IMVANEX

EU RISK MANAGEMENT PLAN

IMVANEX® (SMALLPOX AND MPOX VACCINE MODIFIED VACCINIA ANKARA-BAVARIAN NORDIC (MVA-BN®) (LIVE ATTENUATED, NON-REPLICATING))

RMP version to be assessed as part of this application:

Data lock point for this RMP	31-Jul-2023	Version number	11.0
Date of final sign off	26-Jul-2024		

Rationale for submitting an updated RMP:

Version 11.0 is submitted in the context of the 2024 annual re-assessment, taking into consideration the completion of the SEMVAc study, which was a PAES as specific obligation in the previous versions.

Summary of significant changes in this RMP:

1. Inclusion of high-level results from SEMVAc post-authorization surveillance study
2. Removal of SEMVAc post-authorization surveillance study from additional pharmacovigilance measures, due to completion of the study

Other RMP versions under evaluation:

Not applicable

Details of the currently approved RMP:

Version number: 9.3

Approved with procedure: EMEA/H/C/002596/II/0081

Date of approval (opinion date): 16-Mar-2023

EU-QPPV[1]:Heinz Weidenthaler **Head of CSPV**: [redacted]

For signatures, please see electronic signature page

[1] QPPV name will not be redacted in case of an access to documents request; see HMA/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	Chicken Embryo Fibroblast
cGMP	Current Good Manufacturing Practice
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

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

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 1: Product Overview

Active substance(s) (INN or common name)	Live Modified Vaccinia Ankara-Bavarian Nordic (MVA-BN®)
Pharmacotherapeutic group (ATC Code)	Other viral vaccines (JO7BX)
Marketing Authorisation Holder	Bavarian Nordic A/S Philip Heymans Alle 3 DK-2900 Hellerup Denmark
Medicinal products to which this RMP refers	Suspension for injection
Invented name(s) in the European Economic Area (EEA)	IMVANEX® (MVA-BN®)
Marketing authorisation procedure	Centralised
Brief description of the product	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 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 $1x10^8$ Inf.U/dose. One standard dose (0.5 mL) of the MVA-BN liquid frozen smallpox and mpox vaccine contains at least $0.5x10^8$ Inf.U/0.5 mL dose throughout its shelf life.

Brief description of the product (continued)	In 2017, the MVA-BN potency assay changed from a $TCID_{50}$ based assay to a flow cytometry based assay, and the units changed from $TCID_{50}$ 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 $TCID_{50}$ to flow cytometry and the unit changed from $TCID_{50}$ to Inf.U, the conversion factor was 1:1, therefore the established limits and specifications remain unchanged. 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 ≥18 years including persons with atopic dermatitis (AD) or allergic rhinitis (AR) and Human Immunodeficiency Virus (HIV) infected individuals (CD4 ≥ 100 cells/µL). 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. A primary vaccination series consists of 2 doses of no less than 5 x 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 x 10^7 Inf.U IMVANEX administered via the SC route in vaccinia and IMVANEX experienced subjects.
Hyperlink to the Product Information	Product Information (eCTD seq0204)
Indication(s) in the EEA	Current: Active immunisation against smallpox, monkeypox and disease caused by vaccinia virus in adults. The use of this vaccine should be in accordance with official recommendations.
	Proposed (if applicable): NA

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

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)

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

Table 2 Indication epidemiology: General population (HIV infected)

Indication/target population	Smallpox vaccination in HIV infected subjects
Incidence of target indication	No smallpox infections reported since 26 Oct 1977
Prevalence of target indication	No smallpox infections reported since 26 Oct 1977
Mortality in target indication	Unknown

Potential health risk	Severe disease, potentially fatal
Demographic profile of target population	≥18 years

Table 3 Indication epidemiology: General population (Atopic Disease)

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

Table 4 Indication epidemiology: Military population

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

Table 5 Indication epidemiology: Laboratory personnel

Indication/target population	Smallpox vaccination in laboratory personnel
Incidence of target indication	No smallpox infections reported since 26 Oct 1977
Prevalence of target indication	No smallpox infections reported since 26 Oct 1977
Mortality in target indication	10-90% (assumed from general population risk)

Potential health risk	Severe disease, potentially fatal
Demographic profile of target population	≥18 years

Table 6 Indication epidemiology: First line responders

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

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

Indication/target population	Mpox vaccination in individuals at risk of exposure to mpox virus
Incidence of target indication	Unknown/evolving (highly dependent on being part of at risk groups)
Prevalence of target indication	Unknown/evolving
Mortality in target indication	4-11%
Potential health risk	Severe disease, potentially fatal
Demographic profile of target population	≥ 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.

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

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

Mpox is a viral zoonosis caused by the monkeypox 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)

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)

In May 2022, an outbreak of mpox appeared suddenly and rapidly spread across Europe, the Americas and then throughout the world. The global outbreak affected primarily (but not only) gay, bisexual, and other men who have sex with men (GBMSM) and has spread person-to-person mainly through sexual networks. On 23 July 2022, the World Health Organization (WHO) Director- General determined the event to constitute a Public Health Emergency of International Concern (PHEIC). After a rapid rise of cases, the outbreak started to decline after July 2022. The reasons why the outbreak waned are unclear. Possible explanations include improved awareness and behavioural change in the population at risk, and acquisition of vaccination- or infection-induced immunity (Brand et al. 2023). On 11 May 2023, the WHO declared that the multi-country mpox outbreak was no longer a PHEIC, given the sustained decline in cases. Standing mpox recommendations were issued by the WHO Director-General in August 2023 that will remain valid for 1 year (WHO 2023c).

Throughout the world, 1165 countries reported over 91,000 confirmed cases, and 1657 deaths (WHO 2023a). As of 06 October 2023, EU/EEA countries have reported a total of 21,398 confirmed mpox cases and 7 deaths (ECDC and WHO 2023).

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 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 orthopoxviruses, 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
Military personnel	None

First-line responders	None
Laboratory personnel	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 4.9×10^8 $TCID_{50}$:

- No mortality or clinical signs indicative of systemic toxicity were observed at dose levels up to 4.9×10^8 $TCID_{50}$ 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 1×10^8 $TCID_{50}$) 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:

- 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.

- 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 x 10^7 and 1 x 10^8 $TCID_{50}$ IMVANEX, were applied in all three reproductive toxicity studies.

1 x 10^8 $TCID_{50}$ 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.

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 ($TCID_{50}$)**	**Study number**
Repeated-dose toxicity			
Rabbits / New Zealand White	2 applications at 8 days interval	4.9×10^8	HPA0006/074055
Rabbits / New Zealand White	3 applications within 42 days	1×10^7, 1×10^8	M254-03
Rabbits / New Zealand White	3 applications within 42 days	1×10^7, 1×10^8	M249-03
Reproductive and developmental toxicity			
Rabbits / New Zealand White	3 immunisations at 2 weeks interval	1×10^7, 1×10^8	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

	0 (Control)	**1 x 10^7**	**1 x 10^8**	**4.9x10^8**
Rabbit				
Macroscopic cardiac findings: Atrium Discoloured	0 / 90	0 / 24	1/ 64 *	0 / 26
Microscopic cardiac findings:		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.

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 $1x10^8$ $TCID_{50}$ 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	$1x10^8$ $TCID_{50}$ 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.

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

Key Safety findings (from non- clinical studies)	Relevance to human usage
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

Safety concerns	
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.

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 orthopoxvirus 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 ≥18 years including persons with atopic dermatitis (AD) or allergic rhinitis (AR) and Human Immunodeficiency Virus (HIV) infected individuals (CD4+ ≥ 100 cells/μL).

A primary vaccination series consists of 2 doses of no less than 5 x 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 x 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.

SIII.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:

- 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 ($2x10^7$ $TCID_{50}$) 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 ($1x10^7$ $TCID_{50}$) 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).

- 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 x 10^7 TCID50 of IMVANEX in the context of clinical trials, as per recommended schedule (2 doses of no less than 5 x 10^7 TCID50 4 weeks apart in vaccinia-naïve subjects; 1 single dose of no less than 5 x 10^7 TCID50 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 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.

SIII.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

Doses	Persons (randomized trials)	Persons (open trials)	Total
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-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

Strength	Persons (randomized trials)	Persons (open trials)	Total
10^6 $TCID_{50}$	18	0	18
10^7 $TCID_{50}$	358	0	358
10^8 $TCID_{50}$	6954	1596	8550 *,**
2 x 10^8 $TCID_{50}$	29	0	29
5 x 10^8 $TCID_{50}$	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

Age group	Male			Female		
	rand. trials	open trials	total	rand. trials	open trials	total
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.

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

Ethnic group	**Persons (randomized trials)**	**Persons (open trials)**
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*, **

Vaccinia	**Persons (randomized trials)**	**Persons (open trials)**
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

	Persons (randomized trials)	Persons (open trials)
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

Ability to detect adverse reactions	Limitation of trial programme	Discussion of implications for target population
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

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	Age range	Safety relevant exclusion criteria, common for all studies
POX-MVA-001	86	20-55	- Uncontrolled serious infection - Malignancy or history of malignancy - History or clinical manifestation of clinically significant and severe hematological, renal, hepatic, pulmonary, central nervous, cardiovascular or gastrointestinal disorders. - History and risk of coronary heart diseases - History of alcohol abuse/intravenous drug abuse - History of anaphylaxis or severe allergic reaction and of allergic disease or reactions likely to be exacerbated by any component of the vaccine.
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	- History or clinical manifestation of immune modifying conditions / diseases or immune modifying therapies
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

Table 23 Exclusion criteria which will remain as contraindications

Exclusion criteria which will remain as contraindications	
Criteria	**Implications for target population**
History of anaphylaxis or severe allergic reaction and of allergic disease or reactions likely to be exacerbated by any component of the vaccine.	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

Exclusion criteria which are NOT proposed to remain as contraindications		
Criteria	**Reason for being an exclusion criterion**	**Justification for not being a contraindication**
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.

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

Type of special population	Exposure
Pregnant women Breastfeeding women	Not included in the clinical development program. **Pregnant women** 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. **Breastfeeding women** It is not known whether IMVANEX is excreted in human milk. IMVANEX should not be used during breastfeeding unless the benefits of immunisation outweigh the risks of infection with Mpox, Vaccinia or Variola virus.

Type of special population	Exposure
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment • Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program
Patients with relevant comorbidities: • Immunocompromised patients	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. Data have been generated in HIV infected individuals with CD4 counts ≥100 cells/µl and ≤750 cells/µl. 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.
Population with relevant different ethnic origin	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.
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program 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.

Type of special population	Exposure
Other Population with atopic disease (atopic dermatitis, atopic rhinitis)	Individuals with atopic dermatitis (AD) developed more local and general symptoms after vaccination. 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. 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.

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 or mpox 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 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,the US, and Switzerland, 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 enendemic countries of sub-Saharan Africa should be considered in the context of the overall public health needs of these countries.

Vaccination with MVA–BN has been a crucial component of the 2022 mpox outbreak control. Given the widespread use of the vaccine (at least 1.8 million doses were administered), several observational studies have been conducted and published, providing a unique opportunity to collect VE data in real-world situation. The use of real-world data (RWD) from literature, medical records, and registries is an acceptable methodology to address research questions, especially when traditional randomised clinical trials are unfeasible or unethical (EMA 2023).

BN therefore conducted a thorough systematic literature review (SLR) to summarise the evidence on the VE of MVA-BN in real-world use during the outbreak, covering the period from January 2022 to November 2023. This SLR assessed the strengths and limitations of each study, to understand how well the VE estimates from these studies may represent the actual real-world effectiveness of the vaccine. Despite significant heterogeneity in study design and at-risk population definitions, the findings from the totality of the data were largely consistent and reflect strong effectiveness of MVA-BN at preventing symptomatic mpox disease.

In real-world observational studies conducted in vaccine-eligible individuals (according to local recommendations), vaccine effectiveness against mpox disease was demonstrated at least 14 days after vaccination, with adjusted vaccine effectiveness estimates ranging from 35% (95% CI, -2-59) to 89% (95% CI, 76-95) after one IMVANEX dose and from 66% (95% CI, 47-78) to 90% (95% CI, 86-92) after two IMVANEX doses.

Further details on the real world effectiveness studies covered by the systematic literature review are provided in the Clinical Overview (Module 2.5).

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

No of doses shipped	Cumulative 31-Jul-2013 to 31-Jan-2024
US	15.533.000
EU/EEA	3.067.460
Canada	4.615.000
UK	154.280
Others[b]	1.428.300

Total	24.798.040

[a] Shipments before Brexit are counted in EU/EEA shipments
[b] Other includes European non-EU countries, and Asia

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-2023, 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.

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 31-Jan-2024

Country	Reported number of doses administered	Source
USA	1,243,378	https://www.cdc.gov/poxvirus/monkeypox/response/2022/vaccines_data.html

Country	Reported number of doses administered	Source
UK	121,000	JCVI statement on mpox vaccination as a routine programme - GOV.UK (www.gov.uk) (data as of latest update on 10-Nov-2023)
EU/EEA countries	336,976	https://www.ecdc.europa.eu/sites/default/files/documents/Public%20health%20considerations%20for%20mpox%20in%20EUEEA%20countries%202023_0.pdf (data as of Apr-2023, no longer updated since then)
Canada	50,000	https://www.canada.ca/en/public-health/news/2022/08/statement-from-the-chief-public-health-officer-of-canada-on-august-12-2022.html
Australia	15,493	https://ausvaxsafety.org.au/vaccine-safety-data/monkeypox-vaccine
Total number of doses	**1,810,318**	

SV.2 Results from Post-Authorization Safety/Efficacy Studies

The SEMVAc study was completed on 31 December 2023 and the final CSR, dated 26 April 2024, is available (Module 5.3.5.2). A more detailed summary of the study results are provided in the Clinical Overview (Module 2.5).

As the SEMVAc study is completed, it is removed from the active PAES in this RMP.

A total of 6265 participants were enrolled between 07-Jul-2022 and 31-Dec-2023 and were included in the final analysis as part of the MSM Cohort. The MSM Cohort includes participants enrolled at the study centres, fulfilling the inclusion criteria and not meeting any exclusion criteria and who were not excluded after enrolment. The Vaccine Efficacy (VE) Cohort included 5434 participants. The Safety Cohort included 4788 participants.

There was a total of 14 MPXV PCR-confirmed and physician-reported infections; all occurred in vaccinated participants. No cases of mpox were reported in the unvaccinated group in the VE cohort. Eleven and two cases of MPXV infection were reported in those with one and two doses of MVA-BN, respectively. The majority of infections were reported early on in the study period, i.e. between July and September 2022.

No estimates of effectiveness of the MVA-BN vaccine could be provided, given the lack of reported mpox cases among unvaccinated participants (significantly fewer unvaccinated persons were recruited in the study, hence the under sampled unvaccinated groups infers a decreased opportunity to detect mpox occurrence).

No more than 18 total Adverse Reactions (ARs) were observed during the follow-up period, and no SARs and AESIs (pericarditis, myocarditis, encephalitis) were reported. The likelihood of experiencing an AR was extremely low and decreased, together with AR severity, in those participants who received a second dose of MVA-BN. The cumulative AR incidence was slightly higher in the HIV+ subgroup compared to the overall Safety Cohort. Additionally, the majority of ARs occurred in participants between 40 and 59 years old, indicating that age may be a relevant factor associated with safety events. Thus, it is possible that both age and health status influence the likelihood of ARs, potentially more so in those persons immunosuppressed (i.e., People Living with HIV [PLWH]). However, these observations should be interpreted with caution due to the low number of events.

Reactogenicity generally decreased from the first to the second MVA-BN dose, with most participants experiencing discomfort or a localised reaction (70.2%) after the first vaccination, which decreased in frequency after the second vaccination (56.8%). The most common symptom was mild pain at the injection site with pressure or movement (46.7%) after the first dose, which reduced to 40.6% after the second dose. Only around 5% of participants reported fever, and in those participants that did report fever, no participants reported fever >40ºC and very few >39ºC. The majority of participants did not report fatigue, myalgia, arthralgia, headache, nausea, or diarrhoea. In those who did, <1.5% across groups and vaccination status reported severe symptoms. Less than 3% of participants reported any severe systemic complaints.

CD4 counts in PLWH were associated with the likelihood of a local or systemic reaction after the first and second vaccination. Results showed a protective effect with increasing CD4 levels and a lower odds of experiencing a local or systemic reaction, which might be explained by a more robust immune response in participants with higher CD4 counts, improving tolerability. Study participants with CD4 counts of less than 200/µl only exhibited significantly increased odds of systemic reactions after the first vaccination (odds ratio 14.98 [95% CI 1.74-129.16]). In this case the value was associated with a very wide CI and consequently a high degree of uncertainty, as the occurrence of mpox in this group was very low (5/6 experienced a systemic reaction). Use of PrEP did not significantly impact the likelihood of local or systemic reaction after the first or second dose.

The abovementioned results are indicative of a low reactogenicity and good tolerability of the MVA-BN vaccine in the overall MSM population and across study subgroups, with improved tolerability after the second dose. Overall, the vaccine was well tolerated and showed a favourable safety profile. Based on the outcomes of the SEMVAc study, the benefit-risk balance for IMVANEX remains positive in its authorised indications.

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

Table 28 Summary of safety concerns

Important identified risks	**None**
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 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 ≥0.1% of Subjects in the Completed IMVANEX Clinical Trials* (N=3432)

Table 29 Adverse reactions observed in clinical trials

System Organ Class **Adverse reaction**	**IMVANEX®** **(n=3,432) in %**
Blood and lymphatic system disorders	
Lymphadenopathy	0.87%
Cardiac disorders	
Bundle branch block	0.12%
Ear and labyrinth disorders	
Vertigo	0.17%
Gastrointestinal disorders	
Diarrhoea	0.5%
Nausea	1.57%
Vomiting	0.17%
General disorders and administration site conditions	
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%
Infections and infestations	
Nasopharyngitis	0.35%
Investigations	
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%
Musculoskeletal and connective tissue disorders	
Arthralgia	0.38%
Muscular weakness	0.12%
Myalgia	2.68%
Neck pain	0.15%
Nervous system disorders	
Dizziness	1.11%
Headache	5.57%
Paraesthesia	0.20%
Respiratory, thoracic and mediastinal disorders	
Cough	0.15%
Oropharyngeal pain	0.26%
Pharyngolaryngeal pain	0.38%
Skin and subcutaneous tissue disorders	
Pruritus	0.32%
Rash	0.41%
Skin discoloration	0.20%
Vascular disorders	
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 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 immuno-suppressive 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 on 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.

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, he 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.

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 (both grandfathers had myocardial infarctions in their 50ies, father had blood clots), as well as overweight with a BMI above 33. A few days before event onset, subject returned from a trip to India with diarrhea and was started on ciprofloxacine 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. 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

Risk	Frequency IMVANEX	Frequency Dryvax	Frequency ACAM2000
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

Risk	Frequency IMVANEX	Frequency Dryvax	Frequency ACAM2000
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 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.

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:

Important potential risk:	**Incorrect route of drug administration**
SOC: Injury, poisoning and procedural complications	
Frequency with 95 % CI	Not applicable (not observed in 8992 subjects in completed clinical trials)
Seriousness/outcomes	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	IMVANEX is not indicated for use in children and adolescents.	IMVANEX has not been studied in subjects below 18 years of age.

Missing information	What is known	Risk-benefit impact:
(<18 years)		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 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. It is not known whether IMVANEX is excreted in human milk. IMVANEX should not be used during breastfeeding	Pregnant women 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.

Missing information	What is known	Risk-benefit impact:
	unless the benefits of immunisation outweigh the risks of infection with Vaccinia or Variola virus.	
Elderly subjects	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).	In case of an outbreak situation, the risk of smallpox infection is considered higher than the potential risk of the vaccine.
Individuals with organ impairment	No information available, as not studied.	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.
Clinically immunocompromised individuals	The safe administration of 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.	In case of an outbreak situation, the risk of smallpox infection is considered higher than the potential risk of the vaccine.

Missing information	What is known	Risk-benefit impact:
Safety experience in mass vaccination due to smallpox outbreak	No information available for smallpox, as not studied. Large scale vaccinations in mpox outbreak showed favourable benefit risk profile	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 mpox, smallpox or vaccinia 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 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

For RMP 10.1, the new important potential risk of virologic blips/failure was added, reflecting post-authorization experience in people living with HIV under antiretroviral treatment, where after administration of MVA-BN, a temporary increase in viral load was reported sporadically.

Also with Version 10.1, the previous important potential risk term “postvaccinal encephalitis” was broadened to “immune-mediated neurologic disorders”, to reflect for a suspect post-authorization case of acute disseminated encephalomyelitis (ADEM), a post-infectious encephalomyelitis.

Immunocompromised populations were deleted from the missing information section, to reflect for the availability of data in subjects with AIDS-related conditions (previous PASS study POX-MVA-037).

Background for inclusion of virologic blips/failure:

Raccagni et al. (2023): The aim of this study was to evaluate whether mpox vaccination with MVA-BN may be associated with viral blips or confirmed virologic failures in people with HIV receiving antiretroviral therapy (ART) and the associated factors. Individuals with HIV-RNA < 50 copies/mL and CD4+ lymphocytes ≥ 200 cells/μL in the 6 months prior to vaccination received MVA-BN and had ≥1 HIV-RNA determination within 3 months from vaccination. The primary outcome was occurrence of viral blips (1 HIV-RNA ≥50 copies/mL) and confirmed virologic failures (1 HIV-RNA ≥ 1000 copies/mL or ≥ 2 consecutive HIV-RNA ≥ 50 copies/mL) following MVA BN. Changes in CD4+ and CD4+/CD8+ were secondary outcomes. Residual viremia was defined as detectable HIV-RNA< 50 copies/mL. Individuals already vaccinated against smallpox received a single-dose MVA-BN. Mann-Whitney rank-sum test or Chi-square/Fisher's test applied. Overall, 187 individuals with HIV were included: 147 received 2 doses of MVA-BN, 40 received 1 dose. Six viral blips [incidence rate (IR) = 1.59/100-person months of follow-up (PMFU); 95% CI, 0.58-3.47] and three confirmed virologic failures (IR = 0.80/100-PMFU; 95% CI, 0.16-2.33) were observed. Two confirmed virologic failures occurred at second dose with presence of detectable HIV-RNA following first one, with high compliance to ART. Individuals with viral blips or confirmed virologic failures had, prior to first vaccination, more frequently residual viremia [77% (n = 7) versus 35% (n = 62), p = 0.01]. No differences in ART (p = 0.42) and number of MVA-BN doses (p = 0.40) were found. In two cases of confirmed virologic failures ART was changed; all viral blips resolved within 1 month. In conclusion, although rare, viral blips and confirmed virologic failures following MVA-BN vaccination among people with HIV receiving ART were identified. Close monitoring of HIV RNA during mpox vaccination should be encouraged.

Background for broadening the term “postvaccinal encephalitis” to “immune-mediated neurologic disorders”:

Prowse and Linsenmeyer (2023): A 30-year-old male patient was hospitalized due to acute disseminated encephalomyelitis (ADEM), 2-3 weeks after vaccination against mpox with the second dose of Jynneos (given via unknown route and at unknown dose). Patient's symptoms included headache, coordination difficulties, aphasia, personality changes. Brain MRI showed bilateral ischemic lesions in corona radiata and posterior corpus callosum, initially interpreted as multifocal strokes with negative workup for common stroke etiology. Initial treatment with aspirin, clopidogrel and statins. After the seventh day of hospitalization, the patient had a decline in verbalization and arousal.

Dysphagia worsened which required NPO status. Patient was unable to follow commands. CMP, CBC and UA were unremarkable. EBV, HIV, CMV, JCV, HSV tests were negative. Repeat head CT showed multifocal supratentorial and infratentorial hypoattenuating lesions (matching the earlier findings). Repeat brain MR showed diffuse cerebral edema with supratentorial. Lumbar puncture showed elevated protein. Based on this data, physicians rejected the diagnosis of multifocal strokes, and diagnosed the patient with ADEM. Plasmapheresis was started. Functionality, mental status and speech improved. Amantadine was given. ADEM is unlisted and unexpected per the CCDS V5.0 and USPI for Jynneos. The patient had no pertinent past medical history. Considering that multiple alternative etiologies were rejected, the event is conservatively assessed as related to Jynneos. The case is serious due to hospitalization and medical significance.

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:

Important potential risk: Myo-/pericarditis 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. In post-authorization setting, less than 1 case of myo-/pericarditis per 100.000 administered doses has been reported. Replicating smallpox vaccines: ACAM2000 5.7 per 1000 primary vaccinees 95% CI: 1.9-13.3)

Important potential risk: Myo-/pericarditis SOC: Cardiac disorders	
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 (Arness, 2004, Halsell, 2003)
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, Gravanis, 1991)
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

Important potential risk: Myo-/pericarditis SOC: Cardiac disorders	
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	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. 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.

Important Potential Risk 2:

Important potential risk: Immune-mediated neurologic disorders SOC: Nervous system disorders	
Frequency with 95 % CI	No cases of postvaccinal encephalitis observed with IMVANEX in 8992 subjects in completed clinical trials 12 cases of postvaccinal encephalitis per million vaccinations with replicating smallpox vaccines (Lane 1970) 1 post-authorization case of acute disseminated encephalomyelitis (ADEM) during the mpox vaccination campaign (Prowse, 2023)
Seriousness/outcomes	No postvaccinal encephalitis cases observed with IMVANEX. The post-authorization case of ADEM led to persistent disability in the affected subject. Replicating smallpox vaccines: postvaccinal encephalitis frequently leads to death, especially in infants and young children
Severity and nature of risk	Replicating smallpox vaccines: Severe. Reported case fatality of postvaccinal encephalitis 9% - 40%, 10% – 25% of surviving patients have permanent neurologic sequelae (Goldstein, 1975) ADEM: Case fatality in adults 4-12%, better prognosis in pediatric population (Prowse 2023)
Background incidence/prevalence	Viral encephalitis in central Europe: 0,2 to 0,4 occurrences per 100.000 inhabitants (Schmutzhard, 2001)
Risk groups or risk factors	Unknown
Potential mechanisms	Dissemination of vaccinia virus (acute cases) or induction of cross-reactivity leading to inflammatory disease of the nervous system including demyelination.

Important potential risk: Immune-mediated neurologic disorders SOC: Nervous system disorders	
Preventability	Postvaccinal encephalitis: Not observed and highly unlikely to occur with IMVANEX, which is replication incompetent in human cells ADEM: Mechanism incompletely understood, therefore no current approach for preventability. Early ascertainment of diagnosis could facilitate treatment with high dose steroid taper and/or plasmapheresis
Impact on individual patient/quality of life	Postvaccinal encephalitis 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 Case report including discussion of potential pathophysiology: Prowse 2023
Impact on risk- benefit balance of the product	Postvaccinal encephalitis: 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. Immune mediated encephalitis, myelitis or peripheral neurologic disorders: Such cases have been observed in limited numbers in the post-authorization use settings. The causality remains unclear. Due to the high effectiveness in protecting from symptomatic disease in the targeted vaccination campaigns during post-authorization use for mpox prevention, the risk benefit balance remains positive.

Important Potential Risk 3:

Important potential risk: Viral blips and virological failure SOC:	
Frequency with 95 % CI	Raccagni, 2023 reported results from a study evaluating the immune-virologic status in 187 patients living with HIV, who had received 1 dose (n=40) or two doses (n=147) of MVA-BN vaccination. The incidence rate of virologic blips was 1.59/100 patient months of follow-up (PMFU) (95% confidence interval (95%CI) 0.58-3.47) and that of confirmed virologic failures 0.80/100-PMFU (95% CI=0.16-2.33).
Seriousness/outcomes	A viral blip was defined as a single determination of HIV-RNA≥ 50 copies/mL; a confirmed virologic failure as a single determination of HIV-RNA ≥ 1000 copies/mL or ≥2 consecutive determinations of HIV-RNA ≥ 50 copies/mL. The reported cases of viral blips resolved within one month. For the reported cases of virologic failure, change in HIV treatment was needed and recovery was achieved within 3 months.
Severity and nature of risk	While the risk to an individual, experiencing a temporary increase of HIV-RNA is low, especially when the lab finding is identified and the treatment adjusted accordingly, there is still an increased risk of HIV transmission in the period of increased viral load, especially in sexually active at-risk individuals (Raccagni, 2023) BN has previously performed clinical trials in HIV positive populations, such as studies POX-MVA-010 (Phase 1 in HIV population), POX-MVA-011 (Phase 2 in HIV population) and POX-MVA-037 (a study to evaluate different doses and schedules in HIV subjects). Those studies included planned measurements of HIV viral load as part of the study schedule, hence these particular studies provide much more meaningful information than any other retrospective projects in rather undefined populations. The single largest BN-sponsored study in HIV populations was POX-MVA-011. A review of clinical trial data for non-serious AEs reported within the trial revealed no events of virologic failure, but 4 events of "Blood HIV RNA increased" in this clinical trial (POX-MVA-011 , Overton 2015), thereof 2 after the first and two after the second vaccination, among 351 vaccinia-naïve and 131 vaccinia experienced HIV-positive trial participants. It has to be noted that those events were observed in a clinical trial specifically designed for HIV positive participants, where viral load monitoring was part of the routine safety laboratory measurements. Therefore, further descriptive monitoring of potential future cases with detailed follow-up by dedicated questionnaires is at the current time the preferred follow-up method.

Important potential risk: Viral blips and virological failure SOC:	
Background incidence/prevalence	In an evaluation of the Swedish national HIV cohort (Sörstedt 2016), viral blips were found in 76/735 included subjects (10.3 %) and in 90/4449 samples (2.0 %). Median blip viral load was 76 copies/mL (range 56–138). Median follow-up time was 170 weeks (range 97–240). A calculation of incidence rates corresponding to a time interval was not provided.
Risk groups or risk factors	Only applicable for people living with HIV under antiretroviral treatment (ART)
Potential mechanisms	It is hypothesized that re-activation of latently infected, dormant immune cells may contribute to a temporary increase of viral RNA in otherwise stable, treated HIV infected subjects (Conway 2011)
Preventability	No immediate preventability, as the target population for recommended mpox vaccination (sexually active high-risk groups) is overlapping with the people living with HIV (PWH) population. However, close monitoring of viral load in the period after vaccinations could contribute to early detection and ART adjustment.
Impact on individual patient/quality of life	Additional burden by repeated blood draws and potential need for adjustment of HIV medication. Otherwise, a temporary increase of viral load during ongoing ART does not necessarily have an immediate impact on patient.
Potential public health impact of safety concern	Increased HIV transmission risk during episodes of increased viral load, in the at-risk population with active high-risk sexual behaviour.
Evidence source	Raccagni 2023 Sörstedt 2016 Conway 2011 Overton 2015

Important potential risk: Viral blips and virological failure SOC:	
Impact on risk- benefit balance of the product	The PWH population and the target population for mpox vaccination are highly overlapping, hence this population has the greatest benefit from mpox vaccination by breaking potential infection chains in the community. As the impact on the individual subject by a temporary increase of viral RNA is low, the benefit risk ratio remains unaffected. However, caution is needed in terms of prevention of potential HIV transmission during episodes of higher viral load, therefore awareness of the potential issue is needed among HCPs, leading to regular lab tests of viral load following vaccinations in general.

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**
Use during pregnancy and breastfeeding	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.
Elderly (>=65 years)	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 (Hägg, 2022). 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.

Missing information	Anticipated risk/consequence of the missing information
Individuals with organ impairment	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.
Interactions with other vaccines and concomitantly administered immunoglobulins	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 subjects. In addition, approx. 1.7 million doses had been administered globally 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

Important identified risks	None
Important potential risk	- Myo-/pericarditis - Immune-mediated neurologic disorders -Viral blips / virologic failure

Missing information	-Use during pregnancy and breastfeeding -Elderly subjects -Individuals with organ impairment -Interactions with other vaccines and concomitantly administered immunoglobulins

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.

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.

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 **Error! Reference source not found.**):

- 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.

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

Data Source	**Frequency of review**
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 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 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 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. BN has access to a dedicated team of data processing employees at its global safety database service provider, that can be scaled up flexibly in case of outbreak or re-emergence situations.

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.

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 "Immune mediated neurologic disorders" a specific Adverse Event Follow-Up Questionnaire has been developed to ensure consistent data capture of all suspected encephalitis/myelitis case reports.
- For the safety concern "Viral blips/virologic failure" a specific Adverse Event Follow-Up Questionnaire-Inflammatory Viral blips/virologic failure has been developed to ensure consistent data capture suspected virologic event 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 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 lace (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.

A packed carton 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

Taking into account the experience of at least approx. 1.8 million doses of MVA-BN administered in the context of the mpox outbreak in May-2022 and going forward, there is real-world evidence of efficacy and safety of the vaccine in a clinical setting of a large scale vaccination program for an orthopoxvirus infection.

Given differences in the vaccination policy between member states in terms of type 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.

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 years: 2,658
45 - 60 years: 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

This is an agreed approach with the regulators per outcome of Procedure No. EMEA/H/C/002596/II/0076

III.3 Summary Table of Additional Pharmacovigilance Activities

Table 34 Mandatory Additional PV activities

Study name/title Status	Summary of activity objectives	Safety concerns addressed	Milestones	Due dates
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				
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 Immune-mediated neurologic disorders Viral blips/virologic failures -Use during pregnancy and breastfeeding -Elderly subjects -Individuals with organ impairment -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

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 (EMEA/H/C /002596/SOB 002)	Endorsed by PRAC on 11 Sep 2014 (EMA/PRAC/540458/2014)
			Interim data:	Biannually with PSURs and in the annual re-assessment application.
			Final report:	Dependent on start of mass vaccination programs

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

Safety concern – Important potential risk	**Myo-/pericarditis**
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 myo-/pericarditis will be followed-up according to the case definitions as published by the Centers of Disease Control and Prevention 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."
	Other routine risk minimization measures None proposed

Additional risk minimization measures	None proposed
Effectiveness of risk minimization measures	
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 frequency above expected background incidence for confirmed cases of myo-/pericarditis has 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 Immune-mediated neurologic disorders

Safety concern – Important potential risk	**Immune-mediated neurologic disorders**
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 Immune-mediated neurologic disorders will be followed-up
	Other routine risk minimization measures None proposed
Additional risk minimization measures	None proposed
Effectiveness of risk minimization measures	

How effectiveness of risk minimization measures for safety concern will be measured	Any significant increase in number of spontaneous ADR cases of Immune-mediated neurologic disorders 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 Immune-mediated neurologic disorders 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	No additional risk minimization activities are considered necessary, therefore no specific effectiveness measurements are in place.
Impact of risk minimization	Not applicable
Comment	None

Table 38 Risk minimization for Viral blips / virologic failures

Safety concern – Important potential risk	**Viral blips / virologic failures**
Objectives of risk minimization measures	Identification of risk factors. Facilitation of appropriate measures.
Routine risk minimization measures	All cases of suspected/possible Viral blips / virologic failures will be followed-up
	Other routine risk minimization measures None proposed
Additional risk minimization measures	None proposed
Effectiveness of risk minimization measures	

How effectiveness of risk minimization measures for safety concern will be measured	Any significant increase in number of spontaneous ADR cases of Viral blips / virologic failures 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 Viral blips / virologic failures 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	No additional risk minimization activities are considered necessary, therefore no specific effectiveness measurements are in place.
Impact of risk minimization	Not applicable
Comment	None

Table 39 Risk minimization for missing information on interactions with vaccines and concomitantly administered immunoglobulins

Safety concern – Important missing information	**Interactions with vaccines and concomitantly administered immunoglobulin**
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
Effectiveness of risk minimization measures	
How effectiveness of risk minimization measures for the safety concern will be measured	Any significant number of spontaneous ADR cases of interactions with vaccines and concomitantly 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 40 Risk minimization for missing information on pregnancy and breastfeeding

Safety concern – Important missing information	**Pregnancy and breastfeeding**
Objectives of risk minimization measures	Continuous assessment of potential safety impact. Facilitation of appropriate measures if risks noted.
	SmPC section 4.6 states it is preferable to avoid the use of IMVANEX during pregnancy and breastfeeding
	Comments None

Routine risk minimization measures	Other routine risk minimization measures None proposed
Additional risk minimization measures	None proposed
Effectiveness of risk minimization measures	
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 41 Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risks (none)	Not applicable	Not applicable
Important potential risk Myo-/pericarditis	Routine risk minimisation measures: • 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 Additional risk minimisation measures: • None proposed	Routine and enhanced pharmacovigilance activities, incl. event specific follow-up questionnaires Additional pharmacovigilance activities: • Study POX-MVA-039 (final study report date dependent on start of mass vaccination programs) •
Important potential risk Immune-mediated neurologic disorders	Routine risk minimisation measures: • All cases of suspected/possible Immune-mediated neurologic disorders will be followed-up Additional risk minimisation measures: • None proposed	Routine and enhanced pharmacovigilance activities, including event specific follow-up questionnaires Additional pharmacovigilance activities: • Study POX-MVA-039 (final study report date dependent on start of mass vaccination programs) •

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important potential risk Viral blips / virologic failure	Routine risk minimisation measures: • All cases of suspected/possible Viral blips / virologic failure will be followed-up Additional risk minimisation measures: None proposed	Routine and enhanced pharmacovigilance activities, including event specific follow-up questionnaires Additional pharmacovigilance activities: • Study POX-MVA-039 (final study report date dependent on start of mass vaccination programs) •
Important missing information Use during pregnancy and breastfeeding	Routine risk minimisation measures: • SmPC Section 4.6 'Fertility, pregnancy and lactation' clearly points out that use during pregnancy and breastfeeding is not recommended. Additional risk minimisation measures: • None proposed	Routine pharmacovigilance activities, including pregancy-specific follow-up questionnaire Additional pharmacovigilance activities: • Study POX-MVA-039 (final study report date dependent on start of mass vaccination programs)
Important missing information Elderly subjects (≥65 years)	None proposed	Routine pharmacovigilance activities Additional pharmacovigilance activities: • Study POX-MVA-039 (final study report date dependent on start of mass vaccination programs)

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important missing information Individuals with organ impairment	None proposed	Routine pharmacovigilance activities Additional pharmacovigilance activities: • Study POX-MVA-039 (final study report date dependent on start of mass vaccination programs) •
Important missing information Interactions with vaccines and concomitantly administered immunoglobulins	Routine risk minimisation 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' Additional risk minimisation measures: None proposed	Routine pharmacovigilance activities Additional pharmacovigilance activities: • Study POX-MVA-039 (final study report date dependent on start of mass vaccination programs) •

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.

Important identified risks	None
Important potential risks	Myo-/pericarditis

	Immune-mediated neurologic disorders Viral blips / virologic failures
Important missing information	 Use during pregnancy and breastfeeding Elderly subjects Individuals with organ impairment Interactions with other vaccines and concomitantly administered

II.B Summary of Important Risks

Important potential risk: Myo-/pericarditis	
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	Routine risk minimisation measures • 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 • As no confirmed cases of myo-/pericarditis have been reported for IMVANEX, no additional risk minimisation activities are considered necessary. Additional risk minimisation measures None proposed

Additional pharmacovigilance activities	Routine and enhanced pharmacovigilance including event specific follow-up questionnaire Additional pharmacovigilance activities: POX-MVA-039 See section II.C of this summary for an overview of the post-authorisation development plan.
Important potential risk: Immune-mediated neurologic disorders	
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	Routine risk minimisation measures • All cases of suspected/possible Immune-mediated neurologic disorderswill be followed-up • As postvaccinal encephalitis has not been reported for IMVANEX, and the frequency of further immune-mediated neurologic events is limited to sporadic cases, no additional risk minimisation activities are considered necessary. Additional risk minimisation measures None proposed
Additional pharmacovigilance activities	Routine and enhanced pharmacovigilance including event specific follow-up questionnaire Additional pharmacovigilance activities: POX-MVA-039 See section II.C of this summary for an overview of the post-authorisation development plan.

Important potential risk: Viral blips / virologic failures	
Evidence for linking the risk to the medicine	Pharmacological class effect for all vaccines, and specific description of experience in a study in mpox vaccinated subjects (Raccagni 2023)
Risk factors and risk groups	Limited to People living with HIV under previously stable and effective antiretroviral treatment
Risk minimisation measures	Routine risk minimisation measures • All cases of suspected/possible Viral blips / virologic failures will be followed-up Additional risk minimisation measures None proposed
Additional pharmacovigilance activities	Routine and enhanced pharmacovigilance including event specific follow-up questionnaire Additional pharmacovigilance activities: POX-MVA-039 See section II.C of this summary for an overview of the post-authorisation development plan.
Missing information: Use during pregnancy and breastfeeding	

Risk minimisation measures	Routine risk minimisation measures SmPC Section 4.6 '**Fertility, pregnancy and lactation** clearly points out that use during pregnancy and breastfeeding is not recommended. Additional risk minimisation measures None proposed
Additional pharmacovigilance activities	Routine pharmacovigilance including event-specific follow-up questionnaire Additional pharmacovigilance activities: POX-MVA-039 See section II.C of this summary for an overview of the post-authorisation development plan.
Missing information: Interactions with other vaccines and concomitantly administered immunoglobulins	
Risk minimisation measures	Routine risk minimisation measures 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' Additional risk minimisation measures None proposed

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.

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

NA

PART VII: ANNEXES

LIST OF ANNEXES

D. SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Annex 4.1 Pregnancy Questionnaire

Pregnancy Questionnaire

☐ Initial Report ☐ Follow up Report Number _____

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

Reporter Information		
Name / Position		
Address		
State/Province/Postal code		
Country		
Phone/Fax		
Email		
Patient Information		
Initials	Date of birth _____/_____/_____ (or age in years)	
Vaccine administered		
Vaccine name and dose description	Date of vaccination _____/_____/_____	Batch no. Route of admin:
Vaccine name and dose description	Date of vaccination _____/_____/_____	Batch no. Route of admin

Pregnancy and Delivery Information
Current Pregnancy Is the pregnancy ongoing? ☐ Yes ☐ No If no, was the termination ☐ Spontaneous abortion Date: _____/_____/_____ ☐ Elective abortion Were any fetal abnormalities diagnosed ☐ Yes ☐ No If yes, please provide further details:

_____

_____

_____

Date of last menstrual period _____/_____/_____

Estimated date of delivery _____/_____/_____

Date of pregnancy confirmation _____/_____/_____

Confirmed by ☐ Serum ☐ Dipstick ☐ Ultrasound

Any relevant medical problems / complications observed during pregnancy? ☐ Yes ☐ No
If yes, please provide further details:

_____

_____

_____

Diagnostic tests performed during pregnancy? ☐ Yes ☐ No
If yes, please provide further details:

_____

_____

_____

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:

1. _____

_____

_____

_

2.

Pregnancy outcome
Maternal status

Actual date of delivery _____/_____/_____ ☐ Vaginal delivery ☐ Caesarean section

Any relevant medical problems or complications during delivery or postpartum periods, such as pre-eclampsia, haemorrhage, hypertension, etc.? ☐ Yes ☐ No
If yes, please provide further details:

_____

_____

_____

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: 1min 5min 10 min

Any complications? ☐ Yes ☐ No Any congenital abnormalities? ☐ Yes ☐ No
If yes, please provide further details:

_____

_____

_____

Any unusual diagnostic findings? ☐ Yes ☐ No
If yes, please provide further details:

_____

_____

_____

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

_____

_____

_____

_____

_____

_____

Follup up - 3 month after birth

Malformation/anomalies diagnosed since last report ☐ Yes ☐ No

Infant illnesses, hospitalizations, drug therapies ☐ Yes ☐ No If yes, please provide further details: _____ _____ _____

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

Signature of person completing form:	Date Completed:

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[a]**	**Serious Criteria[b]**	**Outcome[c]**
Key symptoms (mark N/A if not present)	**Start Date**	**Stop Date**	**CTCAE Grade[a]**	**Serious Criteria[b]**	**Outcome[c]**
Dyspnea					
Palpitations					
Cardiac chest pain					
Typical chest pain made worse when lying down and relieved by sitting up					

Key:	CTCAE Grade[a] 1 = Grade 1 (mild) 2 = Grade 2 (moderate) 3 = Grade 3 (severe) 4 = Grade 4 (life-threatening) 5 = Fatal	Serious Criteria[b] D = Death L = Life-threatening H = Hospitalization/prolonged hospitalization S = Significant disability M = Medically significant	Outcome[c] 1 = Recovered/resolved 2 = Recovering/resolving 3 = Not recovered/not resolved 4 = Recovered/resolved with sequelae 5 = Fatal
		N/A = Not applicable (non-serious)	

If one of the events resulted in death	Date of death:	Cause:
Was an autopsy performed?	No	Yes (if available please attach report)
Hospitalization	Admission date:	Discharge Date:

Cardiac Diagnostic Results – enter N/A if not performed		
Test Method	**Test Date**	**Test Results** (please include reference range for lab values)
Auscultation		
ECG		
Echocardiography		
Troponin I or T		
Cardiac MRI		
Other diagnostic tests (please specify, e.g. Angiography, Ergometry, etc.)		

Was any pericardial effusion identified?	Yes No	If yes, please provide details (date, how diagnosed, estimated volume etc.):
Was an endomyocardial biopsy performed?	Yes No	If yes, please provide details (date, histology results etc.):

Minimum left ventricular ejection	%	Date and method of measurement:

Were vasopressors or positive inotropic agents administered? Yes No

Name of treatment	Route	Dose	Therapy Dates	Response

Were any other agents to treat heart failure administered? Yes No

(e.g. diuretics, vasodilators, ACE inhibitors, ß-blocking agents, etc.)

Name of treatment	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

Risk factors (list below) or No risk factors		
Recent episodes of viral (e.g. adeno, coxsackie), bacterial or fungal infections	Yes No	If yes, please provide details
Chronic infections (e.g. HIV, tuberculosis, Hepatitis B/C)	Yes No	If yes, please provide details
Previous hypersensitivities (incl. but not limited to sulfonamides, NSAIDs etc.)?	Yes No	If yes, please provide details
Previous autoimmune disorders (e.g. celiac disease, rheumatoid diseases,etc.)	Yes No	If yes, please provide details
History of malignancies (e.g. incl. anthracyclin treatment)	Yes No	If yes, please provide details

Known ischemic disorders, incl. cardiac/coronary	Yes No	If yes, please provide details
Chronic alcohol or tobacco use	Yes No	If yes, please provide details
Recent pregnancy (female patients)	Yes No	If yes, please provide details
Family history of inflammatory cardiac disorders?	Yes No	If yes, please provide details
Other risk factors (specify):	Yes No	If yes, please provide details

Medical History potentially relevant for assessment of cardiac conditions, in addition to the risk factors specifically listed above:

Condition	Start date, intensity, treatments, further relevant details

Additional Medications (including concomitant medications) If space is not sufficient, please include a printout of the patient's medications.

Drug Name	Indication	Dose and Frequency	Start Date	Stop Date

Additional Event Information		
In your opinion, what is the causal relationship between the inflammatory cardiac adverse event and the IMVANEX vaccination? Related Not Related	If not related, what was the cause of the inflammatory cardiac adverse event?	
Were alternate causes for the signs and symptoms ruled out?	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 M F	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

Neurologic Adverse Event(s) – enter a diagnosis or signs/symptoms if a diagnosis is not available					
Neurologic Adverse Events(s)	**Start Date**	**Stop Date**	**CTCAE Grade[a]**	**Serious Criteria[b]**	**Outcome[c]**
Key symptoms (mark N/A if not present)	**Start Date**	**Stop Date**	**CTCAE Grade[a]**	**Serious Criteria[b]**	**Outcome[c]**
Decreased level of consciousness					
Seizures					
Paraesthesia / Hypoaesthesia					
Paralysis/Palsy of					

Key:	CTCAE Grade[a] 1 = Grade 1 (mild) 2 = Grade 2 (moderate) 3 = Grade 3 (severe) 4 = Grade 4 (life-threatening) 5 = Fatal	Serious Criteria[b] D = Death L = Life-threatening H = Hospitalization/prolonged hospitalization S = Significant disability M = Medically significant	Outcome[c] 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

If one of the events resulted in death	Date of death:	Cause:
Was an autopsy performed?	No	Yes (if available please attach report)
Hospitalization	Admission date:	Discharge Date:

Brain Imaging and/or Other Diagnostic Results – enter N/A if not performed

Test Method	Test Date	Test Results (please include reference range for lab values)
Cerebral spinal fluid examination		
MRI		
EEG		
Nerve conduction velocity /		
Other diagnostic tests (please specify). Please include key findings of complete neurologic examination.		

Was any cerebral edema identified?	Yes No	If yes, please describe how it was identified:		
Were anti-epileptic drugs administered? Yes No				
Name of antiepileptic	**Route**	**Dose**	**Therapy Dates**	**Response**
Were corticosteroids (CS) administered? 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**

Relevant Medical History (list below) or No medical history

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.

Condition	Start date, intensity, treatments, further relevant details

Additional Medications (including concomitant medications) If space is not sufficient, please include a printout of the patient's medications.				
Drug Name	**Indication**	**Dose and Frequency**	**Start Date**	**Stop Date**

Additional Event Information		
In your opinion, what is the causal relationship between the neurologic adverse event and the IMVANEX vaccination? Related Not Related	If not related, what was the cause of the neurologic adverse event?	
Were alternate causes for the signs and symptoms ruled out?	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 Adverse Event Follow-Up Questionnaire – Viral blips/virologic failure

Adverse Event Follow-Up Questionnaire – Viral blips/virologic failure

Please enter all dates in the following format: DD-MMM-YYYY (e.g. 01-MAR-2024)

Patient			
Initials	Sex ☐ M ☐ F ☐ Other:	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

Virologic Adverse Event(s) – enter a diagnosis or signs/symptoms if a diagnosis is not available					
Virologic Adverse Events(s)	**Start Date**	**Stop Date**	**CTCAE Grade[a]**	**Serious Criteria[b]**	**Outcome[c]**
Symptoms of increased viral load (mark N/A if not present)	**Start Date**	**Stop Date**	**CTCAE Grade[a]**	**Serious Criteria[b]**	**Outcome[c]**
Fever					
Infection (specify:)					
Other(specify:)					

Key:	CTCAE Grade[a] 1 = Grade 1 (mild) 2 = Grade 2 (moderate) 3 = Grade 3 (severe) 4 = Grade 4 (life-threatening) 5 = Fatal	Serious Criteria[b] D = Death L = Life-threatening H = Hospitalization/prolonged hospitalization S = Significant disability M = Medically significant N/A = Not applicable (non-serious)	Outcome[c] 1 = Recovered/resolved 2 = Recovering/resolving 3 = Not recovered/not resolved 4 = Recovered/resolved with sequelae 5 = Fatal 6 = Unknown
If one of the events resulted in death Date of death: Cause: **Was an autopsy performed?** ☐ No ☐ Yes (if available please attach report)			
Hospitalization Admission date: Discharge Date:			

HIV history				
Date of first HIV diagnosis				
Viral load at time of first diagnosis				
History of AIDS defining conditions **(Please provide dates and diagnosis of signs and symptoms)** **(mark N/A if never present)**				
HIV treatment (please provide current and previous antiretroviral treatment)				
Name of ART	**Route**	**Dose**	**Therapy Dates**	**Response**
Reasons for discontinuing/switching previous ART regimens **e.g. malcompliance, toxicity etc.**				
Handling of current virologic event				
Please provide all relevant information on how the increased viral load was managed.				
Change of ART				
Education of patient re. avoidance of HIV transmission				
Repeat viral load testing				
Other				
Concomitant drugs and vaccine administrations				
Name of Drug/Vaccine	**Indication**	**Dose/Frequency**	**Start Dates**	**Stop Date**

Viral load measurements (please provide at least the last test before Jynneos vaccination and all tests since vaccination)			
Test Date	**Test Result**	**Test Date**	**Test Result**

Other diagnostic tests (please specify). Please include key results.		
Test Method	**Test Date**	**Test Results (please include reference range for lab values)**

Relevant Other Medical History (list below) or ☐ No medical history If yes, please specify. Please in particular focus on previous episodes of viral load increase, (opportunistic) infections, or other signs potentially associated with HIV treatment failure	
Condition	**Start date, intensity, treatments, further relevant details**

Additional Event Information		
In your opinion, what is the causal relationship between the virologic adverse event and the JYNNEOS vaccination? ☐ Related ☐ Not Related	If not related, what was the cause of the virologic adverse event?	
Were alternate causes for the signs and symptoms ruled out? (e.g. malcompliance with ART)	☐Yes ☐No	If yes, please describe how these were ruled out:
Please provide any other additional, relevant information, if applicable		

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

Address (Institution, Street, City, Postal code, Province/State, Country) (Print):	
Email:	Phone:

Annex 4.5 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 1st dd/mm/yyyy 2nd	Reaction		from	until	Overall outcome (e.g. recovered or ongoing):
	___/___								
	Reaction(s) was/were ~Fatal ~Immediately life threatening ~Leading to or prolonging hospitalization ~Leading to persistent or significant disability								
Vaccinee 2	Initials (first/last)	Gender male/female	Age (years)	Vaccination date 1st dd/mm/yyyy 2nd	Reaction		from	until	Overall outcome (e.g. recovered or ongoing):
	___/___								
	Reaction(s) was/were ~Fatal ~Immediately life threatening ~Leading to or prolonging hospitalization ~Leading to persistent or significant disability								
Vaccinee 3	Initials (first/last)	Gender male/female	Age (years)	Vaccination date 1st dd/mm/yyyy 2nd	Reaction		from	until	Overall outcome (e.g. recovered or ongoing):
	___/___								
	Reaction(s) was/were ~Fatal ~Immediately life threatening ~Leading to or prolonging hospitalization ~Leading to persistent or significant disability								
Vaccinee 4	Initials (first/last)	Gender male/female	Age (years)	Vaccination date 1st dd/mm/yyyy 2nd	Reaction		from	until	Overall outcome (e.g. recovered or ongoing):
	___/___								

	Reaction(s) was/were ~Fatal ~Immediately life threatening ~Leading to or prolonging hospitalization ~Leading to persistent or significant disability								
Vaccine 5	Initials (first/last)	Gender male/female	Age (years)	Vaccination date 1st dd/mm/yyyy 2nd	Reaction		from	until	Overall outcome (e.g. recovered or ongoing):
	__/___								

Please provide any additional information you feel relevant:

Date: _____ **Signature:**

F. DETAILS OF PROPOSED ADDITIONAL RISK MINIMIZATION ACTIVITIES (IF APPLICABLE)

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

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