A Phase 2a Study to Evaluate the Safety, Tolerability, and Immunogenicity of One Dose of NDV-3A Vaccine in Patients With STAT3-Mutated Hyper-IgE Syndrome

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List of Abbreviations

AD-HIES	autosomal-dominant hyper IgE syndrome
AE	adverse event
Als3	agglutinin-like sequence 3
AlOH	Aluminum hydroxide
ALP	alkaline phosphatase
ALT	alanine transaminase
AR	adverse reaction
AST	aspartate transaminase
CC	Clinical Center
CFR	Code of Federal Regulations
CHI	Center for Human Immunology, Autoimmunity and Inflammation
CRIS	Clinical Research Information System
CRIMSON	Clinical Research Information Management System of the NIAID
CSO	Clinical Safety Office
DCR	Division of Clinical Research
ED_{50}	median effective dose
ELISA	enzyme-linked immunosorbent assay
ELISpot	enzyme-linked immunospot
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HRPP	Human Research Protections Program
ICH	International Council on Harmonisation
ID	intradermal(ly)
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IND	Investigational New Drug
IM	intramuscular(ly)
IRB	Institutional Review Board
LCID	Laboratory of Clinical Infectious Disease
NHLBI	National Heart, Lung and Blood Institute
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
OCRPRO	Office of Clinical Research Policy and Regulatory Operations
OHRP	Office of Human Research Protections
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PI	principal investigator
r	recombinant
SAE	serious adverse event
SAR	suspected adverse reaction
SCORAD	SCORing Atopic Dermatitis
SERF	Safety Expedited Report Form
SMC	Safety Monitoring Committee
SRCP	Safety Review and Communications Plan
SUSAR	serious and unexpected suspected adverse reaction
ULN	upper limit of normal
UP	unanticipated problem
UPnonAE	unanticipated problem that is not an adverse event
VVC	vulvovaginal candidiasis

Protocol Summary

Short Title:	NDV-3A Vaccine Study
Clinical Phase:	2a
Sample Size:	N = 40; 20 with autosomal-dominant hyper-IgE syndrome (AD-HIES) and 20 healthy volunteers
Accrual Ceiling:	N = 50
Study Population:	Adults (18-55 years), either healthy volunteers or diagnosed with AD-HIES
Accrual Period:	12 months (Subsequent data analysis until approximately December 2019.)
Study Duration:	Start Date: May 2017 End Date: December 2019 Total length of individual subject participation: approximately 6-7 months
Study Design:	This is a single-dose, open-label study to evaluate the safety, tolerability, and immunogenicity of the NDV-3A vaccine in healthy adult volunteers and adult volunteers with AD-HIES
Study Agent/ Intervention Description:	NDV-3A, a vaccine containing recombinant *Candida albicans* agglutinin-like sequence 3 (rAls3) protein as the antigen, formulated with aluminum hydroxide (AlOH) adjuvant in phosphate-buffered saline. Participants will receive a single 0.5-mL dose containing 300 µg of rAls3 and 0.5 mg of aluminum as AlOH, delivered via intramuscular injection.
Primary Objective:	To assess anti-rAls3 antibody titers in response to the study vaccine 14 days after vaccination.
Secondary Objectives:	1. To evaluate the safety of the study vaccine in adults with AD-HIES. 2. To assess anti-rAls3 antibody titers in response to the study vaccine 6 months after vaccination.
Primary Endpoint:	Percent of each group with at least a four-fold increase in anti-rAls3 antibody titer 2 weeks after vaccination.

Secondary Endpoints:

1. Frequency of injection site and systemic AEs in AD-HIES affected patients and healthy volunteers.
2. Anti-Als3 antibody titers at 6 months after vaccination in patients with AD-HIES and healthy volunteers.

Précis

Autosomal-dominant hyper-IgE syndrome (AD-HIES) is characterized by recurrent *Staphylococcus aureus* and *Candida* epithelial infections, which is thought to be due, in part, to a lack of Th17 cell differentiation, thus impairing epithelial immunity. Treatment of AD-HIES is primarily supportive with prophylactic antibiotics; however, this is limited by microbial resistance and intolerance of medications, and infections do still occur. Immunological intervention with a vaccine could improve quality of life by preventing these infections altogether.

The NDV-3A vaccine consists of a recombinant protein derived from the *Candida* Als3 adhesion protein. This protein is homologous to surface proteins on *S aureus* and has been shown in preclinical studies to protect against both intravascular and subcutaneous challenge with *S aureus*. Therefore, NDV-3A represents not only the first antifungal vaccine, but also the first vaccine to provide cross-kingdom protection. In Phase 1 and Phase 2 studies in healthy volunteers (150 receiving vaccine), the safety profile of this vaccine is very reassuring as the vaccine elicits a strong antibody response after a single dose in all vaccinees as well as a Th1 and/or Th17 response in the majority of vaccinees. We will enroll 20 healthy adult volunteers and 20 adults with AD-HIES in an open-label, single-dose study to assess the immunological response to and the safety/tolerability of the NDV-3A vaccine. We anticipate an increase in baseline anti-Als3 IgG within 2 weeks post-vaccination.

1 Background Information and Scientific Rationale

1.1 Background Information

1.1.1 Description of the Study Agent

The NDV-3 and NDV-3A vaccines (NovaDigm Therapeutics [Grand Forks, ND, USA]) were initially developed for the prevention of *Candida sp* infections. The vaccines contain a purified recombinant protein derived from the 416-residue N-terminal region of the *C albicans* agglutinin-like sequence 3 protein (Als3). Als3 is an adhesin and an invasin that helps *C albicans* adhere to and invade host cells.[1] The recombinant (r) Als3 antigen increases survival in mice given a systemic challenge with *C albicans*,[2] reduces kidney fungal burden in mice given a systemic challenge with any of the five most common species of *Candida* (Ibrahim, unpublished data), and reduces vaginal fungal burden in mice given an intravaginal challenge with *C albicans*.[3] Surprisingly, rAls3 shows substantial homology to 2 surface proteins on *Staphylococcus aureus*.[4] In preclinical mouse studies, the vaccine has been highly protective against tail vein or subcutaneous challenge with *S aureus* , including infections caused by methicillin-resistant strains.[5] This is one of the first examples of cross-kingdom protection conveyed by a vaccine, likely exemplifying convergent evolution of a mechanism of adherence and invasion to human cells by two different human pathogens.[6]

The NDV-3 vaccine contains the rAls3 protein with an N-terminal 15-amino acid addition. This addition contains a six-histidine tag to facilitate purification. The NDV-3A vaccine contains the rAls3 protein without the extra amino acid residues. Both recombinant proteins are expressed in a *Saccharomyces cerevisiae* system. Other licensed vaccines, such as Gardasil for human papillomavirus and Recombivax HB for hepatitis B (Merck & Co, Inc [Kenilworth, NJ, USA]), are also derived from yeast expression systems.[7]

The NDV-3 and NDV-3A vaccines are formulated in an AlOH suspension that serves as an adjuvant.[7]

1.1.2 Summary of Preclinical Studies of NDV-3 and NDV-3A

Pharmacology studies in mice demonstrated a protective effect of rAls3 against infection by *Candida sp* and *S aureus*. In one study, mice that were inoculated with rAls3 + adjuvant and then challenged with *S aureus* demonstrated an increased survival rate relative to mice inoculated with adjuvant alone.[7] In a second study, mice were inoculated with 2 doses of rAls3 + adjuvant or adjuvant alone, and then CD3+ T cells and B220+ B cells were collected. Female Balb/c mice then received either the harvested T or B cells, and then were challenged with *C albicans* or *S aureus*. Mice that received T cells from mice vaccinated with rAls3 + adjuvant demonstrated significantly ($p < 0.01$) enhanced survival for both challenges relative to mice who received B cells from vaccinated mice and either T or B cells from unvaccinated mice.[7] In a third study,

female mice vaccinated with two doses of NDV-3A and then challenged with *C albicans* showed substantial reductions in vaginal fungal burden relative to control mice that only received the adjuvant.[7]

Rhesus macaques inoculated with rAls3 + adjuvant displayed a dramatic increase in anti-rAls3 antibody titers post-vaccination relative to monkeys inoculated with adjuvant alone.[7]

Two other studies were conducted to compare the activity of the NDV-3 and NDV-3A vaccines in mice. In the first, mice were vaccinated on study days 0 and 21 with up to 100 µg of antigen. An immunogenicity assay to measure the geometric mean of serum IgG titer of each dose group showed that IgG response for both antigens plateaued at doses of approximately 5 µg.

In the second study, mice received 2 doses of NDV-3 or NDV-3A, separated by 3 weeks, at doses ranging from 0.02 to 5 µg of antigen. The median effective dose (ED_{50}) for NDV-3 was approximately 0.57 µg, while the ED_{50} for NDV-3A was approximately 0.10 µg. The lower ED_{50} for NDV-3A means that less antigen was required for mice who received that vaccine to seroconvert than was required for mice vaccinated with NDV-3. The results of these studies as well as the intravaginal challenge study described above demonstrate that NDV-3 and NDV-3A have similar biological activity in mouse models.

A Good Laboratory Practice–compliant toxicology study was conducted in New Zealand white rabbits. Rabbits received either a 300-µg dose of the NDV-3 vaccine or placebo at Days 1, 15, and 29 via intramuscular (IM) injection. No test article–related effects were noted for in-life examination (survival, clinical observations, body weight and temperature, skin irritation, and ophthalmoscopic evaluations) and clinical pathology (hematology, clinical chemistry, C-reactive protein, serum protein electrophoresis, and urinalysis).

There was an observable decrease in the weights of adrenal glands between males who received the vaccine and the other groups. However, because this difference was sex-specific and there was no microscopic correlation, this effect was not likely to be the result of the vaccine.

Red discoloration of the skeletal muscle was observed at two of the injection sites of rabbits that received the vaccine. This correlated with microscopic findings of skeletal muscle myofiber degeneration/necrosis, hemorrhage, and presence of inflammatory heterophils, mononuclear cells, and foamy macrophages. These changes resolved at recovery, except for the continued increase in incidence and/or severity of foamy macrophages. All of these changes indicated a typical injection site inflammatory reaction.

The FDA did not require a separate toxicology study of NDV-3A as they considered NDV-3 and NDV-3A to be biologically equivalent based on the in vitro and in vivo preclinical data provided.

1.1.3 Summary of Relevant Clinical Studies of NDV-3 and NDV-3A

Two phase 1 clinical studies of NDV-3 have been completed to date. Additionally, a phase 1b/2a study has completed enrollment.

In the first phase 1 study, 40 healthy adults, ages 19 to 47 years, were randomized into one of three dose groups: placebo (n = 10), 30-µg rAls3 (n = 15), or 300-µg rAls3 (n = 15). Injections were administered IM. Several research participants who had received the vaccine received a booster after 6 months at the same dose as the initial injection. The most common complaint among all groups at both the first and second doses was injection site reactions. All reactions resolved over time with no further complications, and no serious adverse events (SAEs) were observed.

All participants who received the vaccine had at least a four-fold increase in plasma anti-Als3 IgG titers against rAls3 at Day 14 compared to placebo-dosed participants. Plasma anti-Als3 IgA titer was similarly increased in vaccinees compared to placebo recipients. Participants who received the 300-µg dose displayed a greater increase than those who received the 30-µg dose. These responses suggest that natural exposure to *Candida* has primed these individuals and that the vaccine induces an anamnestic immune response. A booster dose at 6 months after the first dose elicited a modest increase in the anti-Als3 IgG and IgA titers.

Additionally, ELISpot assays of harvested PBMCs demonstrated that within a few weeks of vaccination the majority of participants who received either dose of the vaccine had an increased number of PBMCs showing Als3-specific production of IFN-γ and/or IL-17A relative to placebo-dosed participants. The response rate was faster in participants dosed at 300 µg than at 30 µg. A booster dose at 6 months after the first dose elicited what appears to be a substantial increase in the percent of vaccinees with an increased number of PBMCs showing Als3-specific production of IFN-γ and/or IL-17A relative to placebo-dosed participants, but there was no significant difference between the two doses.

In the second phase 1 study, 160 healthy adult volunteers were randomized to one of four dose groups (n = ~40 per group) each receiving a single dose of vaccine: placebo, 30 µg rAls3 without alum adjuvant administered via intradermal (ID) injection, or 300 µg rAls3 (with or without alum adjuvant) administered via IM injection. Injection site reactions were the most common type of adverse event (AE). All were mild or moderate and resolved within a few days. Participants who received 30 µg ID had a higher rate of erythema and pruritus than other groups, and participants who received 300 µg with adjuvant IM had a higher rate of injection site pain than other groups. Other systemic AEs were also observed. Participants dosed with 30 µg ID had an increased rate of nausea, fatigue, headache, and myalgia relative to the control group, but participants dosed with 300 µg IM (with and without adjuvant) had only a slight increase in nausea relative to the control group.

All groups that received NDV-3 displayed an increase in serum and vaginal mucosal IgG and IgA1 titers against rAls3 after vaccination, relative to the control group. Those receiving a 300-µg IM dose with AlOH adjuvant had serum anti-Als3 IgG and IgA titers that were on average 2-3-fold higher than those that received the 300-µg IM dose without AlOH adjuvant. An opsonophagocytic killing assay, which is typically use to evaluate bacterial vaccines but is also relevant for fungal vaccines, showed a clear association between serum anti-rAls3 antibody titer level and *C albicans* killing. These data demonstrate that the anti-rAls3 antibodies can direct an immune response against *C albicans* and thus the vaccine with the AlOH adjuvant is the preferred formulation for further study.

An ELISpot assay of harvested PBMCs showed that for the groups dosed with 300 µg IM (with or without adjuvant), IFN-γ signal was higher at Day 7 than in the group dosed with 30 µg ID. Signals were similar between these three groups at Days 14 and 90. Signal for IL-17A in the 300-µg IM groups (both with and without adjuvant) peaked at Day 7 and declined through Days 14 and 90. For the 30-µg ID group, IL-17A signal was lower than the 300-µg groups but more persistent through the duration of the study.

The Phase 1b/2a study was designed to directly compare NDV-3 and NDV-3A for safety and immunogenicity and to evaluate NDV-3A for efficacy in reducing recurrences of vulvovaginal candidiasis (VVC) in women with recurrent infection. This study enrolled 188 women with recurrent VVC, all of whom have completed the study. Inclusion criteria required that all participants have a documented history of recurrent VVC and present with an active vaginal infection that is positive for *C albicans*. Final results show that 1) NDV-3 and NDV-3A are not substantially different for safety and immunogenicity, 2) NDV-3A is safe and induces a robust immune response in women with recurrent VVC, similar to what was seen in healthy women receiving NDV-3, 3) there were no serious AEs associated with administration of NDV-3 or NDV-3A, and 4) at 12 months post-vaccination of women with RVVC 42% who received NDV-3A were recurrence free whereas only 22% of placebo recipients were recurrence free. This translates to a point estimate of efficacy of approximately 30% ($p = 0.029$).

1.1.4 Summary of Relevant Clinical Studies of Other Vaccines

Aside from the studies described above for NDV-3 and NDV-3A, only one other effort was made in the past 28 years to evaluate a vaccine targeting a fungal pathogen in a placebo-controlled clinical study, that being a Phase 1 study by Pevion Biotech AG (Ittigen, Switzerland) of their vaccine candidate containing recombinant secreted aspartyl proteinase 2 conjugated to an influenza virosome. The vaccine was shown to be safe but only mildly immunogenic following intravaginal administration.

Over 20 different vaccine antigens targeting *S aureus* have been evaluated in placebo-controlled Phase 1-3 clinical studies.[6] All were safe and immunogenic in Phase 1 studies. Vaccine candidates that advanced into Phase 2/3 studies are as follows:

- Nabi evaluated a bivalent polysaccharide-protein conjugate vaccine based on serotypes 5 and 8 in patients undergoing chronic hemodialysis. The vaccine induced a robust immune response that endured for > 1 year, and trended toward but did not reach statistical significance in reducing invasive infection.[8,9]
- Inhibitex evaluated passive protection using antibody to clumping factor A in patients with established staphylococcemia. While antibody levels were durable, there was a trend toward but no statistically significant reduction in the risk of invasive infection.[10]
- Merck evaluated a recombinant iron surface determinant B protein in cardiothoracic sternotomy patients. While the antibody response was evident, the vaccine was potentially associated with serious post-operative complications.[11,12] Data from other studies suggests that this safety issue may be specific to this vaccine antigen and/or patient population.
- Pfizer is currently evaluating a quadrivalent vaccine (polysaccharide-protein conjugates for serotypes 5 and 8 plus recombinant clumping factor A and manganese transporter C proteins in a Phase 2/3 study in patients having elective posterior instrumented lumbar spinal fusion procedure. Results have not been reported yet though earlier studies showed the vaccine to be safe and immunogenic.[13]

In contrast to this study, which will target mucocutaneous *Candida* and *S aureus* infections, the above studies were all targeting patients at risk of invasive *S aureus* infection.

1.2 Rationale

This exploratory study is designed to evaluate the immunological and safety response to NDV-3A in 20 AD-HIES patients and 20 healthy control participants.

Autosomal-dominant hyper-IgE syndrome (AD-HIES, also referred to as Job's syndrome) results from a dominant-negative mutation in *STAT3*.[14] This condition causes an impairment of IL-17 production by T-lymphocytes. Patients with AD-HIES are prone to mucocutaneous infection with both *Candida* and *Staphylococcus*. There is a large cohort of AD-HIES patients who are enrolled in a NIAID-sponsored natural history study at the NIH Clinical Center (CC). *S aureus* and *C albicans* are two pathogens of great concern to this patient population. Mucocutaneous infections are quite frequent and are typically controlled with chronic antibiotics and antifungals. However, resistance to standard antibiotics and antifungals is a growing problem. The potential of immunological intervention with a vaccine, particularly with one that has been shown to affect *C albicans* as well as *S aureus* disease, is very compelling.

One of the major mechanisms of action of the NDV-3A vaccine is the stimulation of a Th17 response by T-cells. Therefore, this vaccine could potentially protect AD-HIES patients against both of these mucocutaneous infections either by inducing protective antibodies or by boosting their impaired Th17 response.

There are many novel aspects to this study:

- This study is the first to look at vaccine immunotherapy in people with AD-HIES.
- There are no fungal vaccines approved for human use; NDV-3A is the only fungal vaccine in clinical development in the world.
- NDV-3A is the only "cross-kingdom" vaccine, offering protection against both a fungal and a bacterial pathogen in preclinical studies, to enter clinical development.
- NDV-3A has the potential to target critical healthcare-associated infections, including methicillin-resistant *S aureus* and fluconazole-resistant *C albicans*; there are no vaccines licensed or any other vaccines in clinical development to address such infections.
- The data obtained from this study may direct future exploration of T-cell–activating adjuvants.

2 Study Objectives

2.1 Primary Objective

To assess anti-rAls3 antibody titers in response to the study vaccine 14 days after vaccination.

2.2 Secondary Objectives

1. To evaluate the safety of the study vaccine in adults with AD-HIES.
2. To assess anti-rAls3 antibody titers in response to the study vaccine 6 months after vaccination.

2.3 Exploratory Objectives

1. To determine the number and severity of *Candida/Staphylococcus* infections after vaccination compared to the historical pattern for each individual.
2. To assess changes in *Candida sp* and *S aureus* colonization for pre- versus post-vaccination samples from skin, the oral, vaginal, and nasal (*S aureus* only) mucus and stool samples.
3. To assess the level of *Candida* killing by mucosal secretions and the level of protective immune factors in mucosal secretions at pre-defined time points before and after vaccination.
4. To assess RNA transcriptome changes 24 hours and 2 weeks after vaccination.
5. To assess inflammatory markers and immunophenotypic changes in serum and PBMCs before and 2 weeks and 6 months post-vaccination, with specific interest in changes in IL-17A and IFN-γ expression.

3 Study Design

3.1 Description of the Study Design

This is an open-label, single-dose study to assess the safety, tolerability, and immunological and microbiological response to the NDV-3A vaccine. Twenty healthy adult volunteers and 20 adults with AD-HIES will be enrolled for this study.

Study personnel will contact participants by telephone at Days 30, 60, 90, 120, and 150 post-vaccination to assess any potential AEs and to conduct a concomitant medication review.

Participants will return to the NIH CC for in-person safety assessments at 1 day, 2 days, 14 days, and 6 months post-vaccination. Additional unscheduled visits will be arranged as needed for evaluation and treatment of underlying conditions. All visits will include a physical exam; collection of blood, mucosal, skin, and stool samples; assessment of any injection site reactions; assessments of any potential AEs; and concomitant medication review. Blood samples will be processed to obtain serum and PBMCs for evaluation of immune response to the vaccine. Mucosal, skin, and stool samples collected will be evaluated for microbiological culture and PCR evidence of colonization by *Candida sp* and *S aureus*.

3.2 Study Endpoints

3.2.1 Primary Endpoint

Percent of each group with at least a four-fold increase in anti-rAls3 antibody titer 2 weeks after vaccination.

3.2.2 Secondary Endpoints

1. Frequency of injection site and systemic AEs in AD-HIES affected patients and healthy volunteers.
2. Anti-rAls3 antibody titers at 6 months after vaccination in patients with AD-HIES and healthy volunteers.

3.2.3 Exploratory Endpoints

1. Decrease in the number of *S aureus* and *Candida sp* infections in patients compared to historical infections in the 6 months prior to vaccination.
2. Improved eczema in AD-HIES patients during the 6 months post-vaccination as evaluated with a SCORing Atopic Dermatitis (SCORAD) eczema severity score.
3. Decrease in the colonization with *S aureus* and *Candida sp* for pre- versus post-vaccination samples from skin, the oral, vaginal, and nasal (*S aureus* only) mucus and stool samples.

4. Improved *Candida sp* killing by mucosal secretions and the level of protective immune factors in mucosal secretions at pre-defined time points before and after vaccination.
5. Inflammatory and immunophenotypic changes at 1 day, 2 weeks and 6 months post-vaccination as assessed using RNAseq, extended flow cytometry and serum inflammatory markers, with specific interest in the IFNgamma and IL-17A responses

4 Study Population

4.1 Recruitment Plan

Adults with AD-HIES (n = 20) will be co-enrolled in NIAID protocol 00-I-0159, "Natural History, Management, and Genetics of the Hyperimmunoglobulin E Recurrent Infection Syndrome (HIES)."

Adult healthy volunteers (n = 20) will be recruited through the NIH Clinical Research Volunteer Program. The healthy volunteers will be recruited once AD-HIES volunteers are identified so they can be age matched within 5 years and gender matched, when possible.

Recruitment of NIH employees: NIH employees and members of their immediate families may participate in this protocol. We will follow the Guidelines for the Inclusion of Employees in NIH Research Studies and will give each employee a copy of the "NIH Information Sheet on Employee Research Participation."

For NIH employees:

- NIH staff may be a vulnerable class of participants.
- Neither participation nor refusal to participate will have an effect, either beneficial or adverse, on the participant's employment or work situation.
- The NIH information sheet regarding NIH employee research participation will be distributed to all potential subjects who are NIH employees.
- The employee subject's privacy and confidentiality will be preserved in accordance with NIH CC and NIAID policies, which define the scope and limitations of the protections.
- For NIH employee subjects, consent will be obtained by an individual independent of the employee's team. Those in a supervisory position to any employee and co-workers of the employee will not obtain consent.
- The importance of maintaining confidentiality when obtaining potentially sensitive and private information from co-workers or subordinates will be reviewed with the study staff at least annually and more often if warranted.

4.2 Subject Inclusion Criteria

1. Age 18-55 years.
2. For healthy volunteers: in general good health, without significant medical illness, physical exam findings, or significant laboratory abnormalities as determined by the investigator.
3. For participants with AD-HIES: confirmation of diagnosis with a STAT3 mutation.
4. Participants who can get pregnant must be willing to use an acceptable form of contraception for the duration of participation and have a negative pregnancy test at screening.
5. Agree to allow storage of biological samples for future research.

Contraception: The effects of the NDV-3A on the developing human fetus are unknown. For this reason, study participants must agree to use adequate contraception when engaging in sexual activities that can result in pregnancy. Acceptable forms of contraception are the following:

- Intrauterine device (IUD) or equivalent.
- Hormonal contraceptives (eg, consistent, timely and continuous use of contraceptive pill, patch, ring, implant, or injection that has reached full efficacy prior to dosing). If the participant uses a contraceptive pill, patch, or ring, then a barrier method (eg, male/female condom, cap, or diaphragm plus spermicide) must also be used at the time of potentially reproductive sexual activity.
- Be in a stable, long-term monogamous relationship, per assessment of the principal investigator (PI), with a partner that does not pose any potential pregnancy risk, eg, has undergone a vasectomy at least 6 months prior to dose of study agent or is of the same sex as the patient.
- Have had a hysterectomy and/or a bilateral tubal ligation or both ovaries removed.

Adequate contraception must be used consistently, beginning 28 days before administration of the vaccine and lasting for the duration of study participation. Participants of childbearing potential must have a negative pregnancy test result before they receive the NDV-3A vaccine. During the course of the study, if a participant becomes pregnant or suspects they are pregnant, then they should inform the study staff and their primary care physician immediately.

4.3 Subject Exclusion Criteria

1. Has a history of allergic response or other serious reaction to aluminum and/or yeast products.
2. Has a history of clinically significant allergy including anaphylaxis or other serious reaction to food, vaccines, or other drugs, that in the opinion of the investigator, might put the participant at undue risk.

3. Has an active infection (such as *S aureus* abscess, pneumonia, acute *Candida* mucocutaneous infection). Baseline state of chronic infections will be considered by the PI (eg, chronic *Pseudomonas* infection in lung).
4. Has an active infection with hepatitis B, hepatitis C, or HIV.
5. Has received or is planning to receive any investigational drug, investigational vaccine, or investigational device within four weeks prior to vaccination, or at any other time during their participation in the study.
6. Has received or is planning to receive any other live vaccine within three weeks before vaccination or for three weeks after vaccination.
7. Self-reported current alcohol abuse or addiction.
8. Self-reported current illicit drug abuse or addiction, or drug screen positive for illicit drugs.
9. Current or planned use, within 3 weeks before vaccination, of any medications or treatments that may alter immune responses to the study vaccine (eg, immunosuppressive medications including systemic corticosteroids, cyclosporine, tacrolimus, cytotoxic drugs, Bacillus Calmette-Guerin, monoclonal antibodies, or radiation therapy). Topical, intranasal, or inhaled immunosuppressants such as corticosteroids will be allowed.
10. Current or planned use within 2 weeks before vaccination of immune globulin replacement.
11. Has any of the following laboratory abnormalities at the screening visit:
    a. Alanine transaminase (ALT), aspartate transaminase (AST), and/or alkaline phosphatase (ALP) > 1.5 times the upper limit of normal (ULN).
    b. Total bilirubin level > 1.5 times the ULN
    c. Serum creatinine level > 1.5 times the ULN
    d. Absolute neutrophil count < 750 cells/µL
    e. Hemoglobin < 9 mg/dL
    f. Platelet count < 100,000
12. Refusal or inability to comply with study procedures to the extent that it is potentially harmful to the participant or to the integrity of the study data.
13. Has donated blood/plasma within four weeks before vaccination.
14. Is pregnant or breastfeeding, or intends to become pregnant over the course of the study.
15. Is unable to commit to the follow-up visits and or has unreliable access to a telephone for follow-up contacts, either by self-admission (self-reporting) or in the opinion of the investigator.
16. Any other condition the investigator believes would interfere with the participant's ability to provide informed consent, comply with study instructions, or that might confound the interpretation of the study results or put the participant at undue risk.

Co-enrollment guidelines: Co-enrollment in other trials is restricted, other than enrollment on observational studies or those evaluating the use of a licensed medication. Study staff should be notified of co-enrollment as it may require the approval of the PI.

4.4 Justification for Exclusion of Special Populations

4.4.1 Exclusion of women

Pregnancy: Pregnant women are excluded from this study because the effects of the NDV-3A vaccine on the developing human fetus are unknown with respect to the potential for teratogenic or abortifacient effects.

Breastfeeding: Because there is an unknown but potential risk for AEs in nursing infants secondary to treatment of the mother with the NDV-3A vaccine, potential participants who are breastfeeding are excluded from this study.

4.4.2 Exclusion of minors

Because there are insufficient data regarding dosing or AEs available in adults to judge the potential risk in minors, minors are excluded from this study.

5 Study Agent/Interventions

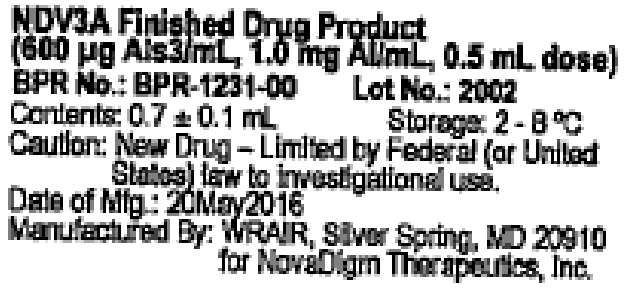
5.1 Disposition and Dispensation

Study agent will be distributed via the NIH pharmacy according to standard pharmacy procedures.

5.1.1 Formulation, Packaging, and Labeling

An example of the label that will be on all vials appears below.

NDV-3A Finished Drug Product
[600 µg Als3/mL, 1.0mg Al/mL, 0.5 mL/dose]
BPR No.:BPR-1231-00 Lot2002
Contents: 0.7 ± 0.1 mL STORE 2-8°C
Caution: New Drug - Limited by Federal
Law to Investigational Use.
Date of Mfg.: 20May2016
Manufactured by: WRAIR, Silver Spring, MD 20910
For NovaDigm Therapeutics Inc.



5.2 Study Agent Storage and Stability

The NDV-3A vaccine will be stored at the NIH pharmacy at 2°C-8°C. Once put into the syringe, the vaccine can be held at room temperature for up to 8 hours.

5.3 Preparation, Administration, and Dosage of Study Agent

The single-dose, 2-mL glass vaccine vials contain 0.7 $\pm$ 0.1 mL of vaccine, which is 600-µg rAls3/mL formulated with 1.0-mg Al/mL as AlOH, in 10-mM sodium phosphate, 154-mM sodium chloride, pH 6.5. The vials will be labeled and stored for use in this study.

Participants will receive a single dose of 0.5 mL (300 µg of rAls3), administered via IM injection. The 300-µg dose has been administered to 201 patients. This dose elicited a robust immune response in adults and did not produce any serious vaccine-attributable AEs.

5.4 Study Product Accountability Procedures

The NIH pharmacy will maintain accurate accountability records. Instructions and the required accountability documentation will be provided to the study pharmacist. When the study is completed, copies of the study drug accountability records will be returned to the sponsor, and the originals maintained at the study site. Copies of the drug accountability records must be maintained with the rest of the documentation for the study. All unused study agent must be disposed of upon authorization by the sponsor. All records regarding the disposition of study drug must be available for inspection by the study monitors and regulatory authorities.

5.5 Assessment of Subject Compliance with Study Agent

The study team will administer a single dose of the NDV-3A vaccine to each participant. Ordered doses of NDV-3A will be documented in the CC Clinical Research Information System (CRIS). The Clinical Research Information Management System of the NIAID (CRIMSON) will be the primary source for dose administration. The dose administration will also be documented in CRIS.

5.6 Concomitant Medications and Procedures

All concomitant prescription and nonprescription (including over-the-counter, herbal supplements, and vitamins) medications taken during study participation will be recorded. For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician.

5.7 Prohibited Medications and Procedures

Use of any medications or treatments that may alter immune responses to the study vaccine throughout the study (eg, cyclosporine, tacrolimus, cytotoxic drugs, Bacillus Calmette-Guerin, monoclonal antibodies, or radiation therapy) is prohibited. Participants may start using these drugs after study participation has ended.

Treatment with antibiotics or antifungals will not be permitted unless discussed with and approved by the PI.

6 Study Schedule and Procedures

All visits will take place at the NIH CC. The study schedule is presented in tabular form in Appendix A. Blood draw volumes are presented in Appendix B.

6.1 Screening (Day −28 to baseline)

Informed consent will be obtained before any study procedures begin.

Participants with AD-HIES will be recruited from NIAID protocol 00-I-0159. The eligibility criteria, including medical history and physical examination findings, will be evaluated from the immunologic, genetic, and/or initial evaluation conducted as part of the referring protocol. Laboratory, history, and exam findings to fulfill eligibility criteria must be collected within 28 days before enrollment in this protocol. If findings are not available from the referring protocol within that timeframe, then physical exam, medical history, sample collection, and pregnancy test will be conducted under this protocol.

Healthy volunteers will undergo the following screening procedures at the screening visit:

1. Physical exam with vital signs
2. Medical history and documentation of concomitant medications
3. Urine drug screening
4. Collection of blood for hepatitis B (antigen and antibody), hepatitis C antibody, and HIV antibody testing; acute, hepatic, and mineral panels; prothrombin/partial thromboplastin time; complete blood count with differential; lymphocyte flow cytometry (BD Multitest 6-Color TBNK Reagent [BD Biosciences, Franklin Lakes, NJ, USA]); and serum immunoglobin quantitation.
5. Serum pregnancy test for participants who are able to become pregnant

6.2 Baseline Visits (Days –3 to 0)

After eligibility is confirmed, all participants will return to the NIH CC for two separate baseline visits. The first baseline will be done 1 to 3 days before vaccination, and the second will be done the day of vaccination (Day 0) before administration of the study vaccine.

At both baseline visits, blood will be collected for harvesting of PBMCs for CHI pre-vaccination analysis: cryopreservation, potential genetic testing, whole transcriptome sequencing, multiplex analysis of inflammatory markers, and immunophenotyping.

Participants of childbearing potential will have a pregnancy test on Day 0. The test must be negative in order for the participant to receive the vaccine.

The following procedures will be conducted at only one of the baseline visits, and will be scheduled depending on the investigators' and participant's convenience:

1. Physical exam with vital signs.
2. Detailed history of *Staphylococcus* and *Candida* infections requiring treatment (eg, additional medications, drainage) in the last 6 months.
3. SCORAD eczema scoring assessment (for participants with AD-HIES only).
4. Collection of blood for research laboratory evaluations that may include but are not limited to ELISA for anti-rAls3 IgG and IgA1.
5. Collection of saliva and/or vaginal secretions for research evaluations: ELISA for anti-rAls3 IgG and IgA1; in vitro killing assay of *C albicans.* Vaginal secretion collection is optional.
6. Collection of stool, skin swab, and oral, nasal, and vaginal mucus may be collected for research evaluations: culture and PCR for *Candida sp* and *S aureus*; microbiome analysis (stool and oral and vaginal mucus only). Vaginal mucus collection and stool samples are optional.

6.3 Visit for Vaccination (Days 0 to 2)

After the baseline evaluations have been conducted on Day 0, participants will receive a single dose of the NDV-3A vaccine (0.5 mL, 300-µg rAls3, 0.5-mg Al as AlOH, in PBS) via IM injection. The study team will observe the participant for 30 minutes post-injection to monitor for potential allergic or anaphylactic reactions. The study team will provide the participant with a 14-day diary card and instructions to record post-injection reactions. Participants will return to the NIH CC for 2 days after the injection (Day 1 and 2) for physical exam with vital signs and assessment of AEs and injection site. They will return the diary card at the Day 14 post-vaccination visit.

On Day 1 only, blood will be collected for storage of PBMCs, serum, and RNA. These samples will be saved for analysis of acute inflammatory responses to the vaccination.

The first 3 participants with AD-HIES will be scheduled for their vaccination visit at least 48 hours apart from each other so there is no overlap. This will allow the study team to monitor for acute AEs in this population before administering NDV-3A to the other AD-HIES participants.

6.4 Follow-up Visits

Participants will return to the NIH CC for in-person follow-up visits at Days 14 (± 3 days) and 180 (± 14 days) Participants will undergo the following procedures at each visit:

1. Physical exam with vital signs.
2. Review of concomitant medications.
3. Assessment of AEs and injection site.
4. Review of diary card (Day 14 only).
5. SCORAD as an eczema severity score (for participants with AD-HIES only).
6. Detailed history of *Staphylococcus* and *Candida* infections requiring treatment (eg, additional medications, drainage) since prior visit.
7. Collection of blood for ELISA for anti-rAls3 IgG and IgA1 and potential other research laboratory evaluations.
8. Collection of saliva and/or vaginal secretions for research evaluations: ELISA for anti-rAls3 IgG and IgA1; in vitro killing assay of *C albicans.* Vaginal secretion collection is optional.
9. Collection of stool, skin swab, and oral, nasal, and vaginal mucus may be collected for research evaluations: culture and PCR for *Candida sp* and *S aureus*; microbiome analysis (stool and oral and vaginal mucus only). Vaginal secretion collection and stool samples are optional.
10. Pregnancy test (Day 14 only).
11. Harvesting of PBMCs for research laboratory evaluations to be performed by CHI:
    a. Cryopreservation of PBMCs after vaccination
    b. Collection of PBMC DNA for potential genetic testing
    c. Whole transcriptome sequencing of PBMCs
    d. Multiplex assays for inflammatory markers
    e. Flow cytometry of PBMCs for immunophenotyping and activation status after vaccination

The participant will be given a memory aid on Day 14 to take home for tracking suspected vaccine-related AEs for the remainder of the study. This memory aid will facilitate accurate AE assessment at the monthly phone calls (see below).

Participants will be strongly encouraged to return to the NIH CC for a follow-up visit on Day 42 (± 7 days), although this visit is optional. AEs will be assessed and serum will be collected for ELISA for anti-rAls3 IgG and IgA1. If traveling to the NIH CC is inconvenient for the participant but they still want to provide samples for this time point, then blood can be drawn from their doctor or local laboratory (eg, Quest Diagnostics) and shipped to the study team.

At Days 30, 60, 90, 120, and 150 (± 3 days), the study team will contact the participant by phone to assess AEs, conduct a concomitant medication review, and assess any infections the participant has experienced in the interim.

Participants and investigators may schedule additional in-person visits to the NIH CC during the 6-month post-vaccination period for evaluation and care of suspected vaccine-related AEs.

Study participation ends after the Day 180 visit.

6.5 Early Termination Visit

All effort will be made to conduct an early termination visit for participants who withdraw from the study. This visit will include all of the procedures performed at the normal end-of-study visit.

6.6 Pregnancy and Follow-up Visit

If a participant becomes pregnant during the course of the study after they receive the vaccine, then they may continue follow-up visits as normal. Blood for research evaluations will not be collected. The study team will ask the participant to notify them of the pregnancy outcome including the weeks of gestation, and pregnancy and birth complications.

7 Potential Risks and Benefits

7.1 Potential Risks

NDV-3A vaccine: The precursor of the study vaccine (NDV-3) has been given to 109 healthy adults and the study vaccine (NDV-3A) has been given to 89 adult women with recurrent VVC in 3 previous clinical trials via IM injection at the same dose to be used in this study. In all studies, the vaccine was well tolerated, and the most common AEs were mild injection site complaints (eg, erythema, induration, pain, and swelling). Systemic AEs included diarrhea, nausea, fatigue, myalgia, and headache. All AEs resolved on their own without sequelae.

The study vaccine was also administered at a lower dose level (30-µg rAls3) in 2 clinical studies. Fifteen subjects received an IM dose with AlOH and experienced similar local and systemic reactions as seen with the 300-µg dose. The vaccine at 30-µg rAls3 without AlOH was also administered ID to 40 subjects, which resulted in a higher incidence of local site and systemic AEs compared to IM injection.

There may be additional risks to NDV-3A that are currently unknown.

Blood draw: The risks of drawing blood include pain, bruising, bleeding, and, rarely, fainting or infection. The amount of blood drawn for research purposes will be within the limits allowed for adult research subjects by the NIH CC (Medical Administrative Policy 95-9, Guidelines for Limits of Blood Drawn for Research Purposes in the Clinical Center: http://cc-internal.cc.nih.gov/policies/PDF/M95-9.pdf).

Genetic Testing: Genetic testing, which may include whole genome, transcriptome, and/or exome sequencing, may be done on collected specimens in an effort to identify genetic components of these diseases and syndromes. Results of genetic testing may have psychological implications for participants such as revelations regarding future health risks, incurable conditions, and/or information contradictory to stated biological relationships. Genetics counseling and advice is available from the NIH to help participants with the implications of findings, where appropriate.

Further testing may be performed on gene variants that are discovered, principally those that are the focus of the main objective of this protocol that have unknown functions or that are believed to have health implications. Depending on how much information is known about a particular gene, such testing may take several years to complete. The results of this testing may require examination in other subjects with immune disorders or may require additional tests to be performed on relatives, particularly parents and siblings. As new information becomes available, existing sequencing data may require reexamination. Genetic counseling and clinical genetics consultation is available at the NIH CC to help patients with the implications of findings, where appropriate.

Following genetic testing, the data will be shared in a controlled-access public database for other investigators to benefit from it (eg, dbGaP, the Database of Genotypes and Phenotypes). However no personal, identifiable information will be shared in this process as the results will be identified only by a code.

Vaginal secretion collection: Vaginal secretions will be collected using a menstrual cup. Participants may experience pressure as the menstrual cup is inserted into the vaginal cavity. The participant should not feel any discomfort during the secretion collection. The test is usually not painful. There is a risk of dislodging an IUD with the menstrual cup, so vaginal fluid collection will NOT be done in participants with IUDs. There is also a risk of toxic shock syndrome when the menstrual cup is left in the vaginal cavity for more than 12 hours. Participants will be instructed to remove the menstrual cup after 1 to 2 hours.

Collection of saliva, skin swab, stool, and oral/nasal/vaginal mucus: Collection of these samples may cause mild discomfort or irritation but there are otherwise no risks associated with collection of these samples.

7.2 Potential Benefits

Participants may not directly benefit from involvement in this study. The information gathered in this study may improve the investigators' understanding of the safety, tolerability, and immunogenicity of the NDV-3A vaccine, and its potential use as a prophylactic against infection from *Candida sp* and *S aureus*.

8 Research Use of Stored Human Samples, Specimens, or Data

Intended Use: Samples and data collected under this protocol may be used to study the safety and immunogenicity of the NDV-3A vaccine. Genetic testing may be performed. A separate signed informed consent document will be obtained for any other research not described in this protocol.

Storage: Access to stored samples will be limited using either a locked room or a locked freezer. Samples and data will be stored using codes assigned by the investigators. Data will be kept in password-protected computers. Only investigators will have access to the samples and data.

Tracking: Samples and data will be tracked using a code that only the study team can trace back to the participants. Clinical data will be entered into CRIMSON.

Disposition at the Completion of the Protocol:

In the future, other investigators (both at NIH and outside) may wish to study these samples and/or data. IRB approval must be sought prior to any sharing of any samples and/or data. Any clinical information shared about the sample would similarly require prior IRB approval. The research use of stored, unlinked, or unidentified samples or data may be exempt from the need for prospective IRB review and approval. Exemption requests will be submitted in writing to the NIH Office of Human Subjects Research Protections, which is authorized to determine whether a research activity is exempt.

At the time of protocol termination, samples will either be destroyed, or after IRB approval, transferred to another existing protocol. Data will be archived by the study team in compliance with requirements for retention of research records; alternatively, after IRB and study sponsor approval, the data may be either destroyed or transferred to another repository.

Reporting the Loss or Destruction of Samples/Specimens/Data to the IRB:

Any loss or unanticipated destruction of samples (for example, as the result of freezer malfunction) or data (for example, misplacing a printout of data with identifiers) that meets the definition of protocol deviation or unanticipated problem (UP) and/or compromises the scientific integrity of the data collected for the study will be reported to the NIAID IRB.

Participants may decide at any point not to have their samples stored. In this case, the PI will destroy all known remaining samples and report what was done to both the participant and to the IRB. This decision will not affect the participant's involvement in this protocol or any other protocols at NIH.

9 Data Sharing Plan

Human data generated in this study will be shared for future research as follows:

- Identified data in the Biomedical Translational Research Information System (BTRIS, automatic for activities in the NIH CC).
- Data sharing may be complicated or limited in certain cases by contractual obligations or agreements with outside collaborators, such as Cooperative Research and Development Agreements, Clinical Trial Agreements, other restraints, etc.

Data will be shared through the following means:

- BTRIS (automatic for activities in the CC).
- Approved outside collaborators under appropriate individual agreements.
- Publication and/or public presentations.

Data will be shared before publication/at the time of publication or shortly thereafter.

10 Remuneration Plan for Participants

Participants will receive compensation as follows:

Visit	**Compensation**
Screening	$40
First baseline (Day −3 to −1)	$100
Second baseline/vaccine administration (Day 0)	$100
Day 1	$60
Day 2	$30
Day 14	$170
Day 42	$50
Day 180	$130
Maximum total	**$680**

Because collections of vaginal mucus and secretions are optional, participants will receive an additional $20 per applicable visit if they provide these samples. These samples are collected at one of the baseline visits and Days 14 and 180, so the maximum additional compensation is $60.

11 Assessment of Safety

11.1 Definitions

Adverse Event: An AE is any untoward or unfavorable medical occurrence in a human research participant, including any abnormal sign (eg, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the participant's participation in the research, whether or not considered related to the research.

Adverse Reaction (AR): An AE that is caused by an investigational agent (drug or biologic).

Suspected Adverse Reaction (SAR): An AE for which there is a reasonable possibility that the investigational agent caused the AE. "Reasonable possibility" means that there is evidence to suggest a causal relationship between the drug and the AE. An SAR implies a lesser degree of certainty about causality than AR, which implies a high degree of certainty.

Serious Adverse Event: An SAE is an AE that results in one or more of the following outcomes:

- death
- a life-threatening event (places the participant at immediate risk of death from the event as it occurred)
- an inpatient hospitalization or prolongation of an existing hospitalization
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- a congenital anomaly/birth defect
- a medically important event*

*Medical and scientific judgment should be exercised in deciding events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the other outcomes listed above.

Unexpected Adverse Event: An AE is unexpected if it is not listed in the Investigator's Brochure or is not listed at the specificity or severity that has been observed. It is the responsibility of the Investigational New Drug (IND) sponsor to make this determination.

Serious and Unexpected Suspected Adverse Reaction (SUSAR): A SUSAR is an SAR that is both serious and unexpected.

Unanticipated Problem (UP): Any incident, experience, or outcome that meets all three of the following criteria:

1. unexpected in terms of nature, severity, or frequency in relation to
   a. the research risks that are described in the IRB-approved research protocol and informed consent document; Investigator's Brochure or other study documents; and
   b. the characteristics of the subject population being studied
2. related or possibly related to participation in the research
3. suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Serious Unanticipated Problem: A UP that meets the definition of an SAE or compromises the safety, welfare or rights of subjects or others.

Unanticipated Problem that is not an Adverse Event (UPnonAE): A UP that does not fit the definition of an AE, but which may, in the opinion of the investigator, involve risk to the subject, affect others in the research study, or significantly impact the integrity of research data. Such events would be considered non-serious UPs. For example, we will report occurrences of breaches of confidentiality, accidental destruction of study records, or unaccounted-for study drug.

Protocol Specified Events: Protocol specified events are AEs specified in the protocol that the PI, IND sponsor, or medical monitor would like to review in real time rather than weeks or months later when they would otherwise appear in various line listings. These events may or may not also be SAEs.

11.2 Documenting, Recording, and Reporting Adverse Events

All AEs occurring from the time the informed consent is signed through the final study visit will be documented, recorded, and reported.

At each contact with the participant, information regarding AEs will be elicited by appropriate questioning and examinations and will be:

- immediately documented in the participant's medical record/source document
- recorded in CRIMSON
  AND
- reported as outlined below (eg, IND sponsor, IRB, and Food and Drug Administration [FDA])

If a diagnosis is clinically evident (or subsequently determined), then the diagnosis rather than the individual signs and symptoms or lab abnormalities will be recorded as the AE.

A laboratory abnormality will not be reported as an AE if ALL of the following criteria are met:

- It is no more than "Grade 1" or "Mild" per the protocol-specified toxicity table (or investigator assessment if not listed on the table); AND
- It does NOT require an intervention (eg, discontinuation of treatment, dose reduction/delay, additional assessments, or treatment); AND
- It is assessed by the PI as NOT related to the study agent(s); AND
- It is assessed by the PI as NOT clinically significant (eg, the abnormal value does NOT suggest a disease or organ toxicity).

All abnormal laboratory findings will be reviewed on a routine basis by the PI to identify potential safety signals. An abnormal lab not included on the toxicity table should be assessed in a similar fashion to the criteria above and per toxicity table guidelines "Instructions for Use."

11.3 Investigator Assessment of Adverse Events

The investigator will assess all AEs with respect to seriousness (criteria listed above), severity (intensity or grade), and causality (relationship to study agent and relationship to research) according to the following guidelines.

11.3.1 Severity

The Investigator will grade the severity of each AE according to the "Division of Aids Table for Grading the Severity of Adult and Pediatric Adverse Events" Version 2.0, November 2014, which can be found at:
http://rsc.tech-res.com/document/safetyandpharmacovigilance/daids_ae_grading_table_v2_nov2014.pdf

Some Grade 1 lab parameters on the DAIDS Toxicity Table (fibrinogen, potassium [low], uric acid [males only, elevated]) fall within the NIH lab reference range for normal values. These normal values will not be reported as Grade 1 AEs. The Grade 1 values for these tests will be reported as follows:

- Fibrinogen: 100-176 mg/dL
- Potassium (low): 3.0-3.3 mmol/L
- Uric acid (males): 8.7-10.0 mg/dL
- Magnesium (low): 0.60-0.65 mmol/L

11.3.2 Causality

Causality (likelihood that the event is caused by the study agent) will be assessed considering the factors listed under the following categories:

Definitely Related

- reasonable temporal relationship
- follows a known response pattern
- clear evidence to suggest a causal relationship
- there is no alternative etiology

Probably Related

- reasonable temporal relationship
- follows a suspected response pattern (based on similar agents)
- no evidence of a more likely alternative etiology

Possibly Related

- reasonable temporal relationship
- little evidence for a more likely alternative etiology

Unlikely Related

- does not have a reasonable temporal relationship
  OR
- good evidence for a more likely alternative etiology

Not Related

- does not have a temporal relationship
  OR
- definitely due to an alternative etiology

Note: Other factors should also be considered for each causality category when appropriate. Causality assessment is based on available information at the time of the assessment of the AE. The investigator may revise the causality assessment as additional information becomes available.

11.4 Investigator Reporting Responsibilities to the Sponsor

11.4.1 Adverse Events

AE data will be submitted to the IND sponsor when requested for periodic safety assessments, review of IND annual reports, review of IND safety reports, and preparation of final study reports.

11.4.2 Reactogenicity

Specified solicited reactogenicity to vaccination will be evaluated per Table 1 below:

Table 1 Evaluation of Vaccine Reactogencity

Local Reaction to Injectable Product	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Erythema/Redness[a]	1.0-4.0 cm	4.1-8.0 cm	> 8.0 cm	Necrosis or exfoliative dermatitis
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Induration[b]	1.0-4.0 cm and does not interfere with activity	4.1-8.0 cm or interferes with activity	> 8.0 cm or prevents daily activity	Necrosis (regardless of size of induration)
Swelling[b]	1.0-4.0 cm and does not interfere with activity	4.1-8.0 cm or interferes with activity	> 8.0 cm or prevents daily activity	Necrosis (regardless of size of swelling)

ER = emergency room.
a In addition to grading the measure local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.
b Induration/swelling should be evaluated and grated using the functional scale as well as the actual measurement.

11.4.3 Serious Adverse Events

All SAEs (regardless of relationship and whether or not they are also UPs) must be reported on the Safety Expedited Report Form (SERF) and sent to the Clinical Safety Office (CSO) by fax or e-mail attachment. Deaths and immediately life-threatening SAEs must be reported to the CSO within 1 business day after the site becomes aware of the event. All other SAEs must be reported within 3 business days of site awareness.

CSO CONTACT INFORMATION:

Clinical Safety Office
5705 Industry Lane
Frederick, MD 21704
Phone: 301-846-5301
Fax: 301-846-6224
E-mail: rchspsafety@mail.nih.gov

SAEs that have not resolved by the end of the follow-up period are followed until final outcome is known. If it is not possible to obtain a final outcome for an SAE (eg, the participant is lost to follow-up), the reason a final outcome could not be obtained will be recorded by the investigator in CRIMSON and the SERF.

SAEs that occur after the 6-month follow-up period that are reported to and are assessed by the investigator to be possibly, probably, or definitely related to study drug must be reported to the CSO.

11.4.4 Unanticipated Problems

UPs that are also AEs must be reported to the CSO by fax or e-mail attachment using the NIH Problem Report Form no later than 7 calendar days of site awareness of the event. UPs that are not AEs are not reported to the CSO.

11.4.5 Pregnancy

All pregnancies will be reported on the Pregnancy Notification/Outcome Form to the CSO within 1 business day from site awareness.

Pregnancy outcome data (eg, delivery outcome, spontaneous or elective termination of the pregnancy) will be reported to the CSO within 3 business days of the site's awareness.

Although pregnancy itself is not an AE, events that meet SAE criteria during pregnancy, delivery, or in the neonate (eg, congenital anomaly/birth defect) are reportable on the SERF.

In the event of pregnancy after administration of the vaccine, the following steps will be taken:

- Continue the study visits, but blood for research evaluations will not be drawn.
- Report to the SMC and/or the IRB.
- Advise participant to notify the obstetrician of study participation and study agent exposure.

11.5 Investigator Reporting Procedures to the NIAID IRB

11.5.1 Definitions

Protocol Deviation: Any change, divergence, or departure from the IRB-approved study procedures in a research protocol. Protocol deviations are designated as serious or non-serious and further characterized as:

1. Those that occur because a member of the research team deviates from the protocol.
2. Those that are identified before they occur, but cannot be prevented.
3. Those that are discovered after they occur.

Serious Protocol Deviation: A deviation that meets the definition of an SAE or compromises the safety, welfare, or rights of subjects or others.

Non-compliance: The failure to comply with applicable NIH Human Research Protections Program (HRPP) policies, IRB requirements, or regulatory requirements for the protection of human subjects. Non-compliance is further characterized as:

1. Serious: non-compliance that:
   a. increases risks, or causes harm, to participants;
   b. decreases potential benefits to participants;
   c. compromises the integrity of the NIH HRPP; or
   d. invalidates the study data.
2. Continuing: non-compliance that is recurring.
3. Minor: non-compliance that is neither serious nor continuing.

11.5.2 Expedited Reporting to the NIAID IRB

Serious and non-serious UPs, deaths, serious deviations, and serious or continuing non-compliance will be reported within 7 calendar days of investigator awareness. SAEs that are possibly, probably, or definitely related to the research will be reported to the NIAID IRB within 7 calendar days of investigator's awareness, regardless of expectedness.

11.5.3 Waiver of Reporting Anticipated Protocol Deviations, Expected UPnonAEs, and Deaths to the NIAID IRB

Anticipated deviations in the conduct of the protocol will not be reported to the IRB unless they occur at a rate greater than anticipated by the study team. Deaths unrelated to any research procedures will be reported at the time of continuing review.

11.5.4 Annual Reporting to the NIAID IRB

The following items will be reported to the NIAID IRB in summary at the time of continuing review:

- Serious and non-serious UPs.
- Expected SAEs that are possibly, probably, or definitely related to the research.
- SAEs that are not related to the research.
- All AEs
- Serious and non-serious protocol deviations.
- Serious, continuing, and minor non-compliance.
- Any trends or events which in the opinion of the investigator should be reported.

11.6 Sponsor's Reporting Responsibilities

SUSARs, as defined in Title 21 of the United States Code of Federal Regulations (CFR) Part 312.32 and determined by the IND sponsor, will be reported to FDA and all participating investigators as IND Safety Reports.

The IND sponsor will also submit an IND Annual Report of the progress of the investigation to the FDA as defined in 21 CFR 312.33.

11.7 Halting Rules for the Protocol

Halting the study requires immediate discontinuation of study agent administered for all participants and suspension of enrollment until a decision is made whether or not to continue enrollment and study agent administration.

The halting rules are:

- 1 or more subjects experience the same or similar SAEs that are unexpected and possibly, probably, or definitely related to the study agent;
  OR
- 2 or more of the same or similar AE in different subjects that are grade 3 or above and are unexpected and possibly, probably, or definitely related to the study agent;
  OR
- any safety issue that the PI and/or the CSO determines should halt the study.

The PI and/or CSO will determine if the study should be halted. In addition, the FDA, IRB, or SMC may halt the study at any time following review of any safety concerns.

11.7.1 Reporting a Study Halt

If a halting rule is met, a description of the AE(s) or safety issue must be reported by the PI within 1 business day to the CSO, the IRB, the SMC, and NovaDigm by fax or email.

11.7.2 Resumption of a Halted Study

The IND sponsor, in collaboration with the PI and the SMC will determine if it is safe to resume the study. The PI will notify the IRB of the decision on resumption of the study.

11.8 Withdrawal Criteria for an Individual Participant

An individual participant will be withdrawn for any of the following:

- An individual participant's decision. (The investigator should attempt to determine the reason for the participant's decision.)
- Non-compliance with study procedures to the extent that it is potentially harmful to the participant or to the integrity of the study data.
- A change in the participant's baseline condition after enrollment but prior to vaccination so that the participant no longer meets the following exclusion criteria:
  - Has a history of clinically significant allergy including anaphylaxis or other serious reaction to food, vaccines, or other drugs, that in the opinion of the investigator, might put the participant at undue risk.
  - Has an active infection (such as S *aureus* abscess, pneumonia, or acute *Candida* mucocutaneous infection). Baseline state of chronic infections will be considered by the PI (eg, chronic *Pseudomonas* infection in lung).
  - Has received or planning to receive any other live vaccine within three weeks before vaccination or for three weeks after vaccination.
  - Has any of the following laboratory abnormalities:
    - ALT, AST, and ALP > 3 times the ULN
    - Total bilirubin level > 2.5 times the ULN
    - Serum creatinine level > 2 times the ULN
    - Absolute neutrophil count < 500 cells/μL
    - Hemoglobin < 9 mg/dL
    - Platelet count < 100,000
- The investigator determines that continued participation in the study would not be in the best interest of the participant.

11.8.1 Replacement of Withdrawn Participant

Only withdrawn participants who have not yet received the study vaccine will be replaced.

11.9 Safety Oversight

11.9.1 Safety Review and Communications Plan

A Safety Review and Communications Plan (SRCP) has been developed for the protocol. The SRCP is an internal communications document between the PI and the CSO, which delineates the safety oversight responsibilities of the PI, the CSO, and other stakeholders. The SRCP also includes the overall plan for conducting periodic safety surveillance assessments.

11.9.2 Sponsor Medical Monitor

A medical monitor, representing the IND sponsor (OCRPRO), has been appointed for oversight of safety in this clinical study. The Sponsor Medical Monitor will be responsible for performing safety assessments as outlined in an SRCP.

11.9.3 Safety Monitoring Committee

An independent SMC consisting of three individuals will review the study prior to initiation and at a specified time agreed upon by the SMC. The SMC will focus on participant safety and will include subject matter experts. The independent experts do not have direct involvement in the conduct of the study and have no significant conflicts of interest as defined by NIAID policy.

Before each SMC review, the PI will submit data as requested by the SMC. After each SMC review, a recommendation as to whether the study is to continue, be modified, or be terminated will be provided in a summary report. All SAEs, all UPs, and all IND Safety Reports will be reported by the PI to the SMC at the same time they are submitted to the IRB or IND sponsor. The SMC will be notified immediately if pausing or halting rules are met, and the SMC will provide a recommendation for continuation, modification, or termination of the study. The PI will submit the written SMC summary reports with recommendations to their IRB.

12 Site Monitoring Plan

According to the International Council on Harmonisation (ICH) E6(R1) Good Clinical Practice (GCP) guidelines (section 5.18) and 21 CFR 312.50, clinical protocols are required to be adequately monitored by the study sponsor. This study monitoring will be conducted according to the "NIAID Intramural Clinical Monitoring Guidelines." Monitors under contract to OCRPRO/NIAID will visit the clinical research site to monitor aspects of the study in accordance with the appropriate regulations and the approved protocol. The objectives of a monitoring visit will be: 1) to verify the existence of signed informed consent documents and documentation of the consent process for each monitored participant; 2) to verify the prompt and accurate recording of all monitored data points, and prompt reporting of all SAEs; 3) to compare CRIMSON data abstracts with individual participants' records and source documents

(participants' charts, laboratory analyses and test results, physicians' progress notes, nurses' notes, and any other relevant original subject information); and 4) to help ensure investigators are in compliance with the protocol. The monitors also will inspect the clinical site regulatory files to ensure that regulatory requirements (Office for Human Research Protections [OHRP]), FDA, and applicable guidelines (ICH GCP) are being followed. During the monitoring visits, the investigator (and/or designee) and other study personnel will be available to discuss the study progress and monitoring visit.

The investigator (and/or designee) will make study documents (eg, consent forms, CRIMSON data abstracts) and pertinent hospital or clinical records readily available for inspection by the IRB, the FDA, the site monitors, and the NIAID staff for confirmation of the study data.

A specific protocol monitoring plan will be discussed with the PI and study staff prior to enrollment. The plan will outline the frequency of monitoring visits based on such factors as study enrollment, data collection status, and regulatory obligations.

13 Statistical Considerations

13.1 Study Hypotheses

NDV-3A will increase anti-Als3 antibody titers from baseline in AD-HIES patients as well as healthy volunteers.

13.2 Sample Size Justification

In this design, a positive response is a 4-fold increase in vaccine-specific IgG from baseline 2 weeks post-vaccination. We assume that we are only interested in exploring NDV-3A further in AD-HIES patients if the response rate is higher than 45%. We will perform a single-arm 2-stage design where there will be 0.9 probability of concluding NDV-3A has activity if the true response rate is 75% and where there will be probability 0.1 of concluding NDV-3A is active when in fact the true response rate is 45%.

13.3 Description of the Analyses

- Safety Analysis: Tables of the proportions of patients with AE's and the grade of AE will be reported.
- Immunogenicity Analysis: At the end of the study if 12 or more (out of 20) positive responses are observed the drug will have shown adequate activity to be considered for further investigation.

13.4 Secondary Endpoints

The following additional secondary endpoints will be examined:

1. Cellular response to vaccine as determined by IFN-γ and IL-17A production by PBMCs after stimulation with rAls3 in AD-HIES affected patients and healthy volunteers.
2. Anti-rAls3 antibody titers at 6 months after vaccination in patients with AD-HIES and healthy volunteers.

14 Ethics/Protection of Human Subjects

14.1 Informed Consent Process

Informed consent is a process where information is presented to enable persons to voluntarily decide whether or not to participate as a research participant. It is an ongoing conversation between the human research participant and the researchers that begins before consent is given and continues until the end of the participant's involvement in the research. Discussions about the research will provide essential information about the study and include purpose, duration, experimental procedures, alternatives, risks, and benefits. Participants will be given the opportunity to ask questions and have them answered.

The participants will sign the informed consent document before undergoing any research procedures. The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The researcher will document the signing of the consent form in the participant's medical record. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

14.1.1 Non–English-Speaking Participants

If a non–English-speaking participant is unexpectedly eligible for enrollment, then the participant will be provided with the CC Short Written Consent Form for Non–English-Speaking Research Participants in the participant's native language and a verbal explanation of the purpose, procedures, and risks of the study as described in Medical Administrative Series Policy M77-2, NIH HRPP SOP 12, and 45 CFR 46.117(b)(2). The IRB-approved English consent form will serve as basis for the verbal explanation of the study. The investigator will obtain an interpreter unless the investigator is fluent in the prospective participant's language. Preferably, the interpreter will be someone who is independent of the participant (ie, not a family member). Interpreters provided by the CC will be used whenever possible. The interpreter will interpret all oral communications (English to target language and conversely) between the investigator and a limited-English-proficient participant, facilitate discussions, and clarify information as necessary.

The IRB-approved English consent form will be signed by the investigator obtaining consent and a witness to the oral presentation. The CC Short Written Consent Form will be signed by the participant and a witness who observed the presentation of information. The interpreter may sign

the consent document as the witness and, in this case, will note "Interpreter" under the signature line. A copy of both signed forms will be provided to the participant to take home.

The investigator obtaining consent will document the consent process in the participant's medical record (CRIMSON), including the name of the interpreter. Further, all instances of use of the CC Short Written Consent Form will be reported to the IRB at the time of annual review. If the CC Short Written Consent Form is used three times or more for the same language, this will be reported to the IRB immediately.

14.2 Participant Confidentiality

All records will be kept confidential to the extent provided by federal, state, and local law. The study monitors and other authorized representatives of the sponsor may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records. Records will be kept locked and all computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by IRB, the FDA, NIAID, OHRP, the pharmaceutical supporter, or the sponsor's designee.

15 Data Handling and Record Keeping

15.1 Data Capture and Management

Study data will be maintained in CRIMSON and collected directly from subjects during study visits and telephone calls, or will be abstracted from subjects' medical records. Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary to confirm the data abstracted for this study. Data entry into CRIMSON will be performed by authorized individuals. The investigator is responsible for assuring that the data collected are complete, accurate, and recorded in a timely manner.

15.2 Record Retention

The investigator is responsible for retaining all essential documents listed in the ICH GCP guidelines. The PI will maintain study records according to the timelines specified in 21 CFR 312.62 or at a minimum of 5 to 7 years and in compliance with institutional, IRB, state, and federal medical records retention requirements, whichever is longest. All stored records will be kept confidential to the extent required by federal, state, and local law.

Should the investigator wish to assign the study records to another party and/or move them to another location, the investigator will provide written notification of such intent to OCRPRO/NIAID with the name of the person who will accept responsibility for the transferred

records and/or their new location. Destruction or relocation of research records will not proceed without written permission from OCRPRO/NIAID.

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Appendix A: Schedule of Procedures/Evaluations

Evaluation	Study day											Early termination visit
	Screening (−28 to baseline)	**Baseline (−3 to -1 and 0)[a]**	**Post-Vaccine (1 to 2)**	**14 (± 3)**	**30[b] (± 3)**	**42[c] (± 7)**	**60[b] (± 3)**	**90[b] (± 3)**	**120[b] (± 3)**	**150[b] (± 3)**	**180 (± 14)**	
Informed consent	X											
Medical history	X[d]	X										
Urine drug screening	X[d]											
Assessment of AEs			X	X	X	X	X	X	X	X	X	X
Vaccination		X[e]										
Physical exam[f]	X[d]	X	X	X							X	X
Review of concomitant medications	X[d]			X	X		X	X	X	X	X	X
Blood for screening[g]	X[d]											
History of Staph and *Candida* infections		X		X							X	X
SCORAD assessment for eczema[h]		X		X							X	X
Diary card[i]				X								
Research blood[j]		X	X[k]	X		X					X	X
Saliva/vaginal secretions[l]		X		X							X	X
Stool, skin swab, oral/nasal/vaginal mucus[l]		X		X							X	X
Research blood draw for CHI labs[m]		X[n]		X							X	X
Serum pregnancy test	X[o]	X[p]		X								

AE = adverse event; PBMC = peripheral blood mononuclear cell; SCORAD = SCORing of atopic dermatitis.

a Unless otherwise noted, baseline procedures will be conducted at only one of the visits, and will be scheduled depending on the investigators' and participant's convenience.

b Evaluations on Days 30, 60, 90, 120, and 150 will be conducted over the phone.

c Visit at Day 42 is optional and can be performed remotely (ie, blood is shipped from doctor or laboratory to NIH) at the convenience of the participant.

d All healthy volunteers will undergo this screening evaluation. For participants with AD-HIES, this screening evaluation will only be conducted if it has not been done under the referring protocol (#00-I-0159) within 28 days before screening.

e Vaccine administration will be conducted on Day 0 after all baseline evaluations are complete.

f Complete physical exam with vital signs.

g Blood for screening is for hepatitis B, hepatitis C, and HIV testing; acute, hepatic, and mineral panels; prothrombin/partial thromboplastin time; complete blood count with differential; lymphocyte flow cytometry; and serum immunoglobin quantitation.

h For participants with AD-HIES only.

i Diary card for recording of post-vaccination reactions will be provided to the participant on Day 0 after they receive the vaccination. The participant will fill out the diary card through Day 14 and then return it to the study team on Day 14.

j Uses of research blood will include but are not limited ELISA for anti-rAls3 IgG and IgA1.

k Day 1 only, for storage of PBMCs, serum, and RNA.

l Vaginal and stool samples are optional. Skin, oral, and nasal may be collected.

m PBMCs will be harvested from whole blood and transferred to the Center for Human Immunology, Autoimmunity and Inflammation (CHI) for storage and analysis. Research tests on PBMCs may include but are not limited to genetic testing, whole transcriptome sequencing, multiplex assays for inflammatory markers, and immunophenotyping.

n Both baseline visits.

o Test must be negative to confirm eligibility.

p Day 0 only. Test must be negative before administration of the vaccine.

Appendix B: Blood Draw Volumes

Evaluation	Study day						
	Screening (−28 to baseline)	**Baseline 1 (−3 to −1)**	**Baseline 2 (0)**	**Post-Vaccine (1)**	**14 (± 3)**	**42[a] (± 7)**	**180 (± 14)**
	Blood draw volume (mL)						
Hepatitis B and C and HIV testing	6[b]						
Chemistry panels (acute, hepatic, and mineral)	4[b]						
PT/PTT	4.5[b]						
CBC with differential	3[b]						
Lymphocyte flow cytometry	5[b]						
Serum immunoglobin quantitation	4[b]						
Serum pregnancy testing	4		4		4		
Serum for ELISA		5[c]		4	5	5	5
PBMCs for cryopreservation, DNA, and flow cytometry		20	20	30	40		30
PBMCs for whole transcriptome sequencing		2.5	2.5	2.5	2.5		2.5
PBMCs for multiplex assays		4	4		4		4
Daily Volume	30.5	51.5	40.5	16.5	55.5	5	41.5
Cumulative Volume	30.5	82.0	122.5	139.0	194.5	199.5	241.0

CBC = complete blood count; CHI = Center for Human Immunology, Autoimmunity and Inflammation; ELISA = enzyme-linked immunosorbent assay; PBMC = peripheral blood mononuclear cell; PT/PTT = prothrombin time/partial thromboplastin time.

a Visit at Day 42 is optional.

b All healthy volunteers will undergo this screening evaluation. For participants with autosomal-dominant hyper-IgE syndrome, this screening evaluation will only be conducted if it has not been done under the referring protocol (#00-I-0159) within 28 days before screening.

c Serum will be collected at only one of baseline visits, depending on the convenience of the participant and investigators.