundredth of the full dose of the vaccine) and 2 will receive the vaccine commonly used BCG (containing 5,000,000 colony forming units). After a 4-week follow-up, a committee of experts independent of the researchers and this institution, known as the "Independent Data Monitoring Committee" (CIMD), will analyze the results in these first volunteers and indicate whether it is appropriate to continue with the next vaccination group (Cohort B), if the vaccination with this dose of vaccine should be repeated in other people (expand or repeat cohort A) or if the study should be stopped. If it is indicated to continue the study, another 6 participants will receive an intermediate dose of the study vaccine (500,000 colony-forming units of the BCG component, equivalent to one-tenth of the full dose) and 2 will receive the commonly used BCG vaccine. After a 4-week follow-up, the CIMD will analyze the safety information and indicate whether it is appropriate to continue with the next vaccination group (Cohort C), if the vaccination with this dose of vaccine should be repeated in other people (expand or repeat cohort B) or whether the study should be stopped. If it is indicated to continue the study, the last 6 participants will receive the full dose of the vaccine (5,000,000 colony-forming units of the BCG component) and 2 will receive the commonly used BCG vaccine. After a 4-week follow-up, CIMD will review all the safety information and issue a final report.

Procedures on participants:

If you agree to participate, you will be scheduled for an initial evaluation visit, to perform a complete medical examination in which your medical history will be evaluated, you will have a complete physical examination, your weight, height, heart rate and arterial pressure will be measured. Your previous BCG vaccination scar(s) will be reviewed, a photograph of them will be taken as initial information and if all this medical evaluation indicates that your health condition is normal and compatible with your safe participation in the study, you will have a blood sample, a urine sample, an electrocardiogram (ECG), and a chest X-ray taken. The blood sample will be obtained by puncturing a vein from the forearm by an experienced nurse, in an amount equivalent to three tablespoons (47 mL). A series of laboratory tests will be performed on your blood and urine samples to confirm that you are healthy and to rule out health conditions that could pose a risk to you (adequate liver and kidney function, immune system, absence of chronic infections). The ECG will show if your heart function is normal, and the X-rays will help us rule out that you have a hidden tuberculosis bacillus infection. This visit will last approximately three hours.
All study visits will take place at the CICUC, located in Portugal 61.

Once we have the results of these tests and all of them are normal, which will occur between one and two weeks after the initial evaluation visit, we will call you to the first study visit, in which you will formally enter this study.

Your medical history, physical exam, and vital signs including your temperature will be updated at the first study visit. If everything is normal, you will be assigned a study number, with which all your history will be registered and you will be randomly assigned which vaccine you will receive. A 30 mL

blood sample will be taken as a baseline sample to study your immune response to the vaccine. Your assigned vaccine will then be administered by intradermal injection into your left arm by a nurse experienced in this procedure. After the vaccination you will be observed for three hours, to detect any immediate adverse reaction that may occur. The research team is prepared to treat eventual reactions and the CICUC has the equipment and medicines for this. Before you leave the center, your temperature and other vital signs will be recorded again, the vaccination site will be reviewed and you will be given a daily card, in which you must record your temperature daily for a week, any eventual discomfort that you may present -both at the vaccination site and in general- and any medications you take for the relief of these discomforts or any other reason.

Subsequently, you will be monitored by the research team for a period of 6 months, during which you will be called by phone 5 times (at 4, 21 and 45 days, and 3 and 5 months after vaccination). You must come to the center for medical evaluation 9 times (on days 1, 2, 3, 7, 14 and 30 and at 2, 4 and 6 months after vaccination). We will give you a calendar with these dates and we will call you prior to each visit to confirm your attendance. Regardless of these visits, you can contact the research team at any time if you have questions or any discomfort, for which we will give you the contact numbers.

At each of the follow-up visits, your medical history will be updated, a complete physical examination will be performed and a blood sample (between 18 and 48 mL), a urine sample and 3 times a saliva sample will be taken, in which tests will be carried out to rule out that the vaccine is causing any alteration in your body, to study the immune response (defenses) that you are producing against RSV and to investigate whether the BCG from the vaccine is present in your body fluids. In addition, pictures will be taken of the vaccination site, where an outbreak (localized inflammation) is expected to occur. At the last visit (6 months post-vaccination), you will have a second chest X-ray taken. At each visit, you will be asked to provide a completed registration card, which will be reviewed by the staff of the investigating team and completed by you if necessary, and you will be given a new registration card (except for the last visit) to record any discomfort or illness that you present and medications that you receive until the next visit.

PROCEDURE FOR SIGNIFICANT RESPIRATORY COMPLICATIONS

If during the study you present an upper respiratory tract infection: nasal secretion, sore throat and/or coughing, associated with significant symptoms, such as fever, respiratory distress or bronchial obstruction, a laboratory test will be performed free of charge to evaluate the presence of respiratory viruses. This test will be performed by a nurse and consists of the introduction of a swab through the nose, until reaching the pharyngeal wall. The swab will be turned around and withdrawn.

Blood, urinary and salivary samples obtained will be solely used for this study, including laboratory tests that could be not considered initially. If the samples were to be used for purposes other than those stipulated for this medical research in the future, your medical consent will be requested. Your genome will not be studied in blood samples. Biological samples will be stored for 15 years in the Immunology Laboratory of the Facultad de Ciencias Biológicas of Pontificia Universidad Católica de Chile, under the responsibility of Dr. Alexis Kalergis.

You will be informed of the results obtained from the laboratory tests. Your attending physician will be informed as well, who will indicate to you the most appropriate medical course of action for you, if necessary.

BENEFITS

Because we do not know if this vaccine protects effectively against RSV, and because the BCG vaccine has been shown not to be effective for tuberculosis prevention in adults, it is probable that this study will not produce a direct benefit for you.

Nonetheless, the results of this study will provide valuable information that could allow continuing the eventual development of this vaccine, which could benefit children affected by RSV in the future.

The complete health evaluation that this study contemplates could be useful for you, in case we detect health conditions that you were not previously aware of.

RISKS

This is the first time this vaccine is used in humans. In this developmental stage of the vaccine, the eventual risks that it could produce are not fully known.

The BCG vaccine, which is the base for the construction of the vaccine in study, produces a small lump in the site of inoculation in 95% of the immunized subjects. This lump consists of a nodule that can develop into a pus-like content, then to a scab, and finally to a scar. This process can be accompanied by a certain degree of local muscular discomfort. In some vaccinated individuals, an armpit lymph node can be inflamed (2% of vaccinated individuals), which can occasionally fester (less than 1% of cases). Long-distance infection with the bacillus contained in the BCG vaccine is rarely described but can be localized on the surface of a bone (osteitis, occurring lower than 1 case per 3,000 vaccinated individuals), or disseminated to the whole organism (near 1 case per a million vaccinated individuals). Bone infection occurs mainly in children, while dissemination occurs in children or adults with grave defects in their immunity or defenses. Your age, medical history, and the exams we perform prior to your entry to the study will help us to further reduce the risk of this happening.

The vaccination component against RSV is a protein. As such, you may develop an allergic reaction when receiving it. Your medical history without records of severe allergic reactions or allergic reactions to previous vaccines will help us reduce this risk.

The Independent Committee for Data Monitoring (Comité Independiente de Monitoreo de Datos, CIMD), conformed by outstanding Chilean professionals that are independent of the researchers, will evaluate periodically the information regarding your security as another way to monitor the possible risks to your health. This committee will have the authority to suspend or allow the

continuity of the participation of either an individual or the whole study, given any indication of risks to the health of the participants or other individuals.

Blood sampling may produce minor local pain and eventual bruising of the puncture site. The quantity of blood that will be extracted will not be enough to produce anemia or other medical complications.

Reproductive effects

Because the BCG vaccine is contraindicated during pregnancy, it has been decided to perform this study only in males. In the face of the rare possibility that this vaccine produced negative effects in sperm cells, **do not participate in this study** if you are trying to conceive a child or have doubts about wanting to conceive a child during the duration of the study.

If you decide to participate in this study, remember that none of the available methods for birth control (either natural or artificial) is free of potential negative effects in sperm cells.

COSTS

All the costs of the procedures included in this study, including the vaccine, medical evaluations, and laboratory tests, will be met by the sponsor.

If the medical and laboratory tests performed in the initial evaluation visit indicate a basal medical condition you were not previously aware of, further treatments or medical evaluations necessary for the treatment of your medical condition will not be financed by the study.

COMPENSATIONS

You will not be economically compensated by your participation in this study – you will not be paid to participate.

HARMS

If you suffer any lesion as a direct result of a procedure related to the study, or because of the vaccine you have received, you must attend the dependencies of the Red de Salud UC – CHRISTUS, so that you can receive adequate and timely medical attention. If necessary, hospitalizations costs are included free of charge.

CONFIDENTIALITY OF INFORMATION

All information obtained about you and your health will be maintained confidential.

Your name will not be revealed to third parties and both your medical chart and biological samples will be labelled with a number or code. Only the staff of the study, and the regulatory authorities in case of needing it, will have access to this confidential information.

It is possible that the results obtained will be published in medical journals and conferences. Nonetheless, your name will not be revealed.

VOLUNTARY

Your participation in this study is completely voluntary.

You have the right not to participate, and to withdraw your consent and retire of this study in any moment you consider convenient, without offering explanations. By doing so, you do not lose any right as a patient of this institution and the quality of the medical attention you deserve will not be affected.

If you withdraw your consent, it may be necessary that we analyze the data obtained from you until that moment for safety reasons. We will do this protecting your confidentiality.

QUESTIONS

If you have any questions regarding this medical study, you can contact Dr. Katia Abarca, Principal Investigator of the study, to phone number 223546825 or cell phone number 96797787.

If you have any questions regarding your rights as a participant during a medical study, you can call Dr. Beatriz Shand Klagges, President of the Scientific Ethical Committee (Comité Ético Científico) of Facultad de Medicina, Pontificia Universidad Católica de Chile, to the phone number 22354-8173, or send an email to etica.investigacion@med.puc.cl.

DECLARATION OF CONSENT

- I understand the purpose of this medical study, the procedures, the risks, benefits and rights I am subject of, and that I can retire of the study at any moment I wish.
- I sign this document voluntarily, without being forced to do so.
- I am not renouncing to any right.
- I will be communicated of any new information related to the vaccine that will arise during the study, and that may have direct importance to my health condition.
- I understand that I have the right to reevaluate my participation in this medical study in my opinion, any moment I wish.
- I authorize the principal investigator and their collaborators to access and use the data contained in my medical chart for the purposes of this medical study.
- I received a signed copy of this document when I signed it.

I,……

(complete name) accept to participate in this medical study.

Signature:..... Date:……

Principal Investigator:

Name:……

Signature:…… Date:……

Director of the Institution, or their Delegate:

Name:……

Signature:…… Date:……