

Appendix VI: Sample Informed Consent Form

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

For protocol: 2018

Randomized Phase I Study of the Infectivity, Safety, and Immunogenicity of a Single Dose of the Recombinant Live-Attenuated Respiratory Syncytial Virus (RSV) Vaccines RSV ΔNS2/Δ1313/I1314L or RSV 276 or Placebo, Delivered as Nose Drops to RSV-Seronegative Infants 6 to 24 Months of Age

Version 1.0, dated 15 June 2017

With changes from Letter of Amendment (LoA) #1 , dated 15 March 2018

SHORT TITLE FOR IMPAACT 2018: Safety and Immunogenicity of a Single Dose of the RSV
ΔNS2/Δ1313/I1314L or RSV 276 Vaccine

INTRODUCTION

You are being asked to allow your baby to take part in this research study to test vaccines to prevent Respiratory Syncytial Virus (RSV) illness in infants. This study is sponsored by the National Institutes of Health (NIH). The doctor in charge of this study at this site is: [*Site: insert name of site investigator*]. Before you decide if you want your baby to be a part of this study, we want you to know about the study.

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

WHY IS THIS STUDY BEING DONE?

The study is being done to look at the safety (side effects) and antibody (germ fighters) response of infants to a single dose of one of two vaccines against a virus called respiratory syncytial virus, or RSV. The study will look at the amount of vaccine virus that is in your child's nose over time. It will tell us how stable and strong the vaccine was during the study. This research study is testing two experimental vaccines. These vaccines have not been licensed by the U.S. Food and Drug Administration (FDA). Your baby was chosen to be in this study because your baby is at least 6 months (180 days) old and less than 25 months (750 days) old, has not had RSV, and is healthy.

RSV is a virus (germ) that can cause breathing problems in infants and children. Symptoms of infection with RSV may include:

- Fever
- Runny nose
- Sore throat
- Ear infection
- Cough
- Croup (barky cough with hoarseness)

RSV can cause serious lung infections such as pneumonia and wheezing. At this time, there is no approved vaccine to prevent RSV illness.

Doctors who develop vaccines at the NIH have made live virus vaccines that may help prevent RSV illness in babies and children. A live virus vaccine contains a weakened, live virus that is made to help your body respond in a way that will protect you from getting sick from the virus. This is called an “immune response.” The investigational RSV vaccines in this study contain a live, weakened form of RSV and are given as nose drops. One of the vaccines has not been tested in humans. However, other RSV vaccines very similar to this one have been tested in both adults and children. The other vaccine has been tested in humans in one other research study. There were not many side effects, and there was an immune response.

We are asking you to allow your baby to participate in this study. If you agree, we will give your baby either 1 dose of one of the vaccines or 1 dose of placebo. The placebo has no vaccine in it. The placebo is made of water, salt, vitamins, and sugar that is gentle on the inside of the nose. It is sterile and approved for use on people. Approximately 80 babies who have not already had an illness caused by RSV virus will take part in the study.

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

The next few paragraphs provide an overview of the study procedures. After that, there are lists of the specific procedures that will be completed at different visits during the study.

At the first visit, your baby’s blood will be tested to see if your baby has had RSV in the past. You will be told the result of the test. If your baby goes on the study, you will be told whether he/she got vaccine or placebo after the end of the study in the spring. You will not receive information about your baby’s response to the vaccine, but you will receive a summary of the overall response to the vaccine for everyone in the study.

If you agree to allow your baby to take part in this study, you will be asked some questions to be sure he/she can be in this study.

Your baby cannot take part in this study if he/she already has antibodies against RSV, which means he/she already had the RSV illness, lives with people who have weak immune systems, or is not well. Your baby cannot take part in this study if he/she lives with or is in a daycare room with babies younger than 6 months of age, unless you are able to keep your baby out of daycare for 28 days after he/she receives vaccine or placebo. Your baby should not get any vaccines, including rotavirus vaccine for at least 14 days and other live vaccines for at least 28 days after getting the study vaccine or placebo. We ask that you talk with the study staff before your baby gets any routine vaccines for the 28 days after the study vaccine or placebo. We ask that your baby does not take part in any other experimental vaccine or drug studies for 8 weeks after they receive vaccine or placebo. We will ask you to review and sign this study consent prior to administering the vaccine/placebo to your baby. At that time, we will ask you to answer questions to see how well you understand the study.

The vaccine/placebo will be given to your baby by gently squirting it inside his/her nose like nose drops. The amount is very small (a few drops). Your baby will need to lie down on his/her back for one minute after getting the vaccine/placebo. About 2 of each 5 enrolled babies will get one of the RSV vaccines, and about 2 of each 5 enrolled babies will get the other RSV vaccine. Approximately 1 of each 5 enrolled babies will get nose drops without vaccine (placebo). Whether your baby gets one of the vaccines or nose drops without vaccine (placebo) will be decided randomly by computer, like flipping a coin. Neither you nor the study doctors or study nurses will know whether your baby got one of the vaccines or placebo until the study ends, but this information can be made available to the study doctor if needed.

Your baby will be in this study until April of the year after he/she started the study. For the first 8 weeks after getting vaccine or placebo, your baby will be followed closely. During this part of the study, there will be about 9 days when your baby is seen by the clinical research staff and 21 days when your baby will not be seen but you will be contacted by telephone or email by the clinical research staff. Your baby will also be followed from [site: insert November 1st until March 31st unless other dates are specified in the MOP for your site] (the winter season after your baby gets the vaccine or placebo). During this winter time, we will contact you [site: insert the methods of contact] each week to ask about your baby's health and arrange for follow-up visits if needed.

Study visits will last about 30 minutes, except on the day when your baby is screened and on the day he/she is given the vaccine or placebo; those 2 visits may take about 1 to 2 hours each.

- If your baby has RSV symptoms, such as runny nose, sore throat, cough, fever or difficulty breathing, he/she might need to be seen for an evaluation, sometimes as soon as within 24 hours.
- Study visits, except the visit where your baby gets the vaccine or placebo, may take place at your home or at one of the research sites/clinics. The visit where your baby receives vaccine or placebo must take place at one of the research sites/clinics where emergency equipment is available.
- For temperature measurements, you will be asked to use a temporal thermometer, which is used on your baby's forehead. You will measure forehead temperatures 3 times in a row, following the directions. The highest of the 3 readings will be recorded on a chart we will give to you. If your baby has a forehead temperature $\geq 100.0^{\circ}\text{F}$, you will be asked to check your baby's rectal temperature within 20 minutes. Forehead and rectal thermometers will be given to you for use during the study.

Screening Visit

The purpose of the screening visit is to find out if your baby may enter the study. It will take about 1 to 2 hours and will include:

- the study staff telling you about the study and asking you questions to be sure you understand the study.
- going over and signing the consent form.
- going over your baby's medical history and doing a physical examination. The physical examination will include checking your baby's temperature, pulse (heart rate), weight, length, and how fast your baby is breathing. If the physical examination results are not normal, the clinical research staff will tell you and refer your baby for follow-up care with your baby's primary medical provider.
- answering questions about the health of your baby and people living in your house.
- collecting a small amount of blood (about 2 teaspoons) to test for antibodies (germ fighters) against RSV and how your baby's cells are reacting to RSV. If your baby had been screened for any study of an RSV vaccine developed by the NIH doctors, we may not need to collect this sample, because we may be able to use the results and blood from the other study.
- if requested, giving written permission to review your baby's medical records.
- if we think your baby may be eligible for the study, your baby will be asked to return for a series of study visits, beginning with the visit when we will confirm that he/she is eligible and then give your baby the vaccine or placebo.

Day Vaccine/Placebo is Given

- We will confirm that your baby has not been ill recently and will check your baby's temperature, pulse (heart rate), and how fast your baby is breathing.

- Your baby will have a nasal wash. To do this, we will gently squirt less than 2 tablespoons of salt water inside your baby's nose and then collect it when it comes back out of the other side of the nose. This is done before the vaccine or placebo is given to check for other viruses and to check for antibodies in the nose. We will also use an absorbent strip to check for antibodies in the nose. The strip will be placed in your baby's nose for about 30 seconds and then removed.
- Your baby will receive 1 dose of vaccine or placebo given as nose drops using a small medicine dropper. Your baby will be lying on his/her back while we give the nose drops and will remain lying down for about 1 minute afterwards. Your baby can be in your lap during this time.
- After the nose drops are given, we will watch your baby in the clinic for 30 minutes.
- We will provide you with the dates of the rest of the visits and telephone/email contact days.
- You will be given a forehead thermometer, a rectal thermometer, and a temperature chart to record your baby's temperature daily for 29 days (including the day the vaccine/placebo is given to your baby), and at any other time you are concerned about fever.

Monitoring for 56 Days after Vaccine/Placebo is Given

- Your baby will have study visits on Days 3, 5, 7, 10, 12, 14, 17, and 28 (each \pm 1 day), after the vaccine or placebo is given. Each visit will take about 30 minutes, and we will:
 - Check your baby's temperature, pulse, and breathing rate.
 - Do a brief clinical assessment.
 - Ask about your baby's health since the last visit.
 - Give your baby a nasal wash using less than 2 tablespoons of salt water, as described above, to check for the virus that's in the study vaccine and other viruses. On Day 28 only, the nasal wash will also be used to check for antibodies in the nose, and we will also use an absorbent strip to check for antibodies in the nose. The strip will be placed in your baby's nose for about 30 seconds and then removed.
 - Because study visits will be less frequent after the first month, on Day 28, we will review when you should contact the study staff in the event your baby becomes ill during the following month.
- The study nurse will contact you on Days 1, 2, 4, 6, 8, 9, 11, 13, 15, 16, and daily from Days 18 to 27, and on Day 29. The study staff will ask you to report your baby's temperatures and any illness your baby has had since the last visit or contact. The contact may be by telephone, text, or email, whichever you prefer.
- Your baby will have a follow-up visit about 56 days after the study nose drops were given. At this visit, we will ask about your baby's health since the last visit and take a small amount of blood (about 2 teaspoons) from your baby to measure antibodies (germ fighters) against RSV and how your baby's blood cells are making antibodies. We will check your baby's temperature, pulse, and breathing rate. We will also use an absorbent strip to check for antibodies in the nose. The strip will be placed in your baby's nose for about 30 seconds and then removed.
- We also ask you to call us right away to tell us about any illness that your baby has from the day he/she receives the nose drops up to the follow-up visit (8 weeks).
- A study nurse or study doctor will be available by telephone to answer your questions 24 hours a day during the 28 days after your baby receives the vaccine or placebo.
- If your baby becomes ill, you may be asked to bring him/her to the clinic for an examination, sometimes as quickly as within 24 hours. We may do a nasal wash at that time to look for the RSV vaccine virus or any other virus that may be in your baby's nose.

Monitoring Before, During, and After RSV Season

- Your baby will also be followed during the winter RSV season [*site: insert (November 1st until March 31st) unless other dates are specified in the MOP for your site*] after getting the study nose

drops. We will be in contact with you each week to inquire about your baby's health. If your baby has a fever, a respiratory illness (a cold), or an ear infection that requires medical care, we will work with you to schedule a visit so that we can perform a nasal wash and clinical assessment.

- We will collect a small amount of blood (about 2 teaspoons) once in [*site: insert October unless another month is specified in the MOP for your site*] before the winter RSV season and once in April after the winter RSV season to look at the antibodies (germ fighters) against natural RSV infection and how your baby's blood cells are making antibodies. We will also use an absorbent strip to check for antibodies in the nose. The strip will be placed in your baby's nose for about 30 seconds and then removed. If your baby's Day 56 Visit occurred on or after [*site: insert October 1 unless another date is specified in the MOP for your site*], a separate visit in [*site: insert October unless another month is specified in the MOP for your site*] will not be required.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

There will be approximately 80 babies taking part in this study.

HOW LONG WILL MY BABY BE IN THIS STUDY?

Your baby will be in this study through next April, which is between 7 and 13 months from now, depending on which month of the year he/she started the study.

WHAT ARE THE RISKS OF THE STUDY?

Risks of the Vaccines

- If the vaccines are not weakened enough, they may cause a runny nose, sore throat, cough, or other signs of a cold. It is also possible that they may cause a sinus infection, croup, ear infection, fever, wheezing, or pneumonia (infection of the lungs). In another study with a similar vaccine, mild respiratory illnesses or colds were observed frequently in babies who received either vaccine or placebo. Runny nose occurred more often in babies who got the vaccine than those who got the placebo.
- Study investigators have used the same placebo for studies of RSV, parainfluenza, and influenza vaccines in several hundred babies and children over the past 20 years. They have not noticed side effects with this placebo.
- There is no specific medicine to treat RSV illness. If any symptoms of RSV occur, such as runny nose, sore throat, cough, or difficulty breathing, your baby will receive prompt medical care.
- The vaccines were made in a way that was designed to minimize the possibility of other ingredients. However, as with all biological products, there is a small chance that they contain unidentified material. There is a very small chance that such material may cause illness, including possibly serious illness.
- There may be other side effects of the vaccines that are not yet known. If new information about possible side effects of the vaccines becomes available, we will let you know.
- It is possible that the vaccine virus could be spread from your baby to other people in the home or daycare and may make them sick. It could be spread to young babies and people with weakened immune systems. We have not seen this type of spread when other vaccines like this one have been studied.
- The vaccines could cause a severe allergic reaction. A severe reaction can cause hives, throat swelling, rapid heart rate, weakness, difficulty breathing, or death. These reactions are rare.

Risks of Nasal Washes

Nasal washes may cause brief discomfort or pain that is like the feeling of getting salt water in the nose and may rarely cause a nosebleed.

Risks of Having Blood Drawn

Blood drawing can cause bleeding, pain, bruising, or infection at the place where the blood is taken. Sometimes, blood drawing can cause your baby to feel lightheaded or to faint. It sometimes takes more than 1 try to get blood from a small baby.

WHY WOULD THE DOCTOR TAKE MY BABY OFF THIS STUDY EARLY?

The study doctors or the sponsor have the right to end your baby's participation in the study at any time without your consent for any of the following reasons:

- For your baby's safety;
- You do not follow study procedures as directed by the study doctors;
- New information becomes available regarding the safety of the vaccine;
- If it is in your baby's best interest;
- You do not consent to continue in the study after being told of changes in the research that may affect your baby;
- The study sponsor, the International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT), the Institutional Review Board (IRB), the Office for Human Research Protections (OHRP), the National Institute of Allergy and Infectious Diseases (NIAID), or the United States Food and Drug Administration (FDA) decide to end the study. (An IRB is a committee that watches over the safety and rights of research participants.)

WHAT HAPPENS IF MY BABY IS INJURED?

If your baby suffers physical injury from this study, the study doctor will provide or will refer your baby for immediate medical treatment. The study doctor will also provide referrals to appropriate health care facilities. The cost for this treatment will be charged to you or your insurance company. There is no program for compensation either through this institution or the National Institutes of Health (NIH). No financial compensation by the doctors that gave your baby the vaccine or placebo will be made for any discomfort suffered because of participation in this study. You will not be giving up any of your legal rights by signing this consent form.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

- Your baby may not receive any direct benefit from being in the study.
- Being in the study may help find a vaccine that works well to prevent serious RSV illness. Such a vaccine may be of future benefit to babies and children in this country and in the rest of the world.

WHAT OTHER CHOICES DO I/DOES MY BABY HAVE BESIDES THIS STUDY?

There are no licensed vaccines to protect against RSV illness at this time. There is no other similar study or licensed vaccine that we can offer your baby. You may choose to not allow your baby to take part in this study.

WHAT ABOUT CONFIDENTIALITY?

To help us protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. With this Certificate, the researchers cannot be forced to disclose information that may identify you, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below. The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA).

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about you or your baby's participation in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate of Confidentiality to withhold that information.

The Certificate of Confidentiality does not prevent the researchers from disclosing voluntarily, without your consent, information that would identify you as a participant in the research project under certain circumstances such as child abuse.

Your baby's name, birth date, and Social Security number are not routinely given to anyone unless required by law. All of the information you give us during this study will be put in locked file cabinets and/or in password-protected computer files. The only people who will have access to this information will be those who are involved in the study.

There will be people involved in the study who need to see your baby's health information. These people may include the researchers, study and laboratory personnel, and other clinical research staff. Others who may see your baby's information are the groups of people who make sure that the study is being done as it should be: Hospital Institutional Review Boards (IRBs), the Center for Immunization Research (CIR), the National Institute of Allergy and Infectious Diseases (NIAID; NIH) Intramural Data and Safety Monitoring Board and others who need to see your baby's information to make sure that the study is going as planned.

Other groups of people who may be involved in the study and may need to see your baby's information are:

- The government agency "Office for Human Research Protections," that makes sure that we are conducting the research as planned, the U.S. FDA, and the European Medicines Agency (EMA)
- The sponsor of the study and people with whom the sponsor may contract for the study, such as study monitors.
- Other US, local, and international regulatory groups

At the end of the study, whatever we learn from the research may be used in a medical journal or used for teaching. Your baby's name or other details about his/her health will not be used in a manner such that anyone can personally identify your baby.

WHAT ARE THE COSTS TO ME?

There are no costs to you or your baby for him/her being in the study. The costs for vaccine/placebo, study visits, or study procedures are covered by the sponsor (NIH/NIAID). However, taking part in this study may lead to added costs to you or your baby and your/your baby's insurance company if medical

complications arise or if your baby's doctor decides extra tests are needed. In some cases, it is possible that your/your baby's insurance company will not pay for these costs, because your baby is taking part in a research study.

WILL MY BABY RECEIVE ANY COMPENSATION?

You will be paid for your baby's participation in this study at the following rate *[Site: insert payment schedule and amount.]*

You will also be paid during the winter RSV surveillance period as follows *[Site: insert payment schedule and amount.]*

[Optional, depending on site: If you stop your baby from taking part in the study early, you will only be paid for the days of the study that your baby completed. Your baby may also receive age-appropriate books or small toys. If needed, bus tokens or parking passes will be given to you.]

You may be required to provide your Social Security number to be paid. If your payment for study participation exceeds \$600 per year, this information must be reported to the Internal Revenue Service.

WHAT ARE MY BABY'S RIGHTS AS A RESEARCH PARTICIPANT?

Taking part in this study is completely voluntary. You may choose not to have your baby take part in this study or leave this study at any time. Your decision will not have any impact on your baby's participation in other studies and will not result in any penalty or loss of benefits to which you or your baby are otherwise entitled.

A study physician, physician assistant, nurse practitioner, or study nurse will inform you of any significant abnormal physical findings and will make appropriate referrals back to your baby's primary care giver, if necessary.

We will tell you about new information from this or other studies that may affect your baby's health, welfare, or willingness to stay in this study. You may be asked to sign a revised consent form if this occurs. If you want the results of the study, let the clinical research staff know.

At the end of the study, you will be told in writing whether your baby was given one of the vaccines or the placebo.

A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>. This website will not include information that can identify your baby. At most, the website will include a summary of the results. You can search this website at any time.

WHAT ARE MY RESPONSIBILITIES?

- If you decide to withdraw your baby from the study early, we ask that you notify the study nurse or study doctor.
- If your baby comes off the study early, we will ask you to bring him/her into the clinic for an early discontinuation visit. At that visit, we will do a final blood draw (about 1 teaspoon) and collect a nasal wash and/or use an absorbent strip to check for antibodies in the nose. The strip will be placed in your baby's nose for about 30 seconds and then removed.

- Any baby who has received the study product will be encouraged to remain in the study so that safety information can be collected.
- It is important that you do not enroll your baby in other studies where your baby receives vaccines or medications for 8 weeks after he/she receives vaccine/placebo.

WHAT DO I DO IF I HAVE QUESTIONS OR PROBLEMS?

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

- *[Site: Insert name of the investigator or other study staff]*
- *[Site: insert telephone number of above]*

For questions about your baby's rights as a research participant, contact:

- *[Site: insert name or title of person on the Institutional Review Board (IRB) or other organization]*
- *[Site: insert telephone number of above]*

GENETIC TESTING

Some of the blood tests done for this study will look at how your baby's genes (DNA) affect his or her response to RSV. Genes are the basic "instruction book" for the cells that make up our bodies. The differences in people's genes can help explain why some people get a disease while others do not. Researchers may use your baby's samples for limited genetic testing. For example, researchers may do "genetic variations" research. They may look at genes that affect how your baby fights infections. Our genes are passed to us from our birth parents. The researchers will not contact you or your baby's regular health care provider with the results of these tests. This is because these tests are often done with experimental procedures and the results should not be used to make decisions about your baby's health care. However, if the researchers decide that a result is important information for your baby's health care, the study doctor will be notified. If you would like to be contacted with this sort of information, you must notify the study staff of any changes of your address and phone number. Your baby's name will not be available to the laboratory or to the scientists who may be doing limited genetic testing.

You may decide that you do not want your baby's blood used for limited genetic testing. Your baby can still be in this study even if you make this decision. Please read the following statement carefully and then mark your initials in the appropriate space provided.

I allow my baby's blood to be used for limited genetic testing, including future limited genetic testing, as part of this study.

Yes: Initials _____ Date _____

No: Initials _____ Date _____

STORAGE AND FUTURE USE OF UNUSED SPECIMENS

If you agree, any unused blood or nasal wash samples taken from your baby will be stored indefinitely (with protectors of identity) once this study is complete. These unused blood and nasal wash samples may be used for future laboratory studies to learn more about RSV and other viruses. This information may lead to other new virus vaccines in the future.

- Your baby's unused blood or nasal wash samples, if any, will be used only for laboratory studies and will not be sold or used directly to make products that will be for sale.
- The samples will be coded so that your baby's name cannot be easily identified.
- Reports about studies done with your baby's unused samples will not be put in your baby's health or study records.
- There will be no direct benefit to your baby in using the samples as noted above, but from studying the unused samples of babies taking part in the studies, we may learn more about the RSV germ or other viruses that cause illness in babies and children.
- Results from future studies using your baby's unused samples may be included in medical papers and meeting reports, but your baby's name will not be used.

You can change your mind at any time about allowing your baby's unused samples to be used for future laboratory studies. If you do change your mind, contact the study doctor or study nurse and let him/her know. Then the samples will no longer be used for laboratory studies and will be destroyed.

PERMISSION FOR STORAGE AND FUTURE USE OF UNUSED SPECIMENS

Your choice will not have any effect on your baby's taking part in this study.

I will allow the use of my baby's unused blood or nasal wash samples to be stored indefinitely and to be used in future laboratory studies for the purposes described above. Your baby's name will not be available to the laboratory or to the scientists who may be doing any future tests. (Please check one and initial below)

Yes: Initials _____ Date _____

No: Initials _____ Date _____

If NO, your baby's study samples will only be used for the testing described in this study.

SIGNATURE

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

Study Participant's Name (print)

Participant's Legal Guardian (print)

Legal Guardian's Signature and Date

Clinical Research Staff Conducting
Consent Discussion (print)

Clinical Research Staff Signature and Date

Witness' Name (print)
(As appropriate)

Witness' Signature and Date

Second Parent/Guardian's Name
(As appropriate)

Signature and Date