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A Non-inferiority Trial to Compare MVA-BN® Smallpox Vaccine to ACAM2000®



The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Read our [disclaimer](#) for details.

ClinicalTrials.gov Identifier: NCT01913353

- [Recruitment Status ⓘ](#) : Completed
- [First Posted ⓘ](#) : August 1, 2013
- [Results First Posted ⓘ](#) : December 5, 2019
- [Last Update Posted ⓘ](#) : December 5, 2019

- Sponsor:**
 - Bavarian Nordic
- Collaborator:**
 - US Army Medical Research Institute of Infectious Diseases
- Information provided by (Responsible Party):**
 - Bavarian Nordic

- Study Details
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Tracking Information	
First Submitted Date ⓘ	July 26, 2013
First Posted Date ⓘ	August 1, 2013

Results First Submitted Date ICMJE	November 18, 2019
Results First Posted Date ICMJE	December 5, 2019
Last Update Posted Date	December 5, 2019
Actual Study Start Date ICMJE	March 2015
Actual Primary Completion Date	March 2017 (Final data collection date for primary outcome measure)
Current Primary Outcome Measures ICMJE (submitted: November 18, 2019)	- Plaque Reduction Neutralization Test (PRNT) Geometric Mean Titer (GMT) at the Peak Visits [Time Frame: Day 42 for Group 1 and Day 28 for Group 2] GMT based on vaccinia-specific PRNT. Titers below the detection limit are included with a value of 1. - Maximum Lesion Area (MLA) in mm² After Scarification With ACAM2000® [Time Frame: Day 6-8, 13-15 after 3rd Vaccination for Group 1 and Day 6-8, 13-15 after 1st vaccination for Group 2] The MLA was defined as the maximum of two measurements: the lesion area measured on Day 6-8 (after scarification) or the lesion area measured on Day 13-15 (after scarification). This was measured using the SilhouetteConnect camera system, and confirmed by the Independent Take Review Committee (ITRC).
Original Primary Outcome Measures ICMJE (submitted: July 30, 2013)	Comparison of the take in Group 1 versus the take in Group 2 The correct measurement of the lesion area will be confirmed by a blinded Independent Take Review Committee (ITRC). [Time Frame: Day 6-8 and day 13-15, respectively and healing time up to 2 weeks after scarification with ACAM2000®.] Comparison of the take in Group 1 versus the take in Group 2 using a composite endpoint measuring the area of lesion in mm² at day 6-8 and day 13-15, respectively and healing time (i.e. number of days until scab separates from the skin) after scarification with ACAM2000®. The correct measurement of the lesion area will be confirmed by a blinded Independent Take Review Committee (ITRC).
Change History	Complete list of historical versions of study NCT01913353 on ClinicalTrials.gov Archive Site
Current Secondary Outcome Measures ICMJE (submitted: November 18, 2019)	- Investigator-measured Maximum Lesion Diameter (MLD) in mm After Scarification With ACAM2000 [Time Frame: Day 6-8 and Day 13-15 after ACAM2000 scarification] The MLD was defined as the largest major diameter measured across the lesion on Day 6-8 (after scarification) or Day 13-15 (after scarification) - Investigator-measured Lesion Diameter in mm at Day 6-8 After Scarification With ACAM2000 [Time Frame: Day 6-8 after ACAM2000 scarification] The lesion diameter at Day 6-8 was defined as the major lesion diameter measured on Day 6-8 (after scarification) - Investigator-measured Lesion Diameter in mm at Day 13-15 After Scarification With ACAM2000 [Time Frame: Day 13-15 after ACAM2000 scarification] The lesion diameter at Day 13-15 was defined as the major lesion diameter measured on Day 13-15 (after scarification) - Individual Take as Classified by a Blinded Independent Take Review Committee (ITRC) [Time Frame: Day 6-8 visit following ACAM2000 vaccination] Take was assessed as either full, partial, or absent take by the ITRC based on Day 6-8 evaluations following ACAM2000 vaccination using subject profiles that contained supportive data up to Day 14 following ACAM2000 vaccination (in accordance with the ITRC Charter). - Lesion Area in mm² at Day 6-8 After Scarification With ACAM2000 [Time Frame: Day 6-8 after ACAM2000 scarification] Lesion area was measured by the Investigator using the SilhouetteConnect camera system and confirmed by the blinded ITRC. - Lesion Area in mm² at Day 13-15 After Scarification With ACAM2000 [Time Frame: Day 13-15 after ACAM2000 scarification] Lesion area was measured by the Investigator using the SilhouetteConnect camera system and confirmed by the blinded ITRC. - Relationship to Vaccine of Any Serious Adverse Event (SAE) [Time Frame: Within 38 weeks for Group 1 and 30 weeks for Group 2] Presentation of SAEs by relationship to study vaccine - Intensity of Any Serious Adverse Event (SAE) [Time Frame: Within 38 weeks for Group 1 and 30 weeks for Group 2]

Presentation of SAEs by intensity

- Incidence of Any Cardiac Sign or Symptom Indicating a Case of Myo-/Pericarditis, i.e. Adverse Events of Special Interest (AESIs) [Time Frame: Within 38 weeks for Group 1 and 30 weeks for Group 2]

In this clinical trial, an AESI was defined as any cardiac sign or symptom developed since the first vaccination, any ECG changes determined to be clinically significant, or any cardiac enzyme results of Troponin I $\geq 2 \times$ ULN.

- Related Grade ≥ 3 Adverse Events [Time Frame: within 29 days after vaccination]

Incidence of any Grade 3 or 4 adverse events (AEs) possibly, probably, or definitely related to the vaccine. Pooled solicited (general only) and unsolicited AEs.

- Relationship to Vaccine of Any Non-serious AEs [Time Frame: within 29 days after vaccination]

Presentation of non-serious AEs by relationship to study vaccine

- Intensity of Any Non-serious AEs [Time Frame: within 29 days after vaccination]

Presentation of non-serious AEs by intensity

- Solicited General AEs [Time Frame: within 15 days after vaccination]

Occurrence, intensity and relationship of solicited general AEs (body temperature [fever], headache, myalgia [muscle pain], chills, nausea, fatigue, malaise)

- Incidence of Lymphadenopathy [Time Frame: within 29 days after vaccination]

Incidence of events of Lymphadenopathy. Pooled solicited and unsolicited events.

- Solicited Local AEs: Intensity [Time Frame: within 15 days after vaccination]

Incidence of solicited local AEs (pain, redness [erythema], swelling, induration, itching [pruritus])

- Major Lesion Size, Major Erythema, and Major Induration Diameter [Time Frame: Within 15 days after scarification with ACAM2000]

Daily measurement of major lesion size, major erythema, and major induration diameter (mm) based on physical appearance of vaccination site as documented in the memory aid. If the shape of the lesion, erythema [excludes lymphangitis], and induration observed was not round but rather asymmetrical, then the largest [or major] cross-sectional measurement was recorded.

- GMTs at the Peak Visits and Individual Peak Measured by Vaccinia-specific ELISA [Time Frame: within 8 weeks (for both groups)]

Peak Visit was defined as Day 42 for Group 1 and Day 28 for Group 2. Individual Peak was the maximum titer per subject from Visit 1 to Visit 7 (Week 8) in Group 1 and maximum titer from Visit 1 to Visit 6 (Week 8) in Group 2. Titers below the detection limit are included with a value of 1.

- GMTs at the Individual Peak Measured by Vaccinia-specific PRNT [Time Frame: within 8 weeks (for both groups)]

Individual Peak was the maximum titer per subject from Visit 1 to Visit 7 (Week 8) in Group 1 and maximum titer from Visit 1 to Visit 6 (Week 8) in Group 2. Titers below the detection limit are included with a value of 1.

- GMTs as Measured by Vaccinia-specific ELISA [Time Frame: within 12 weeks]

GMT based on vaccinia-specific ELISA. Titers below the detection limit are included with a value of '1'.

- GMTs as Measured by Vaccinia-specific PRNT [Time Frame: within 12 weeks]

GMT based on vaccinia-specific PRNT. Titers below the detection limit are included with a value of '1'.

- PRNT Seroconversion Rates at Peak Visits [Time Frame: Group 1 at Week 6; Group 2 at Week 4]

Seroconversion rate based on PRNT. Seroconversion is defined as the appearance of antibody titers "greater than or equal" detection limit (2) for initially seronegative subjects, or a doubling or more of the antibody titer compared to Baseline titer for initially seropositive subjects. Percentages based on number of subjects with data available.

	ELISA Seroconversion Rates at Peak Visits [Time Frame: Group 1 at Week 6; Group 2 at Week 4] Seroconversion rate based on ELISA. Seroconversion is defined as the appearance of antibody titers "greater than or equal" detection limit (50) for initially seronegative subjects, or a doubling or more of the antibody titer compared to Baseline titer for initially seropositive subjects. Percentages based on number of subjects with data available.
Original Secondary Outcome Measures ICMJE	<i>Not Provided</i>
Current Other Pre-specified Outcome Measures	<i>Not Provided</i>
Original Other Pre-specified Outcome Measures	<i>Not Provided</i>
Descriptive Information	
Brief Title ICMJE	A Non-inferiority Trial to Compare MVA-BN® Smallpox Vaccine to ACAM2000®
Official Title ICMJE	A Randomized, Open-label Phase III Non-inferiority Trial to Compare Indicators of Efficacy for MVA-BN® Smallpox Vaccine to ACAM2000® in 18-42 Year Old Healthy Vaccinia-naïve Subjects
Brief Summary	To demonstrate the efficacy of MVA-BN® in terms of vaccinia-specific Plaque Reduction Neutralization Test (PRNT) antibody response and by showing that vaccination prior to administration of ACAM2000® results in an attenuated take.
Detailed Description	To demonstrate the efficacy of MVA-BN® by assessing non-inferiority of MVA-BN® compared to ACAM2000® in terms of vaccinia-specific Plaque Reduction Neutralization Test (PRNT) antibody response at the Peak Visits (Day 42 for Group 1 and Day 28 for Group 2) and by showing that vaccination with MVA-BN® prior to administration of ACAM2000® results in an attenuation of take.
Study Type ICMJE	Interventional
Study Phase ICMJE	Phase 3
Study Design ICMJE	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Single (Outcomes Assessor) Primary Purpose: Prevention
Condition ICMJE	18-42 Year Old Healthy Vaccinia-naïve Subjects
Intervention ICMJE	- Biological: MVA BN® 0.5 ml MVA BN® with a nominal titer of 1x10E8 TCID50, administered as a subcutaneous injection Other Names: - IMVAMUNE - IMVANEX - Biological: ACAM2000® 0.0025 ml ACAM2000®, consisting of 2.5-12.5x10E5 plaque forming units of live vaccinia virus (VACV). Picked up with a bifurcated needle and administered by the percutaneous route (scarification) using 15 jabs of that bifurcated needle.
Study Arms ICMJE	Experimental: Group 1

	Two vaccinations; MVA BN®; administered 4 weeks apart (Day 0 and Day 28) followed by a single vaccination of ACAM2000® vaccine 4 weeks after the second MVA BN® vaccination (Day 56). Interventions: ○ Biological: MVA BN® ○ Biological: ACAM2000® • Active Comparator: Group 2 A single vaccination of ACAM2000® will be administered at Day 0. Intervention: Biological: ACAM2000®
Publications *	Pittman PR, Hahn M, Lee HS, Koca C, Samy N, Schmidt D, Hornung J, Weidenthaler H, Heery CR, Meyer TPH, Silbernagl G, MacLennan J, Chaplin P. Phase 3 Efficacy Trial of Modified Vaccinia Ankara as a Vaccine against Smallpox. N Engl J Med. 2019 Nov 14;381(20):1897-1908. doi: 10.1056/NEJMoa1817307.
* Includes publications given by the data provider as well as publications identified by ClinicalTrials.gov Identifier (NCT Number) in Medline.	
Recruitment Information	
Recruitment Status ICMJE	Completed
Actual Enrollment ICMJE (submitted: January 20, 2015)	440
Original Enrollment ICMJE	<i>Not Provided</i>
Actual Study Completion Date ICMJE	August 2017
Actual Primary Completion Date	March 2017 (Final data collection date for primary outcome measure)
Eligibility Criteria ICMJE	Inclusion Criteria: 1. Healthy male and female subjects, 18-42 years of age 2. The subject has read, signed and dated the Informed Consent, having been advised of the risks and benefits of the trial in a language understood by the subject and prior to performance of any trial specific procedure 3. Acceptable medical history by screening evaluation and physical examination 4. BMI greater or equal than 18.5 and smaller than 35 5. Women of childbearing potential (WOCBP) must have a negative serum pregnancy test at Screening and a negative urine or serum pregnancy test within 24 hours prior to each vaccination 6. WOCBP must have used an acceptable method of contraception for 28 days prior to the first vaccination, must agree to use an acceptable method of contraception during the trial, and must avoid becoming pregnant for at least 28 days after the last vaccination. A woman is considered of childbearing potential unless post-menopausal or surgically sterilized. (Acceptable contraception methods are restricted to abstinence, barrier contraceptives, intrauterine contraceptive devices or licensed hormonal products) 7. Human Immunodeficiency Virus (HIV) antibody negative, hepatitis B surface antigen negative and negative antibody test to hepatitis C virus 8. White blood cells greater or equal than 2500/mm³ and smaller than 11,000/mm³ 9. Hemoglobin within normal limits 10. Platelets greater or equal than lower normal limits 11. Adequate renal function defined as a calculated Creatinine Clearance (CrCl) greater than 60 ml/min as estimated by the Cockcroft-Gault equation

12. Adequate hepatic function in the absence of other evidence of significant liver disease defined as:

- Total bilirubin greater than 1.5 x Upper Limit Normal (ULN)
- Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST) greater than 1.5 x ULN
- Alkaline Phosphatase (Alk Phos) greater than 1.5 x ULN

13. Troponin I smaller than 2 x ULN

14. Electrocardiogram (ECG) without clinically significant findings, e.g. any kind of atrioventricular or intraventricular conditions or blocks such as complete left or right bundle branch block, atrioventricular node block, QTc or PR prolongation, premature atrial contractions or other atrial arrhythmia, sustained ventricular arrhythmia, two premature ventricular contractions in a row, ST elevation consistent with ischemia

Exclusion Criteria:

1. Pregnant or breast-feeding women
2. Typical vaccinia scar
3. Known or suspected history of smallpox vaccination defined as visible vaccination scar or documentation of smallpox vaccination or as reported by the subject
4. History of vaccination with any poxvirus-based vaccine
5. History of any serious medical condition, which in the opinion of the investigator would compromise the safety of the subject
6. History of or active immunodeficiency or immunosuppression caused by acquired or congenital diseases or caused by ongoing treatments such as chronic (greater than 14 days) high-dose corticosteroids (smaller than 5 mg prednisone [or equivalent] per day applied systemically, i.e. parenterally or orally), chronic or planned treatment with steroid eye drops or ointment at time of enrollment or radiation, or immunosuppressive drugs; low-dose corticosteroid topical products and nasal sprays used sporadically, i.e. pro re nata (according to circumstances) are permissible
7. Having had radiation or X-ray treatment (not routine X-rays) within the last 3 months
8. Post organ and bone-marrow transplant subjects whether or not receiving chronic immunosuppressive therapy
9. Eye surgery within 4 weeks prior to trial vaccination
10. History of or active autoimmune disease. Persons with vitiligo or thyroid disease taking thyroid hormone replacement are not excluded
11. Uncontrolled serious infection, i.e. not responding to antimicrobial therapy
12. History of malignancy, other than squamous cell or basal cell skin cancer, unless there has been surgical excision considered to have achieved cure. Subjects with history of skin cancer must not be vaccinated at the previous site of cancer
13. History of keloid formation
14. History or clinical manifestation of severe hematological, renal, hepatic, pulmonary, central nervous, cardiovascular or gastrointestinal disorders
15. History of coronary heart disease, myocardial infarction, angina, congestive heart failure, cardiomyopathy, stroke or transient ischemic attack, uncontrolled high blood pressure, or any other heart condition under the care of a doctor
16. Chest pain (that is diagnosed as cardiac related) or trouble breathing on exertion
17. Ten percent or greater risk of developing a myocardial infarction or coronary death within the next 10 years using the National Cholesterol Education Program's Risk Assessment Tool: <http://hin.nhlbi.nih.gov/atpiii/calculator.asp> NOTE: This criterion applies only to subjects 20 years of age and older
18. History of an immediate family member (father, mother, brother, or sister) who has had onset of ischemic heart disease before the age of 50 years
19. Clinically significant psychological disorder not adequately controlled by medical treatment
20. Active or history of chronic alcohol abuse and/or intravenous and/or nasal drug abuse (within the past 6 months)
21. History of anaphylaxis or any severe allergic reaction or serious adverse reaction to a vaccine

	22. Eczema of any degree or history of eczema 23. People with active atopic dermatitis (AD) [characterized by pruritus, eczematous lesions, xerosis (dry skin), and lichenification (thickening of the skin and an increase in skin markings)] or with a history of AD 24. People with chronic exfoliative skin disorders/conditions 25. People with active current Varicella zoster, Herpes zoster, impetigo, uncontrolled acne, Darier's disease or any acute skin disorders of large magnitude, e.g., laceration requiring sutures 26. People with a tattoo that covers the vaccination injection area (preventing assessment of the area and interfering with a vaccination site photograph) 27. Having received any vaccinations or planned vaccinations with a live vaccine within 28 days prior to or after trial vaccination 28. Having received any vaccinations or planned vaccinations with a killed vaccine within 14 days prior to or after trial vaccination 29. Administration or planned administration of immunoglobulins and/or any blood products during a period starting from three months prior to administration of the vaccine and ending at trial conclusion 30. Use of any investigational or non-registered drug or vaccine other than the trial vaccines within 28 days preceding the first dose of the trial vaccine or planned administration of such a drug /vaccine during the trial period 31. Blood donation for the duration of the trial 32. Acute disease (illness with or without a fever) at the time of enrollment 33. Temperature $\geq 100.4^{\circ}\text{F}$ (38.0°C) at the time of enrollment 34. Known household contacts with, or occupational exposure (other than minimal contact) to any of the following: ○ Pregnant women ○ Children <12 months of age ○ People with eczema or a history of eczema ○ People with active AD or history of AD ○ People with chronic exfoliative skin disorders/conditions ○ People with active Varicella zoster, Herpes zoster, impetigo, uncontrolled acne, Darier's disease or any acute skin disorders of large magnitude, e.g., laceration requiring sutures, burn with areas greater than 2x2 cm ○ People with active or recent immunodeficiency disease or use of immunosuppressive medications, for example: have or take medication for HIV, AIDS, leukemia, lymphoma, or chronic liver problem, have or take medication for Crohn's disease, lupus, arthritis, or other immune disease; have had radiation or X-ray treatment (not routine X-rays) within the last 3 months; have ever had a bone-marrow or organ transplant (or take medication for that); or have another problem that requires steroids, prednisone or a cancer drug for treatment ○ People having had eye surgery within the last 4 weeks 35. Known allergy to MVA-BN® vaccine or any of its constituents, e.g. tris(hydroxymethyl)-amino methane, including known allergy to egg or aminoglycoside (gentamycin) 36. Known allergies to ACAM2000® and its diluents including polymyxin B sulfate, neomycin sulfate, and phenol 37. Known allergies to vaccinia immunoglobulin (VIG) including thimerosal or previous allergic reaction to immunoglobulins 38. Known allergies to cidofovir, sulfa drugs, or probenecid 39. Trial personnel
Sex/Gender ^{ICMJE}	Sexes Eligible for Study: All
Ages ^{ICMJE}	18 Years to 42 Years (Adult)
Accepts Healthy Volunteers ^{ICMJE}	Yes

Contacts ^{ICMJE}	Contact information is only displayed when the study is recruiting subjects
Listed Location Countries ^{ICMJE}	Korea, Republic of
Removed Location Countries	
Administrative Information	
NCT Number ^{ICMJE}	NCT01913353
Other Study ID Numbers ^{ICMJE}	POX-MVA-006
Has Data Monitoring Committee	Yes
U.S. FDA-regulated Product	Not Provided
IPD Sharing Statement ^{ICMJE}	Not Provided
Responsible Party	Bavarian Nordic
Study Sponsor ^{ICMJE}	Bavarian Nordic
Collaborators ^{ICMJE}	US Army Medical Research Institute of Infectious Diseases
Investigators ^{ICMJE}	Principal Investigator: Phillip R Pittman, MD, MPH US Army Medical Research Institute of Infectious Diseases
PRS Account	Bavarian Nordic
Verification Date	November 2019
^{ICMJE} Data element required by the International Committee of Medical Journal Editors and the World Health Organization ICTRP	