

**EU RISK MANAGEMENT PLAN**  
**IMVANEX<sup>®</sup> (SMALLPOX AND MPOX VACCINE**  
**MODIFIED VACCINIA ANKARA-BAVARIAN NORDIC**  
**(MVA-BN<sup>®</sup>) (LIVE ATTENUATED, NON-**  
**REPLICATING))**

**RMP version to be assessed as part of this application:**

Data lock point for this RMP

31-Jul-2022

Version number

9.3

Date of final sign off

06-Mar-2023

**Rationale for submitting an updated RMP:**

Considering the mpox outbreak in May 2022 and based on currently available safety information the indication of IMVANEX in EU is extended to include mpox and disease caused by vaccinia virus in adults in an accelerated procedure and approved on 22-Jul-2022. This version implements the PRAC recommendations received as part of the procedure EMEA/H/C/002596/II/0076.

**Summary of significant changes in this RMP:**

1. Indication extension to include mpox and disease caused by vaccinia virus in adults
2. Children and adolescents (<18 years) removed from the safety specification as this subpopulation is not included in the targeted indication
3. The term ‘safety experience in a mass vaccination due to a smallpox outbreak’ removed from the safety specification
4. Section SVI.2 Potential for medication errors deleted since requirement from superseded RMP template guidance. Safety concern “incorrect route of drug administration” deleted thus as well

5. Complete re-structuring of Part III.1 Routine Pharmacovigilance activities to comply to latest guidance” Core requirement for RMPs of COVID-19 vaccines” and other RMPs of authorised COVID-19 vaccines to align activities as much as possible
6. Addition of additional Pharmacovigilance activity: non-BN sponsored clinical study SEMVAc
7. Deletion of paediatric study POX-MVA-035. Paediatric studies are included in the Paediatric Investigation Plan of IMVANEX (EMA-001161-PIP02-11) and are therefore removed from this RMP

**Other RMP versions under evaluation:**

Not applicable

**Details of the currently approved RMP:**

Version number: 8.0

Approved with procedure: EMA/H/C/PSUSA/00010119/202107

Date of approval (opinion date): 10-Mar-2022

**EU-QPPV<sup>1</sup>:** Dr. Anna Stahl

**CSPV Physician:**

**Signature:**

**Signature:**

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<sup>1</sup> QPPV name will not be redacted in case of an access to documents request; see EMA/EMA Guidance document on the identification of commercially confidential information and personal data within the structure of the marketing-authorisation application; available on EMA website <http://www.ema.europa.eu>

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**ABBREVIATIONS**

AD	Atopic Dermatitis
ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
AR	Allergic Rhinitis
BN	Bavarian Nordic
CCDS	Company Core Data Sheet
CDC	Centers for Disease Control and Prevention
CEF Practice	Chicken Embryo FibroblastcGMP Current Good Manufacturing
CI	Confidence Interval
CSPV	Clinical Safety and Pharmacovigilance
DoD	Department of Defense
DRC	Democratic Republic of Congo
EEA	European Economic Area
ECDC	European Centre for Disease Prevention and Control
ECG	Electrocardiogram
EDLM	Electronic Data Logging Monitors
EPAR	European Public Assessment Report
eRMR	Electronic Reaction Monitoring Report.
EU	European Union
EVDAS	EudraVigilance Data Analysis System
GSDB	Global Safety Database
GVP	Good Pharmacovigilance Practices
HERA	European Health Emergency Preparedness and Response Authority

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HIV	Human Immunodeficiency Virus
HLT	High Level Term
ICH	International Conference on Harmonisation
ICSR	Individual Case Safety Report
ID	intradermal
IM	intramuscular
IMP	Investigational Medicinal Product
Inf.U	Infectious Units
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare Products Regulatory Agency
MPXV	Monkeypox Virus
MSM	Men who have Sex with Men
MVA-BN®	Modified Vaccinia Ankara – Bavarian Nordic
N	Number
NA	Not applicable
NIH	US National Institutes of Health
NYCBH	New York City Board of Health
O/E	Observed versus expected
PASS	Post-authorisation Safety Study
PAES	Post-authorisation Efficacy Study
PC	Product Complaint Report
PIP	Pediatric Investigation Plan
PrEP	Pre-exposure Prophylaxis
PRNT	Plaque Reduction Neutralization Test
PSUR	Periodic Safety Update Report

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PT	Preferred Term
PVA	Pharmacovigilance Agreement
RMP	Risk Management Plan
SAE	Serious Adverse Event
SC	subcutaneous
SDEA	Safety Data Exchange Agreement
SmPC	Summary of product characteristics
SMQ	Standardised MedDRA Queries
SOC	System Organ Class
SSR	Summary Safety Reports
STI	Sexually Transmitted Infection
SUSAR	Suspected Unexpected Serious Adverse Reaction
TCID	tissue culture infectious dose
UK	United Kingdom
US	United States
VAERS	Vaccine Adverse Event Reporting System
VE	Vaccine effectiveness
VV	Vaccinia Virus
WHO	World Health Organisation

**PART I: PRODUCT(S) OVERVIEW****Table 0.1: Product Overview**

<b>Active substance(s) (INN or common name)</b>	Live Modified Vaccinia Ankara-Bavarian Nordic (MVA-BN <sup>®</sup> )
<b>Pharmacotherapeutic group (ATC Code)</b>	Other viral vaccines (J07BX)
<b>Marketing Authorisation Holder</b>	Bavarian Nordic A/S Philip Heymans Allé 3 DK-2900 Hellerup Denmark
<b>Medicinal products to which this RMP refers</b>	Suspension for injection
<b>Invented name(s) in the European Economic Area (EEA)</b>	IMVANEX <sup>®</sup> (MVA-BN <sup>®</sup> )
<b>Marketing authorisation procedure</b>	Centralised
<b>Brief description of the product</b>	Chemical class: Other viral vaccines (J07BX)
	Summary of mode of action: IMVANEX is a live viral vaccine produced from the strain Modified Vaccinia Ankara-Bavarian Nordic (MVA-BN), a highly attenuated orthopox virus. MVA-BN is grown in chicken embryo fibroblast cells, harvested, purified and suspended in a Tris buffer (10 mM Tris, 140 mM NaCl, pH 7.7). The vaccine contains trace amounts of host cell DNA, protein, benzonase <sup>®</sup> and, the antibiotics gentamicin and ciprofloxacin. No preservative or adjuvant is added to the formulation.
	Important information about its composition:  The vaccine is filled with a nominal virus titer of $1 \times 10^8$ Inf.U/dose. One standard dose (0.5 mL) of the MVA-BN liquid frozen smallpox and mpox vaccine contains at least $0.5 \times 10^8$ Inf.U/0.5 mL dose throughout its shelf life.

<b>Brief description of the product (continued)</b>	<p>In 2017, the MVA-BN potency assay changed from a TCID<sub>50</sub> based assay to a flow cytometry based assay, and the units changed from TCID<sub>50</sub> to infectious units (Inf.U) (procedure EMEA/H/C/002596/II/0027, positive opinion 14-Sep-2017 EMA/CHMP/605563/2017). It should be emphasized that although the method of the potency assay changed from TCID<sub>50</sub> to flow cytometry and the unit changed from TCID<sub>50</sub> to Inf.U, the conversion factor was 1:1, therefore the established limits and specifications remain unchanged.</p> <p>The non-replicating smallpox vaccine was developed by BN for active immunisation for the prevention of smallpox virus infections and protection against smallpox disease in adults <math>\geq 18</math> years including persons with atopic dermatitis (AD) or allergic rhinitis (AR) and Human Immunodeficiency Virus (HIV) infected individuals (<math>CD4 \geq 100</math> cells/<math>\mu</math>L).</p> <p>Each 0.5 ml dose of vaccine is supplied as a liquid frozen suspension in a 2-ml type I glass vial for subcutaneous use.</p> <p>A primary vaccination series consists of 2 doses of no less than <math>5 \times 10^7</math> Inf.U IMVANEX, each dose administered 4 weeks apart via the subcutaneous (SC) route in vaccinia-naïve subjects, and a single booster dose of no less than <math>5 \times 10^7</math> Inf.U IMVANEX administered via the SC route in vaccinia and IMVANEX experienced subjects.</p>
<b>Hyperlink to the Product Information</b>	<a href="#">Product Information (eCTD seq 0172)</a>
<b>Indication(s) in the EEA</b>	<p>Current:</p> <p>Active immunisation against smallpox, monkeypox and disease caused by vaccinia virus in adults.</p> <p>The use of this vaccine should be in accordance with official recommendations.</p>
	<p>Proposed (if applicable):</p> <p>NA</p>

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<b>Dosage in the EEA</b>	<p>Current:</p> <p>One dose of 0.5 ml contains no less than <math>5 \times 10^7</math> Inf.U (infectious units)</p>
	<p>Proposed (if applicable):</p> <p>NA</p>
<b>Pharmaceutical form(s) and strengths</b>	<p>Current (if applicable):</p> <p>Suspension for injection. One dose (0.5 ml) contains:</p> <p>Modified Vaccinia Ankara – Bavarian Nordic Live virus<sup>1</sup> no less than <math>5 \times 10^7</math> Inf.U*</p> <p>*infectious units</p> <p><sup>1</sup> Produced in chick embryo cells</p>
	<p>Proposed (if applicable): NA</p>
<b>Is/will the product be subject to additional monitoring in the EU?</b>	<p>Yes</p>

**PART II SAFETY SPECIFICATION****PART II: MODULE SI EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)**

The indication for IMVANEX is active immunisation against smallpox, mpox and disease caused by vaccinia virus in adults.

The use of this vaccine should be in accordance with official recommendations.

**Incidence, Prevalence, Demographics of the population in the approved indication:**

The target population of IMVANEX is considered identical with the general population. In addition, due to the non-replicating properties, IMVANEX is expected to be used in individuals not eligible for vaccination with replicating smallpox vaccines like immunocompromised individuals and individuals with atopic dermatitis.

**Table 1 Indication epidemiology: General population (Healthy)**

<b>Indication/target population</b>	Smallpox vaccination of general population
<b>Incidence of target indication</b>	No smallpox infections reported since 26 Oct 1977
<b>Prevalence of target indication</b>	No smallpox infections reported since 26 Oct 1977
<b>Mortality in target indication</b>	10-90% (historic data)
<b>Potential health risk</b>	Severe, often fatal disease
<b>Demographic profile of target population</b>	≥18 years

**Table 2 Indication epidemiology: General population (HIV infected)**

<b>Indication/target population</b>	Smallpox vaccination in HIV infected subjects
<b>Incidence of target indication</b>	No smallpox infections reported since 26 Oct 1977
<b>Prevalence of target indication</b>	No smallpox infections reported since 26 Oct 1977
<b>Mortality in target indication</b>	Unknown
<b>Potential health risk</b>	Severe disease, potentially fatal

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<b>Demographic profile of target population</b>	≥18 years
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**Table 3 Indication epidemiology: General population (Atopic Disease)**

<b>Indication/target population</b>	Smallpox vaccination in subjects with atopy / atopic syndrome
<b>Incidence of target indication</b>	No smallpox infections reported since 26 Oct 1977
<b>Prevalence of target indication</b>	No smallpox infections reported since 26 Oct 1977
<b>Mortality in target indication</b>	Unknown
<b>Potential health risk</b>	Severe disease, potentially fatal
<b>Demographic profile of target population</b>	Young adults (incidence decreasing with age)

**Table 4 Indication epidemiology: Military population**

<b>Indication/target population</b>	Smallpox vaccination in military personnel
<b>Incidence of target indication</b>	No smallpox infections reported since 26 Oct 1977
<b>Prevalence of target indication</b>	No smallpox infections reported since 26 Oct 1977
<b>Mortality in target indication</b>	10-90% (assumed from general population risk)
<b>Potential health risk</b>	Severe disease, potentially fatal
<b>Demographic profile of target population</b>	≥18 years

**Table 5 Indication epidemiology: Laboratory personnel**

<b>Indication/target population</b>	Smallpox vaccination in laboratory personnel
<b>Incidence of target indication</b>	No smallpox infections reported since 26 Oct 1977
<b>Prevalence of target indication</b>	No smallpox infections reported since 26 Oct 1977
<b>Mortality in target indication</b>	10-90% (assumed from general population risk)
<b>Potential health risk</b>	Severe disease, potentially fatal

<b>Demographic profile of target population</b>	≥18 years
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Table 6 Indication epidemiology: First line responders

<b>Indication/target population</b>	Smallpox vaccination in first line responders
<b>Incidence of target indication</b>	No smallpox infections reported since 26 Oct 1977
<b>Prevalence of target indication</b>	No smallpox infections reported since 26 Oct 1977
<b>Mortality in target indication</b>	10-90% (assumed from general population risk)
<b>Potential health risk</b>	Severe disease, potentially fatal
<b>Demographic profile of target population</b>	≥18 years

Table 7 Indication epidemiology: Individuals at risk of exposure to mpox virus

<b>Indication/target population</b>	Mpox vaccination in individuals at risk of exposure to mpox virus
<b>Incidence of target indication</b>	Unknown/evolving
<b>Prevalence of target indication</b>	Unknown/evolving
<b>Mortality in target indication</b>	4-11%
<b>Potential health risk</b>	Severe disease, potentially fatal
<b>Demographic profile of target population</b>	≥ 18 years

### Natural history of smallpox, mpox and related orthopox, including vaccinia virus, in the untreated population and treatment options

Smallpox is caused by variola virus, an orthopoxvirus of the poxviridae family. Variola virus occurred in two variants: variola major, leading to the classical smallpox disease with a case fatality rate of 30–40%; and variola minor (alastrim) observed in the late phase of the smallpox era, leading to a less severe form with a case fatality rate of 1–2% (Fenner, 1988). Variola virus infects only humans, does not persist in humans and has no animal reservoir. It is transmitted from person-to-person, mainly via the respiratory route.

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Following an incubation period of approximately 12 to 14 days, early symptoms are characterized by sudden onset of fever, malaise, headache, backache and prostration. Two to 3 days later, the fever drops and a maculopapular rash with deeply embedded lesions appear on the mucosa of the mouth and on the face, hands and forearms, eventually progressing to the trunk, legs and feet in a centrifugal distribution pattern. The lesions appear in crops and progress to vesicular and pustular stages. Eight to 14 days after the onset of rash, scabs form, which can eventually lead to depressed, depigmented, pitted scars. Typical complications of smallpox are bacterial co-infections, keratitis with consecutive blindness, encephalitis, as well as spontaneous abortion and stillbirth in pregnant women. As such, smallpox is a serious disease associated with morbidity that has substantial impact on day to- day functioning and high likelihood to result in death or permanent disability.

A summary of the various forms of smallpox disease in humans is provided in [Table 8](#).

**Table 8 Summary of the Various Forms of Smallpox Disease in Man**

	<b>Form of smallpox disease</b>		
	<b>Haemorrhagic</b>	<b>Confluent</b>	<b>Discrete</b>
<b>Symptoms</b>	Head/Backache, vomiting, rash, anorexia, fever	Rash, eruptions, papules, vesicles	Rash, eruptions, papules, vesicles
<b>Time of symptoms to death (Days)</b>	4-7	15	>15
<b>Death rate (%)</b>	90-100	40	<10
<b>Time until diagnosis (Days)</b>	Up to 30 days after first case	>15	>15

Mpox is a viral zoonosis caused by the mypox virus, a member of the orthopoxvirus family. It was first identified in 1958 and the first cases of human mpox were reported in the 1970s in the Central African region. Mpox has since then been observed repeatedly in humans throughout Sub-saharan Africa, including West Africa and Central Africa ([McCollum, 2014](#)) The incidence of human mpox in the Democratic Republic of Congo (DRC) seems to be rising following the cessation of smallpox vaccination campaigns. In endemic countries incidences of human mpox virus infections in pediatric age groups are higher than in adult age groups ([Rimoin, 2010](#)) which might correlate with the lack of smallpox vaccine coverage as compared to older populations. However, in the last decades, the age of human mpox cases has gradually increased, probably in part due to growing proportions of the population without vaccination coverage ([Bunge, 2022](#))

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Since the first documentation of the large Nigerian mpox outbreak in 2017, cases exported to Western World countries were observed in 2018 in the UK and Israel, then again 2019 in the UK and Singapore ([Mauldin, 2022](#)) In 2020, no exported cases were reported, possibly due to COVID-19 related travel restrictions. With only limited resumption of international travel, new cases were observed in 2021 in the US and the UK ([Hobson, 2021](#)); ([Rao, 2022](#)) In the long-term perspective, Nigeria's working age population will be more than doubling to >240 million people by 2050, according to World Bank estimates, leading to advocacy for Nigeria to be part of the Global Skill Partnership program, which would support legal labor migration of Nigerians to Western World countries over the next decades ([Adhikari, 2019](#)). International long-distance travel to and from West and Central Africa is therefore projected to rise sharply over the next decades. At the same time, due to further waning of population immunity over time and population growth globally, disease modelling suggested (even before the current outbreak) that human mpox may soon reach pandemic potential, with a basic reproduction number above 1 when the proportion of unvaccinated individuals in a population falls below approx. 30% ([Grant, 2020](#))

Since May-2022, a multi-country outbreak of human mpox in a large number of previously non-endemic countries is going on, with yet unknown perspectives about the further course ([Saxena, 2022](#)). Results from a mathematical model, posted prior to peer review, suggest (based on still weak assumptions) that a very small number of sexually associated transmissions among the MSM (Men who have Sex with Men) population are sufficient to cause a large outbreak over the MSM sexual network. All scenarios projected that, without interventions or changes to sexual behaviour, a major outbreak in the MSM population (defined as  $\geq 10,000$  cases excluding initial cases) is highly likely given the current outbreak size. In contrast, sustained transmission in the non-MSM population is unlikely in all scenarios considered due to the less heavy tail of the corresponding partnership distribution, although from 10 up to 10,000 additional cases may be observed if a substantial number of infections are introduced into the non-MSM sexual contact network ([Endo, 2022](#)). A recent guidance document published by WHO recommends use of smallpox vaccines in the context of the mpox outbreak dependent on individual risk assessment in both, pre- and post-exposure prophylaxis scenarios ([WHO, 2022](#)).

In laboratories working with replicating orthopoxviruses such as vaccinia, accidental exposure of laboratory personnel is an occupational health risk. Cases of needlestick injuries or similar accidents leading to local infections with replicating vaccinia have repeatedly been reported (([Campe, 2009](#))[Whitehouse, 2019](#), [Isaacs, 2019](#), [Sennayake, 2009](#), [Hsu, 2015](#), [Wei, 2013](#), [Mousstaché, 2003](#)).

In addition, there are rare case reports of other orthopoxvirus transmissions, such as human cowpox infections, mostly from pet rodents or cats of questionable origin ([Campe, 2009](#), [Eder, 2015](#)). A

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previous smallpox vaccination decades ago was shown to lead to a milder clinical course in one of the reported cases.

Furthermore, the recently published de novo synthesis of horsepox virus may have direct implications for biosecurity by facilitating potential synthesis of other orthopox viruses, including variola, increasing the risk for emergence of new orthopoxvirus diseases ([Koblentz, 2017](#), [Noyce, 2018](#)).

In summary, there is a medical need for vaccines protective across the whole orthopoxvirus spectrum. The cross-protectivity of orthopoxvirus vaccines has been first described by Edward Jenner in 1798 and was the basis for the successful smallpox eradication campaign.

In the EU, no other prophylactic vaccines are specifically licensed for mpox or other orthopoxvirus infections. IMVANEX is currently approved in the EU for prevention of smallpox, mpox and disease caused by vaccinia in adults. In the US, it is approved under the tradename JYNNEOS for prevention of mpox. In Canada it is approved under the tradename IMVAMUNE, the approval includes the indications against mpox and related orthopoxviruses.

Symptomatic treatment of orthopoxvirus infections includes close supervision of the patient and fluid replacement. Antibiotics are restricted to patients with bacterial superinfection. Available therapies for smallpox (and other orthopox) include the approved TPOXX (tecovirimat developed by SIGA Technologies Inc.) and the antiviral agent cidofovir (Gilead Sciences, Inc), as well as the potential use of CNJ-016 (Vaccinia Immune Globulin Intravenous [Human]; Cangene Corporation) and of the (currently) investigational antiviral agent brincidofovir (Chimerix, Inc.).

Historically, as a passive immunization method, intravenous vaccinia immunoglobulin (IVIG) produced from sera of recently vaccinated individuals was available to treat complications of replicating vaccinia vaccinations, such as generalized spread of vaccinia.

#### Important co-morbidities:

Table 9 Important co-morbidity in different target populations

Indication/target population	Important co-morbidity
General population	As per general population, e.g. cardiovascular and malignancies
HIV individuals	Hepatitis, malignancies, opportunistic infections, hyperlipidemia, atherosclerosis, coronary artery disease, cardiomyopathy
Atopic individuals	Asthma, rhinitis, conjunctivitis

<b>Military personnel</b>	None
<b>First-line responders</b>	None
<b>Laboratory personnel</b>	None

## PART II: MODULE SII NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Key safety findings from non-clinical studies and relevance to human usage:

### SII.1 Toxicity

- Key issues identified from acute or repeated-dose toxicity studies

IMVANEX has been shown to be safe and well tolerated in a toxicity programme conducted in rats and rabbits, investigating acute and repeated dose toxicity, local tolerance, as well as reproduction toxicity with segment II (teratology) and segment III (peri- and postnatal toxicity) studies. Moreover, a bio-distribution study supports the *in-vitro* finding that IMVANEX is replication deficient (Suter, 2009), since it only remained detectable for the first few days post administration.

Taken together, all preclinical studies show a good safety profile following up to four administrations via various routes (intramuscular [IM] or subcutaneously [SC]) at doses as high as  $4.9 \times 10^8$  TCID<sub>50</sub>:

- No mortality or clinical signs indicative of systemic toxicity were observed at dose levels up to  $4.9 \times 10^8$  TCID<sub>50</sub> of IMVANEX.
- Repeated administrations (SC and IM) of IMVANEX resulted in injection site irritations and some lymphoid changes in both rats and rabbits. However, these effects were minimal and reversible and are therefore not considered to be dose-limiting.
- In developmental toxicity studies IMVANEX (up to  $1 \times 10^8$  TCID<sub>50</sub>) neither induced a teratogenic effect nor caused intrauterine toxicity to conceptuses.
- IMVANEX did not have any adverse effect on dams or the intrauterine development of embryos. Furthermore, it did not have any effect on lactating females or their developing offspring.

In addition, the following results on immunogenicity and efficacy were collected in the toxicity programme:

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- Vaccination with IMVANEX via SC and IM routes resulted in a dose related immune response to vaccinia in rats and rabbits.
- Vaccination with IMVANEX yielded a robust, dose dependent antibody response in dams and conferred passive immunity to their litters.
- IMVANEX has also been shown to induce an efficacy comparable to replicating smallpox vaccines in relevant mouse and non-human primate models. Since results of the reproductive toxicity and bio-distribution studies are of particular interest for this product, details of these studies are provided below.

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- Reproductive/developmental toxicity

Four reproductive studies on embryo-fetal toxicity were performed in two species, rat and rabbits, and included segment II and III studies. The same dose levels,  $1 \times 10^7$  and  $1 \times 10^8$  TCID<sub>50</sub> IMVANEX, were applied in all three reproductive toxicity studies.

$1 \times 10^8$  TCID<sub>50</sub> IMVANEX is also the maximum human dose; the route of administration, SC, mimics the clinical route of administration.

The following treatment schedules aimed at maximizing exposure of the developing fetus to the vaccine and to the immune response induced. As for other vaccines, the priming dose was applied prior to mating, and additional doses were applied during the period of gestation; in detail:

- Segment II – rat: two vaccinations, Day –14, and Day 0; (day 0: day of sperm positivity)
- Segment II – rabbit: three vaccinations, Day –14, Day 0, and Day 14;
- Segment III – rat: two vaccinations, Day –14, and Day 0;
- Segment II – rat: two vaccinations, Day 0 and Day 6;

In these studies, traditionally used endpoints were chosen to evaluate the potential for developmental effects. IMVANEX had no adverse effects on gestation, lactation or maternal behaviour in female dams nor 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 IMVANEX 14 days prior to the day of sperm positivity (Day –14), on the day of sperm positivity (Day 0) and on gestation day 6 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 of rabbit pregnancy.

As the same dose level and treatment frequency was used in the rat segment II and III studies, reference regarding embryo-fetal exposure to MVA-specific antibodies during organogenesis between the two studies seems justified and the data confirm the presence of MVA-specific antibodies in milk and fetal serum up to day 28 *post partum*.

Altogether, the results (further supported by immune response data collected as part of the repeated dose studies) confirm these species as relevant animal model for toxicity testing and confirm that dams were exposed to the immune response, which is the active principle of the vaccine, during organogenesis of the embryos.

Direct exposure to the test item, the vaccine antigen, was addressed in the peri-/postnatal study.

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In this study follow up of the pups from birth to day 28 *post partum* was performed to assess normal growth, nursing activity, body weight gain, and viability, and developmental landmarks (surface-righting reflex, pinna detachment, incisors' eruption, and eye opening), which are considered the best currently available indicators for normal development. Pups were further subjected to necropsy, and gross pathology investigations on the presence of any abnormalities/malformations. These parameters did not reveal vaccine-induced adverse effects in either pregnant or lactating animals, embryo or fetal development, or development of offspring. In addition, all components of the formulation are well known and direct embryotoxic effects of any excipient of the vaccine formulation can be excluded; the formulation does not contain any adjuvant.

## SII.2 Safety pharmacology

### Cardiovascular system

**Myocardial findings:** During nonclinical development of IMVANEX macroscopic and microscopic cardiac evaluations were included in the rabbit studies displayed in [Table 10](#) below. All studies were conducted under Good laboratory practice conditions. Except for study M249-03 (intramuscular administration), all animals were treated subcutaneously (SC).

**Table 10 Cardiac evaluations in rabbit studies with IMVANEX**

Species / strain	Duration of dosing	Dose Level (TCID <sub>50</sub> )	Study number
<b>Repeated-dose toxicity</b>			
Rabbits / New Zealand White	2 applications at 8 days interval	4.9 x 10 <sup>8</sup>	HPA0006/074055
Rabbits / New Zealand White	3 applications within 42 days	1 x 10 <sup>7</sup> , 1 x 10 <sup>8</sup>	M254-03
Rabbits / New Zealand White	3 applications within 42 days	1 x 10 <sup>7</sup> , 1 x 10 <sup>8</sup>	M249-03
<b>Reproductive and developmental toxicity</b>			
Rabbits / New Zealand White	3 immunisations at 2 weeks interval	1 x 10 <sup>7</sup> , 1 x 10 <sup>8</sup>	BN-PRE-06-004

A summary of all findings on the heart, irrespective of necropsy time point and study type, is given below:

**Table 11 Findings on the heart, irrespective of necropsy time point and study type**

	<b>0 (Control)</b>	<b>1 x 10<sup>7</sup></b>	<b>1 x 10<sup>8</sup></b>	<b>4.9x10<sup>8</sup></b>
<b>Rabbit</b>				
<b>Macroscopic cardiac findings:</b>				
Atrium Discoloured	0 / 90	0 / 24	1 / 64 *	0 / 26
<b>Microscopic cardiac findings:</b>		n.a.		
Degeneration, Myofiber	0 / 66		1 / 40*	-
Inflammation	2 / 66		3 / 40*	-
Myocardial Inflammatory Cell Infiltrate	0 / 66		-	4 / 26
Adipose Tissue-Inflammatory Cell Infiltrate	1 / 66		-	0 / 26
Inflammation, Endocardium	0 / 66		1 / 40	1 / 26
Inflammation, Pericardium	2 / 66		0 / 40	-
Inflammation, Chronic, Pericardium	1 / 66		0 / 40	
Subacute Inflammation	0 / 66		1 / 40	-
Chronic Inflammation	0 / 66		1 / 40	-

- not detected

\* at terminal sacrifice, the right atrium of the heart of the high dosed male (number 52 in study M254-03) was discoloured pink and the left atrium was pale; microscopic findings of myofiber degeneration and inflammation were observed in this tissue. The spleen of the same animal was described as slightly small at necropsy, but there were no correlative microscopic findings in this tissue.

The table above shows a very low frequency of findings, supporting the conclusion that cardiac findings in animal number 52 in study M254-03 are considered a spontaneous background finding in rabbits.

However, to reduce any potential safety risk, heart sections of this study were re-examined by two histopathologists (control and high dosed groups): This re-examination followed the specific intent of recording any observations, including those that were so slight and that were considered normal in the initial evaluation. Although additional observations were made noting tissue inflammation, the severity and distribution in the tissues examined were minimal. There were no modifications to the initial interpretation of clinical histopathology findings for this study: Both histopathologists came to the conclusion, that these minor findings in the heart sections were sporadic and are therefore not attributed to the vaccinia vaccination. They also did not find any positive correlation between the cardiac findings and inflammation response at the injection site, or any other pathological correlate.

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In conclusion, with respect to the usage of the vaccine the findings in animal toxicology studies do not suggest any risk for cardiotoxicity to humans following SC vaccination with IMVANEX.

### **SII.3 Safety concerns that have not been adequately addressed by clinical data or which are of unknown significance**

There are no safety concerns from nonclinical studies.

Bavarian Nordic (BN) had agreed to conduct an additional Segment II study in rats as a post-authorisation commitment. The study followed the Note for guidance on the development of vaccinia virus-based vaccines against smallpox (CPMP/1100/02), as suggested, with the exception that instead of a single intradermal vaccination, two doses of  $1 \times 10^8$  TCID<sub>50</sub> of IMVANEX were administered subcutaneously. The first immunisation occurred on the day of conception (sperm positivity) and the second immunisation was performed 6 days after conception with the aim to target the first trimester of pregnancy.

**Table 12 Study design**

Group	Number of dams	Control/Test Article
1	25	Saline Control
2	25	$1 \times 10^8$ TCID <sub>50</sub> IMVANEX

**Table 13 Study schedule**

Day	Procedure
0*	Bleed and first administration of control/test article
6	Bleed and second administration of control/test article
20	Bleed, C-section and sacrifice

\* Day of sperm positivity

This study (BN-PRE-13-012) was completed and identified no effect on maternal or developmental toxicity.

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**Table 14 Key safety findings (from non-clinical studies)**

<b>Key Safety findings (from non- clinical studies)</b>	<b>Relevance to human usage</b>
Toxicity including: Single and repeated-dose toxicity, reproductive (must be discussed if medicine might be used in women of child-bearing potential) developmental toxicity nephrotoxicity hepatotoxicity genotoxicity carcinogenicity	None
General safety pharmacology: cardiovascular (including potential for QT interval prolongation) nervous system etc.	None
Mechanisms for drug interactions	Not applicable
Other toxicity-related information or data	Not applicable

### **Need for additional non-clinical data if the product is to be used in special populations**

There is no targeted special population requiring specific nonclinical data.

## SII.4 Conclusions on non-clinical data

Reproduction and developmental toxicity studies did not reveal vaccine-induced adverse effects in either pregnant or lactating animals, embryo or fetal development, or development of offspring. In conclusion, with respect to the usage of the vaccine the findings in animal toxicology studies do not suggest any risk for cardiotoxicity to humans following SC vaccination with IMVANEX.

However, given that myo-/pericarditis is a known adverse drug reaction to replicating smallpox vaccines, it will be considered an important potential risk.

There are no safety concerns from non-clinical studies that have been confirmed by clinical data, have not been adequately refuted by clinical data, which are of unknown significance, or which need to be analysed further.

There are no safety concerns from nonclinical studies.

**Table 15 Safety concerns**

<b>Safety concerns</b>	
Important identified risks (confirmed by clinical data)	None
Important potential risks (not refuted by clinical data or which are of unknown significance)	None
Important missing information	None

## PART II: MODULE SIII CLINICAL TRIAL EXPOSURE

### SIII.1 Brief overview of development

The original, replicating smallpox vaccines were based on a number of different VV strains, e.g. the Lister-Elstree strain used primarily in Europe or the Dryvax® New York City Board of Health (NYCBH) strain used in the United States (US) and in Canada. These first-generation vaccines were produced using outdated production methods (i.e. growing the virus on the skin of calves prior to harvest and lyophilisation), which would not comply with today's current Good Manufacturing Practice (cGMP) requirements. Remaining lots of Dryvax expired in 2008.

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In the US, Dryvax has been replaced by ACAM2000® a replicating smallpox vaccine based on the Dryvax NYCBH strain and manufactured in cell cultures according to cGMP standards. ACAM2000 is indicated for active immunisation against smallpox disease for persons determined to be at risk for smallpox infection and is not commercially available to the public. Although replicating smallpox vaccines proved to be highly effective immunising agents making the eradication of smallpox possible, they also show considerable side effects. Due to the formation of a virus filled pustule and replication of the VV they can cause severe and even life-threatening complications, particularly in people with immune deficiencies and skin disorders. Furthermore, in clinical trials an unexpected high frequency of myo-/pericarditis was observed for Dryvax and ACAM2000 (incidence of 10.38 events/thousand and 5.73 events/thousand, respectively).

Bavarian Nordic (BN) has developed a non-replicating vaccine which represents a safer alternative to the first- and second-generation smallpox vaccines.

BN's non-replicating vaccine against smallpox, mpox and disease caused by vaccinia, IMVANEX, is prepared from the Modified Vaccinia Ankara – Bavarian Nordic (MVA-BN) strain, which is a highly attenuated orthopox virus strain, propagated in Chicken Embryo Fibroblast (CEF) cells.

The non-replicating vaccine against smallpox, mpox and disease caused by vaccinia, was developed by BN for active immunisation for the prevention of smallpox virus infections and protection against smallpox disease in adults  $\geq 18$  years including persons with atopic dermatitis (AD) or allergic rhinitis (AR) and Human Immunodeficiency Virus (HIV) infected individuals ( $CD4^+ \geq 100$  cells/ $\mu$ L).

A primary vaccination series consists of 2 doses of no less than  $5 \times 10^7$  Inf.U IMVANEX each dose administered 4 weeks apart via the subcutaneous (SC) route in vaccinia-naïve subjects, and a single booster dose of no less than  $5 \times 10^7$  Inf.U IMVANEX administered via the SC route in vaccinia- and IMVANEX-experienced subjects.

IMVANEX was centrally authorised in July 2013. At present, one pharmaceutical form is authorised.

## SIIL.2 Clinical trial exposure

BN has collected data of 26 completed clinical trials (17 sponsored by BN, 9 non-BN sponsored) evaluating the safety and immunogenicity of IMVANEX in both healthy subjects and special populations with contraindications to replicating smallpox vaccines; namely individuals diagnosed with atopic dermatitis or infected with HIV.

These include:

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- three dose ranging trials in healthy subjects (POX-MVA-001, POX-MVA-002 and POX-MVA-004; POX-MVA-002 was NIH sponsored and also included a direct comparison of MVA-BN to Dryvax as well as an efficacy evaluation of MVA-BN).
- a phase 1/2 and a phase 2 trial comparing the safety and immunogenicity of MVA-BN in HIV infected subjects to healthy subjects (POX-MVA-010 and POX-MVA-011).
- a phase 1 and a phase 2 trial comparing the safety and immunogenicity of MVA-BN in subjects diagnosed with AD to healthy subjects (POX-MVA-007 and POX-MVA-008).
- a placebo-controlled phase 2 trial in healthy subjects (POX-MVA-005).
- a phase 2 trial investigating the booster response of MVA-BN two years following previous vaccination of healthy subjects enrolled in POX-MVA-005 (POX-MVA-023).
- a phase 2 trial to evaluate MVA-BN in an older adult (aged 56 to 80 years) population (POX-MVA-024).
- a phase 1/2 trial (NIH sponsored) evaluating different vaccination regimens of MVA-BN in healthy adults (POX-MVA-009).
- a phase 2 trial (NIH sponsored) comparing the safety and immunogenicity of a high dose and a standard dose of MVA-BN in healthy vaccinia-naïve individuals (POX-MVA-028).  
a phase 2 trial (NIH sponsored) comparing the safety and immunogenicity of lyophilized MVA-BN (standard dose) versus liquid formulation MVA-BN (standard dose) administered by the SC route and a lower dose liquid formulation MVA-BN ( $2 \times 10^7$  TCID<sub>50</sub>) administered by the ID route in healthy vaccinia-naïve individuals (POX-MVA-029).
- a placebo-controlled phase 1 trial (NIH sponsored) evaluating the safety and immunogenicity of MVA-BN after administration of either a low dose ( $1 \times 10^7$  TCID<sub>50</sub>) or the standard dose in persons with prior hematopoietic stem cell transplantation (HSCT) (POX-MVA-030).
- a randomized, double-blind, placebo-controlled phase 3 trial to evaluate immunogenicity and safety of three consecutive production lots of MVA-BN smallpox vaccine in healthy, vaccinia-naïve subjects, receiving MVA-BN in a 3:1 ratio versus Placebo (POX-MVA-013).
- POX-MVA-006, a pivotal, randomized, open-label phase 3 non-inferiority trial to compare indicators of efficacy for MVA-BN smallpox vaccine to ACAM2000 in 18-42 year old healthy vaccinia-naïve subjects.
- a randomized, double-blind, multicenter phase 2 trial to compare the immunogenicity and safety of a liquid frozen and a freeze-dried formulation of MVA-BN smallpox vaccine in vaccinia-naïve healthy subjects (POX-MVA-027).

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- a phase 2 (NIH sponsored), randomized, open-label trial to evaluate the safety and immunogenicity of MVA-BN smallpox vaccine using three immunization schedules and two modes of delivery (POX-MVA-036).
- POX-MVA-037, a randomized, open-label phase 2 trial to assess the safety and immunogenicity of MVA-BN smallpox vaccine when increasing the number of injections compared to the standard regimen in immunocompromised subjects with HIV infection.
- POX-MVA-031, a randomized, double-blind, multicenter phase 3 trial to evaluate the immunogenicity and safety of three consecutive production lots of a freeze-dried formulation of MVA-BN smallpox vaccine in healthy, vaccinia-naïve subjects.
- POX-MVA-03X, a BN sponsored Special Access Program providing prophylactic vaccination with MVA-BN for personnel working directly with or in the vicinity of replicating vaccinia virus (included 22 male and female volunteers, aged 18 to 65).
- Public Health England (PHE) introduced an observational surveillance type of study named “A Cohort Study of serological responses to MVA-BN Smallpox Vaccine (IMVANEX) Administered During a Monkeypox Outbreak in the UK” with a planned number of 120 participants.
- MVA-BN has been used as a control arm in HIV infected subjects in two phase 1/2 trials evaluating the safety and immunogenicity of two recombinant MVA-based vaccines. One trial (HIV-NEF-004) compared MVA-BN to a recombinant MVA-based vaccine encoding the nef gene from HIV (MVA-Nef), while a second trial (HIV-POL-002) compared MVA-BN to a recombinant MVA-vaccine encoding multiple T cell epitopes from various HIV genes (MVA-HIV polytope).
- MVA-BN has been administered in the control arm of healthy subjects in a phase 1 double-blind, placebo-controlled study (NIH sponsored) to evaluate the safety and immunogenicity of a recombinant MVA-BN yellow fever vaccine candidate (MVA-BN-YF), with and without the montanide ISA 720 adjuvant, using different immunization schedules.
- A non-BN-sponsored clinical trial, the open label phase 0 study titled “A Study Exploring the Use of Vaccine and Antigen Challenges for Immune Monitoring in Healthy Participants” sponsored by Janssen Research & Development LLC. This study investigated immune status changes provoked by several interventions, including administration of IMVANEX.

In total, the number of subjects having received the final dose of no less than  $5 \times 10^7$  TCID<sub>50</sub> of IMVANEX in the context of clinical trials, as per recommended schedule (2 doses of no less than  $5 \times 10^7$  TCID<sub>50</sub> 4 weeks apart in vaccinia-naïve subjects; 1 single dose of no less than  $5 \times 10^7$  TCID<sub>50</sub> in vaccinia-experienced subjects) is 7490. Five of the BN sponsored clinical trials included at-risk populations for which replicating smallpox vaccines such as Dryvax and

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ACAM2000 are contraindicated, e.g. individuals with atopic dermatitis or HIV infected subjects. Current clinical experience until the DLP of the RMP covers a total of N=9116 in completed trials and other studies with IMVANEX (including 152 vaccinees that were included twice, as having been part of studies POX-MVA-005 and POX-MVA-023); N=8992 in completed clinical trials. No trends for unexpected and/or serious adverse reactions were detected and no difference in the safety profile has been observed between vaccinia-naïve and vaccinia-experienced subjects receiving IMVANEX. The safe administration of IMVANEX in the general population (18-55 years of age) is further substantiated by safety data from immunocompromised populations that have contraindications for receiving conventional smallpox vaccines, e.g. individuals with HIV or AD. The available data in these subjects as well as in healthy individuals revealed no special risks or safety concerns following IMVANEX administration (reviewed in Kennedy, 2009; Jones, 2008). In addition, safe administration of IMVANEX has also been demonstrated in the elderly population 56-80 years of age (total of 120 vaccinees). Based on currently available clinical data, vaccination with IMVANEX is safe and well tolerated. The majority of adverse drug reactions (ADRs) are related to local, injection-site reactions of mild to moderate intensity, which were completely reversible within days.

### III.3 Clinical trial exposure

Randomized trials referred to in the following tables are: POX-MVA-001, POX-MVA-002, POX-MVA-004, POX-MVA-005, POX-MVA-006, POX-MVA-009, POX-MVA-013, POX-MVA-024, POX-MVA-027, POX-MVA-028, POX-MVA-029, POX-MVA-030, POX-MVA-031, POX-MVA-036, POX-MVA-037, HIV-POL-002, HIV-NEF-004.

Open trials referred to in the following tables are: POX-MVA-007, POX-MVA-008, POX-MVA-010, POX-MVA-011, POX-MVA-023, POX-MVA-03X.

**Table “Duration of exposure” is not applicable for a vaccine, as there is no administration over a time period.**

**Table 16 Exposure to IMVANEX by number of doses**

<b>Doses</b>	<b>Persons (randomized trials)</b>	<b>Persons (open trials)</b>	<b>Total</b>
1	1002	314	1316*
2	6337	1282	7619**
3	65	0	65

\* Please note that the total number of subjects exposed is strictly speaking lower, as 152 vaccinees were exposed twice, first in the randomized trial POX-MVA-005, and later in the open trial POX-MVA-023. \*\* 8 subjects exposed but not included in analysis. 7 subjects in POX-MVA-009 received Dryvax either on the same day or within 7 days after MVA-

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BN administration and were therefore not included to avoid a potential bias in the adverse event reporting. 1 subject in POX-MVA-029 was not vaccinated according to the randomization, therefore removed from analysis set.

**Table 17 Exposure to IMVANEX by dose strength**

<b>Strength</b>	<b>Persons (randomized trials)</b>	<b>Persons (open trials)</b>	<b>Total</b>
10 <sup>6</sup> TCID <sub>50</sub>	18	0	18
10 <sup>7</sup> TCID <sub>50</sub>	358	0	358
10 <sup>8</sup> TCID <sub>50</sub>	6954	1596	8550 *,**
2 x 10 <sup>8</sup> TCID <sub>50</sub>	29	0	29
5 x 10 <sup>8</sup> TCID <sub>50</sub>	45	0	45

\* Please note that the total number of subjects exposed is strictly speaking lower, as 152 vaccinees were exposed twice, first in the randomized trial POX-MVA-005, and later in the open trial POX-MVA-023. \*\* 8 subjects exposed but not included in analysis. 7 subjects in POX-MVA-009 received Dryvax either on the same day or within 7 days after MVA-BN administration and were therefore not included to avoid a potential bias in the adverse event reporting. 1 subject in POX-MVA-029 was not vaccinated according to the randomization, therefore removed from analysis set.

**Table 18 Clinical exposure to IMVANEX (BN sponsored trials) by age group and sex**

<b>Age group</b>	<b>Male</b>			<b>Female</b>		
	<b>rand. trials</b>	<b>open trials</b>	<b>total</b>	<b>rand. trials</b>	<b>open trials</b>	<b>total</b>
Adult (age range 18-55 years)	3598	888	4486*,**	3680	706	4386*,**
Elderly (age range 56-80 years)	49	2	51	77	0	77
Total	3647	890	4537*,**	3757	706	4463*,**

\* Please note that the total number of subjects exposed is strictly speaking lower, as 152 vaccinees (67 males, 85 females) were exposed twice, first in the randomized trial POX-MVA-005, and later in the open trial POX-MVA-023. \*\* 8 subjects exposed but not included in analysis. 7 subjects in POX-MVA-009 received Dryvax either on the same day or within 7 days after MVA-BN administration and were therefore not included to avoid a potential bias in the adverse event reporting. 1 subject in POX-MVA-029 was not vaccinated according to the randomization, therefore removed from analysis set.

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**Table 19 Exposure to IMVANEX by ethnic origin\*, \*\*, \*\*\***

<b>Ethnic group</b>	<b>Persons (randomized trials)</b>	<b>Persons (open trials)</b>
Caucasians (incl. others)	6091	1220
Black	1096	284
Asian	183	92

\* Please note that the total number of subjects exposed is strictly speaking lower, as 152 vaccinees (67 males, 85 females) were exposed twice, first in the randomized trial POX-MVA-005, and later in the open trial POX-MVA-023.

\*\* 8 subjects exposed but not included in analysis. 7 subjects in POX-MVA-009 received Dryvax either on the same day or within 7 days after MVA-BN administration and were therefore not included to avoid a potential bias in the adverse event reporting. 1 subject in POX-MVA-029 was not vaccinated according to the randomization, therefore removed from analysis set.

\*\*\* The overall number of subjects in this table amounts to 8966. The remaining 34 subjects either had ethnic origin not reported or were of “other” ethnic groups than those displayed in this table.

**Table 20 Exposure to IMVANEX by past Vaccinia exposure\*, \*\***

<b>Vaccinia</b>	<b>Persons (randomized trials)</b>	<b>Persons (open trials)</b>
Naïve	7029	1209
Experienced	375	387

\* Please note that the total number of subjects exposed is strictly speaking lower, as 152 vaccinees (67 males, 85 females) were exposed twice, first in the randomized trial POX-MVA-005, and later in the open trial POX-MVA-023.

\*\* 8 subjects exposed but not included in analysis. 7 subjects in POX-MVA-009 received Dryvax either on the same day or within 7 days after MVA-BN administration and were therefore not included to avoid a potential bias in the adverse event reporting. 1 subject in POX-MVA-029 was not vaccinated according to the randomization, therefore removed from analysis set.

**Table 21 Exposure to IMVANEX - Special populations**

	<b>Persons (randomized trials)</b>	<b>Persons (open trials)</b>
Allergy / atopic dermatitis	0	381
HIV	123	573

In addition, 32 female vaccinees became pregnant after vaccination.

Epidemiological study exposure

No epidemiologic studies have been performed with IMVANEX.

## **PART II: MODULE SIV POPULATIONS NOT STUDIED IN CLINICAL TRIALS**

### **SIV.1 Limitations of ADR detection common to clinical trial development programmes**

<b>Ability to detect adverse reactions</b>	<b>Limitation of trial programme</b>	<b>Discussion of implications for target population</b>
Which are rare	8992 individuals were exposed during the whole CT programme	ADRs with frequency greater than 1 in 2627 could be detected if there were no background incidence
Which have a long latency	Follow-up period in most clinical trials was 6 months, except for POX-MVA-023, where subjects that had previously received vaccinations in POX-MVA-005 had booster vaccines 2 years later	Neither 6 months nor 2 year-data suggest any late onset adverse reactions.
In special patient groups	Geriatric (aged 65+)	ADRs with frequency greater than 1 in 42 could be detected if there were no background incidence
	Allergy / atopic dermatitis	ADRs with frequency greater than 1 in 127 could be detected if there were no background incidence
	HIV	ADRs with frequency greater than 1 in 232 could be detected if there were no background incidence

## 1.8.2 Risk Management Plan

### SIV.2 Exclusion criteria in pivotal clinical studies within the development programme

The table below lists safety relevant exclusion criteria for pivotal and supporting clinical trials. Since these are the common exclusion criteria applied for all clinical trials they are only listed once.

**Table 22 Population in clinical studies: Main exclusion criteria**

Study number	Individuals exposed to product	Age range	Safety relevant exclusion criteria, common for all studies
POX-MVA-001	86	20-55	<ul style="list-style-type: none"> <li>- Uncontrolled serious infection</li> <li>- Malignancy or history of malignancy</li> <li>- History or clinical manifestation of clinically significant and severe hematological, renal, hepatic, pulmonary, central nervous, cardiovascular or gastrointestinal disorders.</li> <li>- History and risk of coronary heart diseases</li> <li>- History of alcohol abuse/intravenous drug abuse</li> <li>- History of anaphylaxis or severe allergic reaction and of allergic disease or reactions likely to be exacerbated by any component of the vaccine.</li> <li>- History or clinical manifestation of immune modifying conditions / diseases or immune modifying therapies</li> </ul>
POX-MVA-002	75	18-32	
POX-MVA-004	164	18-30	
POX-MVA-005	564	18-55	
POX-MVA-006	220	18-42	
POX-MVA-007*	60	18-40	
POX-MVA-008*	632	18-40	
POX-MVA-009	199	18-35	
POX-MVA-010*#	151	18-49	
POX-MVA-011*#	579	18-55	
POX-MVA-013	3003	18-40	
POX-MVA-023*	152	20-57	
POX-MVA-024	119	56-80	
POX-MVA-027	651	18-55	
POX-MVA-028	91	18-37	
POX-MVA-029	524	18-38	
POX-MVA-030	20	18-60	
POX-MVA-031	1129	18-45	
POX-MVA-036	435	18-40	
POX-MVA-037#	87	18-45	
HIV-NEF-004#	26	18-60	
HIV-POL-002#	10	18-50	
POX-MVA-03X*	22	18-65	

\*open label studies

# for these studies, HIV infection was not an exclusion, but an inclusion criterion

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**Table 23 Exclusion criteria which will remain as contraindications**

<b>Exclusion criteria which will remain as contraindications</b>	
<b>Criteria</b>	<b>Implications for target population</b>
History of anaphylaxis or severe allergic reaction and of allergic disease or reactions likely to be exacerbated by any component of	Subjects allergic to any of the components will be excluded to avoid allergic reactions. (see section 4.3 of SmPC)
Uncontrolled serious infection	Immunisation should be postponed in individuals suffering from an acute severe febrile illness or acute infection. (see section 4.4 of SmPC)

**Table 24 Exclusion criteria which are NOT proposed to remain as contraindications**

<b>Exclusion criteria which are NOT proposed to remain as contraindications</b>		
<b>Criteria</b>	<b>Reason for being an exclusion criterion</b>	<b>Justification for not being a contraindication</b>
Malignancy or history of malignancy	only healthy subjects to be included in trial	
History or clinical manifestation of clinically significant and severe hematological, renal, hepatic, pulmonary, central nervous, cardiovascular or gastrointestinal disorders	Only healthy subjects to be included in trial	
History and risk of coronary heart diseases	Only healthy subjects to be included in trial	No confirmed case of myo-/pericarditis in completed clinical trials (N=8992)
History of alcohol abuse/intravenous drug abuse	Risk of poor compliance during trial	Compliance not relevant for vaccination setting outside a clinical trial
History or clinical manifestation of immune modifying conditions / diseases or immune modifying therapies	Risk of decreased immune response in vaccinee; Only healthy subjects to be included in trial	Additional trial in immunocompromised population completed with favorable safety and immunogenicity results

Information is still considered as missing for persons with organ impairment and limited for immunocompromised patients.

### **SIV.3 Limitations to detect adverse reactions in clinical trial development programmes**

The clinical development programme is unlikely to detect certain types of adverse reactions such as adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

### **SIV.4 Limitations in respect to populations typically under-represented in clinical trial development programmes**

No studies have been undertaken in

- Children and adolescents (<18 years)
- Pregnant and breastfeeding women
- Individuals with relevant co-morbidity such as clinically significant renal, hepatic or cardiac impairment

Limited data is available in

- Geriatric subjects (age 65+) (N = 120)
- Immunocompromised patients (HIV infected subjects N = 696)

#### **Fertile patients**

Animal studies did not reveal any evidence of impaired female fertility.

#### **Patients driving cars and working with machines**

Some of the undesirable effects (such as dizziness) may affect the ability to drive or operate machinery.

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**Table 25 Exposure of special populations included or not in clinical trial development programmes**

Type of special population	Exposure
<p>Pregnant women</p> <p>Breastfeeding women</p>	<p>Not included in the clinical development program.</p> <p><b>Pregnant women</b></p> <p>There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of IMVANEX in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. As a precautionary measure, it is preferable to avoid the use of IMVANEX during pregnancy unless the benefits of immunisation outweigh the risks of infection with Vaccinia or Variola virus.</p> <p><b>Breastfeeding women</b></p> <p>It is not known whether IMVANEX is excreted in human milk.</p> <p>IMVANEX should not be used during breastfeeding unless the benefits of immunisation outweigh the risks of infection with Vaccinia or Variola virus.</p>
<p>Patients with relevant comorbidities:</p> <ul style="list-style-type: none"> <li>• Patients with hepatic impairment</li> <li>• Patients with renal impairment</li> <li>• Patients with cardiovascular impairment</li> <li>• Patients with a disease severity different from inclusion criteria in clinical trials</li> </ul>	<p>Not included in the clinical development program</p>

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Type of special population	Exposure
<p>Patients with relevant comorbidities:</p> <ul style="list-style-type: none"> <li>Immunocompromised patients</li> </ul>	<p>Immunocompromised patients (e.g. HIV infected, patients under immunosuppressive therapy) who have been previously vaccinated against smallpox should receive two booster doses. The second booster vaccination should be given no less than 28 days after the first dose.</p> <p>Data have been generated in HIV infected individuals with CD4 counts <math>\geq 100</math> cells/<math>\mu</math>l and <math>\leq 750</math> cells/<math>\mu</math>l. Lower immune response data have been observed in HIV infected individuals compared to healthy individuals (see section 5.1). There are no data on the immune response to IMVANEX in other immunosuppressed individuals.</p>
<p>Population with relevant different ethnic origin</p>	<p>No effect of different racial/ethnic origin is expected on the effect of a vaccine. These parameters are more relevant for the drug metabolism of drugs that are repeatedly administered, rather than for the one or two times administration of IMVANEX.</p>
<p>Subpopulations carrying relevant genetic polymorphisms</p>	<p>Not included in the clinical development program</p> <p>No effect of genetic polymorphisms is expected on the effect of a vaccine. These parameters are more relevant for the drug metabolism of drugs that are repeatedly administered, rather than for the one or two times administration of IMVANEX.</p>

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Type of special population	Exposure
Other  Population with atopic disease (atopic dermatitis, atopic rhinitis)	<p>Individuals with atopic dermatitis (AD) developed more local and general symptoms after vaccination.</p> <p>In a non-placebo controlled clinical trial that compared the safety of IMVANEX 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 IMVANEX experienced a flare-up or worsening of their skin condition during the course of the trial.</p> <p>The trial revealed no particular safety concerns for IMVANEX in subjects with atopic dermatitis (history or active). Furthermore, no indication or trend could be detected that vaccination with MVA-BN worsened the intensity of AD.</p>

### Conclusions on populations not studied and other limitations of clinical trial development programme

The target population for IMVANEX divides into four subgroups:

- General population at risk of smallpox, mpox or vaccinia virus infection,
- first-line responders (medical personnel, civil defence) in case of (imminent) smallpox outbreak (emergency situation),
- military personnel pre-deployment, and
- laboratory personnel potentially exposed to vaccinia or other orthopox viruses.

Military personnel are generally required to be in good health status for deployment, whereas personnel with occupational exposure to infectious agents are at least required to be free of serious diseases, potentially afflicting their immune system or potentially aggravating after accidental contact with infectious agents.

Pregnancy and breastfeeding can be excluded for pre-deployment military personnel. With regard to laboratory personnel, vaccination can be scheduled adequately, as pregnant and

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breastfeeding women should not be exposed to vaccinia and other orthopox viruses at all and therefore do not require vaccination.

With regard to the general population and first-line responders, this limitation is not considered relevant in case of an imminent or actual smallpox, mpox or vaccinia virus outbreak, compared to the risk of the diseases themselves.

## **PART II: MODULE SV POST-AUTHORISATION EXPERIENCE**

### **SV.1 Post-Authorisation Exposure**

#### **SV.1.1 Method Used to Calculate Exposure**

Patient exposure is calculated based on world-wide sales volume per 0.5 ml dose of vaccine during a given period.

#### **SV.1.2 Exposure**

##### **Projected post-authorisation usage data**

Following authorisation in the EU, UK, Canada and the US, IMVANEX (also marketed as IMVAMUNE or JYNNEOS) was either intended for

- Stockpiling at Government and military facilities and for limited distribution for vaccination of laboratory personnel. Pre-deployment vaccination of military personnel and first-line responders is foreseen. In the event of a deliberate release of smallpox, vaccination of the general population (including immunocompromised subjects such as HIV individuals and subjects with AD) is also foreseen.
- Pre-deployment vaccination is not applicable to the general population. Laboratory personnel with potential exposure to vaccinia and poxviruses are a very limited population.

While for smallpox, an actual use for an eradicated disease is currently not foreseen in vaccination guidelines, the human-to-human transmission of mpox, both in endemic countries as well as in the multi-country outbreak which started in May 2022, has led to the publication of various national and international guidelines for pre- and post-exposure prophylaxis of individuals considered at high risk. In the long term, also an evaluation of the public health needs for vaccination to prevent mpox in endemic countries of sub-Saharan Africa should be considered in the context of the overall public health needs of these countries.

To date some effectiveness data starts to be published providing initial reassurance that the vaccine will have an effect on disease and the evolution of the outbreak.

As of September 28, 2022, a total of 25,341 mpox cases have been reported in the United States. To examine the incidence of mpox among persons who were unvaccinated and those who had received  $\geq 1$  JYNNEOS vaccine dose, 5,402 reported mpox cases occurring among

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males aged 18–49 years during July 31–September 3, 2022, were analyzed by vaccination status across 32 U.S. jurisdictions. Average mpox incidence (cases per 100,000) among unvaccinated persons was 14.3 (95% CI = 5.0–41.0) times that among persons who received 1 dose of JYNNEOS vaccine  $\geq 14$  days earlier. This early finding suggests that a single dose of JYNNEOS vaccine provides some protection against mpox infection. The degree and durability of such protection is unknown. (Incidence of Monkeypox Among Unvaccinated Persons Compared with Persons Receiving  $\geq 1$  JYNNEOS Vaccine Dose — 32 U.S. Jurisdictions, July 31–September 3, 2022 | MMWR (cdc.gov))

A study in the Clalit Health Services (CHS) of Israel, including subjects eligible for JYNNEOS as defined by the Israeli Ministry of Health commenced on July 31, 2022, when the vaccination campaign was initiated in CHS, and participants were followed until September 12, 2022. A Cox proportional-hazards regression model with time-dependent covariates was used to estimate the association between vaccination and MPXV infections with adjustment for sociodemographic and clinical risk factors. A total of 1,970 subjects met the study eligibility criteria (0.04% of CHS members). Of them, 873 (44%) were vaccinated with MVA and completed at least 25 days of follow-up. 18 infections were confirmed in CHS during the study period, 3 in vaccinated and 15 in unvaccinated status (40.0 versus 6.4 per 100,000 person days). Vaccine effectiveness (VE) was estimated at 79% (95% CI: 24%–94%). These results suggest that a single dose of MVA is associated with a significantly lower risk for MPVX infection in high-risk individuals. (Arbel et al., 2022; DOI: <https://doi.org/10.21203/rs.3.rs-1976861/v2>)

More studies are ongoing and will further document the impact of the vaccine and the vaccination of individual at risk of acquiring mpox.

The following table provides an overview of worldwide shipments of the vaccine cumulatively since IBD, which was 31-Jul-2013:

**Table 26 Worldwide Shipments of IMVANEX**

#### **Actual post-authorisation usage data**

To date, about 28 million doses of IMVANEX have been delivered to the US Strategic National Stockpile (parts already before July 2013, which is the cut-off date for the tables above). Approximately 833,000 doses have been delivered to several governmental and military facilities outside the US. However, as some of the recipients are military organisations, they will not report the actual use of IMVANEX to Bavarian Nordic, but will only report serious adverse reactions, should they be observed.

As of 31-Jul-2022, the MAH has distributed significant number of doses in several countries, including those from the European Union, and in the UK, for the purpose of immediate use as a public health measure to handle the current mpox outbreak. Several of these implementation plans have been initiated and will be rolled out in the weeks and months to come.

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In 2022, the MAH supplied vaccine doses to the European Health Emergency Preparedness and Response Authority (HERA), which made vaccine doses available to EU member states, Norway and Iceland. As per a contractual agreement, HERA will receive data on the use of the vaccine from the countries and will share this information with the MAH for inclusion in upcoming PSURs.

In addition to this, in order to obtain actual exposure data, the MAH also actively screens local health authority webpages for data concerning the use of the product, including information of doses administered, first versus second dose, stratified by region (by country within the EU), gender and age groups and where available. The data received from these publicly available sources and received from reports such as from HERA, are summarized in overview tables in the PSURs.

**Table 27 Number of doses administered during mpox outbreak as of January 17<sup>th</sup>, 2023\***

Country	Reported number of doses administered	Source
USA	1,163,716	<a href="https://www.cdc.gov/poxvirus/monkeypox/response/2022/vaccines_data.html">https://www.cdc.gov/poxvirus/monkeypox/response/2022/vaccines_data.html</a>
UK	45,000	<a href="https://www.gov.uk/government/news/second-vaccine-doses-to-be-offered-to-those-at-highest-risk-from-monkeypox">https://www.gov.uk/government/news/second-vaccine-doses-to-be-offered-to-those-at-highest-risk-from-monkeypox</a>
Germany	50,333	<a href="https://www.rki.de/DE/Content/Infekt/Impfen/ImpfungenAZ/Affenpocken/Affenpocken-Impfmonitoring.pdf?__blob=publicationFile">https://www.rki.de/DE/Content/Infekt/Impfen/ImpfungenAZ/Affenpocken/Affenpocken-Impfmonitoring.pdf?__blob=publicationFile</a>
Canada	50,000	<a href="https://www.canada.ca/en/public-health/news/2022/08/statement-from-the-chief-public-health-officer-of-canada-on-august-12-2022.html">https://www.canada.ca/en/public-health/news/2022/08/statement-from-the-chief-public-health-officer-of-canada-on-august-12-2022.html</a>
Netherlands	29,765	<a href="https://www.rivm.nl/en/monkeypox/vaccination">https://www.rivm.nl/en/monkeypox/vaccination</a>
France	142,478	<a href="https://solidarites-sante.gouv.fr/soins-et-maladies/maladies/maladies-infectieuses/monkeypox/cas-groupes-d-infection-par-le-virus-monkeypox">https://solidarites-sante.gouv.fr/soins-et-maladies/maladies/maladies-infectieuses/monkeypox/cas-groupes-d-infection-par-le-virus-monkeypox</a>
Australia	11,892	<a href="https://ausvaxsafety.org.au/vaccine-safety-data/monkeypox-vaccine">https://ausvaxsafety.org.au/vaccine-safety-data/monkeypox-vaccine</a>
<b>Total number of doses</b>	<b>1,493,184</b>	

\*: DLP for this table is 17 Jan 2023

## **PART II: MODULE SVI ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION**

### **Potential for misuse for illegal purposes**

The product is largely not available on the regular market but licensed for stockpiling to be used under controlled conditions in special populations (e.g. military and first-line responders). However, in the multi-country mpox outbreak in May 2022, the product is being used to vaccinate individuals at high risk for exposure to mpox and their contacts. Illegal use or misuse is unlikely and therefore no specific measures are warranted.

Due to its properties it is unsuitable as a biological weapon since the risk for reversion and/or recombination to a replication competent virus strain can be virtually excluded due to the genetic properties of the product ([Suter, 2009](#)).

## **PART II: MODULE SVII IDENTIFIED AND POTENTIAL RISKS**

There have been no new risks identified as important potential or identified risks, based on the summary information prepared and submitted for IMVANEX to date.

### **SVII.1 Identification of Safety Concerns in the Initial RMP Submission**

The safety concerns of MVA-BN vaccine in the initial RMP are listed in Table 28 Summary of safety concerns.

All safety data available from the MVA-BN clinical development programme were evaluated in order to formulate the initial list of identified risks (adverse drug reactions), in addition to the important potential risks described within the initial approved version of this Risk Management Plan (RMP) (Version 1). Risks that were not included in the initial list of safety concerns are presented in Section [SVII.1.1](#), with safety concerns relevant for inclusion in the initial approved RMP and their justifications presented in Section [SVII.1.2](#)

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**Table 28 Summary of safety concerns**

<b>Important identified risks</b>	<b>None</b>
Important potential risks	Myo-/pericarditis Generalized vaccinia Encephalitis / myelitis Vaccinia virus infection Erythema multiforme, eczema vaccinatum Postvaccinal encephalitis Incorrect route of drug administration
Missing information	Children and Adolescents (<18 years) Use during pregnancy and breastfeeding Elderly subjects Individuals with organ impairment Clinically immunocompromised individuals Safety experience in mass vaccination due to smallpox outbreak Interactions with other vaccines and concomitantly administered immunoglobulins

#### **SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP**

The following topics were not considered relevant for inclusion in the list of safety concerns at the time of initial EU RMP approval:

Not all potential or identified risks for the vaccine are considered to meet the level of importance necessitating inclusion in the list of safety concerns in the RMP. Reasons for not including an identified or potential risk in the list of safety concerns in this RMP include:

Risks with minimal and temporary clinical impact on patients (in relation to the severity of the disease prevented). The main risk associated with administration of MVA-BN is the development of local reactions at the vaccination site (e.g. pain, erythema, induration, swelling

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and pruritus at the injection site) as well as of generalized symptoms like fatigue, headache, myalgia, and nausea).

Very rare potential risks for any medicinal treatment, including vaccines, which are well known to healthcare professionals are not included in the list of safety concerns.

The following table summarises adverse reactions observed in more than 1% (1:100) of exposed subjects in clinical trials with IMVANEX (N=3432).

Suspected Adverse Drug Reactions Reported by  $\geq 0.1\%$  of Subjects in the Completed IMVANEX Clinical Trials\* (N=3432)

**Table 29 Adverse reactions observed in clinical trials**

<b>System Organ Class Adverse reaction</b>	<b>IMVANEX® (n=3,432) in %</b>
<b>Blood and lymphatic system disorders</b>	
Lymphadenopathy	0.87%
<b>Cardiac disorders</b>	
Bundle branch block	0.12%
<b>Ear and labyrinth disorders</b>	
Vertigo	0.17%
<b>Gastrointestinal disorders</b>	
Diarrhoea	0.5%
Nausea	1.57%
Vomiting	0.17%
<b>General disorders and administration site</b>	
Asthenia	0.12%
Axillary pain	0.15%
Fatigue	6.29%
Injection site erythema	16.75%
Injection site induration	14.13%
Injection site pain	17.42%
Injection site pruritus	12.53%
Injection site reactions (other)	14.25%
Injection site swelling	13.43%
Malaise	0.15%
Pyrexia	1.95%
<b>Infections and infestations</b>	
Nasopharyngitis	0.35%
<b>Investigations</b>	
ALT increased	0.20%
CD4 lymphocytes increased	0.12%
Mean platelet volume decreased	0.26%
Neutrophil count decreased	0.20%
Troponin I increased	0.41%
<b>Musculoskeletal and connective tissue disorders</b>	
Arthralgia	0.38%
Muscular weakness	0.12%
Myalgia	2.68%

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Neck pain	0.15%
<b>Nervous system disorders</b>	
Dizziness	1.11%
Headache	5.57%
Paraesthesia	0.20%
<b>Respiratory, thoracic and mediastinal disorders</b>	
Cough	0.15%
Oropharyngeal pain	0.26%
Pharyngolaryngeal pain	0.38%
<b>Skin and subcutaneous tissue disorders</b>	
Pruritus	0.32%
Rash	0.41%
Skin discoloration	0.20%
<b>Vascular disorders</b>	
Haematoma	0.15%
Hot flushes	0.15%

\* POX-MVA-001, POX-MVA-002, POX-MVA-004, POX-MVA-005, POX-MVA-007, POX-MVA-008, POX-MVA-009, POX-MVA-010, POX-MVA-011, POX-MVA-023, POX-MVA-024, POX-MVA-028, POX-MVA-029, HIV-POL-002, HIV-NEF-004; 7 subjects in POX-MVA-009 received Dryvax either on the same day or within 7 days after MVA-BN administration and were therefore not included to avoid a potential bias in adverse event reporting.

In addition to the reactions reported above, a total of 7 Serious Adverse Events (SAEs) have been reported for IMVANEX, which were assessed as possibly related by the investigator. The SAEs

- Pneumonia,
- Sarcoidosis,
- Extraocular muscle paresis,
- Crohn's disease, and
- Cardiomyopathy
- Throat tightness and other hypersensitivity symptoms such as hives, pruritus, tender vaccination site, swollen axilla, angioedema of forearms
- Non-ST segment elevation myocardial infarction

have been thoroughly reviewed and it is the opinion of the MAH that there is no reasonable evidence for a causal relationship with IMVANEX.

Regarding immunologic effects caused by vaccines, no evidence can be found in the literature referring to the observed events ([Salemi, 2010](#)), ([Orbach, 2010](#)) It is more likely that the

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observed potentially immunologically stimulated events (sarcoidosis, extraocular muscle paresis and Crohn's disease) are incidental events with no causal relationship.

The observed pneumonia is caused by bacteria; the early time to onset after vaccination in this case basically excludes an immunosuppressive effect. Moreover, such an effect should have been observed more likely in the HIV individuals or elderly subjects in the respective studies. The cardiomyopathy reported has been observed in a HIV patient. HIV is associated with cardiomyopathy in 10-15% and is therefore a rather plausible reason for the event ([Barbaro, 2011](#)).

**Pneumonia:** (Study POX-MVA-011) A vaccinia-naïve (18-55 year-old) HIV infected female was admitted to the hospital with pneumonia the day after the second vaccination. She recovered without sequelae, was discharged after 3 days and continued the study as planned. The investigator assessed the pneumonia as possibly related to study medication, since the event began within one day after injection and the subject was asymptomatic and had no abnormal physical findings on the day of vaccination.

Comment: Bacterial pneumonia is not caused by viral vaccines; a hypothetical immunosuppressive effect can be excluded given the short interval of one day.

**Sarcoidosis:** (Study POX-MVA-005) A 18-55 year-old man suffered from arthralgia, 10 weeks after second vaccination and reported fever up to 38°C and night sweat. Based on bronchoscopy and biopsy 42 days later subject was diagnosed with sarcoidosis. Investigator classified the event as an important medical event and as possibly related to the study vaccine or other condition or treatment. He was treated with 600 mg ibuprofen five times daily for a month. Event was ongoing by time of report.

**Extraocular muscle paresis:** (Study POX-MVA-008) A 18-55 year-old female received the first study vaccination on Study Day 1 and the second vaccination on Study Day 30. She experienced extraocular muscle paresis 8 days after the second vaccination.

She experienced constant mixed horizontal and vertical diplopia. Upon examination by an ophthalmologist on Study Day 43 a discreet paresis of the right lower oculomotor muscle was diagnosed. The event was treated; on Study Day 48, right hypertropia was improving; and diplopia was less bothersome. On Study Day 52 subject presented with a red eye and increased palpebral volume; hyperemic eye conjunctive with papules was found. Bacterial conjunctivitis was diagnosed. By Study Day 55 paresis had virtually recovered. Neither diplopia nor hypertropia were evident. By Study Day 69 diplopia had disappeared completely. There was no ocular mobility limitation; conjunctivitis was resolved.

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The treating ophthalmologist mentioned that in the literature there have been isolated cases reported of transitory oculomotor paresis due to viral infections or to the use of different vaccines. In the absence of other risk factors, the ophthalmologist considered the paresis to be probably related to the study vaccine. The attending neurologist considered the event as a possible vaccination adverse reaction.

Comment: In the scientific literature numerous cases of optic neuritis have been reported following administration of rubella, measles, hepatitis B, influenza as well as anthrax vaccines. However, in the current case the ophthalmologist did not report that the optic nerve was involved; rather the impairment seemed to have been limited to the extraocular inferior rectal muscle.

To date, no other cases of any type of paralysis or similar events have been observed following administration of the study vaccine.

**Crohn's disease:** This case did not occur during the study period of POX-MVA-005, but rather was reported as a post study SUSAR, two years after last vaccination. Information is rather limited, as case was found during the screening for a booster study.

Comment: Given the long interval and the lack of scientific evidence for a causal link between vaccination and Morbus Crohn case is assessed as not related (no reasonable evidence) to study vaccine.

**Cardiomyopathy:** (Study POX-MVA-010) The event involved a 18-55 year-old, HIV-infected female, who was hospitalized 133 days following her second/last vaccination with the study vaccine and was diagnosed with congestive heart failure due to cardiomyopathy. The diagnosis was confirmed by a cardiologist, in addition to several other "current problems", i.e. shortness of breath, pleural effusion, hypertension, obesity, dyspnea on exertion, glaucoma and osteopenia. She was released after 10 days from the hospital in stable condition with cardiac medications.

Subject had been concomitantly participating in a growth hormone releasing hormone (GH-RH) study for treatment of lipodystrophy; she had denied this fact during screening for the Bavarian Nordic trial, otherwise this would have excluded her participation. The lipodystrophy study investigator also assessed the event "congestive cardiac failure" as being possibly related to the study drug GH-RH.

Comment: Due to the latency period of 133 days since the last administration of the study vaccine in combination with the other more likely predisposing factors of HIV infection and concomitant treatment with GH-RH, Bavarian Nordic assessed the development of congestive heart failure due to cardiomyopathy to be unlikely related to the study vaccine.

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**Throat tightness and other hypersensitivity symptoms (Trial POX-MVA-036):** The subject received her second dose of IMVANEX 21 days after the first dose and after 2 hours developed symptoms such as skin reactions and throat tightness which was responsive to epinephrine treatment. She had no wheezing and was not hypotensive. Symptoms subsided after several days under prednisone and diphenhydramine treatment. She has a family history of allergies and a medical history of shingles. She has received multiple vaccines before but never had previous hives or other problems with vaccines.

**Non-ST segment elevation myocardial infarction (Trial POX-MVA-036):** Positive family history for cardiovascular diseases (myocardial infarctions, blood clots), as well as overweight with a BMI above 33. A few days before event onset, subject presented with diarrhea and was started on ciprofloxacin treatment (which per US prescribing information is associated with angina pectoris and myocardial infarction). He showed chest pain and increased troponin I, but no ST segment changes in the ECG and no coronary artery disease in cardiac catheterization. A post-infectious myocarditis (published case reports exist for campylobacter, shigella, salmonella) was considered as alternative etiology for the reported event.

Please note that the information provided above is included to enable an overview of the clinical safety profile of IMVANEX. As no safety concerns have emerged from these data, upcoming revisions of the Risk Management Plan may no longer detail clinical data, unless any safety signals or safety concerns are found.

**Reason for not including an identified or potential risk in the list of safety concerns in the RMP:** Not applicable

#### **SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP**

##### **Important Identified Risk:**

There were no important identified risks for IMVANEX at the time of initial EU RMP approval.

##### **Important Potential Risks:**

The following topics were classified as important potential risks for IMVANEX at the time of initial EU RMP approval:

##### Risk benefit impact:

Safety concerns from clinical experience with conventional, replicating vaccinia vaccines such as replicating first generation vaccines used during the smallpox eradication programme (e.g.

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Dryvax) and also the replicating second generation smallpox vaccine ACAM2000 currently licensed in the US are summarised in Table 30 Pharmacological class effects of smallpox vaccines

**Table 30 Pharmacological class effects of smallpox vaccines**

<b>Risk</b>	<b>Frequency IMVANEX</b>	<b>Frequency Dryvax</b>	<b>Frequency ACAM2000</b>
Myo-/pericarditis	Nil	10.38 per 1000 vaccinations (Halsell, 2003; Cassimatis, 2004; (Arness, 2004; (Eckart, 2004)	5.73 per 1000 vaccinations (ACAM2000, 2007)
Generalized vaccinia	Nil	9 – 241 per 1 million vaccinations (Dryvax, 2002)	Nil (ACAM2000, 2007)
Encephalitis / myelitis	Nil	2 – 12 per 1 million vaccinations (Dryvax, 2002)	1 per 1 million vaccinations (ACAM2000, 2007)
Vaccinia virus infection	Nil	9 – 241 per 1 million vaccinations (Dryvax, 2002)	Nil (ACAM2000, 2007)
Erythema multiforme, eczema vaccinatum	Nil	No data available	No data available
Postvaccinal encephalitis	Nil	12.3 per 1 million vaccinations (Dryvax, 2002)	No data available

Suspected cases of myocarditis and/or pericarditis have been observed in healthy adult vaccinees.

An increased incidence of myo-/pericarditis compared to the general population has been observed following recent smallpox vaccination programs using Dryvax among US military personnel and in clinical trials comparing ACAM2000 to Dryvax (Halsell, 2003; Cassimatis, 2004; Arness, 2004; Eckart, 2004; ACAM2000, 2007).

In clinical trials, the reported incidence rates for developing myo-/pericarditis were 10.38 events per 1000 vaccinations following vaccination with the replicating smallpox vaccine Dryvax, and 5.73 events per 1000 vaccinations with ACAM 2000 (ACAM2000, 2007). All cases of myocarditis or myo-/pericarditis were considered to be at least possibly related to (replicating) study vaccine.

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Given this class effect, myo-/pericarditis has been added as an important potential risk for IMVANEX.

Encephalitis, encephalomyelitis, progressive and generalized vaccinia, and erythema multiforme major (including Stevens-Johnson syndrome) and eczema vaccinatum resulting in permanent sequelae or death, ocular complications, blindness, and fetal death have occurred following either primary vaccination or revaccination with replication-competent smallpox vaccines.

These risks, seen in use of replicating vaccines, are increased in vaccinees with the following conditions and may result in severe disability, permanent neurological sequelae and/or death:

- Cardiac disease or a history of cardiac disease
- Eye disease treated with topical steroids
- Congenital or acquired immune deficiency disorders, including those taking immunosuppressive medications
- Eczema and persons with a history of eczema or other acute or chronic exfoliative skin conditions
- Infants less than 12 months of age
- Pregnancy

Live vaccinia virus can be transmitted to persons who have close contact with the vaccinee and the risks in contacts are the same as those for the vaccinee.

IMVANEX is a live, highly attenuated strain of vaccinia that has been shown not to replicate in human cells and therefore cannot be transmitted or cause dispersed vaccinia-infection.

In addition, the recommended administration of IMVANEX via the SC or IM route also excludes the risk of autoinoculation and viral spread.

Therefore, the effects described above and related contraindications for replicating, replication-competent vaccinia vaccines like Dryvax and ACAM2000 have neither been observed so far with IMVANEX nor are they expected with future use.

The pharmacological class effects described above are proposed as important potential risks. They are not specific to any subgroup, i.e. they are specific to the active substance (and its class); hence stratification by a specific formulation, indication or route of administration, by a specific target population, or switch to non-prescription status (highly unlikely) is not applicable.

#### **Other Important Potential Risk:**

### 1.8.2 Risk Management Plan

<b>Important potential risk:</b> <b>Incorrect route of drug administration</b>	
SOC: Injury, poisoning and procedural complications	
Frequency with 95 % CI	Not applicable (not observed in 8992 subjects in completed clinical trials)
Seriousness/outcome	Non serious; no cases observed at time of this report
Severity and nature of risk	Non severe; no cases observed at time of this report

The following topics were classified as important missing information for IMVANEX at the time of initial EU RMP approval:

#### Missing information

##### Risk-benefit impact:

The table below presents important missing information and the risk-benefit impact.

Missing information	What is known	Risk-benefit impact:
Children and adolescents (<18 years)	IMVANEX is not indicated for use in children and adolescents.	IMVANEX 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.  Children are not within the target population (military, first-line responders, lab workers). In case of an outbreak situation, the risk of smallpox infection is considered higher than the potential risk of the vaccine.
Pregnant and lactating women	Animal studies did not reveal any evidence of impaired female fertility.  There are no or limited amount of data (less than	Pregnant women are not within the target population military, first-line responders, lab workers). In case of an outbreak

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Missing information	What is known	Risk-benefit impact:
	<p>300 pregnancy outcomes) from the use of IMVANEX in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. As a precautionary measure, it is preferable to avoid the use of IMVANEX during pregnancy unless the benefits of immunisation outweigh the risks of infection with Vaccinia or Variola virus.</p> <p>It is not known whether IMVANEX is excreted in human milk.</p> <p>IMVANEX should not be used during breastfeeding unless the benefits of immunisation outweigh the risks of infection with Vaccinia or Variola virus.</p>	<p>situation, the risk of smallpox infection is considered higher than the potential risk of the vaccine.</p>
Elderly subjects	<p>Limited data is available. Safe administration of IMVANEX has also been demonstrated in the elderly population 56-80 years of age (total of 125 vaccinees).</p>	<p>In case of an outbreak situation, the risk of smallpox infection is considered higher than the potential risk of the vaccine.</p>
Individuals with organ impairment	<p>No information available, as not studied.</p>	<p>Subjects with organ impairment are not within the primary target population (military, first-line responders, lab workers). In case of an outbreak situation, the risk of smallpox infection is considered higher than the potential risk of the vaccine.</p>
Clinically	<p>The safe administration of</p>	<p>In case of an outbreak situation, the risk of</p>

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<b>Missing information</b>	<b>What is known</b>	<b>Risk-benefit impact:</b>
immunocompromised individuals	IMVANEX in the general population (18-55 years of age) is further substantiated by safety data from immunocompromised populations (696 vaccinees) that have contraindications for receiving conventional smallpox vaccines, e.g. individuals with HIV or AD. The available data in these subjects as well as in healthy individuals revealed no special risks or safety concerns following IMVANEX administration.	smallpox infection is considered higher than the potential risk of the vaccine.
Safety experience in mass vaccination due to smallpox outbreak	No information available, as not studied.	In case of an outbreak situation, the risk of smallpox infection is considered higher than the potential risk of the vaccine
Interactions with other vaccines and concomitantly administered immunoglobulins	No interactions are known for IMVANEX.	In case of an outbreak situation, the risk of smallpox infection is considered higher than the potential risk of the vaccine and possible interactions with other vaccines and concomitantly administered immunoglobulins.

### SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

For RMP 8.0, the deletion of the important potential risks/safety concerns vaccinia rash, eczema vaccinatum, generalised vaccinia, progressive vaccinia, erythema multiforme and incorrect route of drug administration were approved. The safety experience of the IMVANEX vaccine through the routine pharmacovigilance activities has not reported any incidences of any of these events. The absence of these events is expected, because IMVANEX is a live, highly attenuated strain of vaccinia that has been shown not to replicate in human cells and

### 1.8.2 Risk Management Plan

therefore cannot be transmitted or cause dispersed vaccinia infection. In addition, the recommended administration of MVA-BN via the SC or IM route excludes the risk of cutaneous autoinoculation and viral spread.

As per regulatory procedure EMEA/H/C/002596/II/0076, the following missing information have been removed from the list of safety concerns for this current RMP:

- Children and adolescents (<18 years) as this subpopulation is not included in the targeted indication
- The term ‘safety experience in a mass vaccination due to a smallpox outbreak’ as per EMA request

## SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

### SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

Table 31 Important potential risks

#### Important Potential Risk 1:

<b>Important potential risk: Myo-/pericarditis</b> SOC: Cardiac disorders	
Frequency with 95% CI	Myocarditis not observed with IMVANEX. One possible albeit doubtful case of pericarditis in 8992 subjects in completed clinical trials.  Replicating smallpox vaccines: ACAM2000 5.7 per 1000 primary vaccinees (95% CI: 1.9-13.3)
Seriousness / outcomes	In the completed clinical trials involving 8992 subjects, no cases of myocarditis have been observed, and only one case of possible albeit doubtful pericarditis. In this case, the only symptom was chest pain being worse when lying down, which met the protocol-specified diagnosis criteria. All further cardiac examinations, including auscultation, ECG, Troponin I, Echocardiography were normal, i.e. there was no pericardial rub or effusion. The subject had no decreased exercise capacity, making the diagnosis of an actual pericarditis doubtful. As possible alternative explanation, a positive Coxsackie-B virus titer was identified during laboratory workup of this condition. The outcome was favourable.  Replicating smallpox vaccines: moderate to severe ( <a href="#">Arness, 2004</a> , <a href="#">Halsell, 2003</a> )

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<b>Important potential risk: Myo-/pericarditis</b> SOC: Cardiac disorders	
Severity and nature of risk	No impact on exercise capacity in the single reported case of possible, albeit doubtful pericarditis. No cases of myocarditis. Replicating smallpox vaccines: Spontaneously resolving, no fatalities. (US DoD 2007)
Background incidence/prevalence	As high as 1.06% (autopsy study, <a href="#">Gravanis, 1991</a> )
Risk groups or risk factors	No risk factors identified, use is currently limited mainly to military personnel
Potential mechanisms	Unknown, immune mediated inflammation suggested based on biopsy findings
Preventability	Unknown
Impact on individual patient/quality of life	Spontaneously resolving, no fatalities
Potential public health impact of safety concern	No impact to public health
Evidence source	Pharmacological class effect, US Department of Defense Smallpox Vaccination Program (US DoD 2007); ACAM2000 package information leaflet

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<b>Important potential risk: Myo-/pericarditis</b> SOC: Cardiac disorders	
Impact on risk-benefit balance of the product	<p>Smallpox vaccines have been associated with myopericarditis. If a vaccinated subject exhibits signs and symptoms potentially associated with cardiac disorder (e.g. chest pain or discomfort, dyspnea, palpitations), ECG and troponin I test should be performed. In case of ECG changes or troponin I elevations, further cardiologic examination should be performed.</p> <p>Health care professionals will be instructed to observe vaccinees for symptoms associated with cardiac disease. If vaccinees become symptomatic (i.e. chest pain, dyspnea), ECG and troponin control will be advised. In view of the fact that the potential risk has never been observed in more than 8992 subjects vaccinated with IMVANEX in contrast to other smallpox vaccines (in clinical trials an unexpected high frequency of myo-/pericarditis was observed for Dryvax and ACAM2000 (incidence of 10.38 events/thousand and 5.73 events/thousand, respectively per 1000 primary vaccinees (95% CI: 1.9-13.3) Pharmacological class effect, US Department of Defense Smallpox Vaccination Program (US DoD 2007); ACAM2000 package information leaflet) it is very unlikely that this class effect is valid for IMVANEX.</p>

### Important Potential Risk 2:

<b>Important potential risk: Postvaccinal encephalitis</b> SOC: Nervous system disorders	
Frequency with 95 % CI	No cases observed with IMVANEX in 8992 subjects in completed clinical trials 12 per million vaccinations with replicating smallpox vaccines ( <a href="#">Lane 1970</a> )
Seriousness/outcomes	No cases observed with IMVANEX replicating smallpox vaccines: Frequently leads to death, especially in infants and young children
Severity and nature of risk	No cases observed with IMVANEX replicating smallpox vaccines: Severe. Reported case fatality 9% - 40%, 10% – 25% of surviving patients have permanent neurologic sequelae ( <a href="#">Goldstein, 1975</a> )
Background incidence/prevalence	Viral encephalitis in central Europe: 0,2 to 0,4 occurrences per 100.000 inhabitants ( <a href="#">Schmutzhard, 2001</a> )

### 1.8.2 Risk Management Plan

<b>Important potential risk: Postvaccinal encephalitis</b> SOC: Nervous system disorders	
Risk groups or risk factors	Unknown
Potential mechanisms	Dissemination of vaccinia virus
Preventability	Not observed and highly unlikely to occur with IMVANEX, which is replication incompetent in human cells
Impact on individual patient/quality of life	Frequently leads to death, especially in infants and young children
Potential public health impact of safety concern	No impact to public health foreseen
Evidence source	Pharmacological class effect, US Department of Defense Smallpox Vaccination Program (US DoD 2007); ACAM2000 package information leaflet
Impact on risk-benefit balance of the product	Live vaccinia virus can be transmitted to persons who have close contact with the vaccinee and the risks in contacts are the same as those for the vaccinee. IMVANEX is a live, highly attenuated strain of vaccinia that has been shown not to replicate in human cells and therefore cannot be transmitted or cause dispersed vaccinia-infection.  Therefore, this risk has neither been observed so far with IMVANEX nor is it expected with future use.

### SVII.3.2 Presentation of the Missing Information

#### Missing information:

#### Anticipated risk/consequence of the missing information:

Missing information	Anticipated risk/consequence of the missing information
<b>Use during pregnancy and breastfeeding</b>	Pregnant women are not within the target population (military, first-line responders, lab workers, individuals at risk for exposure to smallpox, mpox or vaccinia virus). In case of an outbreak situation, the risk of smallpox, mpox or vaccinia virus infection is considered higher than the potential risk of the vaccine.

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<b>Missing information</b>	<b>Anticipated risk/consequence of the missing information</b>
<b>Elderly (&gt;=65 years)</b>	Elderly are not within the target population (military, first-line responders, lab workers, individuals at risk for exposure to smallpox, mpox or vaccinia virus. In the current mpox outbreak, the vast majority of the affected subjects are young adults). Immune function declines with age in a process called immunosenescence. Both the innate and the adaptive immune system show reduced function of natural killer cells and dendritic cells and reduced diversity and memory of T and B cells. This may render vaccines less efficacious in this population ( <a href="#">Hägg, 2022</a> ). In case of an outbreak situation, the risk of smallpox, mpox or vaccinia virus infection is considered higher than the potential risk of the vaccine.
<b>Individuals with organ impairment</b>	Individuals with organ impairment are not within the primary target population (military, first-line responders, lab workers, individuals at risk for exposure to smallpox, mpox or vaccinia virus). Their condition or the treatment of their condition might impact efficacy of the vaccine. Although there is no evidence that the safety profile of this population receiving MVA-BN will be different to that of the general population, given the paucity of data, the possibility cannot be excluded. In case of an outbreak situation, the risk of smallpox, mpox or vaccinia virus infection is considered higher than the potential risk of the vaccine.
<b>Immunocompromised patients</b>	Immunocompromised patients are not within the primary target population (military, first-line responders, lab workers, individuals at risk for exposure to smallpox, or vaccinia virus). For mpox, major parts of the target population may be immunocompromised, i.e. HIV positive. In case of an outbreak situation, the risk of smallpox, mpox or vaccinia virus infection is considered higher than the potential risk of the vaccine.
<b>Interactions with other vaccines and concomitantly administered immunoglobulins</b>	In case of an outbreak situation, the risk of smallpox, mpox or vaccinia virus infection is considered higher than the potential risk of the vaccine and possible interactions with other vaccines and concomitantly administered immunoglobulins. The concomitant administration of MVA-BN vaccine and immunoglobulins may alter the immune response of the vaccine. No interactions are known for IMVANEX.

## PART II: MODULE SVIII SUMMARY OF THE SAFETY CONCERNS

As of the date of this report, BN oversees 8992 subjects exposed with IMVANEX in completed clinical trials, including at-risk populations for which replicating smallpox vaccines such as Dryvax and ACAM2000 are contraindicated, e.g. individuals with AD or HIV infected

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subjects. In addition, more than 110.000 doses had been administered in the US by the data lock point of this RMP. Latest numbers are disclosed in [Table 27 . \(\)](#).

No trends for unexpected and/or serious adverse reactions were detected and no difference in the safety profile has been observed between vaccinia-naïve and vaccinia-experienced subjects receiving IMVANEX.

**Table 32 Summary of Safety Concerns**

<b>Important identified risks</b>	None
<b>Important potential risks</b>	<ul style="list-style-type: none"><li>□ Myo-/pericarditis</li><li>□ Postvaccinal encephalitis</li></ul>
<b>Missing information</b>	<ul style="list-style-type: none"><li>-Use during pregnancy and breastfeeding</li><li>-Elderly subjects</li><li>-Individuals with organ impairment</li><li>-Immunocompromised patients</li><li>-Interactions with other vaccines and concomitantly administered immunoglobulins</li></ul>

## **PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)**

### **III.1 Routine Pharmacovigilance Activities**

#### **Safety concerns and overview of previous pharmacovigilance actions**

- As specified in the approved Paediatric Investigation Plan (PIP) BN commits to approach the European Centre for Disease Prevention and Control (ECDC) and/or the public health institution of a member state to support the planning and set up of post-licensure studies to be applied in case of a declared smallpox or mpox outbreak. The PIP is being modified. The request for modification is related to the proposed extension of the indication of IMVANEX to “active immunisation against smallpox, mpox and related orthopoxvirus infection and disease”. Since May 2022, a mpox outbreak began spreading globally, mostly affecting countries from the EU/EEA. Although there have been only very limited confirmed paediatric cases in this mpox outbreak and the risk to human health and to the general public remains low, there is the potential for increased health impact with wider dissemination in vulnerable groups, including children. Infection with mpox virus during pregnancy may also lead to adverse outcomes for the foetus or newborn infant.

Severe and life-threatening adverse reactions such as inadvertent inoculation, eczema vaccinatum, progressive vaccinia, generalized vaccinia, and postvaccinal encephalitis that have been observed after the administration of conventional smallpox vaccines are due to the replication of the vaccinia strains. IMVANEX is replication incompetent in human cells and consequently has a better safety and tolerability profile. It is essentially impossible that IMVANEX could induce the severe side effects listed above associated with replication competent vaccinia viruses. Furthermore, with an overall rate (all age groups; data historically reported for Dryvax) of 529.2 cases/million vaccinations for inadvertent inoculation, 38.5 cases/million vaccinations for eczema vaccinatum, 241.5 cases/million vaccinations for generalized vaccinia, 1.5 cases/million vaccinations for progressive vaccinia and 12.3 cases/million vaccinations for postvaccinal encephalitis in primary (vaccinia-naïve) vaccinees, these rare events are highly unlikely to be captured in a clinical trial and true monitoring may therefore only be possible during a post-market surveillance. Nevertheless, all these events would constitute an SAE and thus be captured via the routine AE reporting procedure within the clinical trials.

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Children and adolescents (<18 years), pregnant and lactating women, individuals with organ impairment or treated with other vaccines or concomitantly administered immunoglobulins were excluded from participating in either of both clinical trials. Nevertheless, pregnancies exposed to the Investigational Medicinal Product (IMP) cannot be excluded with certainty and would have been followed up until delivery.

- Since it was not possible to assess effectiveness, at time of licensure, seroconversion was measured as a surrogate parameter at least in a subset of subjects in clinical trials and the special access program.
- Regular updates on safety and efficacy of IMVANEX since approval were provided in PSURs in a 6-month cycle.

#### **Overview of routine pharmacovigilance activities**

It is needed to differentiate between routine pharmacovigilance activities in case of a mass vaccination campaign e.g. during a smallpox outbreak and vaccination of a specific target population. These are two different scenarios demanding different approaches. It is considered that for the current mpox outbreak routine pharmacovigilance activities such as ICSR reporting to EudraVigilance according to the legally binding timelines and regular PSURs are sufficient, whereas in a mass vaccination campaign e.g. during a smallpox outbreak with major impact on health systems and important infrastructure more focused pharmacovigilance activities may be needed.

Bavarian Nordic undertakes routine pharmacovigilance activities consistent with the International Conference on Harmonisation (ICH) E2E Pharmacovigilance Planning Guideline.

Routine pharmacovigilance activities (as defined by standard operating procedures and guidelines) are designed to rapidly assess the ongoing safety profile of IMVANEX throughout clinical development and in the post-authorisation period in order to characterise and communicate pertinent safety data appropriately.

In addition to ICH requirements, Bavarian Nordic's routine pharmacovigilance activities in relation to IMVANEX are also aligned with the measures described in GVP IX.

Routine activities to specifically address the challenges in the context of mass vaccination are described in the sections below.

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### **Enhanced PV activities**

#### **III.1.1 Signal Detection**

Given the specific requirements of vaccines and the need to rapidly identify potential safety issues during mass vaccination, routine signal detection activities are supplemented as described below.

#### **Adverse events of special interest**

For the purpose of the RMP and summary safety reports, an AESI list is defined taking into consideration the available lists of AESIs from the following expert groups and regulatory authorities:

- Brighton Collaboration (SPEAC) ([Law, 2020](#))
- ACCESS protocol ([ACCESS, 2020](#))
- US CDC (preliminary list of AESI for VAERS surveillance) ([Shimabukuro, 2020](#))
- MHRA (unpublished guideline)

The AESI list is comprised of medical conditions to allow for changes and customisations of MedDRA terms as directed by AE reports and the evolving safety profile of the vaccine. The terms searched (using MedDRA SMQ search terms) in the safety database to identify cases of potential AESIs are presented by System Organ Class. Medical concepts that are captured in the AESI list include (case definitions of these AESIs are presented in [Annex 1](#)):

- Myocarditis
- Pericarditis
- Encephalitis
- Anaphylaxis
- Lack Of Efficacy/vaccination failure

The AESI list will be reviewed on an ongoing basis and will be updated as necessary.

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Data sources that are used for signal detection and the frequency of their review are listed in Table 33

**Table 33 Data sources for signal detection and frequency of review**

<b>Data Source</b>	<b>Frequency of review</b>
Global Safety Database (GSDB) (Argus) which includes BN sponsored and non-BN sponsored clinical trial SAEs and all post marketing case reports received by BN and License Partners (including adverse events of special interest and case reports from MHRA, VAERS, Canada Vigilance and EU [EudraVigilance])	Weekly
EudraVigilance Data Analysis System (EVDAS),	Monthly
Medical and scientific literature (Pubmed and Embase)	Weekly
Any relevant study data including investigator-initiated research	Weekly
Expanded Access Programs/compassionate use and named patient use as applicable	As applicable, then weekly
Invalid /Deleted cases (GSDB outputs)	Weekly
Product Complaint Reports (PCs)	Weekly
Batch analysis	Weekly
Medical Information Enquiries associated with safety and/or efficacy relevant information	Weekly
Market Research	As applicable, as per SDEA
Internet/social media	Weekly

Multiple methods for the evaluation of data retrieved from the above data sources are utilised for signal detection. Further detail on methodologies is provided below.

#### Quantitative methodology

Due to the nature of the license and thus the vaccine having been mainly used for governmental stock piling and the initial indication being for smallpox infection and disease only (which was officially declared eradicated in 1980 by the WHO), a low case volume was

### 1.8.2 Risk Management Plan

received in the post-marketing setting just until recently. Signal assessment was performed considering all possible sources for safety relevant information periodically and was summarized in aggregate reports. During clinical development, adverse events were reviewed during trial duration, analyzed in clinical trial reports and aggregate reports.

Up until 2021, cumulatively there were nine (9) post market cases received since license grant in 31 Jul 2013. Considering the amount of data available for MVA-BN since the license was first granted and with the finalization of clinical development it was further decided to evaluate the safety data as per review periods in order to identify trends.

Disproportionality analysis is primarily a tool to generate hypotheses on possible causal relations between drugs and adverse effects, to be followed up by clinical assessment of the underlying individual case reports by dedicated pharmacovigilance professionals. It is still the predominant statistical and computational method; however, disproportionality analysis is generally recommended and necessary for large databases. Since the beginning of the recent mpox outbreak the case volume increased but the total number of cases in the GSDB is still close under 1000 cases in total.

Within BN, following quantitative method is used:

#### Disproportionality analysis using EudraVigilance

EudraVigilance data are downloaded and integrated into the GSDB on a daily basis. These data are included in the weekly data review. Additionally, an eRMR is generated on a monthly basis and is included as a part of routine signal detection reports. The eRMR report is generated using the Active Substance High Level value of “MODIFIED VACCINIA ANKARA – BAVARIAN NORDIC LIVE VIRUS”.

Filters are then applied to the eRMR to identify events requiring review. Examples of these filters include events that are statistically significant ( $RoR > 1.0$ ), or are Important Medical Events, Designated Medical Events per EMA, or have an increase in the number of reported cases.

#### Qualitative methodology

Routine safety data review: Data from Bavarian Nordic’s global safety database (GSDB) are extracted weekly in the form of specific listings and reviewed weekly as part of routine surveillance activities. In addition, daily listings may be generated for cases not yet closed/locked in the safety database to allow for early identification of any potential safety issue. These listings include, besides all AEs, regardless of outcome and listedness also reports

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from special situations (such as reports of medication error, overdose/underdose, lack of efficacy, and potential interactions with other vaccines administered concomitantly).

Monthly signal reports are created with listings that provide both per period and cumulative event counts, and comparisons with previous event counts are conducted to determine if there are any sudden increases or unusual patterns of AE reporting, as population-level exposure to MVA-BN is expected to increase over time. These reports also support the identification of potential serious but rare adverse reactions that may be associated with MVA-BN use.

Batch related trends: The majority of recorded batch/lot numbers in the GSDB still stems from clinical trial cases. Batch numbers are tabulated per reported AEs and compared for trends in order to identify any safety issues potentially related to the quality of MVA-BN in the routine reports.

Time-series analysis: In order to identify changes in case reporting over time, time-series analyses will be considered based on necessity, and subject to the availability of baseline data.

Observed versus expected (O/E) analysis: This signal detection methodology is currently under evaluation. O/E analysis will be conducted for events/medical concepts provided on the AESI list (see [Section III.1](#)). The stratified background rates publicly available from the ACCESS program and other industry groups (as applicable) will be analysed against the observed reports received in the MAH's GSDB, using distribution data and/or exposure data collected from EU member countries when made publicly available, on a monthly basis. To account for potential under reporting of AEs, sensitivity analysis will be performed. Where appropriate, standard statistical testing methodology will also be applied. To further enhance background rate identification additional literature review may be conducted if ACCESS data is insufficient or unavailable.

Time-to-onset analysis: An additional signal detection methodology currently under evaluation is time-to-onset analysis. This methodology will consider the amount of time from vaccine administration to event onset for a given event compared to onset time for all other vaccines for that event.

#### Mixed methodology

Cluster Analysis: Cluster analyses will be performed ad hoc based on the results of routine surveillance methods described above. Should a cluster analysis be performed as part of the signal detection process, this will be included in the Summary Safety Report (see [Section](#)

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III.1.1 Signal Detection). Rationales will be described for such analyses, and all PTs will be provided.

The MAH will attempt to acquire exposure data based on administered doses, first versus second dose, stratified by region (by country within the EU), gender and age groups, where available. Where such data are not available, exposure data will be included in the report based on doses distributed in each market by the MAH and its license partners, as part of SDEAs/PVAs.

With regards to AESIs, safety concerns and fatal AEs, the total number of any such events are discussed in the context of O/E analyses, which is conducted as part of signal detection activities.

### III.1.1.1 Signal Evaluation

Each evaluation of a signal should include information regarding the source or trigger of the signal, relevant background, method(s) of evaluation (including data sources, search criteria and standard definition for diagnoses), results (a summary and critical analysis of the data considered), discussion and conclusion. The conclusion of a signal evaluation can either refute that signal or determine that there is a potential or identified risk associated with the product. Risks are further categorised as non-important or important depending on the severity, reversibility, and other safety aspects. All validated signals will be presented in the Summary Safety Report (see [\(see Section III.1.1 Signal Detection\)](#)).

Following validation of any signal, a further internal safety review will take place based on BN's standard operating procedures. Following this, should there be a reasonable possibility of a causal relationship with MVA-BN, appropriate updates will be made to the core product information, which will subsequently be shared with Competent Authorities through standard regulatory processes.

### III.1.2 ICSR Reporting in case of mass vaccination

To address the challenges associated with a mass vaccination campaign it is necessary to ensure that the necessary pharmacovigilance infrastructure is in place to address the expected rapid increase in post-marketing individual case safety reports (ICSRs) for processing and regulatory reporting. This will in turn facilitate the rapid provision of high-quality data to support the detection and evaluation of potential safety issues.

Measures to be put in place include scaling of infrastructure and systems, recruitment and training of additional resources, and implementation of specific processes and procedures.

Spontaneous cases of confirmed lack of efficacy when MVA-BN is used in accordance with its authorisation, will be reported within the required 15 days of receipt.

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### III.1.3 Specific Adverse Reaction Follow-Up Questionnaires

- For the safety concern “important missing information: Use during pregnancy and breastfeeding” a specific Pregnancy Questionnaire was developed to ensure consistent data capture of pregnancy reports (documentation and follow up [pregnancy tracking]).
- For the safety concern “Myo-/Pericarditis” a specific Adverse Event Follow-Up Questionnaire-Inflammatory cardiac disorders has been developed to ensure consistent data capture suspected myocarditis case reports.
- For the safety concern “Postvaccinal encephalitis” a specific Adverse Event Follow-Up Questionnaire – Immune mediated neurologic disorders has been developed to ensure consistent data capture of all suspected encephalitis case reports.

All the above-mentioned questionnaires are provided in Annex 4.

### III.1.4 Summary Safety Reports

In case of mass vaccination in, for example, a smallpox outbreak scenario, in addition to the submission of Periodic Safety Update Reports (PSURs) at 6-monthly intervals, Summary Safety Reports (SSR) will be compiled as a complement to the submission of PSURs at initially monthly intervals for MVA-BN. This is to support timely and continuous benefit risk evaluations. Topics and frequency for the first SSR should be agreed with the regulators and will include as a minimum:

- Interval and cumulative number of reports per HLT and SOC. Interval and cumulative number
- Interval and cumulative number of reports of fatal events and case reports involving PT of sudden death
- Interval and cumulative number of reports, stratified by report type (medically confirmed/not) and by seriousness (including fatal separately)
- Overview of data presented in tabulations (Observed versus Expected analyses, AESIs, safety concerns, vaccination errors associated with harm and/or where risk minimisation activities are considered warranted, batch analysis and lack of efficacy)
- Interval and cumulative number of pregnancies
- Reports per EU country
- Estimated exposure data from post-marketing experience
- Changes to reference safety information in the interval, and current CCDS
- Ongoing and closed signals in the interval
- Conclusion and actions (reflecting risk-benefit considerations)

For the first few SSR submissions a discussion if any unusual pattern of fatal reports is observed during initial post-marketing use will be included. Data on medication errors will be

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included only if a pattern of errors leading to harm is identified and/or risk minimisation activities are considered.

The MAH will attempt to acquire exposure data based on administered doses, first versus second dose, stratified by region (by country within the EU), gender and age groups, where available. Where such data are not available, exposure data will be included in the report based on doses distributed in each market by the MAH and its license partners, as part of SDEAs/PVAs.

With regards to AESIs, safety concerns and fatal AEs, the total number of any such events are discussed in the context of O/E analyses, which is conducted as part of signal detection activities.

### III.1.4 Enhanced Passive Surveillance

Enhanced passive surveillance activities are not planned as other additional pharmacovigilance measures are in place (see [Section III.2](#)).

### III.1.5 Traceability, shipping and transport conditions

Traceability:

Where regional practices permit, the batch number for MVA-BN, if not already provided, is systematically followed up for each post marketing ICSR. When available, batch information is included in the GSDB. The SmPC, includes instructions for healthcare professionals to clearly record the name and batch number of the administered vaccine to improve traceability (section 4.4).

The Bavarian Nordic packaging/tracking configuration for IMVANEX/IMVAMUNE/JYNNEOS follows Standard Operating procedures and is as follows:

- Primary: Labels on vials includes batch/Lot number
- Secondary: Vials are packed in cartons of 20 and the cartons are serialized
- Tertiary: Cartons are packed in cases of 70 and the cases are serialized

The serialization includes all relevant information.

During packaging, vial labels are printed with batch specific data and applied to the vials. The labelled vials are placed in an insert and a leaflet applied. Inserts with vials and leaflet are then put in cartons, and the carton ends glued to secure tamper evidence of the carton. The cartons are printed with batch specific and serialization data and put in a case, where the cartons are aggregated to the case. The cases are closed with tape, a case label with serialization data for the case is applied, and the case is put on a pallet.

After the batch has been started on the line, the control functions of the packaging line are tested. Samples of printed packaging materials will be collected from the packaging line when these have been imprinted and controlled by the Vision system. The samples will be controlled for appearance and correct imprint by an operator and added to the batch journal.

In process controls at vial- and carton level are taken during start-up, hourly and before ending the batch to continuously verify correctness and quality of print and packaging.

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A packed carton with 20 vials will be collected at the end of the batch as a retention sample for Quality Assurance.

Traceability is also available for every shipment of MVA-BN smallpox/mpox vaccine through correlation of relevant shipment information (packing list, sales order/invoice, freightbill etc.) and shipped batch/quantity. Each shipment is equipped with Electronic Data Logging Monitors (EDLMs) for registration of temperature during shipment. The EDLMs are traceable to unique serial nos. which are logged prior to and after shipment to ensure matching information. EDLM serial nos. are available on the temperature readouts.

#### Shipping and transport conditions

MVA-BN smallpox/mpox vaccines require storage and shipping at ultra-cold conditions and per standard procedures are shipped in qualified shipping equipment and transport modes. EDLMs are used to monitor and ensure that the temperature during shipment has been maintained within the required conditions throughout as per pre-defined specifications. In case excursions from the required conditions take place, escalation for product impact assessment is effectuated with the aim to report back to consignee soonest possible whether received shipment is still acceptable for use. Temperature excursions are identified through a combination of evaluating when the shipment took place and how the temperature readout appears in the relevant period. Alarm limits are programmed into the EDLMs to point to potential shipment temperature excursions.

## **III.2 Additional Pharmacovigilance Activities**

Given differences in the vaccination policy between member states in terms of vaccine used, target population prioritised for vaccination, setting of vaccination and surveillance systems already in place, it is considered that a single method cannot be proposed.

### **PASS/PAES POX-MVA-039 summary:**

#### Study short name and title:

POX-MVA-039: An observational post-authorization safety and efficacy study for the prophylactic vaccination with IMVANEX following re-emergence of circulating smallpox infections

#### Rationale and study objectives:

The primary objective of the study will be to monitor and characterise incidence of serious adverse events and/or medically attended adverse events in patients exposed to IMVANEX in accordance with a national public health vaccination program and/or other real-life use, in case of a smallpox outbreak.

## 1.8.2 Risk Management Plan

Effectiveness endpoints will also be included in the PASS/PAES.

### Study design:

A prospective non-interventional cohort study (POX-MVA-039) will be started as soon as the vaccine is used in mass vaccination in a smallpox outbreak situation. Concurrent cohorts of non-exposed individuals are not required given the conditions of an outbreak situation.

### Study population:

The recruitment procedure will ensure that an adequate number of subjects will be included in each age category. The following numbers of subjects to be studied are considered a minimum sample size:

<18 years: please refer to PIP (P/0038/2012), 342

18 - 44 2,658

45 - 60 3000

>60 years: 3000.

Please note: safety data of PIP and PASS will be combined for evaluation.

For practical reasons, flexibility in the age categories is allowed. The total sample size of 9000 subjects would be able to rule out events occurring with a frequency of 1 per 3000 if no event is observed (provided the event may occur in all age categories).

### Milestones:

At this time it is not possible to plan for even first steps (incl. which registries to use, establish first contacts to potential investigators etc.) since a mass vaccination would be performed in case of a smallpox outbreak. However, it cannot be foreseen where in the world such an outbreak would occur.

### **Non-BN sponsored Postmarketing Safety and Efficacy Studies in the context of the current mpox outbreak**

Given the fast evolution of the current outbreak, incompatible with the timelines to set up a PAES, it would be unfeasible for Bavarian Nordic to set-up a study that provides effectiveness and safety data in a timely manner, especially since the vaccine supply situation and the mpox outbreak dynamics is continuously changing since the start of the outbreak and might continue to change substantially over the next months. This is an agreed approach with the regulators per outcome of Procedure No. EMEA/H/C/002596/II/0076

### **SEMVAc study summary:**

### 1.8.2 Risk Management Plan

Bavarian Nordic has agreed with the investigators of the SEMVAc study (a prospective, non-interventional, multicentric cohort study to determine the vaccine effectiveness and safety of MVA-BN against symptomatic mpox virus infections - study synopsis in Annex 3) to be able to share the data of the study as part of its commitments.

#### Study short name and title:

Sicherheit und Effektivität der MVA-BN Impfung gegen MPXV-Infektion bei Risikopersonen in Deutschland (SEMVAc)  
(Safety and Effectiveness of MVA-BN vaccination against MPXV infection in at-risk individuals in Germany)

Note: The study protocol still contains the term monkeypox instead of mpox. At Bavarian Nordic, we change the names wherever possible, but as Bavarian Nordic is not the sponsor of the SEMVAc study, we can only recommend the principal investigator changing the protocol terminology asap.

#### Rationale and study objectives:

The primary outcome measure is vaccine effectiveness of MVA-BN against symptomatic PCR-detected mpox disease, defined as reduction in risk of disease in vaccinated versus unvaccinated individuals. Safety and tolerability of MVA-BN vaccination will be assessed through questionnaires as one of the secondary outcome measures.

#### Study design:

This is a prospective non-interventional observational cohort study without randomization. Baseline demographic characteristics will be collected, and the risk behaviour of participants be collected (sexual behaviour, occurrence of STIs) and quantified (number of contact). All study participants will be prospectively observed for 1 year, for estimate of vaccine effectiveness (calculated based on symptomatic PCR-detected mpox disease), and safety. In a subset of participants (1000 vaccinated and 1000 unvaccinated), serology response to mpox will be analysed.

#### Study population:

The study population is healthy MSM, with indication for PrEP of IMVANEX and without known exposure to mpox, but individuals with existing medical conditions (HIV, STIs, atopic dermatitis) and medication (HIV PrEP) are allowed to be recruited. The study will include subjects at high risk for a mpox infection, 5'000 who received MVA-BN and 10'000 controls that will not be vaccinated.

#### Milestones:

### 1.8.2 Risk Management Plan

Study start was on 07 Jul 2022. Last Participant Out is planned to be in December 2023, with study end planned on 31 Dec 2023. The total duration of the study is planned to be 18 months.

## III.3 Summary Table of Additional Pharmacovigilance Activities

**Category 1** – Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation

Not applicable, as no additional PV activities were mandated or imposed.

**Category 2** – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances

**Category 3** - Required additional pharmacovigilance activities

Not applicable

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**Table 34 Mandatory Additional PV activities**

Study name/title Status	Summary of activity objectives	Safety concerns addressed	Milestones	Due dates
<b>Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorisation under exceptional circumstances</b>				
POX-MVA-039: An observational post-authorisation safety and efficacy study for the prophylactic vaccination with IMVANEX following re-emergence of circulating smallpox infections  planned	To assess safety and efficacy for the prophylactic vaccination with IMVANEX following re-emergence of circulating smallpox infections	Myo-/pericarditis Postvaccinal encephalitis -Use during pregnancy and breastfeeding -Elderly subjects -Individuals with organ impairment -Immunocompromised patients -Interactions with other vaccines and concomitantly administered immunoglobulins	Protocol submission	11 Sep 2014
			Interim data	Biannually with PSURs and in the annual re-assessment application
			Final report	Dependent on start of mass vaccination programs
SEMVAc: Sicherheit und Effektivität der MVA-BN	To determine the vaccine effectiveness and safety of MVA-BN against symptomatic MPXV infections	Myo-/pericarditis Postvaccinal encephalitis	<i>This trial is not sponsored by the MAH</i>	Jul-2022

### 1.8.2 Risk Management Plan

Impfung gegen MPXV-Infektion bei Risikopersonen in Deutschland  (Safety and Effectiveness of MVA-BN vaccination against MPXV infection in at- risk individuals in Germany)  ongoing		-Individuals with organ impairment  -Immunocompromised patients  -Interactions with other vaccines and concomitantly administered immunoglobulins	Study design concept submission	Protocol submitted to EMA on 04-Aug- 2022
			Interim data	Biannually with PSURs and in the annual re-assessment application
			Final data	Not before 31-Dec- 2023

## PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

**Table 35 Planned and on-going post-authorisation efficacy studies that are conditions of the marketing Authorization or that are specific obligations.**

Study/ Status	Summary of objectives	Efficacy uncertainties addressed	Milestones	Due Date
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
POX-MVA-039: An observational post-authorization safety and efficacy study for the prophylactic vaccination with IMVANEX following re-emergence of circulating smallpox infections planned	Post-authorisation safety and efficacy study for the prophylactic vaccination with IMVANEX following re-emergence of circulating smallpox infections	Efficacy experience in mass vaccination due to smallpox outbreak after re-emergence of circulating smallpox infections	Protocol including EMA requests (EMA/H/C /002596/S O B 002)	Endorsed by PRAC on 11 Sep 2014 (EMA/PRAC/5 40458/2014)
			Interim data:	Biannually with PSURs and in the annual re-assessment application.
			Final report:	Dependent on start of mass vaccination programs
SEMVAc: Sicherheit und Effektivität der MVA-BN Impfung gegen MPXV-Infektion bei Risikopersonen	To determine the vaccine effectiveness and safety of MVA-BN against symptomatic MPXV infections	Efficacy of MVA-BN against symptomatic MPXV infections	Interim data:  <i>This trial is not sponsored by the MAH</i>	Biannually with PSURs and in the annual re-assessment application

in Deutschland (SEMVAc) (Safety and Effectiveness of MVA-BN vaccination against MPXV infection in at- risk individuals in Germany)  ongoing			Final data:  <i>This trial is not sponsored by the MAH</i>	Not before 31- Dec-2023
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## **PART V: RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)**

### **Risk Minimisation Plan**

IMVANEX has been shown to be safe and well tolerated, revealing no risks requiring risk minimization activities by safety concern. Moreover, IMVANEX is not intended for regular marketing (government use programmes only).

### **V.1 Routine Risk Minimisation Measures**

**Table 36 Description of Routine Risk Minimization Measures by Safety Concern**

<b>Safety concern – Important potential risk</b>	<b>Myo-/pericarditis</b>
Objectives of risk minimization measures	Identification of risk factors. Facilitation of appropriate measures if increased risk is noted.
Routine risk minimization measures	<p>All cases of suspected/possible myo-/pericarditis will be followed-up according to the case definitions as published by the Centers of Disease Control and Prevention</p> <p>In the event that information should become available to suggest that myo/pericarditis must be regarded as an identified risk for IMVANEX, the Applicant is committed to include a respective warning in the product information. In this context, the Applicant will use the definition for “identified risk” as provided in GVP module V, i.e. “an untoward occurrence for which there is adequate evidence of an association with the medicinal product of interest”. In the case of IMVANEX, such adequate evidence would be generated in particular by “a number of well-documented spontaneous reports where causality is strongly supported by temporal relationship and biological plausibility.”</p>
	<p>Other routine risk minimization measures</p> <p>None proposed</p>
Additional risk minimization measures	None proposed
<b>Effectiveness of risk minimization measures</b>	

How effectiveness of risk minimization measures for safety concern will be measured	Any significant number of spontaneous ADR cases of myo-/pericarditis received – or corresponding information in published literature – would indicate possible lack of efficacy of current risk minimization measures.
Criteria for judging success of proposed risk minimization measures	If there is no evidence for an increase in the number of spontaneous ADR cases of myo-/pericarditis received – or corresponding information in published literature – this would be considered evidence for efficacy of current risk minimization measures.
Planned dates for assessment	As per submission due date of each PSUR.
Results of effectiveness measurement	As no confirmed cases of myo-/pericarditis have been reported for IMVANEX, no additional risk minimization activities are considered necessary.
Impact of risk minimization	Not applicable
Comment	None

**Table 37 Risk minimization for Post vaccinal encephalitis**

<b>Safety concern – Important potential risk</b>	<b>Post vaccinal encephalitis</b>
Objectives of risk minimization measures	Identification of risk factors. Facilitation of appropriate measures if increased risk is noted.
Routine risk minimization measures	All cases of suspected/possible post vaccinal encephalitis will be followed-up
	Other routine risk minimization measures None proposed
Additional risk minimization measures	None proposed
<b>Effectiveness of risk minimization measures</b>	
How effectiveness of risk minimization measures for safety concern will be measured	Any significant increase in number of spontaneous ADR cases of post vaccinal encephalitis received – or corresponding information in published literature – would indicate possible lack of efficacy of current risk minimization measures.

Criteria for judging success of proposed risk minimization measures	If there is no evidence for an increase in the number of spontaneous ADR cases of post vaccinal encephalitis received – or corresponding information in published literature – this would be considered evidence for efficacy of current risk minimization measures.
Planned dates for assessment	As per submission due date of each PSUR.
Results of effectiveness measurement	As post vaccinal encephalitis has not been reported for IMVANEX, no additional risk minimization activities are considered necessary.
Impact of risk minimization	Not applicable
Comment	None

**Table 38 Risk minimization for missing information on interactions with vaccines and concomitantly administered immunoglobulins**

<b>Safety concern – Important missing information</b>	<b>Interactions with vaccines and concomitantly administered immunoglobulin</b>
Objectives of risk minimization measures	Continuous assessment of potential safety impact. Facilitation of appropriate measures if risks noted.
Routine risk minimization measures	SmPC section 4.5 states: ‘No interaction studies with other vaccines or medicinal products have been performed. Therefore, concomitant administration of IMVANEX with other vaccines should be avoided. The concomitant administration of the vaccine with any immunoglobulin including Vaccinia Immune Globulin (VIG) has not been studied and should be avoided’
	Comments None
	Other routine risk minimization measures None proposed
Additional risk minimization measures	None proposed
<b>Effectiveness of risk minimization measures</b>	
How effectiveness of risk minimization measures for	Any significant number of spontaneous ADR cases of interactions with vaccines and concomitantly

the safety concern will be measured	administered immunoglobulins received – or corresponding information in published literature – would indicate possible lack of efficacy of current risk minimization measures.
Criteria for judging the success of the proposed risk minimization measures	If there is no evidence (e.g. no or very few cases) from spontaneous ADR cases of interactions with vaccines and concomitantly administered immunoglobulins received – or corresponding information in published literature – this would be considered evidence for efficacy of current risk minimization measures.
Planned dates for assessment	As per submission due date of each PSUR.
Results of effectiveness measurement	As interactions with vaccines and concomitantly administered immunoglobulins have not been reported for IMVANEX, no additional risk minimization activities are considered necessary.
Impact of risk minimization	Not applicable
Comment	None

**Table 39 Risk minimization for missing information on pregnancy and breastfeeding**

<b>Safety concern – Important missing information</b>	<b>Pregnancy and breastfeeding</b>
Objectives of risk minimization measures	Continuous assessment of potential safety impact. Facilitation of appropriate measures if risks noted.
Routine risk minimization measures	SmPC section 4.6 states it is preferable to avoid the use of IMVANEX during pregnancy and breastfeeding
	Comments None
	Other routine risk minimization measures None proposed
Additional risk minimization measures	None proposed
<b>Effectiveness of risk minimization measures</b>	

How effectiveness of risk minimization measures for the safety concern will be measured	Any significant number of spontaneous ADR cases in pregnant or breastfeeding women– or corresponding information in published literature – would indicate possible lack of efficacy of current risk minimization measures.
Criteria for judging the success of the proposed risk minimization measures	If there is no evidence of substantial use (e.g. no or very few cases) from spontaneous ADR cases in pregnant or breastfeeding women– or corresponding information in published literature– this would be considered evidence for efficacy of current risk minimization measures.
Planned dates for assessment	As per submission due date of each PSUR.
Results of effectiveness measurement	As only few cases of spontaneous ADRs in pregnant or breastfeeding women have been reported for IMVANEX, no additional risk minimization activities are considered necessary.
Impact of risk minimization	Not applicable
Comment	None

No table is applicable for important missing information on elderly subjects, on individuals with organ impairment, and on immunocompromised patients as no risk minimization measures are proposed.

## V.2 Additional Risk Minimization Measures

Routine risk minimization activities as described in Part [V.1](#) are sufficient to manage the safety concerns of the medicinal product.

## V.3 Summary of Risk Minimization Measures

**Table 40**      **Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern**

Safety concern	Risk minimisation measures	Pharmacovigilance activities
<b>Important identified risks</b> (none)	Not applicable	Not applicable
<b>Important potential risk</b> Myo-/pericarditis	Routine risk minimisation measures: <ul style="list-style-type: none"> <li>All cases of suspected/possible myo-/pericarditis will be followed-up according to the case definitions as published by the Centers of Disease Control and Prevention</li> </ul> Additional risk minimisation measures: <ul style="list-style-type: none"> <li>None proposed</li> </ul>	Additional pharmacovigilance activities: <ul style="list-style-type: none"> <li>Study POX-MVA-039 (final study report date dependent on start of mass vaccination programs)</li> <li>Study SEMVAc (final study report date not before 31 Dec 2023)</li> </ul>
<b>Important potential risk</b> Postvaccinal encephalitis	Routine risk minimisation measures: <ul style="list-style-type: none"> <li>All cases of suspected/possible post vaccinal encephalitis will be followed-up</li> </ul> Additional risk minimisation measures: <ul style="list-style-type: none"> <li>None proposed</li> </ul>	Additional pharmacovigilance activities: <ul style="list-style-type: none"> <li>Study POX-MVA-039 (final study report date dependent on start of mass vaccination programs)</li> <li>Study SEMVAc (final study report date not before 31 Dec 2023)</li> </ul>
<b>Important missing information</b> Use during pregnancy and breastfeeding	Routine risk minimisation measures: <ul style="list-style-type: none"> <li>SmPC Section 4.6 'Fertility, pregnancy and lactation' clearly points out that use during pregnancy and breastfeeding is not recommended.</li> </ul> Additional risk minimisation measures: <ul style="list-style-type: none"> <li>None proposed</li> </ul>	Additional pharmacovigilance activities: <ul style="list-style-type: none"> <li>Study POX-MVA-039 (final study report date dependent on start of mass vaccination programs)</li> </ul>
<b>Important missing information</b> Elderly subjects (≥65 years)	None proposed	Additional pharmacovigilance activities: <ul style="list-style-type: none"> <li>Study POX-MVA-039 (final study report date dependent on start of mass vaccination programs)</li> </ul>

Safety concern	Risk minimisation measures	Pharmacovigilance activities
<b>Important missing information</b> Individuals with organ impairment	None proposed	Additional pharmacovigilance activities: <ul style="list-style-type: none"> <li>• Study POX-MVA-039 (final study report date dependent on start of mass vaccination programs)</li> <li>• Study SEMVAc (final study report date not before 31 Dec 2023)</li> </ul>
<b>Important missing information</b> Immunocompromised patients	None proposed	Additional pharmacovigilance activities: <ul style="list-style-type: none"> <li>• Study POX-MVA-039 (final study report date dependent on start of mass vaccination programs)</li> <li>• Study SEMVAc (final study report date not before 31 Dec 2023)</li> </ul>
<b>Important missing information</b> Interactions with vaccines and concomitantly administered immunoglobulins	Routine risk minimisation measures: <ul style="list-style-type: none"> <li>• SmPC section 4.5 states: ‘No interaction studies with other vaccines or medicinal products have been performed. Therefore, concomitant administration of IMVANEX with other vaccines should be avoided. The concomitant administration of the vaccine with any immunoglobulin including Vaccinia Immune Globulin (VIG) has not been studied and should be avoided’</li> </ul> Additional risk minimisation measures: <ul style="list-style-type: none"> <li>• None proposed</li> </ul>	Additional pharmacovigilance activities: <ul style="list-style-type: none"> <li>• Study POX-MVA-039 (final study report date dependent on start of mass vaccination programs)</li> <li>• Study SEMVAc (final study report date not before 31 Dec 2023)</li> </ul>

## **PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN**

### **SUMMARY OF RISK MANAGEMENT PLAN FOR IMVANEX® (SMALLPOX AND MPOX VACCINE MODIFIED VACCINIA ANKARA- BAVARIAN NORDIC (MVA-BN®) (LIVE ATTENUATED, NON- REPLICATING))**

This is a summary of the risk management plan (RMP) for IMVANEX. The RMP details important risks of IMVANEX, and how more information will be obtained about IMVANEX's risks and uncertainties (missing information).

IMVANEX's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how IMVANEX should be used.

This summary of the RMP for IMVANEX should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of IMVANEX's RMP.

#### **I THE MEDICINE AND WHAT IT IS USED FOR**

IMVANEX is authorised for active immunisation against smallpox, mpox and disease caused by vaccinia virus in adults (see SmPC for the full indications). It contains smallpox vaccine live Modified Vaccinia Ankara-Bavarian Nordic (MVA-BN®) (live attenuated, non-replicating) as the active substance and it is given by subcutaneous (SC) injection.

Further information about the evaluation of IMVANEX's benefits can be found in IMVANEX's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage

<https://www.ema.europa.eu/en/medicines/human/EPAR/imvanex>.

#### **II RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERIZE THE RISKS**

Important risks of IMVANEX, together with measures to minimise such risks and the proposed studies for learning more about IMVANEX's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

If important information that may affect the safe use of IMVANEX is not yet available, it is listed under 'missing information' below.

## II.A List of Important Risks and Missing Information

Important risks of IMVANEX are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of IMVANEX. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

As of the date of this report, BN oversees 8992 subjects exposed with IMVANEX, including at-risk populations for which replicating smallpox vaccines such as Dryvax and ACAM2000 are contraindicated, e.g. individuals with AD or HIV infected subjects. (late breaking: more than 900.000 doses have been administered in the US in the ongoing mpox outbreak as of 11-Oct-2022, numbers from other countries are still being compiled).

No trends for unexpected and/or serious adverse reactions were detected and no difference in the safety profile has been observed between vaccinia-naïve and vaccinia-experienced subjects receiving IMVANEX.

<b>Important identified risks</b>	None
<b>Important potential risks</b>	<input type="checkbox"/> Myo-/pericarditis <input type="checkbox"/> Postvaccinal encephalitis
<b>Important missing information</b>	<input type="checkbox"/> <input type="checkbox"/> Use during pregnancy and breastfeeding <input type="checkbox"/> Elderly subjects

	<ul style="list-style-type: none"> <li>□ Individuals with organ impairment</li> <li>□ Immunocompromised patients</li> <li>□ Interactions with other vaccines and concomitantly administered immunoglobulins</li> </ul>
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## II.B Summary of Important Risks

<b>Important potential risk: Myo-/pericarditis</b>	
Evidence for linking the risk to the medicine	Pharmacological class effect, US Department of Defense Smallpox Vaccination Program (US DoD 2007); ACAM2000 package information leaflet
Risk factors and risk groups	No risk factors identified;
Risk minimisation measures	<p>Routine risk minimisation measures</p> <ul style="list-style-type: none"> <li>• All cases of suspected/possible myo-/pericarditis will be followed-up according to the case definitions as published by the Centers of Disease Control and Prevention</li> <li>• As no confirmed cases of myo-/pericarditis have been reported for IMVANEX, no additional risk minimisation activities are considered necessary.</li> </ul> <p>Additional risk minimisation measures</p> <p>None proposed</p>
Additional pharmacovigilance activities	<p>Additional pharmacovigilance activities:</p> <p>POX-MVA-039</p> <p>SEMVAc study</p> <p>See section II.C of this summary for an overview of the post-authorisation development plan.</p>
<b>Important potential risk: Postvaccinal encephalitis</b>	

Evidence for linking the risk to the medicine	Pharmacological class effect, US Department of Defense Smallpox Vaccination Program (US DoD 2007); ACAM2000 package information leaflet
Risk factors and risk groups	Unknown
Risk minimisation measures	<p>Routine risk minimisation measures</p> <ul style="list-style-type: none"> <li>• All cases of suspected/possible postvaccinal encephalitis will be followed-up</li> <li>• As postvaccinal encephalitis has not been reported for IMVANEX, no additional risk minimisation activities are considered necessary.</li> </ul> <p>Additional risk minimisation measures</p> <p>None proposed</p>
Additional pharmacovigilance activities	<p>Additional pharmacovigilance activities:</p> <p>POX-MVA-039</p> <p>SEMVAc study</p> <p>See section II.C of this summary for an overview of the post-authorisation development plan.</p>
<b>Missing information: Use during pregnancy and breastfeeding</b>	
Risk minimisation measures	<p>Routine risk minimisation measures</p> <p>SmPC Section 4.6 '<b>Fertility, pregnancy and lactation</b> clearly points out that use during pregnancy and breastfeeding is not recommended.</p> <p>Additional risk minimisation measures</p> <p>None proposed</p>
Additional pharmacovigilance activities	<p>Additional pharmacovigilance activities:</p> <p>POX-MVA-039</p>

<b>Missing information: Interactions with other vaccines and concomitantly administered immunoglobulins</b>	
Risk minimisation measures	<p>Routine risk minimisation measures</p> <p>SmPC section Interaction with other medicinal products and other forms of interaction states: ‘No interaction studies with other vaccines or medicinal products have been performed. Therefore, concomitant administration of IMVANEX with other vaccines should be avoided. The concomitant administration of the vaccine with any immunoglobulin including Vaccinia Immune Globulin (VIG) has not been studied and should be avoided’</p> <p>Additional risk minimisation measures</p> <p>None proposed</p>

No table is applicable for important missing information on elderly subjects, on individuals with organ impairment, and on immunocompromised patients, as no risk minimization measures are proposed.

## **II.C Post-Authorisation Development Plan**

### **II.C.1 Studies Which Are Conditions of the Marketing Authorization**

**Study short name: PASS/PAES POX-MVA-039:** An observational post-authorization safety and efficacy study for the prophylactic vaccination with IMVANEX following re-emergence of circulating smallpox infections

Purpose of the study: The primary objective of the study will be to monitor and characterise incidence of serious adverse events and/or medically attended adverse events in patients exposed to IMVANEX in accordance with a national public health vaccination program and/or other real-life use.

Effectiveness endpoints will also be included in the PASS/PAES.

The POX-MVA-039 study is not designed or operationally feasible to adapt during current mpox outbreak, due to the difference between smallpox and mpox mode of transmission and the present implementation of vaccination campaigns to target a limited number of people in close contact with mpox cases and people at high risk of exposure.

**Study short name:** SEMVAc (Sicherheit und Effektivität der MVA-BN Impfung gegen MPXV-Infektion bei Risikopersonen in Deutschland) (Safety and Effectiveness of MVA-BN vaccination against MPXV infection in at-risk individuals in Germany)

**Purpose of the study:** This is a prospective, non-interventional, multicentric cohort study. It is a non-BN sponsored clinical study. The primary outcome measure is vaccine effectiveness of IMVANEX against symptomatic PCR-detected mpox disease, defined as reduction in risk of disease in vaccinated versus unvaccinated individuals. Safety and tolerability of IMVANEX vaccination will be assessed through questionnaires as one of the secondary outcome measures.

The study has started on 07-Jul-2022.

## **II.C.2 Other Studies in Post-Authorisation Development Plan**

NA

## **PART VII: ANNEXES**

## Annex 4.1 Pregnancy Questionnaire

1

## Pregnancy Questionnaire

IMVANEX®

### Pregnancy History

Total # pregnancies \_\_\_\_\_ Full term \_\_\_\_\_ Premature deliveries \_\_\_\_\_  
 Ectopic pregnancies \_\_\_\_\_ Stillbirths \_\_\_\_\_ Spontaneous abortions \_\_\_\_\_ Elective abortions \_\_\_\_\_

Any family history of birth defects, genetic disorders, fetal abnormalities, or pregnancy complications known?

If yes, please provide further details:

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### Pregnancy outcome

#### Maternal status

Actual date of delivery \_\_\_\_/\_\_\_\_/\_\_\_\_ ☐ Vaginal delivery ☐ Caesarean section

Any relevant medical problems or complications during delivery or postpartum period, such as pre-eclampsia, haemorrhage, hypertension, etc.? ☐ yes ☐ no

If yes, please provide further details:

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#### Infant status

Live birth? ☐ yes ☐ no Fetal death/stillborn? ☐ yes ☐ no ☐ male ☐ female

Gestational age at delivery: \_\_\_\_ weeks Birth weight: \_\_\_\_ (g/ pounds) Length: \_\_\_\_ (cm/ inches)

APGAR Score: \_\_\_\_ 1 min. \_\_\_\_ 5 min. \_\_\_\_ 10 min.

Any complications? ☐ yes ☐ no Any congenital anomalies? ☐ yes ☐ no

If yes, please provide further details:

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Any unusual diagnostic findings? ☐ yes ☐ no

If yes, please provide further details:

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### Relevant additional information (medical history, concomitant medication, etc.):

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**Follow up – 3 months after birth**

Malformation/anomalies diagnosed since last report      yes no

Infant illnesses, hospitalisations, drug therapies      yes no

If yes, please provide further details:

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Date / Signature

Please forward completed form to

or email to

## Annex 4.2 Adverse Event Follow-Up Questionnaire – Cardiac events

### Adverse Event Follow-Up Questionnaire – Inflammatory cardiac disorders

Please enter all dates in the following format: DD/MMM/YYYY (e.g. 01/MAR/2019)

Patient			
Initials	Sex	M	DOB
Study ID (if applicable)			
Suspect Product Administration			
IMVANEX (MVA-BN)	Date of first dose	Batch no.	
IMVANEX (MVA-BN)	Date of second dose	Batch no.	
Other (specify):	Therapy dates	Dose/frequency :	Indication
Other (specify):	Therapy dates	Dose/frequency :	Indication

Cardiovascular Adverse Event(s) – enter a diagnosis or signs/symptoms if a diagnosis is not available					
Cardiovascular Adverse Events(s)	Start Date	Stop Date	CTCAE Grade <sup>a</sup>	Serious Criteria <sup>b</sup>	Outcome <sup>c</sup>
Key symptoms (mark N/A if not present)	Start Date	Stop Date	CTCAE Grade <sup>a</sup>	Serious Criteria <sup>b</sup>	Outcome <sup>c</sup>
Dyspnea					
Palpitations					
Cardiac chest pain					
Typical chest pain made worse when lying down and relieved by sitting up					

<b>Key:</b>	CTCAE Grade <sup>a</sup> 1 = Grade 1 (mild) 2 = Grade 2 (moderate) 3 = Grade 3 (severe) 4 = Grade 4 (life-threatening) 5 = Fatal	Serious Criteria <sup>b</sup> D = Death L = Life-threatening H = Hospitalization/prolonged hospitalization S = Significant disability M = Medically significant	Outcome <sup>c</sup> 1 = Recovered/resolved 2 = Recovering/resolving 3 = Not recovered/not resolved 4 = Recovered/resolved with sequelae 5 = Fatal 6 = Unknown
		N/A = Not applicable (non-serious)	
<b>If one of the events resulted in death</b> Date of death: Cause: <b>Was an autopsy performed?</b> No Yes (if available please attach report)			
<b>Hospitalization</b> Admission date: Discharge Date:			
<b>Cardiac Diagnostic Results – enter N/A if not performed</b>			
<b>Test Method</b>	<b>Test Date</b>	<b>Test Results</b> (please include reference range for lab values)	
Auscultation			
ECG			
Echocardiography			
Troponin I or T			
Cardiac MRI			
<b>Other diagnostic tests (please specify, e.g. Angiography, Ergometry, etc.)</b>			
<b>Was any pericardial effusion identified?</b>	Yes No	If yes, please provide details (date, how diagnosed, estimated volume etc.):	
<b>Was an endomyocardial biopsy performed?</b>	Yes No	If yes, please provide details (date, histology results etc.):	

<b>Minimum left ventricular ejection fraction (LV-EF)</b>	<b>%</b>	<b>Date and method of measurement:</b>		
<b>Were vasopressors or positive inotropic agents administered?    Yes   No</b>				
<b>Name of treatment</b>	<b>Route</b>	<b>Dose</b>	<b>Therapy Dates</b>	<b>Response</b>
<b>Were any other agents to treat heart failure administered?    Yes   No</b> (e.g. diuretics, vasodilators, ACE inhibitors, $\beta$ -blocking agents, etc.)				
<b>Name of treatment</b>	<b>Route</b>	<b>Dose</b>	<b>Therapy Dates</b>	<b>Response</b>
<b>Were any other treatments administered?    Yes   No</b>				
<b>Name of treatment</b>	<b>Route</b>	<b>Dose</b>	<b>Therapy Dates</b>	<b>Response</b>
<b>Were any non-drug treatments applied?    Yes   No</b>				
<b>Description of treatment</b>			<b>Therapy Dates</b>	<b>Response</b>
<b>Risk factors (list below) or No risk factors</b>				
<b>Recent episodes of viral (e.g. adeno, coxsackie), bacterial or fungal infections</b>	Yes No	If yes, please provide details		
<b>Chronic infections (e.g. HIV, tuberculosis, Hepatitis B/C)</b>	Yes No	If yes, please provide details		
<b>Previous hypersensitivities (incl. but not limited to sulfonamides, NSAIDs etc.)?</b>	Yes No	If yes, please provide details		
<b>Previous autoimmune disorders (e.g. celiac disease, rheumatoid diseases, etc.)</b>	Yes No	If yes, please provide details		

<b>History of malignancies (e.g. incl. anthracyclin treatment)</b>	Yes No	If yes, please provide details		
<b>Known ischemic disorders, incl. cardiac/coronary</b>	Yes No	If yes, please provide details		
<b>Chronic alcohol or tobacco use</b>	Yes No	If yes, please provide details		
<b>Recent pregnancy (female patients)</b>	Yes No	If yes, please provide details		
<b>Family history of inflammatory cardiac disorders?</b>	Yes No	If yes, please provide details		
<b>Other risk factors (specify):</b>	Yes No	If yes, please provide details		
<b>Medical History potentially relevant for assessment of cardiac conditions, in addition to the risk factors specifically listed above:</b>				
<b>Condition</b>		<b>Start date, intensity, treatments, further relevant details</b>		
<b>Additional Medications (including concomitant medications) If space is not sufficient, please include a printout of the patient's medications.</b>				
<b>Drug Name</b>	<b>Indication</b>	<b>Dose and Frequency</b>	<b>Start Date</b>	<b>Stop Date</b>

Additional Event Information		
<b>In your opinion, what is the causal relationship between the inflammatory cardiac adverse event and the IMVANEX vaccination?</b> <div style="display: flex; justify-content: space-around;"> <span>Related</span> <span>Not Related</span> </div>	If not related, what was the cause of the inflammatory cardiac adverse event?	
<b>Were alternate causes for the signs and symptoms ruled out?</b>	Yes No	If yes, please describe how these were ruled out:

Please provide any additional, relevant information on a separate page.

Signature of person completing form:	Date Completed:
Name and function of person completing form (Print):	
Email:	Phon

***Annex 4.3 Adverse Event Follow-Up Questionnaire – Immune mediated neurologic disorders***

**Adverse Event Follow-Up Questionnaire – Immune mediated neurologic disorder**

Please enter all dates in the following format: DD/MMM/YYYY (e.g. 01/MAR/2019)

Patient			
Initials	Sex	DOB	Study ID (if applicable)
	M F		

<b>Suspect Product Administration</b>			
IMVANEX (MVA-BN)	Date of first dose		Batch no.
IMVANEX (MVA-BN)	Date of second dose		Batch no.
Other (specify):	Therapy dates	Dose/frequency :	Indication
Other (specify):	Therapy dates	Dose/frequency :	Indication

<b>Neurologic Adverse Event(s) – enter a diagnosis or signs/symptoms if a diagnosis is not available</b>					
Neurologic Adverse Events(s)	Start Date	Stop Date	CTCAE Grade <sup>a</sup>	Serious Criteria <sup>b</sup>	Outcome <sup>c</sup>
Key symptoms (mark N/A if not present)	Start Date	Stop Date	CTCAE Grade <sup>a</sup>	Serious Criteria <sup>b</sup>	Outcome <sup>c</sup>
Decreased level of consciousness					
Seizures					
Paraesthesia / Hypoaesthesia					
Paralysis/Palsy of					
<b>Key:</b>	CTCAE Grade <sup>a</sup> 1 = Grade 1 (mild) 2 = Grade 2 (moderate) 3 = Grade 3 (severe) 4 = Grade 4 (life-threatening) 5 = Fatal		Serious Criteria <sup>b</sup> D = Death L = Life-threatening H = Hospitalization/prolonged hospitalization S = Significant disability M = Medically significant		Outcome <sup>c</sup> 1 = Recovered/resolved 2 = Recovering/resolving 3 = Not recovered/not resolved 4 = Recovered/resolved with sequelae 5 = Fatal

		N/A = Not applicable (non-serious)	6 = Unknown	
<b>If one of the events resulted in death</b>		Date of death: Cause:		
<b>Was an autopsy performed?</b>		No Yes (if available please attach report)		
<b>Hospitalization</b>		Admission date:		Discharge Date:
<b>Brain Imaging and/or Other Diagnostic Results – enter N/A if not performed</b>				
<b>Test Method</b>	<b>Test Date</b>	<b>Test Results</b> (please include reference range for lab values)		
Cerebral spinal fluid examination				
MRI				
EEG				
Nerve conduction velocity / Electromyography				
<b>Other diagnostic tests (please specify). Please include key findings of complete neurologic examination.</b>				
<b>Was any cerebral edema identified?</b>	Yes No	If yes, please describe how it was identified:		
<b>Were anti-epileptic drugs administered?</b> Yes No				
<b>Name of antiepileptic</b>	<b>Route</b>	<b>Dose</b>	<b>Therapy Dates</b>	<b>Response</b>
<b>Were corticosteroids (CS) administered?</b> Yes No				

Name of CS	Route	Dose	Therapy Dates	Response
Were any other treatments administered?    Yes   No				
Name of treatment	Route	Dose	Therapy Dates	Response
Were any non-drug treatments applied?    Yes   No				
Description of treatment			Therapy Dates	Response
<b>Relevant Medical History (list below) or No medical history</b> <b>If yes, please specify if any history of seizure disorder or other neurologic disorders, autoimmune disorder, malignancies (including potential CNS involvement), or presence of implants or medical devices in the CNS.</b>				
Condition		Start date, intensity, treatments, further relevant details		
<b>Additional Medications (including concomitant medications) If space is not sufficient, please include a printout of the patient's medications.</b>				
Drug Name	Indication	Dose and Frequency	Start Date	Stop Date

<b>Additional Event Information</b>
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<b>In your opinion, what is the causal relationship between the neurologic adverse event and the IMVANEX vaccination?</b>  <div style="display: flex; justify-content: space-around;"> <span>Related</span> <span>Not Related</span> </div>	If not related, what was the cause of the neurologic adverse event?	
<b>Were alternate causes for the signs and symptoms ruled out?</b>	Yes No	If yes, please describe how these were ruled out:

Please provide any additional, relevant information on a separate page.

Signature of person completing form:	Date Completed:
Name and function of person completing form (Print):	
Email:	Phone:

***Annex 4.4 Summary ADR Reporting Form***

***(on following pages)***

Reporter

Name: \_\_\_\_\_ Phone/Fax: \_\_\_\_\_ Email: \_\_\_\_\_

Address: \_\_\_\_\_

Health Care Professional? \_\_\_\_\_ Yes/no if no, please describe: \_\_\_\_\_

Vaccinee 1	Initials (first/last)	Gender male/female	Age (years)	Vaccination date 1 <sup>st</sup> dd/mm/yyyy 2 <sup>nd</sup>	Reaction		from	until	Overall outcome (e.g. recovered or ongoing):
	____/____								
	Reaction(s) was/were ~Fatal disability ~Immediately life threatening ~Leading to or prolonging hospitalization ~Leading to persistent or significant								
	Initials (first/last)	Gender male/female	Age (years)	Vaccination date 1 <sup>st</sup> dd/mm/yyyy 2 <sup>nd</sup>	Reaction		from	until	Overall outcome (e.g. recovered or ongoing):
____/____									
Reaction(s) was/were ~Fatal disability ~Immediately life threatening ~Leading to or prolonging hospitalization ~Leading to persistent or significant									
Vaccinee 3	Initials (first/last)	Gender male/female	Age (years)	Vaccination date 1 <sup>st</sup> dd/mm/yyyy 2 <sup>nd</sup>	Reaction		from	until	Overall outcome (e.g. recovered or ongoing):
	____/____								
	Reaction(s) was/were ~Fatal disability ~Immediately life threatening ~Leading to or prolonging hospitalization ~Leading to persistent or significant								
	Vaccinee 4	Initials (first/last)	Gender male/female	Age (years)	Vaccination date 1 <sup>st</sup> dd/mm/yyyy 2 <sup>nd</sup>	Reaction		from	until
____/____									
Reaction(s) was/were ~Fatal disability ~Immediately life threatening ~Leading to or prolonging hospitalization ~Leading to persistent or significant									

Vaccine 5	Initials (first/last)	Gender male/female	Age (years)	Vaccination date 1 <sup>st</sup> dd/mm/yyyy 2 <sup>nd</sup>	Reaction		from	until	Overall outcome (e.g. recovered or ongoing):
	/								

Please provide any additional information you feel relevant:

Date: \_\_\_\_\_

Signature: \_\_\_\_\_

## **ANNEX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMIZATION ACTIVITIES (IF APPLICABLE)**

Not applicable, as there are no additional risk minimisation measures proposed.

## **ANNEX 1 OTHER SUPPORTING DATA (INCLUDING REFERENCED MATERIAL)**

## LITERATURE REFERENCES

Acambis Inc. ACAM2000™ (Smallpox (Vaccinia) Vaccine, Live). Prescribing information. 2007

ACCESS Protocol Background rates of adverse events of special interest for monitoring COVID-19 vaccines, version 1.1, 21 Sep 2020. <https://vac4eu.org/covid-19-vaccinemonitoring/> Adhikari S, Dempster H. Using regularized labor migration to promote Nigeria's development aims. Washington: The World Bank; 2019 [Available from <https://blogs.worldbank.org/developmenttalk/using-regularized-labor-migration-promote-nigerias-development-aims>]

Arness MK, Eckart RE, Love SS, Atwood JE, Wells TS, Engler RJM, Collins LC, Ludwig SL, Riddle JR, Grabenstein JD, Tornberg DN: Myopericarditis following Smallpox Vaccination. *American Journal of Epidemiology* 2004; 160: 642-51

Barbaro G, Barbarini G. Human immunodeficiency virus & cardiovascular risk. *Indian J Med Res* 2011 Dec;134(6):898-903

Bunge EM, Hoet B, Chen L, et al. The changing epidemiology of human monkeypox-A potential threat? A systematic review. *PLoS Negl Trop Dis*. 2022;16(2):e0010141. Published 2022 Feb 11. doi:10.1371/journal.pntd.0010141

Campe H, Zimmermann P, Glos K, et al. Cowpox virus transmission from pet rats to humans, Germany. *Emerg Infect Dis*. 2009;15(5):777-780. doi:10.3201/eid1505.090159

Casey C, Vellozzi C, Mootrey GT, Chapman LE, McCauley M, Roper MH, et al. Surveillance guidelines for smallpox vaccine (vaccinia) adverse reactions. *MMWR Recomm Rep* 2006;55:1–16.

Cassimatis DC, Atwood JE, Engler RM, Linz PE, Grabenstein JD, Vernalis MN: Smallpox vaccination and myopericarditis: a clinical review. *J.Am.Coll.Cardiol*. 2004; 43: 1503-10

Centers for Disease Control and Prevention (CDC). Update: cardiac-related events during the civilian smallpox vaccination program—United States, 2003. *MMWR Morb Mortal Wkly Rep*. 2003;52:492–6.

Eckart RE, Love SS, Atwood JE, Arness MK, Cassimatis DC, Campbell CL, Boyd SY, Murphy JG, Swerdlow DL, Collins LC, Riddle JR, Tornberg DN, Grabenstein JD, Engler RJ: Incidence and follow-up of inflammatory cardiac complications after smallpox vaccination. *J.Am.Coll.Cardiol*. 2004; 44: 201-5

Eder I, Vollmar P, Pfeffer M, Naether P, Rodloff AC, Meyer H. Two Distinct Clinical Courses of Human Cowpox, Germany, 2015. *Viruses*. 2017;9(12):375. Published 2017 Dec 7. doi:10.3390/v9120375

Endo A, Murayama H, Abbott S, Ratnayake R, Pearson CAB, Edmunds WJ, et al. Heavy-tailed sexual contact networks and the epidemiology of monkeypox outbreak in non-endemic regions, May 2022. *medRxiv : the preprint server for health sciences*. 2022:2022.06.13.22276353.

Eurosurveillance. 2021 Jones, T., (2008). IMVANEX, as attenuated modified vaccinia Ankara virus vaccine for smallpox infection. *Curr Opin Mol Ther* 10, 407-417

Fenner F, Henderson DA, Arita I, et al. Smallpox and its eradication. World Health Organization, Geneva. 1988; 1-1460.

Gold MS, Amarasinghe A, Greenhawt M, Kelso JM, Kochhar S, Yu-Hor Thong B, Top KA, Turner PJ, Worm M, Law B. Anaphylaxis: Revision of the Brighton collaboration case definition. *Vaccine*. 2022 Nov 24;S0264-410X(22)01425-6. doi: 10.1016/j.vaccine.2022.11.027.

Goldstein JA, Neff JM, Lane JM, Koplan JP. Smallpox vaccination reactions, prophylaxis, and therapy of complications. *Pediatrics*. 1975; 55:342–347

Grant R, Nguyen LL, Breban R. Modelling human-to-human transmission of monkeypox. *Bull World Health Organ*. 2020;98(9):638-640. doi:10.2471/BLT.19.242347

Gravanis MB, Sternby NH. Incidence of myocarditis. A 10-year autopsy study from Malmö, Sweden. *Arch Pathol Lab Med* 1991; 115(4):390-2.

Hägg, S., Religa, D. COVID vaccination in older adults. *Nat Microbiol* 7, 1106–1107 (2022). <https://doi.org/10.1038/s41564-022-01166-0>

Halsell JS, Riddle JR, Atwood JE, Gardner P, Shope R, Poland GA, Gray GC, Ostroff S, Eckart RE, Hospenhal DR, Gibson RL, Grabenstein JD, Arness MK, Tornberg DN: Myopericarditis Following Smallpox Vaccination Among Vaccinia-Naïve US Military Personnel. *JAMA: The Journal of the American Medical Association* 2003; 289: 3283-9

Hobson G, Adamson J, Adler H, Firth R, Gould S, Houlihan C, et al. Family cluster of three cases of monkeypox imported from Nigeria to the United Kingdom, May 2021.

Hsu CH, Farland J, Winters T, et al. Laboratory-acquired vaccinia virus infection in a recently immunized person--Massachusetts, 2013. *MMWR Morb Mortal Wkly Rep*. 2015;64(16):435-438.

Isaacs SN. Working safely with vaccinia virus: laboratory technique and review of published cases of accidental laboratory infections. *Methods Mol Biol*. 2012;890:1-22. doi:10.1007/978-1-61779-876-4\_1

Kennedy, J. S., and Greenberg, R. N. (2009). IMVANEX: modified vaccinia Ankara strain as an attenuated smallpox vaccine. *Expert Rev Vaccines* 8, 13-24

Koblentz, G. D. The *De Novo* Synthesis of Horsepox Virus: Implications for Biosecurity and Recommendations for Preventing the Reemergence of Smallpox. *Health Secur*, 2017, 15, 620628

Law B, Sturkenboom M. D2.3 priority list of adverse events of special interest: COVID19. In: WP2 standards and tools. V2.0. 25-05-2020. Brighton Collaboration. Decatur, GA: Safety Platform for Emergency vACCines; 2020: 52 pages.

Mauldin MR, McCollum AM, Nakazawa YJ, et al. Exportation of Monkeypox Virus From the African Continent. *J Infect Dis*. 2022;225(8):1367-1376. doi:10.1093/infdis/jiaa559

McCollum AM, Damon IK. Human monkeypox [published correction appears in *Clin Infect Dis*. 2014 Jun;58(12):1792]. *Clin Infect Dis*. 2014;58(2):260-267. doi:10.1093/cid/cit703

Moussatché N, Tuyama M, Kato SE, et al. Accidental infection of laboratory worker with vaccinia virus. *Emerg Infect Dis*. 2003;9(6):724-726. doi:10.3201/eid0906.020732

Noyce, R. S., Lederman, S. & Evans, D. H. 2018. Construction of an infectious horsepox virus vaccine from chemically synthesized DNA fragments. PLoS One. 2018 Jan 19;13(1):e0188453. doi: 10.1371/journal.pone.0188453

Orbach H, Agmon-Levin N, Zandman-Goddard G. Vaccines and autoimmune diseases of the adult. Discov Med 2010 Feb;9(45):90-7.

Petersen, B. W., Damon, I. K., Pertowski, C. A., *et al.* Clinical guidance for smallpox vaccine use in a postevent vaccination program. MMWR Recomm Rep, 2015, 64, 1-26

Rao AK, Schulte J, Chen TH, et al. Monkeypox in a Traveler Returning from Nigeria - Dallas, Texas, July 2021. MMWR Morb Mortal Wkly Rep. 2022;71(14):509-516. Published 2022 Apr 8. doi:10.15585/mmwr.mm7114a1

Rimoin AW, Mulembakani PM, Johnston SC, et al. Major increase in human monkeypox incidence 30 years after smallpox vaccination campaigns cease in the Democratic Republic of Congo. Proc Natl Acad Sci U S A. 2010;107(37):16262-16267. doi:10.1073/pnas.1005769107

Salemi S, D'Amelio R. Could autoimmunity be induced by vaccination? Int Rev Immunol 2010 Jun;29(3):247-69

Saxena SK, Ansari S, Maurya VK, et al. Re-emerging human monkeypox: a major public-health debacle [published online ahead of print, 2022 Jun 1]. J Med Virol. 2022;10.1002/jmv.27902. doi:10.1002/jmv.27902

Schmutzhard E. Viral infections of the CNS with special emphasis on herpes simplex infections. J Neurol. 2001 Jun;248(6):469-77

Sejvar JJ, Kohl KS, Bilynsky R, Blumberg D, Cvetkovich T, Galama J, Gidudu J, Katikaneni L, Khuri-Bulos N, Oleske J, Tapiainen T, Wiznitzer M; Brighton Collaboration Encephalitis Working Group. Encephalitis, myelitis, and acute disseminated encephalomyelitis (ADEM): case definitions and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine. 2007 Aug 1;25(31):5771-92. doi: 10.1016/j.vaccine.2007.04.060. Epub 2007 May 11

Senanayake SN. Needlestick injury with smallpox vaccine. Med J Aust. 2009;191(11-12):657. doi:10.5694/j.1326-5377.2009.tb03368.x

Shimabukuro T. Enhanced safety monitoring for COVID-19 vaccines in early phase vaccination. In: ACIP presentation. Atlanta, GA: National Center for Immunization & Respiratory Diseases; 2020: 21 pages. Suter M, Meisinger-Henschel C, Tzatzaris M, Hülsemann V, Lukassen S, Wulff NH, Hausmann J, Howley P, Chaplin P: Modified vaccinia Ankara strains with identical coding sequences actually represent complex mixtures of viruses that determine the biological properties of each strain. Vaccine 2009; 27: 7442-50

Wei Q, Lu XC, Wu GZ. [Analysis on status and characteristics of laboratory-acquired vaccinia virus infections cases]. Zhonghua Shi Yan He Lin Chuang Bing Du Xue Za Zhi. 2013 Feb;27(1):73-5. Chinese. PMID: 23855138.] Wei Q, Lu XC, Wu GZ. Zhonghua Shi Yan He Lin Chuang Bing Du Xue Za Zhi. [Analysis on status and characteristics of laboratory-acquired vaccinia virus infections cases]

Whitehouse ER, Rao AK, Yu YC, et al. Novel Treatment of a Vaccinia Virus Infection from an Occupational Needlestick - San Diego, California, 2019. MMWR Morb Mortal Wkly Rep. 2019;68(42):943-946. Published 2019 Oct 25. doi:10.15585/mmwr.mm6842a2

Wyeth Laboratories, Dryvax™ (Dried Smallpox Vaccine). Prescribing information 2002