PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

IMVAMUNE®

Smallpox and mpox Vaccine
Modified Vaccinia Ankara-Bavarian Nordic®
(live-attenuated, non-replicating)

Suspension for Injection

at least 0.5 x 10^8 Inf.U/ per 0.5 mL single dose

Pharmacotherapeutic group: Other viral vaccines
ATC code: J07BX

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RECENT MAJOR LABEL CHANGES

Since September 2019, major label changes related to safety and efficacy have been made under the following sections:

1 Indications	11/2020
3 Serious Warnings and Precautions Box	11/2020
4 Dosage and Administration_4.5 Missed Dose	11/2020
7 Warnings and Precautions_7.1 Special Populations	11/2020

TABLE OF CONTENTS

PART I: HEALTH PROFESSIONAL INFORMATION

Health Canada has authorized the sale of IMVAMUNE based on limited clinical testing in humans under the provision of the Extraordinary Use New Drug regulations. The authorization is based on the Health Canada review of the available quality, non-clinical and clinical data. Health Canada considers that the benefit/risk profile of IMVAMUNE is favourable for

- active immunization against smallpox, mpox and related *orthopoxvirus* infection and disease in adults 18 years of age and older determined to be at high risk for exposure.

As part of the authorization for sale of IMVAMUNE, Health Canada has requested the sponsor agree to post-market commitments. Adherence to these commitments, as well as updates to information on quality, non-clinical, and clinical data will be continuously monitored by Health Canada.

1 INDICATIONS

IMVAMUNE is indicated for:

- active immunization against smallpox, mpox and related *orthopoxvirus* infection and disease in adults 18 years of age and older determined to be at high risk for exposure.

The vaccine may be used for both primary vaccination and revaccination.

1.1 Pediatrics

Pediatrics (< 18 years of age): IMVAMUNE has not been studied in subjects below 18 years of age (Section 7.1.3).

1.2 Geriatrics

Geriatrics (≥ 56 years of age): IMVAMUNE has been administered to 120 subjects 56 to 80 years of age. No overall differences in safety and immunogenicity were observed between these subjects and those < 56 years of age (Section 7.1.4).

2 CONTRAINDICATIONS

- Patients who are hypersensitive to this vaccine or to any ingredient in the formulation or component of the container. For a complete listing, see Dosage Forms, Strengths, Composition and Packaging.
- Individuals who show hypersensitivity reactions after receiving the first dose of the vaccine should not be given the second dose.
- As with other vaccines, vaccination with IMVAMUNE must be postponed in persons with acute febrile conditions if used for non-emergency (pre-event) prophylaxis.

3 SERIOUS WARNINGS AND PRECAUTIONS

At the time of authorization, there are no known serious warnings or precautions associated with this product.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

IMVAMUNE should be administered by subcutaneous injection, preferably in the upper arm. The vaccine must not be administered intravascularly.

4.2 Recommended Dose and Dosage Adjustment

Primary Dose:

The primary vaccination schedule in Vaccinia-naïve individuals consists of two doses of 0.5 mL four weeks apart administered by the subcutaneous route.

Booster Dose:

Individuals previously vaccinated against smallpox with either a replicating smallpox vaccine or IMVAMUNE can be re-vaccinated with a single subcutaneous 0.5 mL dose of IMVAMUNE to boost their immune response.

Since no persistency data beyond two years after priming are available for IMVAMUNE-experienced persons, the recommended booster schedule is to administer a single dose of IMVAMUNE every two years (see CLINICAL TRIALS, Study Results POX-MVA-023).

IMVAMUNE has not been studied for pediatric use (Section 7.1.3).

4.4 Administration

Each vial is for single use only and should not be used for more than one individual. The entire contents of the vial should be injected.

In the absence of compatibility studies this vaccine must not be mixed with other medicinal products.

4.5 Missed Dose

If the primary vaccination schedule in Vaccinia-naïve individuals is not completed full protection might not be achieved against smallpox, mpox, or other related *orthopoxvirus*. The second dose, if missed, should be given as soon as possible (see CLINICAL TRIALS, Study Results POX-MVA-005).

5 OVERDOSAGE

No case of overdose has been reported.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

To help ensure the traceability of vaccines for patient immunization record-keeping as well as safety monitoring, health professionals should record the time and date of administration, quantity of administered dose (if applicable), anatomical site and route of administration, brand name and generic name of the vaccine, the product lot number and expiry date.

Dosage Form
Suspension for injection

Composition
Each single-dose vial of liquid-frozen IMVAMUNE is formulated to have a titer of at least 0.5 x 10^8 infectious units (Inf.U) per 0.5 mL (1 dose) of MVA-BN (see Section 13).
Each dose contains 0.61 mg trometamol and 4.1 mg sodium chloride. The vaccine contains trace amounts of host cell DNA and protein, benzonase, gentamicin and ciprofloxacin. The product contains no preservatives and no adjuvants.

Packaging
IMVAMUNE is supplied as a single dose in a 2-mL type I borosilicate glass vial closed with a sterile bromobutyl rubber stopper, crimped with an aluminum cap and covered with a polypropylene closure.

IMVAMUNE is supplied in a package of ten or twenty 2-mL single dose vials. Not all pack sizes may be marketed.

Table 1 Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients*
Subcutaneous injection (s.c.)	Suspension for injection ≥ 0.5 x 10^8 Inf.U/ 0.5 mL	Tris buffer (10 mM Tris containing 140 mM NaCl, pH 7.7): Tris-hydroxymethyl-amino methane, sodium chloride, water for injection and hydrochloric acid Trometamol (Tris-hydroxymethyl-amino methane), sodium chloride, water for injection

* The vaccine contains trace amounts of host cell DNA and protein, benzonase, gentamicin and ciprofloxacin

7 WARNINGS AND PRECAUTIONS

General
- As with any other vaccine, vaccination with IMVAMUNE may not result in protection in all cases.
- As with all vaccines, appropriate medical treatment and supervision should always be available to treat rare cases of anaphylactic reactions following the administration of the vaccine.
- IMVAMUNE should not be administered intravascularly

Monitoring and Laboratory Tests
Replicating smallpox vaccines have been associated with myopericarditis. If a vaccinated subject exhibits signs and symptoms potentially associated with a cardiac disorder (e.g. chest pain or discomfort, dyspnea, or palpitations), ECG and troponin I tests should be performed. In case of ECG changes or troponin I elevations, further cardiologic examination should be performed.

7.1 Special Populations

7.1.1 Pregnant Women

Available human data on IMVAMUNE administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy. Animal reproductive studies did not reveal any evidence of impaired fertility or harm to the fetus.

IMVAMUNE should be administered to pregnant women only if they are at risk of infection with variola virus or other *orthopoxviruses*, and if the benefit of immunization outweighs the potential risks to the mother and fetus.

7.1.2 Breast-feeding

Safety during lactation has not been established. It is unknown if vaccine antigens or antibodies are excreted in human milk.

IMVAMUNE should be administered to women who are breastfeeding only if they are at risk of infection with variola virus or other *orthopoxviruses*, and if the benefit of immunization outweighs the potential risks.

7.1.3 Pediatrics

Pediatrics (< 18 years of age): IMVAMUNE has not been studied in subjects below 18 years of age. Before the eradication of smallpox disease, smallpox vaccination was administered routinely during childhood since the benefits were considered to outweigh the risks.

IMVAMUNE should be administered to children only if they are at risk of infection with variola virus or other *orthopoxviruses*, and if the benefit of immunization outweighs the potential risks to the child.

7.1.4 Geriatrics

Geriatrics (≥ 56 years of age): IMVAMUNE® has been administered to 120 subjects 56 to 80 years of age. No overall differences in safety and immunogenicity were observed between these subjects and those < 56 years of age.

7.1.5 Immunosuppressed Individuals

The use of IMVAMUNE in immunosuppressed patients is supported by clinical trials which include individuals who are human immunodeficiency virus (HIV) infected (CD4 ≥ 100 cells/μL), and individuals with atopic dermatitis (AD). (See Section 14.1 for more details). An adequate

immune response may be diminished in HIV positive individuals as well as in other patients with immunodeficiency or patients receiving immunosuppressive therapy.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Safety was assessed in 20 completed clinical trials where approximately 13,700 doses were given to 7414 subjects. The most common local adverse drug reactions at the injection site after vaccine administration are pain, erythema, induration and swelling. The most common systemic adverse drug reactions observed after vaccination are fatigue, headache, myalgia, and nausea. Most of the reported adverse drug reactions were of mild to moderate intensity and resolved within the first seven days following vaccination. No trends have been identified suggesting the occurrence of any particular unexpected adverse reactions or classes of adverse reactions following the administration of IMVAMUNE.

Cardiac AESIs were reported to occur in 1.4% (91/6,640) of IMVAMUNE recipients and 0.2% (3/1,206) of placebo recipients who were smallpox vaccine-naïve. Cardiac AESIs were reported to occur in 2.1% (16/762) of IMVAMUNE recipients who were smallpox vaccine-experienced. The higher proportion of IMVAMUNE recipients who experienced cardiac AESIs was driven by 28 cases of asymptomatic post-vaccination elevation of troponin-I in two studies, that used a different troponin assay than was used in the other previous studies, and had no placebo controls. The clinical significance of these asymptomatic post-vaccination elevations of troponin-I is unknown. Among the cardiac AESIs reported, 6 cases (0.08%) were considered to be causally related to IMVAMUNE vaccination and included tachycardia, electrocardiogram T wave inversion, abnormal electrocardiogram, electrocardiogram ST segment elevation, abnormal electrocardiogram T wave, and palpitations. None of the cardiac AESIs considered causally related to study vaccination were considered serious. Furthermore, despite close cardiac monitoring, no confirmed case of myocarditis, pericarditis, endocarditis or any other type of cardiac inflammatory disease (or related syndromes) was recorded.

In addition, IMVAMUNE has been tested in individuals with contraindications to receiving replicating smallpox vaccines, i.e. HIV infected persons and AD patients. The safety profile of IMVAMUNE in immune compromised subjects has been shown to be comparable to that recorded for healthy individuals. IMVAMUNE has been studied in more than 690 subjects infected with HIV to evaluate its immunogenicity and safety in an immunocompromised population. Since HIV directly infects T helper cells, and also indirectly impairs other immune system responses, HIV infection can be considered as being exemplary also for other forms of immunodeficiency.

AD subjects developed slightly more frequent and more intense reactions than are typically observed after vaccination (local skin reactions such as injection site erythema, injection site swelling and injection site pruritus; general symptoms like headache, myalgia, chills, nausea, and fatigue). No indication or trend could be detected that a vaccination with IMVAMUNE worsens the intensity of AD.

8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from

clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Data sources: Summarized 6-month safety data of all completed clinical Phase I trials POX-MVA-001, POX-MVA-002, POX-MVA-007, POX-MVA-030; Phase I/II trials POX-MVA-010, POX-MVA-009 and HIV-POL-002 (IMVAMUNE control group only); Phase II trials POX-MVA-004, POX-MVA-005, POX-MVA-008, POX-MVA-011, POX-MVA-023, POX-MVA-024, POX-MVA-028, POX-MVA-029, POX-MVA-037 and HIV-NEF-004 (IMVAMUNE control group only); and Phase III trials POX-MVA-013 and POX-MVA-006 (total N=6755)

Doses ranging from 1 x 10^6 to 1 x 10^8 Inf.U were administered in studies POX-MVA-001, POX-MVA-002 and POX-MVA-004; in all remaining studies, the standard dose was generally utilized. The following populations were included:

- Vaccinia-naïve, healthy, 18-55 years of age
- Vaccinia-experienced, healthy, 18-55 years of age
- IMVAMUNE -experienced, healthy, 20-57 years of age
- Vaccinia-experienced, healthy, elderly 56-80 years of age
- Vaccinia-naïve, HIV-1 infected, 18-55 years of age
- Vaccinia-experienced, HIV-1 infected, 18-55 years of age
- Vaccinia-naïve, atopic dermatitis (AD), 18-40 years of age
- Vaccinia-naïve, allergic rhinitis (AR), 18-40 years of age

The following frequencies of Adverse Drug Reactions (n= 6755) have been reported in these completed clinical trials with IMVAMUNE (Table 2).

Table 2 Adverse Drug Reactions Reported in Completed IMVAMUNE Clinical Trials (N=6755)

MedDRA System Organ Class	Very common (≥ 1/10)	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1,000 to < 1/100)	Rare (≥ 1/10,000 to < 1/1,000)
Infections and Infestations	–	–	Nasopharyngitis Upper respiratory tract infection	Sinusitis Conjunctivitis Influenza
Blood and Lymphatic System Disorders	–	–	Lymphadenopathy	–
Metabolism and Nutrition Disorders	–	Appetite disorder	–	–
Psychiatric Disorders	–	–	Sleep disorder	–
Nervous System Disorders	Headache	–	Dizziness Paresthesia	Migraine Peripheral sensory neuropathy
Ear and Labyrinth Disorders	–	–	–	Vertigo

MedDRA System Organ Class	**Very common (≥ 1/10)**	**Common (≥ 1/100 to < 1/10)**	**Uncommon (≥ 1/1,000 to < 1/100)**	**Rare (≥ 1/10,000 to < 1/1,000)**
Cardiac Disorders	–	–	–	Tachycardia
Respiratory, Thoracic and Mediastinal Disorders	–	–	Pharyngolaryngeal pain Rhinitis Cough	Oropharyngeal pain
Gastrointestinal Disorders	Nausea	–	Diarrhea Vomiting Dry mouth	Abdominal Pain
Skin and Subcutaneous Tissue Disorders	–	–	Rash Pruritus Dermatitis Skin discolouration	Urticaria Ecchymosis Hyperhidrosis Night sweats Subcutaneous nodule Angioedema
Musculoskeletal and Connective Tissue Disorders	Myalgia	Pain in extremity Arthralgia	Musculoskeletal stiffness Back pain Neck pain	Muscle spasms Musculoskeletal pain Muscular weakness
General Disorders and Administration Site Conditions	Injection site pain Injection site erythema Injection site swelling Injection site induration Injection site pruritus Fatigue	Rigor/Chills Injection site nodule Injection site discolouration Injection site haematoma Injection site warmth	Underarm swelling Malaise Injection site irritation Injection site haemorrhage Flushing Axillary pain Chest pain Injection site exfoliation Injection site inflammation Injection site paraesthesia Injection site reaction	Injection site rash Oedema peripheral Asthenia Influenza like illness Injection site anesthesia Injection site dryness Injection site movement impairment Injection site vesicles

MedDRA System Organ Class	Very common (≥ 1/10)	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1,000 to < 1/100)	Rare (≥ 1/10,000 to < 1/1,000)
Investigations	–	Body temperature increased Pyrexia	Troponin I increased Hepatic enzyme increased White blood cell count decreased Mean platelet volume decreased	White blood cell count increased
Injury, Poisoning and Procedural Complications	–	–	Contusion	–

Individuals with atopic dermatitis (AD)
In a non-placebo controlled clinical trial that compared the safety of IMVAMUNE in individuals with AD to healthy individuals, individuals with AD reported erythema (61.2%) and swelling (52.2%) at the injection site with a higher frequency than healthy individuals (49.3% and 40.8%, respectively). The following general symptoms were reported more frequently in individuals with AD compared to healthy individuals: headache (33.1% vs. 24.8%), myalgia (31.8% vs. 22.3%), chills (10.7% vs. 3.8 %), nausea (11.9% vs. 6.8%), and fatigue (21.4% vs. 14.4%). 7% of the individuals with AD in clinical trials with IMVAMUNE experienced a flare-up or worsening of their skin condition during the course of the trial.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

There were no safety concerns with regard to haematological parameters, clinical chemistry or urine analysis across studies.

8.5 Post-market adverse reactions

The following adverse events have been observed during the post authorization use of the vaccine:
Cardiac disorders: myocarditis, pericarditis.
The causality of the adverse events has not been established.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Concomitant administration of combination antiretroviral therapy in the majority of the HIV-1 infected study population did not reveal any undesirable interaction regarding the efficacy and safety of IMVAMUNE.

9.4 Drug-Drug Interactions

Use with other vaccines:
Interactions with other vaccines have not been established. Therefore, concomitant administration of other vaccines should be avoided. If co-administration with another vaccine is indicated, immunization should be carried out on separate limbs. To minimize the potential risk of interactions, it is recommended to administer killed vaccines > 2 weeks and live vaccines ≥ 4 weeks before or after administration of IMVAMUNE.

Use with immunoglobulins:
Interaction with concomitant administration of immunoglobulins has not been established.

Interactions with other drugs have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

IMVAMUNE is a live, attenuated, and non-replicating viral vaccine produced from the *orthopoxvirus* strain Modified Vaccinia Ankara-Bavarian Nordic (MVA-BN) (see Section 13 - Product Characteristics).

Clinical and pre-clinical studies have shown that both humoral and cellular immune responses induced with IMVAMUNE in animal species (i.e. mice and monkeys) and human individuals vaccinated with IMVAMUNE are comparable to immune responses induced by replicating smallpox vaccines used to eradicate smallpox. Furthermore, animal model challenge studies performed in mice and monkeys have shown that IMVAMUNE confers protection against *orthopoxvirus* infections including mpox and vaccinia infections.

Special Populations and Conditions

Please refer to Section 7.1.

11 STORAGE, STABILITY AND DISPOSAL

Store frozen at -20°C ± 5°C or -50°C ± 10°C or -80°C ± 10°C.
Expiry date depends on storage temperature

Can be stored at 2°C – 8°C for up to 2 months.

After thawing, the vaccine can be stored at 2°C – 8°C for up to 2 months prior to use.

Do not refreeze a vial once it has been thawed.

Store in the original package in order to protect from light.

Do not use after the expiry date shown on the label, unless batch certification documentation allows for use based on an updated expiry date.

12 SPECIAL HANDLING INSTRUCTIONS

Thaw at room temperature. To ensure homogeneity upon thawing, the vial should be swirled gently (not shaken) for at least 30 seconds. After thawing, the drug product should appear as a pale milky colored homogeneous suspension. The liquid vaccine should be visually inspected for any foreign particulate matter prior to administration. In case of foreign particulate matter being visible, the vaccine must not be used.

After thawing, the vaccine can be stored at 2°C – 8°C for up to 2 months prior to use.

Do not re-freeze a vial once it has been thawed.

Store in the original package in order to protect from light.

The injection volume of 0.5 mL per dose should be withdrawn with a syringe using an injection needle long enough to reach the bottom of the vial. After withdrawal of the vaccine, the injection needle should be changed to a s.c. injection needle and the vaccine administered to the subject immediately.

Sterile needles should be used for withdrawal and administration of IMVAMUNE.

Needles and vial should be properly disposed.

IMVAMUNE is a vaccine suspension and is supplied in a package of ten or twenty 2-mL injection vials each containing one single standard dose (at least $0.5x10^8$ Inf.U per dose) of liquid-frozen vaccine. Not all pack sizes may be marketed.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance
Proper name: Smallpox and mpox Vaccine
Modified Vaccinia Ankara-Bavarian Nordic (live-attenuated, non-replicating)

Product Characteristics
IMVAMUNE is a live, attenuated, and non-replicating viral vaccine produced from the orthopoxvirus strain Modified Vaccinia Ankara-Bavarian Nordic (MVA-BN). MVA-BN has a restricted host-range and fails to reproductively replicate in human cells due to multiple genomic deletions and other mutations that block viral assembly and egress in the cells. MVA-BN is grown in chicken embryo fibroblast cells, harvested, concentrated, purified and suspended in a Tris buffer (10 mM Tris containing 140 mM NaCl, pH 7.7). The vaccine contains trace amounts of host cell DNA and protein, benzonase, gentamicin and ciprofloxacin. No preservative or adjuvant is added to the formulation.

Each vial of liquid-frozen IMVAMUNE is formulated to have a titer of at least $0.5x10^8$ Inf.U per dose (0.5 mL) of MVA BN (standard dose).

14 CLINICAL TRIALS

An overview of the pivotal clinical trial (POX-MVA-006) and the main 7 clinical trials supporting efficacy (POX-MVA-005, POX-MVA-008, POX-MVA-011, POX-MVA-023, POX-MVA-024, POX-MVA-013 and POX-MVA-037) with IMVAMUNE is given below (Table 3). Twelve other clinical trials have also been completed to gather data about IMVAMUNE.

14.1 Trial Design and Study Demographics

Clinical trials included vaccinia-naïve and vaccinia-experienced adults (age 18 – 55) and vaccinia-experienced elderly (age 56 – 80) subjects. IMVAMUNE has been studied in healthy subjects, > 690 subjects infected with HIV and in 381 subjects with atopic dermatitis.

Table 3 Trial Design and Demographics

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Sex
POX-MVA-006	Phase III, randomized, open-label, active-controlled, non-inferiority study Safety and indicator of efficacy (immunogenicity and clinical take attenuation) of IMVAMUNE compared with ACAM2000[1] in healthy in vaccinia-naïve subjects (18-42 years).	Two standard doses of IMVAMUNE s.c. administration at Day 0 and 28 followed by one dose of ACAM2000 via scarification at Day 56; or one dose of ACAM2000 via scarification at Day 0 **Group 1:** 2 doses IMVAMUNE, 1 dose ACAM2000 **Group 2:** 1 dose ACAM2000	**n total = 433**	**Overall** 23.5 years (18–42)	**Overall** M: 365 (84.3%) F: 68 (15.7%)
			Group 1 n = 220	**Group 1** 23.5 years (18–42)	**Group 1** M: 181 (82.3%) F: 39 (17.7%)
			Group 2 n = 213	**Group 2** 23.4 years (18–41)	**Group 2** M: 184 (86.4%) F: 29 (13.6%)
POX-MVA-005	Phase II, partially double-blind, partially randomized, placebo-controlled, non-inferiority study Safety and immunogenicity of IMVAMUNE in healthy vaccinia-naïve and vaccinia-experienced subjects (18-55 years)	One or two standard doses of IMVAMUNE s.c. administration at Day 0 (1 dose schedule) or Day 0 and 28 (2 dose schedule) **Group 1:** 2 doses IMVAMUNE **Group 2**: 1 dose IMVAMUNE, 1 dose Placebo **Group 3**: Placebo **Group 4:** 1 dose IMVAMUNE	**n total = 745** **Vaccinia-naïve Group 1** n=183	**Overall** 29.8 years (18-55) **Vaccinia-naïve Group 1** 25.3 years (18- 50)	**Overall** M:314 (42.1%) F:431 (57.9%) **Vaccinia-naïve Group 1** M: 86 (47.0%) F: 97 (53.0%)
			Group 2 n= 181	**Group 2** 25.4 years (18- 44)	**Group 2** M: 69 (38.1%) F: 112 (61.9%)
			Group 3 n=181	**Group 3** 26.0 years (18- 50)	**Group 3** M: 74 (40.9%) F: 107 (59.1%)
			Vaccinia-experienced Group 4 n=200	**Vaccinia-experienced Group 4** 41.5 years (22- 55)	**Vaccinia-experienced Group 4** M: 85 (42.5%) F: 115 (57.5%)

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Sex
POX-MVA-023	Phase II, open-label booster study Safety and immunogenicity of single booster with IMVAMUNE in former POX-MVA-005 vaccinees	One standard dose of IMVAMUNE two years after priming with either one or two doses of IMVAMUNE s.c. administration at Day 0	**Booster Set[2]** n total = 152 **Group 1** n = 75 **Group 2** n = 77 **Persistence Set[3]** n total = 304 (152 + 152) **Group 1** n = 92 (75+17) **Group 2** n = 91 (77+14) **Group 4** n = 121	**Booster Set[2]** **Overall** 27.6 years (20-52) **Group 1** 27.3 years (20-52) **Group 2** 27.9 years (20- 46) **Persistence Set[3]** **Overall** 34.6 years (20 -57) **Group 1** 27.7 years (20- 52) **Group 2** 27.7 years (20-46) **Group 4** 44.9 years (26- 57)	**Booster Set[2]** **Overall** M: 67 (44.1%) F: 85 (55.9%) **Group 1** M: 35 (46.7%) F: 40 (53.3%) **Group 2** M: 32 (41.6%) F: 45 (58.4%) **Persistence Set[3]** **Overall** M: 132 (43.4%) F: 172 (56.6%) **Group 1** M: 42 (45.7%) F: 50 (54.3%) **Group 2** M: 36 (39.6%) F: 55 (60.4%) **Group 4** M: 54 (44.6%) F: 67 (55.4%)
POX-MVA-008	Phase II, open-label, controlled, multicenter Safety and immunogenicity of IMVAMUNE in vaccinia-naïve AD subjects compared to healthy subjects	Two standard doses of IMVAMUNE s.c. administration at Day 0 and 28	**n total = 632** **AD subjects** n = 350 **Healthy subjects** n = 282	**AD subjects** 27.9 years (18-42) **Healthy subjects** 27.4 years (18-41)	**AD Subjects** M: 127 (36.3%) F: 223 (63.7%) **Healthy subjects** M: 132 (46.8%) F: 150 (53.2%)

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Sex
POX-MVA-011	Phase II Safety and immunogenicity of IMVAMUNE in vaccinia-naïve and vaccinia-experienced HIV infected subjects compared to healthy subjects	Two standard doses of IMVAMUNE s.c. administration at Day 0 and 28	**n total= 579** **Healthy** naïve n = 88 **Healthy experienced** n = 9 **HIV infected naïve** n = 351 **HIV infected experienced** n = 131	 **Healthy naïve** 28.9 years (18-52) **Healthy experienced** 45.6 years (25-56) **HIV infected naïve** 36.8 years (18-54) **HIV infected experienced** 44.6 years (25-55)	 **Healthy naïve** M: 38 (43.2%) F: 50 (56.8%) **Healthy experienced** M: 5 (55.6%) F: 4 (44.4%) **HIV infected naïve** M: 287 (81.8%) F: 64 (18.2%) **HIV infected experienced** M: 110 (84.0%) F: 21 (16.0%)
POX MVA-024	Phase II Safety and immunogenicity of one and two doses of IMVAMUNE smallpox vaccine in 56-80 year old vaccinia-experienced subjects	Two standard doses of IMVAMUNE or one Placebo dose and one standard dose of IMVAMUNE s.c. administration at Day 0 and 28	**n total = 120**[4] **2 doses IMVAMUNE** n = 62 **1 dose Placebo/ 1 dose IMVAMUNE** n = 58	**Overall** 63.7 years (56-80) **2 doses IMVAMUNE** 64.6 years (56-77) **1 dose Placebo/ 1 dose IMVAMUNE** 62.6 years (56-80)	**Overall** M: 43 (35.8 %) F: 77 (64.2 %) **2 doses IMVAMUNE** M: 25 (40.3 %) F: 37 (59.7%) **1 dose Placebo/ 1 dose IMVAMUNE** M: 18 (31.0%) F: 40 (69.0%)

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Sex
POX-MVA-013	Phase III, randomised, double-blind, placebo-controlled, non-inferiority trial Immunogenicity and safety of three consecutive production lots of IMVAMUNE in healthy, vaccinia-naïve subjects	Two standard doses of IMVAMUNE or two Placebo doses s.c. administration at Day 0 and 28	**n total = 4005** **2 doses IMVAMUNE** n = 3003 **2 doses Placebo** n = 1002	**Overall** 27.7 years (18-40) **2 doses IMVAMUNE** 27.7 years (18-40) **2 doses Placebo** 27.7 years (18-40)	**Overall** M: 1919 (47.9%) F: 2086 (52.1%) **2 doses IMVAMUNE** M: 1456 (48.5%) F: 1547 (51.5%) **2 doses Placebo** M: 463 (46.2%) F: 539 (53.8%)
POX-MVA-037	Phase II, randomized, open-label study Safety and immunogenicity of IMVAMUNE when increasing the dose or the number of injections in HIV-infected, vaccinia-naïve subjects (18–45 years)	Two, three or four standard doses of IMVAMUNE s.c. administration (**two dose schedule**: 1 injection each at Day 0 and 28; **three dose booster schedule**: 1 injection each at Day 0, 28 and 84; or **four dose schedule**: 2 injections each at Day 0 and 28) **Group 1**: 2 doses IMVAMUNE **Group 2**: 4 doses IMVAMUNE **Group 3**: 3 doses IMVAMUNE	**n total =87**	**Overall** 35.0 years (22–45 years)	**Overall** M: 75 (86.2%) F: 12 (13.8%)
			Group 1 n = 27	**Group 1** 35.1 years (22–45 years)	**Group 1** M: 23 (85.2%) F: 4 (14.8%)
			Group 2 n = 29	**Group 2** 33.1 years (22–45 years)	**Group 2** M: 24 (82.8%) F: 5 (17.2%)
			Group 3 n = 31	**Group 3** 36.6 years (26–45 years)	**Group 3** M: 28 (90.3%) F: 3 (9.7%)

[1] ACAM2000® is the US licensed smallpox vaccine.
[2]Subjects of Groups 1 and 2 who received a booster vaccination in study POX-MVA-023.
[3] Subjects of Groups 1 and 2 who received a booster vaccination (booster set) in study POX-MVA-023 plus Group 1, 2 and 4 subjects who had a blood draw only in POX-MVA-023.
[4]A total of 120 subjects received at least one vaccination but one subject had no baseline data and was excluded from the FAS.
Abbreviations: AD = Atopic Dermatitis; F = Female; HIV = Human Immunodeficiency Virus; M = Male; N = Number of subjects; s.c. = Subcutaneous; US = United States of America.

14.2 Study Results

Efficacy in humans

Vaccine efficacy was evaluated by comparing the immunogenicity of IMVAMUNE with a licensed smallpox vaccine (ACAM2000®) and assessing the attenuation of clinical takes when ACAM2000 was administered following IMVAMUNE vaccination. These evaluations were performed in a randomized, open-label non-inferiority Phase III clinical trial in healthy smallpox vaccine-naïve 18 through 42-year-old adults (US military personnel only) (see study POX-MVA-006, summarized in Table 3).

For the first co-primary efficacy endpoint, the trial compared vaccinia-specific Plaque Reduction Neutralization Test (PRNT) antibody responses at the peak visits (week 6 after first vaccination for IMVAMUNE [where the subjects received two doses according to the standard vaccination schedule] versus week 4 in subjects who received one dose of ACAM2000). Non-inferiority of IMVAMUNE to ACAM2000 was met if the two-sided 95% confidence interval of the ratio of the GMTs was entirely above 0.5.

Peak visit is Day 42 (Week 6; Visit 6) for Group 1 i.e. following receipt of two IMVAMUNE vaccinations according to the two-dose vaccination regimen and Day 28 (Visit 4) for Group 2, i.e. Week 4 post vaccination in alignment with published data for replicating smallpox vaccines reaching a peak four weeks post vaccination.

IMVAMUNE induced a peak neutralizing antibody GMT of 153.5, which was non-inferior to that obtained after scarification with ACAM2000 (79.3) (Table 4).

At 2 weeks post vaccination with ACAM2000, a time when a protective response had been induced as judged by the induction of a vaccine “take,” the neutralizing antibody GMT induced by a single dose of IMVAMUNE was non-inferior when applying the same statistical boundary as pre-determined for the comparison of peak visits.

Table 4 Comparison of Neutralizing Antibody GMTs for IMVAMUNE and ACAM2000 in Adults 18 – 42 Years of Age, POX-MVA-006 (Per Protocol Set for Immunogenicity[1])

	Group 1 (IMVAMUNE) N=185			Group 2 (ACAM2000) N=186			Ratio of GMTs Group 1 / Group 2	
Week	**n**	**GMT**	**95% CI**	**n**	**GMT**	**95% CI**	**Ratio**	**95% CI**
0	185	1.0	[1.0, 1.1]	186	1.0	[1.0, 1.0]	NA	NA
2	184	16.2	[13.0, 20.1]	184	16.2	[13.1, 20.0]	0.997	[0.738, 1.348]
4	185	16.9	[13.7, 20.8]	186	79.3	[67.1, 93.8]	NA	NA
6	185	153.5	[134.3, 175.6]	181	64.7	[54.9, 76.2]	NA	NA
Peak Visit[2]	185	153.5	[134.3, 175.6]	186	79.3	[67.1, 93.8]	1.935	[1.562, 2.397]

[1] PPS for Immunogenicity: Per Protocol Set for Immunogenicity, included subjects who received all vaccinations, completed all visits up until Visit 7 for Group 1 and Visit 4 for Group 2, and adhered to all protocol conditions pertaining to immunogenicity.

[2] The Peak Visits were at Week 6 for IMVAMUNE (2 weeks following the second IMVAMUNE vaccination) and Week 4 for ACAM2000 (4 weeks following the only vaccination).

N: Number of subjects in the specified group, n: Number of subjects with data available; NA: not applicable; GMT: Geometric Mean Titer; %: 95% CI: 95% confidence interval, lower limit and upper limit.

For the second co-primary efficacy endpoint, an evaluation was performed to determine whether vaccination with IMVAMUNE prior to administration of ACAM2000 (Group 1) resulted in an attenuation of the "take" of ACAM2000 in terms of maximum lesion area (MLA). 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). The primary analysis assessed whether the area attenuation ratio (AAR), which reflects the reduction in the MLA, was significantly above 40%. This shows that IMVAMUNE is able to suppress the viral replication induced by ACAM2000, providing evidence of the efficacy afforded by IMVAMUNE to protect against smallpox.

There was a significant relative reduction in MLA of far more than the pre-specified threshold for clinical relevance of 40% for subjects that received IMVAMUNE priming prior to ACAM2000 scarification compared to those who did not (AAR for MLA: 97.9%) (Table 5).

Table 5 Maximum Lesion Area (MLA), POX-MVA-006 (Per Protocol Set[1])

	Group 1 (IMVAMUNE) N=165		**Group 2 (ACAM2000) N=161**			
Visit	**Median**	**95% CI***	**Median**	**95% CI***	**AAR**	**95% CI+**
Day 6-8	0.0	0.0, 1.0	37.0	33.0, 42.0	95.2%	[93.8, 96.2]
Day 13-15	0.0	0.0, 0.0	75.0	69.0, 85.0	98.2%	[97.7, 98.4]
Maximum	0.0	0.0, 2.0	76.0	70.0, 87.0	97.9%	[96.6, 98.3]

[1] PPS: Per Protocol Set, included subjects who received all vaccinations, completed all visits up until Visit 10 for Group 1 and Visit 4 for Group 2, adhered to all clinical protocol conditions;
N: Number of subjects in the specified group; AAR: Area Attenuation rate =1 – (Median IMVAMUNE) / (Median ACAM2000); 95% CI*: Non-parametric 95% confidence interval of the median, lower limit and upper limit; 95% CI+: Hodges-Lehmann based 95% confidence interval of the AAR, lower limit and upper limit.

A Phase I study (POX-MVA-002) performed at a time when Dryvax was still licensed in the US and permitted for use in clinical trials demonstrated that the peak and long-term immune responses (ELISA and PRNT) induced by IMVAMUNE were comparable to those induced by Dryvax in healthy vaccinia-naïve subjects. In the same Phase I study, prior vaccination of healthy, vaccinia-naïve subjects with two doses of IMVAMUNE prevented or attenuated the vaccine take following a subsequent vaccination with Dryvax as judged by either the absence of or a significant reduction in redness/swelling, healing time and VV titers in the skin pustule. The prevention and/or attenuation of the Dryvax lesion has historically been associated with pre-existing immunity against smallpox infections, acquired either by previous vaccination(s) using conventional smallpox vaccines or a prior smallpox infection.

IMVAMUNE induced comparable variola virus neutralizing titers compared to subjects vaccinated with Dryvax. In vitro evaluation of the peak response sera obtained from study POX-MVA-002 demonstrated that the immune response elicited by IMVAMUNE, measured by the ability to neutralize variola virus in a PRNT, was comparable to that elicited by Dryvax. In addition, 90% neutralization at serum dilutions > 1:160 was only observed with IMVAMUNE and not with Dryvax. The responses generated using the variola-specific PRNT were highly correlated to results generated using the BN ELISA and vaccinia-specific PRNT.

Vaccine effectiveness

Twelve observational studies were conducted to evaluate vaccine effectiveness in real-world settings during the 2022-2023 mpox outbreak. The studies were conducted in the US, Spain, Canada, the UK, the Netherlands, and Israel, in vaccine-eligible individuals as per local recommendations, for pre-exposure or post-exposure prophylaxis vaccination. These studies employed various designs, including case-control, case coverage methods, as well as retrospective and prospective cohorts. Vaccine effectiveness against mpox disease was observed at least 14 days after vaccination[a], with adjusted vaccine effectiveness estimates ranging from 35% (95% CI, -2-59) to 89% (95% CI, 76-95) after one IMVAMUNE dose and from 66% (95% CI, 47-78) to 90% (95% CI, 86-92) after two IMVAMUNE doses.

[a]PEP administered ≤ 14 days after exposure. Subcutaneous and/or intradermal administration was possible in some studies.

Impact on hospitalization

In a surveillance study conducted from May 2022 to May 2023 in the US, IMVAMUNE was shown to reduce the risks of mpox-related hospitalization. Compared with unvaccinated mpox patients, the odds of hospitalization were 0.27 (95% CI, 0.08-0.65) after one IMVAMUNE dose, and 0.20 (95% CI, 0.01-0.90) after two IMVAMUNE doses. The estimated relative risk reduction was 73% after one IMVAMUNE dose and 80% after two IMVAMUNE doses [see Module 2.5 Section 1.3.1].

Immunogenicity in humans

Seroconversion rates in vaccinia-naïve healthy and special populations

The vaccinia-naïve study population included healthy individuals as well as individuals with HIV infection and AD who received 2 doses of IMVAMUNE 4 weeks apart. Seroconversion rates in vaccinia-naïve individuals was defined as appearance of antibody titers equal or greater than the assay cut-off value following receipt of two doses of IMVAMUNE. Seroconversion by ELISA and PRNT are summarized in Table. However, because clinical trials were conducted under varying populations, doses, and assay versions, response rates observed in a trial cannot be directly compared with rates in another trial.

Table 6 Seroconversion Rates in Vaccinia-naïve Healthy and Special Populations who Received 2 Standard Doses

SCR - ELISA			Day 7/14[1]	Day 28[1]	Day 42[1]
Study	**Health status**	**N**	**SCR % (95% CI)**	**SCR % (95% CI)**	**SCR % (95% CI)**
POX-MVA-005[2]	Healthy	183	70.9 (63.7, 77.4)	88.9 (83.4, 93.1)	98.9 (96.0, 99.9)
POX-MVA-006[3]	Healthy	185	91.8 (86.9, 95.4)	94.6 (90.3, 97.4)	100 (98.0, 100)
POX-MVA-008[4]	Healthy	194	12.5 (8.1, 18.2)	85.4 (79.6, 90.1)	98.5 (95.5, 99.7)
	AD	257	22.9 (17.8, 28.6)	85.4 (80.5, 89.5)	97.3 (94.5, 98.9)
POX-MVA-011[2]	Healthy	88	29.6 (20.0, 40.8)	83.7 (74.2, 90.8)	98.7 (93.1, 100)
	HIV	351	29.2 (24.3, 34.5)	67.5 (62.1, 72.5)	96.2 (93.4, 98.0)
POX-MVA-013[5]	Healthy	2119[6]	NA[7]	NA[7]	99.7 (99.4, 99.9)
POX-MVA-037[3]	HIV	20	NA[7]	75.0 (50.9, 91.3)	100 (83.2, 100)

SCR - PRNT			Day 7/14[1]	Day 28[1]	Day 42[1]
Study	**Health Status**	**N**	**SCR % (95% CI)**	**SCR % (95% CI**	**SCR % (95% CI)**
POX-MVA-005[2]	Healthy	183	45.1 (37.7, 52.6)	56.7 (49.1, 64.0)	89.2 (83.7, 93.4)
POX-MVA-006[3]	Healthy	185	90.8 (85.6, 94.5)	94.1 (89.6, 97.0)	100 (98.0, 100)
POX-MVA-008[4]	Healthy	194	5.4 (2.6, 9.8)	24.5 (18.6, 31.2)	86.6 (81.0, 91.1)
	AD	257	5.6 (3.1, 9.3)	26.8 (21.4, 32.7)	90.3 (86.0, 93.6)
POX-MVA-011[2]	Healthy	88	11.1 (5.2, 20.0)	20.9 (12.9, 31.0)	77.2 (66.4, 85.9)
	HIV	351	15.7 (11.9, 20.1)	22.5 (18.1, 27.4)	60.3 (54.7, 65.8)
POX-MVA-013[5]	Healthy	2119[6]	NA[7]	NA[7]	99.8 (99.5, 99.9)
POX-MVA-037[3]	HIV	20	NA[7]	60.0 (36.1, 80.9)	100 (83.2, 100)

[1]Day 7/14 corresponding to 1 or 2 weeks after the first IMVAMUNE dose (Day 7 was the only analysis timepoint prior to Day 28 in studies POX-MVA-008 and POX-MVA-011; Day 14 is provided for studies POX-MVA-005 and POX-MVA-006); Day 28 corresponding to 4 weeks after the first IMVAMUNE dose; Day 42 corresponding to 2 weeks following the second dose of IMVAMUNE; SCR = Seroconversion rate; [2] Full Analysis Set (FAS); [3] Per Protocol Set for Immunogenicity; 4Per Protocol Analysis Set (PPS);[5] Immunogenicity Analysis Set (IAS) subset used for immunogenicity analysis (first 700 subjects enrolled per group); [6] combined Groups 1-3; [7] no immunogenicity sample taken.

Seroconversion rates in Vaccinia-experienced healthy and special populations
The vaccinia-experienced study population included healthy individuals as well as individuals with HIV infection. Seroconversion in Vaccinia-experienced individuals is defined as at least a two-fold increase in base titers following a single vaccination with IMVAMUNE and is summarized below for subjects who received a total of 1 IMVAMUNE vaccination (subgroups from studies POX-MVA-005 and POX-MVA-024) or 2 IMVAMUNE vaccinations (POX-MVA-011) (Table 6).

Table 6 Seroconversion rates in Vaccinia-experienced healthy and special populations who received 1 or 2 standard doses

SCR - ELISA			Day 7/14[1]	Day 28[1]	Day 42[1]
Study	**Health status**	**N**	**SCR % (95% CI)**	**SCR % (95% CI)**	**SCR % (95% CI)**
POX-MVA-005[2]	Healthy	200	95.5 (91.6, 97.9)	93.0 (88.5, 96.1)	NA
POX-MVA-024[2]	Healthy	61	83.6 (71.9, 91.8)	79.7 (67.2, 89.0)	NA
POX-MVA-011[2]	Healthy	9	62.5 (24.5, 91.5)	100 (63.1, 100)	100 (59.0, 100.0)
	HIV	131	57.3 (48.1, 66.1)	76.6 (68.2, 83.7)	92.7 (86.6, 96.6)

SCR - PRNT			Day 7/14[1]	Day 28[1]	Day 42[1]
Study	**Health status**	**N**	**SCR % (95% CI)**	**SCR % (95% CI)**	**SCR % (95% CI)**
POX-MVA-005[2]	Healthy	200	78.5 (72.2, 84.0)	69.8 (63.0, 76.1)	NA
POX-MVA-024[2]	Healthy	61	73.8 (60.9, 84.2)	71.2 (57.9, 82.2)	NA
POX-MVA-011[2]	Healthy	9	75.0 (34.9, 96.8)	62.5 (24.5, 91.5)	85.7 (42.1, 99.6)
	HIV	131	46.0 (37.0, 55.1)	59.7 (50.5, 68.4)	75.6 (67.0, 82.9)

[1]Day 0 corresponding to day of vaccination with IMVAMUNE; Day 7/14 corresponding to 1 or 2 weeks after vaccination with IMVAMUNE (first post vaccination analysis at Day 7 in study POX-MVA-011, and at Day 14 in studies POX-MVA-005 and POX-MVA-024); Day 28 corresponding to 4 weeks after vaccination with IMVAMUNE; SCR = Seroconversion rate; [2] Full Analysis Set (FAS)

Long-term immunity in humans

Limited data on long-term immunity covering a period of 24 months following primary vaccination of vaccinia-naïve individuals with IMVAMUNE are currently available, as shown below (Table 7). Although antibody titers tend to decrease to low levels two years after priming, these can be readily boosted following a single booster dose of IMVAMUNE to even higher peak GMT responses (ELISA and PRNT) compared to the primary response. Repeated exposure to IMVAMUNE (booster vaccination) increases the antibody titers (3.4-fold higher GMTs by ELISA and 2.7-fold higher GMT by PRNT) compared to the priming vaccination.

Table 7 Long-term immunity in humans (POX-MVA-005 and POX-MVA-023; Full Analysis Set)

		ELISA		PRNT	
Month	**N**	**SCR % (95% CI)**	**GMT (95% CI)**	**SCR % (95% CI)**	**GMT (95% CI)**
2	178	98.9 (96.0, 99.9)	328.7 (288.5, 374.4)	86.0 (80.0, 90.7)	34.0 (26.4, 43.9)
6	178	73.0 (65.9, 79.4)	27.9 (20.7, 37.6)	65.2 (57.7, 72.1)	7.2 (5.6, 9.4)
24*	92	71.7 (61.4, 80.6)	23.3 (15.2, 35.9)	5.4 (1.8, 12.2)	1.3 (1.0, 1.5)

ELISA = enzyme-linked immunosorbent assay; GMT= geometric mean titer; N = number of subjects in the specific study group; PRNT = plaque reduction neutralization test; SCR = seroconversion rate;
*represents seropositivity rates

Booster Dose

Two clinical studies have demonstrated that IMVAMUNE is able to boost a pre-existing immunological memory response, induced by either licensed smallpox vaccines ≥5 years ago or two years after IMVAMUNE (Table 8). IMVAMUNE provided a strong recall response (ELISA and PRNT) in healthy and HIV infected subjects previously vaccinated with a smallpox vaccine of proven efficacy against smallpox.

A single dose of IMVAMUNE in vaccinia-naive subjects induces a long-lived B cell memory that can be boosted to the same antibody levels as in subjects vaccinated according to the standard schedule (two IMVAMUNE doses): 2 years after priming with either one or two doses of IMVAMUNE, the recall response (ELISA and PRNT) to a single booster dose of IMVAMUNE is rapid (within 7 days), stronger compared to the primary responses (> 2.5-fold), and comparable to that observed in individuals previously vaccinated with a licensed smallpox vaccine with proven efficacy (POX-MVA-023).

Table 8 Booster Dose (POX-MVA-005 and POX-MVA-023; Full Analysis Set)

Primary immunization		**N**	**Day 0[1]**		**N**	**Day 7[1]**		**Day 14[1]**	
	ELISA		**S+ %**	**GMT**		**S+ %**	**GMT**	**S+ %**	**GMT**
2 doses of IMVAMUNE		92	72	23	75	100	738	100	1688
Licensed smallpox vaccine		200	79	39	195	-	-	98	621

	PRNT		S+ %	GMT		S+ %	GMT	S+ %	GMT
2 doses of IMVAMUNE		92	5.4	1	75	92	54	99	125
Licensed smallpox vaccine		200	77	22	195	-	-	98	190

[1]Day 0 corresponding to day of booster vaccination with IMVAMUNE (pre-booster); Day 7 and 14 corresponding to 1 or 2 weeks after booster vaccination with IMVAMUNE; N = number of subjects in the specific study group; ELISA = enzyme-linked immunosorbent assay; PRNT = plaque reduction neutralization test; S+ = Seropositivity rate; GMT = geometric mean titer.

16 NON-CLINICAL PHARMACOLOGY AND TOXICOLOGY

Due to the absence of naturally occurring smallpox, the clinical efficacy of a smallpox vaccine cannot be directly demonstrated in humans, since it is not feasible and would not be ethical to expose people to an artificial smallpox infection (challenge). Therefore, clinical efficacy was inferred from nonclinical studies using animal challenge models (Section 16.1 and Section 10.2) as well as in clinical studies where immune responses induced by IMVAMUNE and by licensed smallpox vaccines were compared (Section 16.2).

16.1 Non-clinical Pharmacology

The pharmacodynamic properties of IMVAMUNE were assessed in mice and non-human primates (NHP). Variola, the causative agent of smallpox in humans, belongs to the *orthopox* family of viruses, which includes a number of closely related poxviruses e.g. mousepox virus (ectromelia virus [ECTV]), cowpox virus, mpox virus (MPXV) and vaccinia virus (VV). It has been well established that exposure to one of the poxviruses provides protection from some of the other *orthopox* family members and indeed, smallpox has been eradicated by a worldwide vaccination campaign using various VV strains e.g. Lister-Elstree or New York City Board of Healthy (e.g. Dryvax®).

Animal efficacy data have been generated in four separate animal models that have been specifically developed to demonstrate the efficacy of IMVAMUNE in comparison to replicating smallpox vaccines.

NHP studies using either a systemic (i.v.) or respiratory (i.t.) lethal challenge with MPXV have demonstrated:

- A single vaccination of IMVAMUNE (1 x 10^8 Inf.U) induces a comparable peak immune response (antibody and T cell) compared to ACAM2000 in cynomolgus macaques. A prime-boost regime of IMVAMUNE induced a higher peak antibody response (by ELISA and PRNT) compared to ACAM2000.
- The efficacy of Imvamune to protect cynomolgus macaques (*Macaca fascicularis*) against a mpox virus (MPXV) challenge was evaluated in several studies. Animals were administered a placebo or Imvamune (1 x 10^8 $TCID_{50}$) sub-cutaneously on day 0 and day 28. On day 63, animals were challenged with MPXV delivered by intravenous (5 x 10^7 pfu) or intratracheal (5 x 10^6 pfu) route. Across all studies, 80-100% of Imvamune-vaccinated animals survived compared to 0-33% of control animals.

Two murine models that utilize a lethal intranasal (i.n.) challenge with either VV Western Reserve (WR) or ECTV that closely mimic smallpox infection in humans were used to test vaccine efficacy. Findings from these studies demonstrated the following:

- A single vaccination with IMVAMUNE induces a comparable immune response (antibody and T cells) as replicating smallpox vaccines (Elstree, Dryvax and ACAM2000).
- A single vaccination with IMVAMUNE induces comparable protection in mice challenged (i.n.) with 50x murine lethal dose 50 (MLD_{50}) VV-WR as replicating smallpox vaccines (Elstree, Dryvax and ACAM2000).
- Similarly, vaccination of IMVAMUNE induces a robust protection in mice challenged (i.n.) with lethal doses of ECTV (58x to 580x MLD_{50}).
- Within 3–4 days of a single IMVAMUNE vaccination, mice are protected from a lethal (50x MLD_{50}) challenge (i.n.) with VV-WR, while animals vaccinated with replicating smallpox vaccines (e.g. Dryvax) are only protected 10–14 days later.
- A single vaccination with IMVAMUNE can induce protection in immune suppressed animals on the same day as a lethal challenge with ECTV. IMVAMUNE can protect all animals when given 2 days post challenge (post exposure) with a lethal dose of ECTV.
- There was a negative correlation between seroconversion (by ELISA) and VV titers in the lungs following a lethal challenge with VV-WR, pointing towards antibody responses as a good predictor for protection. Seroconversion by ELISA was correlated to the ability to predict protection in the mouse VV-WR challenge model. Using the optimal dose of IMVAMUNE (1 x 10^8 Inf.U) or 10-fold less, seroconversion by PRNT also correlated with protection.

16.2 Non-clinical Toxicology

The toxicity of IMVAMUNE was evaluated in repeated dose studies in rats and rabbits. Embryo-fetal development studies (segment II) were performed in rats and rabbits, and a peri- and postnatal development toxicity study (segment III) was performed in rats. The local tolerance of IMVAMUNE was evaluated as part of the repeat-dose toxicity studies.

Table 9 Toxicology Studies Overview

Type of Study	Species	Route of Administration	Dosing level (Inf.U)	Schedule/Duration
Repeat-dose toxicity	Rats / Crl:CD(SD)	Subcutaneous	4.9 x 10^8	4 applications within 22 days
	Rabbits / New Zealand White	Subcutaneous	4.9 x 10^8	2 applications at 8 days interval
	Rabbits / New Zealand White	Subcutaneous	1 x 10^7, 1 x 10^8	3 applications within 42 days
	Rabbits / New Zealand White	Subcutaneous	1 x 10^7, 1 x 10^8	3 applications within 42 days
Reproductive and develop-mental toxicity	Rats / Crl(Wi)BR-Wistar	Subcutaneous	1 x 10^7, 1 x 10^8	2 immunizations at 2 weeks interval
	Rabbits / New Zealand White	Subcutaneous	1 x 10^7, 1 x 10^8	3 immunizations at 2 weeks interval
	Rats / Crl:(Wi)BR-Wistar	Subcutaneous	1 x 10^7, 1 x 10^8	3 immunizations at 2 weeks interval

IMVAMUNE did not cause any life-threatening toxicity and there were no adverse changes in observed clinical signs, ophthalmology, clinical chemistry, urinalyses, gross tissue evaluation, organ weights or histopathologic tissue evaluation indicative of direct target organ toxicity when administered to rats and rabbits at doses up to 4.9 x 10^8 Inf.U applied up to 4 times within a period of 42 days. The dose of 4.9 x 10^8 Inf.U is approximately 5 times the dose (in absolute terms) and 20 - 200 times the dose (based on mg/kg) to be used in humans (i.e. 1 x 10^8 Inf.U of IMVAMUNE; two-dose vaccination regimen).

Haematological parameters did not provide any evidence for immunotoxic effects.

Local tolerance was evaluated in biodistribution studies as well as in the repeat-dose toxicity studies. The only reported clinical observations were swelling and red discoloration at the injection site.

In development toxicity studies, IMVAMUNE (up to 1 x 10^8 Inf.U; highest tested dose) had no adverse effect on gestation, lactation and maternal behaviour in female dams and on the behavioural/functional development of the offspring (F1 generation) of treated female rats and rabbits. No adverse effects on embryo-fetal development were observed when dosing IMVAMUNE 14 days prior to the day of sperm positivity (Day –14) and on the day of sperm positivity (Day 0) in rats and at 14 days prior to the day of sperm positivity (Day –14), on the day of sperm positivity (gestation Day 0), and on gestation Day 14 in rabbits. Vaccination with IMVAMUNE yielded a robust, dose dependent antibody response in dams and conferred passive immunity to their litters, confirming this species as relevant animal model for toxicity testing. Overall, nonclinical studies provided no evidence of perinatal toxicity or teratogenicity IMVAMUNE.

No specific juvenile animal studies were performed.

The toxicity study results demonstrate that IMVAMUNE induces reversible and vaccine expected side effects.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

IMVAMUNE®
Smallpox and mpox Vaccine
Modified Vaccinia Ankara-Bavarian Nordic® (live-attenuated, non-replicating)

Health Canada has authorized the sale of IMVAMUNE based on limited clinical testing in humans under the provision of the Extraordinary Use New Drug regulations. The authorization is based on the Health Canada review of the available quality, non-clinical and clinical data. Health Canada considers that the benefit/risk profile of IMVAMUNE is favourable for:

- active immunization against smallpox, mpox and related *orthopoxvirus* infection and disease in adults 18 years of age and older determined to be at high risk for exposure.

As part of the authorization for sale for IMVAMUNE Health Canada has requested the sponsor agree to post-market commitments. Adherence to these commitments, as well as updates to information on quality, non-clinical, and clinical data will be continuously monitored by Health Canada.
This vaccine is for exclusive use by the Canadian Government.

Read this carefully before you receive **IMVAMUNE**. This leaflet is a summary and will not tell you everything about this vaccine. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **IMVAMUNE**.

What is IMVAMUNE used for?

- IMVAMUNE is a vaccine that helps protect against smallpox, mpox and related *orthopoxvirus* infection and disease
- IMVAMUNE is indicated for individuals 18 years of age and older. This could include individuals:
  - Who are human immunodeficiency virus infected (CD4 ≥ 100 cells/μL)
  - Who have atopic dermatitis

How does IMVAMUNE work?

IMVAMUNE is used for vaccination (active immunization) against smallpox, mpox, and other orthopoxviruses. IMVAMUNE activates your immune system to help protect you from smallpox, mpox and *orthopoxvirus* infection and disease.
IMVAMUNE does not contain replicating viruses and cannot spread or cause orthopoxvirus disease (including smallpox and mpox).

What are the ingredients in IMVAMUNE?

Medicinal ingredients: Smallpox and mpox Vaccine
Modified Vaccinia Ankara-BN (live-attenuated, non-replicating)

Non-medicinal ingredients: sodium chloride
Trometamol
Water for injection
Traces of residual host cell DNA and protein, benzonase, gentamicin and ciprofloxacin

IMVAMUNE comes in the following dosage forms:

Suspension for injection, at least 0.5 x 10^8 Inf.U MVA-BN / dose

Do not use IMVAMUNE if:
- **You are below 18 years of age**

Individuals with the following conditions should discuss vaccination with their physician, who will be able to advise on safe vaccination or on alternative preventative measures to avoid infection with smallpox,mpox or other *orthopoxviruses*:
- Pregnant or breast feeding woman
- Persons with fever (temperature above 38.5°C)
- Persons with allergies to the active substance or any of the excipients (see ingredients)

To help avoid side effects and ensure proper use, talk to your healthcare professional before you receive IMVAMUNE. Talk about any health conditions or problems you may have, including if you:
- are or think you are pregnant or if you are breast feeding
- have any known allergies
- have a fever or you think you may be getting a fever

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines or vaccines.

How to receive IMVAMUNE:
The vaccine is to be given as a single dose by injection under the skin.

DO NOT INJECT INTRAVASCULARLY

Usual dose:
The primary vaccination series consists of two doses of 0.5 mL each according to the following schedule:
First dose: Day 0
Second dose: 28 days after first dose
Your doctor will advise on the need for a booster dose.

Overdose:
No case of overdose has been reported.

If you think you have received too much IMVAMUNE, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
Make sure you finish the complete vaccination course of two injections. If not, you may not be fully protected against the disease. If you miss a scheduled injection, talk to your doctor and arrange another visit.

What are possible side effects from using IMVAMUNE?

These are not all the possible side effects you may feel when receiving IMVAMUNE. If you experience any side effects not listed here, contact your healthcare professional.
Like all vaccines, IMVAMUNE can cause side effects, although not everybody gets them.

Anaphylactic shock is a rare but very serious event. Although no cases have been observed during clinical development of IMVAMUNE, these events may occur with any injectable vaccine. An allergic reaction causes symptoms in many parts of the body, often starting with tingling or swelling around the mouth and lips. The face and neck may swell and breathing may become difficult. Heartbeat is fast and may be irregular. A rash, hives or redness of the skin may occur and there may be diarrhea. If these symptoms occur, contact your physician or call your emergency services immediately.

The adverse reactions listed below have been observed during clinical studies. The most common side effects reported were at the injection site. Most of the reported adverse reactions are mild to moderate in intensity and resolving without intervention within seven days following vaccination.

Very common side effects reported in at least 1 in 10 persons were:
Pain, redness, swelling, hardness, or itching at the injection site.
Tiredness, headache, aching muscles, nausea.

Common side effects reported in at least 1 in 100 but less than 1 in 10 persons were:
Nodule, discolouration, bruising, warmth at the injection site, chills, fever, pain in extremity, joint pain, or loss of appetite.

Uncommon side effects reported in at least 1 in 1000 but less than 1 in 100 persons were:
Irritation, bleeding, scaling, inflammation, sensibility disorder, or reaction at the injection site. Underarm swelling, malaise, flushing, axillary pain, chest pain, dizziness, sensibility disorder, musculoskeletal stiffness, back pain, neck pain, rash, pruritus, dermatitis, skin discolouration, diarrhea, vomiting, dry mouth, throat pain, flu-like symptoms, cough, sleep disorder, clinically not relevant increase of cardiac enzymes, hepatic enzyme increased, white blood cell count decreased, mean platelet volume decreased, contusion, nose and throat infection, upper respiratory tract infection or temporarily enlarged lymph nodes.

Rare side effects reported in less than 1 in 1000 persons were:
Rash, anesthesia, dryness, movement impairment or vesicles at the injection site.
Weakness, influenza like illness, oedema peripheral, migraine, peripheral nerve sensations, muscle spasms, musculoskeletal pain, muscular weakness, urticarial, ecchymosis, increased sweating, night sweats, subcutaneous nodule, angioedema, abdominal pain, increased heartbeat, sinusitis, pink eye, mouth and throat pain, influenza, white blood cell count increased, vertigo.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
RARE Angioedema (swelling of the face, mouth and throat)		✓	✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough

to interfere with your daily activities, talk to your healthcare professional.

Reporting Suspected Vaccine Side Effects

For the general public: Should you experience a side effect following immunization, please report it to your doctor, nurse, pharmacist, or immunization provider.

Should you require information related to the management of the side effect, please contact your healthcare provider. The Public Health Agency of Canada, Health Canada and Bavarian Nordic cannot provide medical advice.

For healthcare professionals: If a patient experiences a side effect following immunization, please complete the Adverse Events Following Immunization (AEFI) Form appropriate for your province/territory (http://www.phac-aspc.gc.ca/im/aefi-essi-form-eng.php) and send it to your local Health Unit, or according to specified public health guidance.

STORAGE:
Your doctor or pharmacist is responsible for storing this vaccine and disposing of any unused product correctly. Do not use after the expiry date stated on the label.
Keep out of reach and sight of children.

If you want more information about IMVAMUNE:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website; the manufacturer's website http://www.bavarian-nordic.com, or by calling +45-3326-8383.

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