21 July 2022
EMA/683534/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Invented name: IMVANEX

Common name: smallpox and monkeypox vaccine (live modified vaccinia virus Ankara)

Procedure No. EMEA/H/C/002596/II/0076

Marketing authorisation holder (MAH): Bavarian Nordic A/S

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AE	Adverse Event
CDC	Centre for Disease Control
CHMP	Committee for Medicinal Products for Human Use
CSR	Clinical Study Report
DLP	Data Lock Point
DRC	Democratic Republic of the Congo
ECTM	Ectromelia virus
ELISA	Enzyme-Linked ImmunoSorbent Assay
EMA	European Medicines Agency
ETF	Emergency Task Force
EU	European Union
GCP	Good Clinical Practices
GLP	Good Laboratory Practices
GMT	Geometric Mean Titre
NHP	Non-Human Primate
IM	Intramuscular
i.n.	Intranasal
IRB	Institutional Review Board
i.t.	Intratracheal
IV	Intravenous
KSPH	Kinshasa School of Public Health
MAA	Marketing Authorization Application
MAH	Marketing Authorization Holder
MPX	Monkeypox
MPXV	Monkeypox virus
MVA-BN	Modified Vaccinia Ankara-Bavarian Nordic
NYCBH	New York City Board of Health
PAES	Post-Authorization Effectiveness Study
PCR	Polymerase Chain Reaction
PEP	Post-Exposure Prophylaxis
Pfu	Plaque-forming units
PIP	Paediatric Investigation Plan
PP	Per Protocol
PRNT	Plaque Reduction Neutralization Test
PSUR	Periodic Safety Update Report
SAE	Serious Adverse Event
SC	Subcutaneous
SCR	Seroconversion rate
WHO	World Health Organization
WR-VV	Western Reserve Vaccinia Virus

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Bavarian Nordic A/S submitted to the European Medicines Agency on 24 June 2022 an application for a variation.

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIA and IIIB

Extension of indication to include active immunisation against monkeypox and related orthopoxvirus infection and disease in adults 18 years of age and older for Imvanex; as a consequence, sections 1, 4.1, 4.2, 4.4, 4.6 and 5.1 of the SmPC are updated. The Package Leaflet and Labelling are updated in accordance. Version 9.0 of the RMP has also been submitted.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0264/2022 on the agreement of a Paediatric Investigation Plan (PIP).

At the time of submission of the application, the PIP P/0264/2022 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was Jan Mueller-Berghaus.

Timetable	Actual dates
Submission date	24-June-2022
Start of the rolling review procedure	27-June-2022
PRAC Rapporteur Assessment Report	08-July-2022
PRAC members comments	n/a
Updated PRAC Rapporteur Assessment Report	n/a
CHMP Rapporteur Assessment Report	14-July-2022
Start of the procedure (after administrative validation)	18-July-2022
CHMP members comments	18-July-2022
ETF meeting	19-July-2022
Updated CHMP Rapporteur Assessment Report	20-July-2022
PRAC Outcome	20-July-2022
CHMP Opinion	21-July-2022

2. Scientific discussion

2.1. Introduction

2.1.1 Problem statement

Disease or condition

Monkeypox

Monkeypox 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 monkeypox in humans were reported in the 1970s in the Central African region. Since then, monkeypox in humans has been reported repeatedly throughout Sub-Saharan Africa, including West Africa and Central Africa, with rising frequency in recent years. Since 2017, seven countries in the WHO Africa region have reported outbreaks and most have continued to occur in forested rural areas. However, countries are increasingly reporting monkeypox in previously unaffected regions; in Nigeria, of the more than 550 cases reported since the outbreak began in 2017 (West Africa clade), many have occurred in urban and peri-urban areas. The Democratic Republic of the Congo (DRC) has reported over 1300 cases just from January 2022 to May 2022 (Congo Basin clade). Surveillance in all countries is expanding rapidly and WHO expects that more cases will be reported.

Most recently, a multi-country monkeypox outbreak is spreading to previously non-endemic countries, mostly in the European region. According to the WHO situation report on Monkeypox on 7 July 2022, 6,027 laboratory-confirmed cases of monkeypox and 3 deaths have been reported to the WHO from 59 countries from the period of 1 January 2022 to 4 July 2022. Approximately 82% of the cases are in Europe, and 15% in the Americas, including more than 1000 confirmed cases in UK (1,351), Spain (1,256) and Germany (1,242), and 300 or more confirmed cases in Health Canada (300) and the United States (460). Based on the gender data available on 4,406 cases, men made up 99.5% of the cases, and men aged 18 to 44 years accounted for 79% of the cases.

In endemic countries, incidences of monkeypox virus infections in paediatric age groups are higher than in adult age groups, which might correlate with the lack of smallpox vaccine coverage as compared to older populations. However, in the last decades, the age of humans having monkeypox cases has gradually increased, probably in part due to growing proportions of the population without vaccination coverage, as smallpox was eradicated in 1980.

The clinical course of monkeypox is similar to smallpox, although milder and with a substantially lower-case fatality rate. After infection, there is an incubation period of roughly 1-2 weeks. Shortly after an initial febrile prodrome, potentially alongside with headache and fatigue, a rash will develop in many patients, as well as lymphadenopathy in cervical, inguinal or maxillary regions. Fever is frequently observed around the time of rash onset. The distinctive pox lesions begin to develop simultaneously and evolve together on any given part of the body, and the evolution of lesions progresses have been described through four stages, as first macular, later papular, then vesicular or pustular, scabbing over and resolving. The illness typically lasts 2-4 weeks. The severity of illness can depend upon the initial health of the individual, the route of exposure, and the strain of the infecting virus (West African vs. Central African virus genetic groups, or clades). West African monkeypox is associated with milder disease, fewer deaths, and limited human-to-human transmission. Human infections with the Central African monkeypox virus clade are typically more severe compared to those with the West African virus clade and have a higher mortality. Person-to-person spread is well-documented for Central African monkeypox virus.

People who live with or have close contact (including sexual contact) with someone who has monkeypox, or who has regular contact with animals who could be infected, are most at risk of infection. Newborn infants, young children and people with underlying immune deficiencies may be at risk of more serious disease.

Other orthopoxviruses

In laboratories working with replicating orthopoxviruses such as vaccinia, accidental exposure of laboratory personnel is an occupational health risk. Cases of needle-stick injuries or similar accidents leading to local infections with replicating vaccinia have repeatedly been reported. 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. Previous smallpox vaccination decades ago was shown to lead to a milder clinical course in one of the reported cases.

In addition, the recently published de novo synthesis of horsepox may have direct implications for biosecurity by facilitating potential synthesis of other orthopoxviruses, including variola, increasing the risk for emergence of new orthopoxvirus diseases.

Other human orthopoxvirus infections, such as cowpox, follow a similar pattern, although the pox lesions may be less frequent and show fewer spread across the body.

Management

Control of monkeypox outbreaks primarily relies on public health measures including surveillance, contact-tracing, isolation and care of patients.

Symptomatic treatment of orthopoxvirus infections includes close supervision of the patient and fluid replacement. Antibiotics are restricted to patients with bacterial superinfection. For specific treatment, tecovirimat is the only medicinal product approved in the European Union for the treatment of smallpox, monkeypox and cowpox in adults and children with body weight at least 13 kg. Tecovirimat works by interfering with a protein called VP37 that is found on the surface of orthopoxviruses. By interacting with this protein, the medicine prevents the viruses from reproducing normally, slowing down the spread of

infection. This medicinal product was approved based on testing in animal models using other orthopoxviruses than smallpox only.

Vaccination with smallpox vaccines is expected to provide some protection against monkeypox, based on history data showing a vaccine efficacy of approximately 85% in a human monkeypox outbreak setting, in previously smallpox vaccinated individuals. A recent guidance document published by WHO recommends use of smallpox vaccines in the context of the monkeypox outbreak, dependent on individual risk assessment in both, pre- and post-exposure prophylaxis scenarios.

In the EU, no prophylactic vaccines are specifically licensed for monkeypox or other orthopoxvirus infections. IMVANEX is currently approved in the EU for prevention of smallpox in adults.

2.1.2. About the product

IMVANEX is a live, highly attenuated, non-replicating viral vaccine for protection against smallpox. The vaccine is suspension for injection. One dose (0.5 mL) contains modified vaccinia Ankara – Bavarian Nordic live virus no less than 5×10^7 infectious unit.

IMVANEX is manufactured based on the manufacturer's proprietary strain of the orthopoxvirus Modified Vaccinia Ankara-Bavarian Nordic (MVA-BN) that is grown in chicken embryo fibroblast cells, harvested, concentrated, and purified.

IMVANEX was approved under exception circumstances in the EU on 31 July 2013 for active immunisation against smallpox in adults.

The primary vaccination schedule consists of 2 doses of the vaccine administered subcutaneously at interval of no less than 28 days, whereas a single dose of 0.5 mL is considered for booster vaccination whenever necessary in individuals previously vaccinated against smallpox. For immunocompromised patients, two booster doses separated by 28 days or longer should be given.

2.2. Non-clinical aspects

2.2.1. Introduction

The non-clinical aspect is restricted to the non-clinical pharmacology aspect, involving the non-clinical overview addendum and non-clinical summary, making a cross-reference to the prior existing non-clinical dossier. In addition, two additional animal efficacy studies were included as a confirmation of the existing non-clinical dossier.

2.2.2. Pharmacology

Summary of monkeypox animal data

As already covered in the non-clinical dossier of IMVANEX, the applicant tested the ability of IMVANEX to protect against lethal challenges with monkeypox virus (MPXV) when this was given by the intravenous, intratracheal or aerosol routes to non-human primates. The percentage of animals surviving the standard dose ($1x10^8$ Inf.U) challenges is summarised in the below Table.

Table 1: Summary of Imvanex-induced protection from death in monkeypox challenge models in NHP

	% Survival (Survivor NHP / Total NHP)		
	Intravenous Challenge	Intratracheal Challenge	Aerosol Challenge
$1x10^8$ $TCID_{50}$ Single Vaccination	100% (6/6)	88% (14/16)	-
$1x10^8$ $TCID_{50}$ Two Dose Regime	100% (5/5) *100% (19/19)*	91% (29/32)	100% (6/6) *100% (18/18)*
$1x10^7$ $TCID_{50}$ Two Dose Regime	100% (5/5)	100% (5/5)	100% (6/6)
$1x10^6$ $TCID_{50}$ Two Dose Regime	60% (6/10)	60% (3/5)	67% (4/6)

Data source: intravenous (2 studies), intratracheal (5 studies) and aerosol (2 studies), liquid-frozen formulation from previous dossier version (high challenge doses only) and additionally updated liquid-frozen treated animal numbers from the additional two studies BN-PRE-12-003 (adding 14 NHP) and BN-PRE-12-028 (adding 12 NHP) in grey. Note: The approved dose and schedule is $1x10^8$ infectious units (Inf.U) two doses four weeks apart, corresponding to the second line in this table. (see also 2.5 Clinical Overview)

Recently, a non MAH-sponsored animal study was performed by the US CDC, to investigate post-exposure prophylaxis of IMVANEX and ACAM2000 (a smallpox (Vaccinia) vaccine, live approved in the US), in the intranasal prairie dog challenge model (Keckler, 2020). Two times lethal dose (LD50) of monkeypox virus was administered intranasally first, followed by vaccination with either IMVANEX or ACAM2000 post-challenge. It was found that 7 out of 8 animals vaccinated with IMVANEX survived the challenge when the post-challenge vaccination was given one day after exposure, in contrast to 4 out of 8 animals vaccinated with ACAM2000. Whereas only 3 out of 8 animals vaccinated with IMVANEX survived the challenge when the post-challenge vaccination was given on the third day post-exposure, contrasting with 5 out of 8 for ACAM2000.

The initial application also covered non-clinical pharmacology studies on mice. Among these studies, there were intranasal challenge studies with a lethal dose of Vaccinia Virus Western Reserve (VV-WR) and Ectromelia Virus (ECTV) in mice. The applicant characterised testing with the challenge virus VV-WR strain given by the intranasal route. A dose-response for morbidity and mortality was shown and a dose equivalent to 50-fold the median lethal dose was taken forward for use in testing the protective efficacy of Imvanex. When mice previously vaccinated with Imvanex were then challenged with this lethal intranasal dose they survived. Subsequently methods were developed to challenge mice with ectromelia, an orthopoxvirus that naturally infects mice. The applicant showed that mice vaccinated with Imvanex were able to survive a lethal challenge with this virus, whereas unvaccinated mice did not.

Two additional non-clinical studies submitted

1. Comparison of the efficacy and immunogenicity of freeze-dried and liquid-frozen formulations of IMVAMUNE in the intravenous Monkeypox challenge model in Cynomolgus Macaques [BN-PRE-12-003]

The objective of this GLP-compliant study was to compare the survival and morbidity of non-vaccinated and liquid-frozen or freeze-dried MVA-BN (indicated as IMVAMUNE in the study report) vaccinated Non-

Human Primates (NHP) after intravenous challenge with MPXV. In addition to efficacy, the immunogenicity of the liquid-frozen and freeze-dried MVA-BN formulations were evaluated.

Groups of NHP received subcutaneous prime-boost vaccinations with $1x10^8$ median Tissue Culture Infectious Dose (TCID50) of either liquid-frozen or freeze-dried MVA-BN, or were inoculated with Tris-Buffered Saline (TBS) as controls on Study Days 0 and 28 (see Table below for study design).

Table 2: Study design (BN-PRE-12-028)

Group	N	Test/Reference Item Administration				Challenge Virus Administration	
		Vaccination	Dose[1] per Administration	Route[2]	Schedule (Study Day)[3]	Target Dose (PFU)	Schedule (Study Day)[4]
1	10	Vehicle Control (TBS)	N/A	SC	0 and 28	$5x10^7$	63
2	14	Liquid-frozen IMVAMUNE®	$1x10^8$ $TCID_{50}$				
3	14	Freeze-dried IMVAMUNE®	$1x10^8$ $TCID_{50}$				

1 = Dose volume 0.5 ml per vehicle control or IMVAMUNE vaccination; 2 = Subcutaneous (SC); 3 = First vaccination on Study Day 0, second vaccination on Study Day 28; 4 = All animals received an intravenous challenge with monkeypox Zaire strain V79-I-005 BEI Resources NR-21738 of $5x10^7$ plaque forming units on Study Day 63.
Abbreviations: N = Number; TCID50 = Median Tissue Culture Infectious Dose; PFU = Plaque Forming Units

Blood samples collected at different time-points prior to challenge were analysed for total vaccinia-specific antibody titres by ELISA and for neutralising antibody titres by PRNT at Bavarian Nordic.

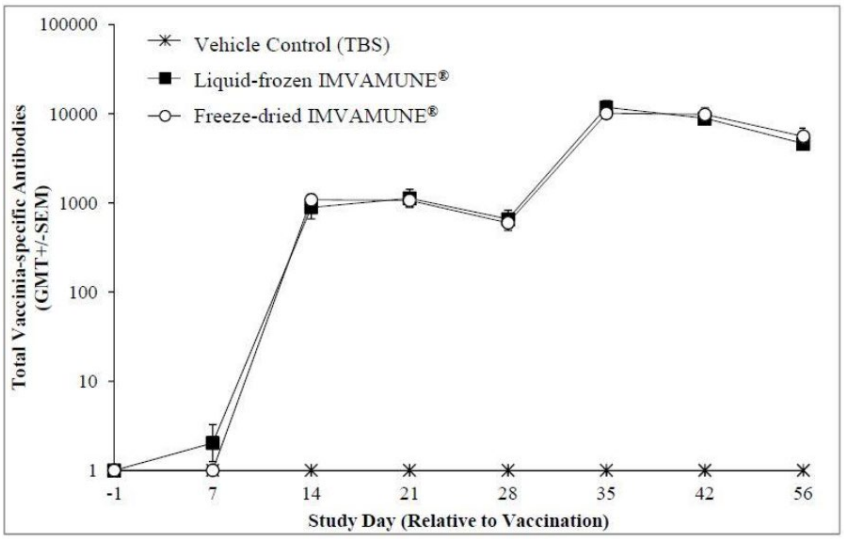
On Study Day 63, animals were challenged by the intravenous route with a target MPXV dose of $5 x10^7$ Plaque Forming Units (PFU).

Animals were examined for morbidity and mortality, clinical observations, body weights, body temperatures, and skin pox lesions. Whole blood and throat swabs were taken at assigned time points and tested for virus load by quantitative PCR assay. All NHPs were euthanized when deemed necessary, i.e., when moribund or on Study Day 91. For all animals found dead or euthanized a complete gross necropsy was conducted.

Results:

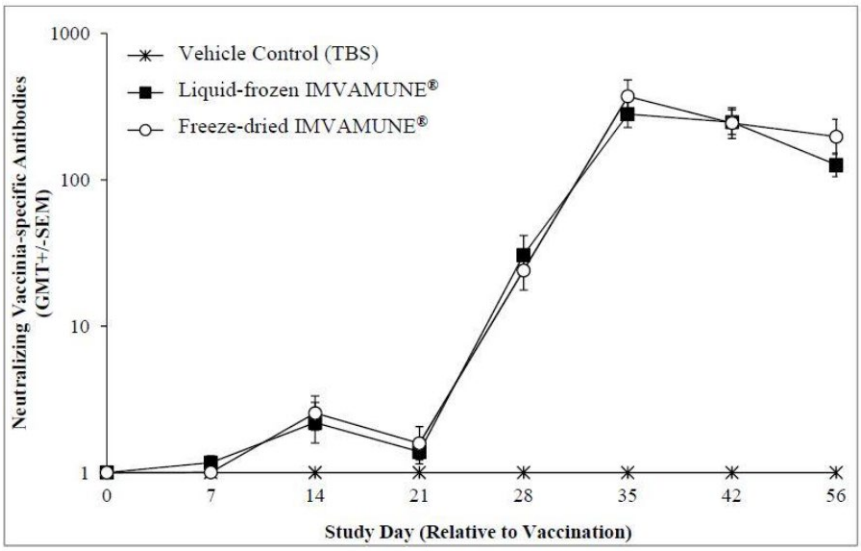
Vaccinia-specific total and neutralising antibody responses

Prime-boost vaccination with $1x10^8$ TCID50 of liquid-frozen MVA-BN (Group 2) or freeze-dried MVA-BN (Group 3) induced 100% seroconversion by ELISA and by PRNT with comparable Geometric Mean Titres (GMTs) between the groups. Statistical analysis of the peak response (Study Day 35) for ELISA and for PRNT revealed no significant difference between the two different formulations comparing Log10 titres measured either by ELISA or by PRNT. Further, vaccinia-specific total and neutralising antibodies responses did significantly correlate as illustrated in the figures below.



NHPs were vaccinated with liquid-frozen or freeze-dried MVA-BN on Study Day 0 and 28, or received Vehicle control (TBS). At various time-points sera were collected and analyzed by ELISA. Results are presented as the GMT together with the Standard Error of the Mean (SEM).

Figure 1: Total Vaccinia-Specific Antibody Responses Quantified by ELISA

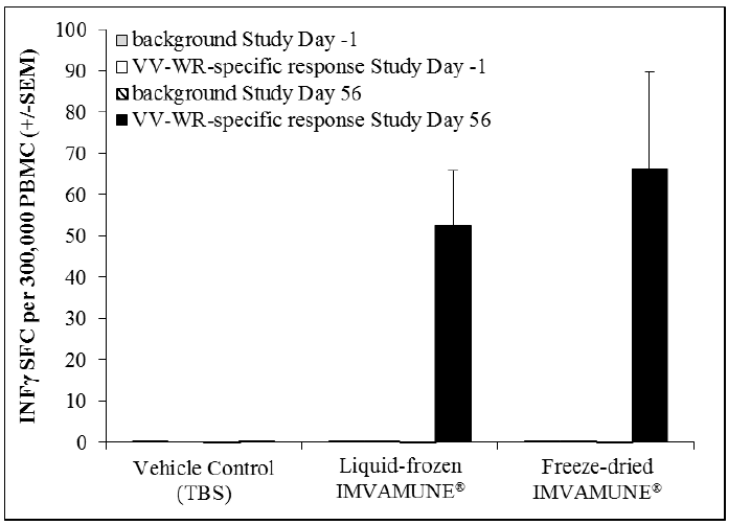


NHPs were vaccinated with liquid-frozen or freeze-dried MVA-BN on Study Day 0 and 28, or received TBS. At various time-points sera were collected and analyzed by PRNT. Results are presented as the GMT together with the SEM

Figure 2: Neutralising Vaccinia-Specific Antibody Responses Quantified by PRNT

T-cell response (IFNγ ELISPOT)

After stimulation of Peripheral Blood Mononuclear Cells (PBMC) with Vaccinia virus Western Reserve (VV-WR), animals vaccinated with liquid-frozen MVA-BN (Group 2) recorded a mean of 53 Spot Forming Cells (SFC) per $3x10^5$ PBMC and animals that received freeze-dried MVA-BN (Group 3) had a mean of 66 SFC per $3x10^5$ PBMC. Responses of both vaccinated groups were not significantly different. Importantly, background responses were absent or very low and non-vaccinated animals (Group 1) did not respond.



PBMC were prepared on Study Day -1 (prior to vaccination) and Study Day 56 (4 weeks post the booster vaccination with MVA-BN and stimulated *in vitro* with either medium alone or with VV-WR (Multiplicity of Infection [MOI] of 1). IFNγ producing cells were analyzed by ELISPOT and data are shown as spot forming cell (SFC) per $3x10^5$ PBMC (±SEM).

Figure 3: Vaccinia-Specific T Cell Responses Quantified by ELISPOT

Appearance post-challenge

A summary of survival following challenge is shown below. 6 of 10 animals in the control groups died. All vaccinated animals survived the challenge irrespective of the formulation. The difference between the survival rate after challenge with MPXV of the control group (Group 1: 40% survival) and both vaccinated groups (Groups 2 and 3: 100% survival) was statistically significant. In the control group the first fatality occurred nine days after challenge, and the last fatalities (other than scheduled Study Day 91 euthanasia) occurred 15 days after challenge.

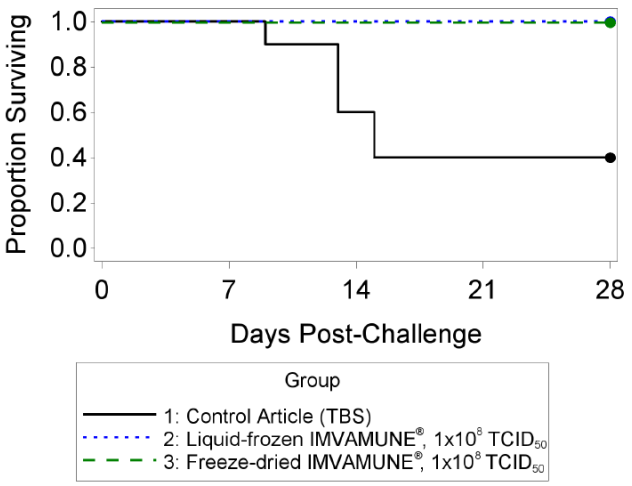
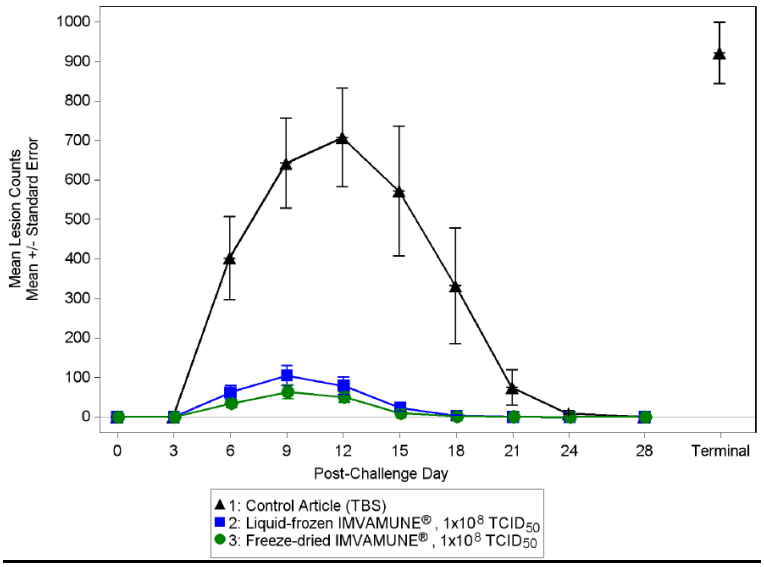


Figure 4: Kaplan-Meier Plot of Survival

The most common clinical signs in all groups were hunched posture, inappetence, oedema and dehydration. In the vaccinated animals (Groups 2 and 3), however, incidence and severity of clinical signs were markedly lower than in the control (Group 1). There was a significant difference between the mean clinical scores of the non-vaccinated control group and both vaccinated groups from days 7 to 20 post challenge. All adverse clinical signs resolved in surviving animals by the end of the study. The protective effect of vaccination was also apparent with regard to pock lesions, which were significantly fewer in vaccinated animals compared to non-vaccinated controls. Lesions in all surviving animals, regardless of group, resolved by the end of the study.

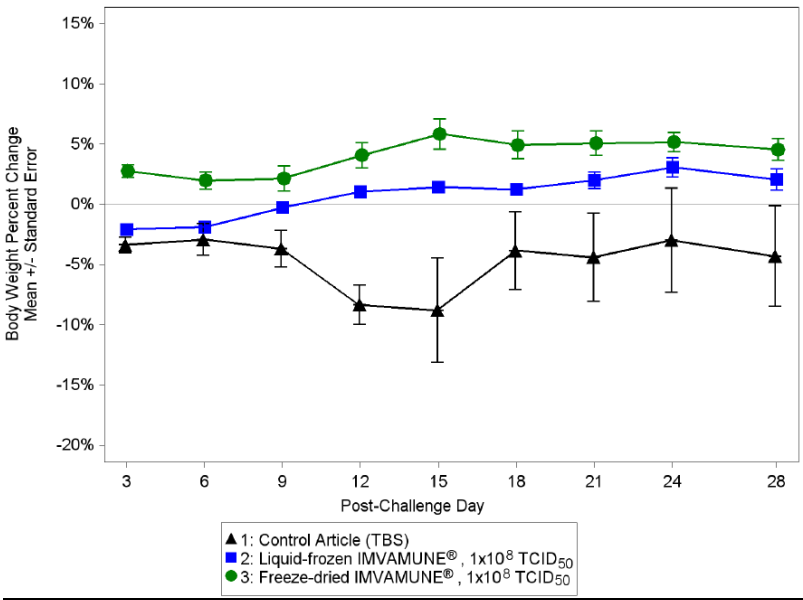


Skin lesions were counted every three days post challenge through Study Day 87 and Study Day 91. Group means (+/- SEM) are shown. Mean terminal values (+/- SEM) are shown for animals that succumbed prior to scheduled euthanasia (Group 1: five animals were euthanized, one animal was found dead).

Figure 5: Group Mean Lesion Counts

Body Weight Changes and Body Temperature Changes Post Challenge

Statistical analysis of body weight and body temperature changes detected significant differences between the control and the two vaccinated groups. Body temperature change was also used as a criterion for euthanasia when the animal loses the ability to regulate its body temperature. There was a statistically significant differences between the vaccinated groups on scattered time points or over time periods in body weight and body temperature change detected. However, compared to differences between the control group and both vaccinated groups, differences between the two vaccinated groups were small and most likely due to variations in the biological system not indicating a tendency for an increased efficacy for one of the vaccines.

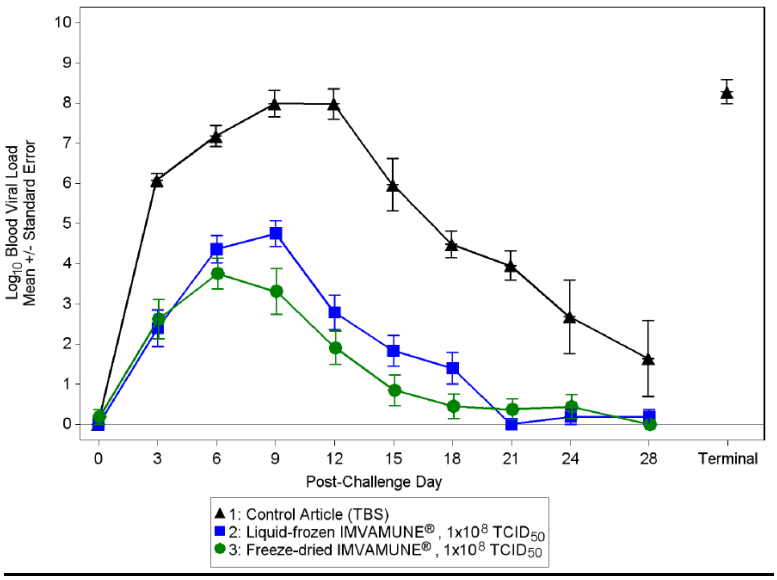


Body weight (in kg) was measured on the day of challenge (baseline prior to challenge) and every three days thereafter until Study Day 87 and Study Day 91. Body weight change (in %) from baseline was calculated and is shown as group mean (+/- SEM).

Figure 6 Group Mean Body Weight Change

Viremia (Whole Blood)

MPXV levels in the blood of vaccinated animals were significantly reduced compared to controls, and virus levels were undetectable in all but one vaccinated animal by the end of the study, whereas two of the four surviving control animals had detectable virus at the end of the study. However, genome numbers consistently decreased from Day 9 post challenge onwards and likely would have been below detectable limits and eliminated had the post challenge observation period been greater than 28 days. On days 6 to 18 post-challenge the mean viral load of Group 3 (freeze-dried MVA-BN) was lower than that of Group 2 (liquid-frozen MVA-BN); when all three groups were compared, on post-challenge day 9 the difference was statistically significant, but analysis comparing just Groups 2 and 3 did not confirm the significant difference.

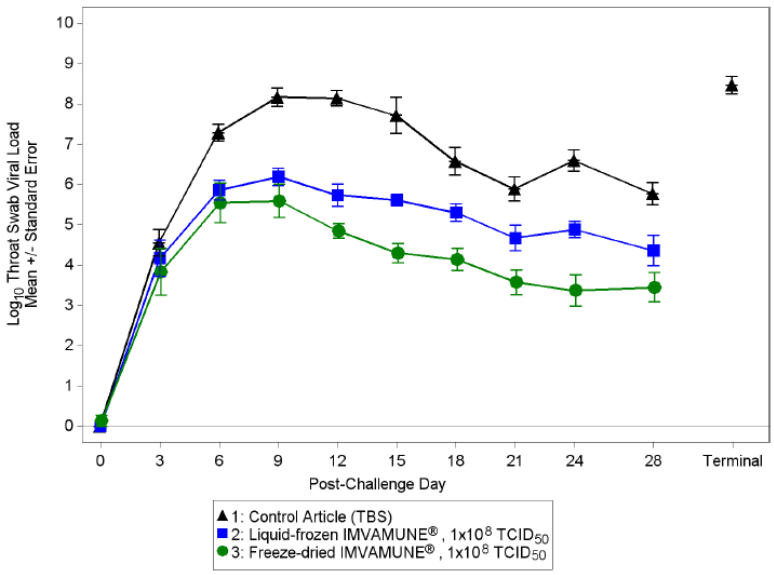


Viral load was measured in blood samples collected on the day of challenge and every three days thereafter until Study Day 87 and Study Day 91. Mean viral loads (log10 genomes/mL +/- SEM) for each group are shown. The Limit Of Quantification (LOQ) was 800 genome copies/mL, i.e. 2.9 log10 scale. For calculation purposes for samples with signals below the quantification limit a value of 400 genomes/mL, i.e. 2.6 log10 was used. Mean terminal values (+/- SEM) are shown for animals that succumbed prior to scheduled euthanasia

Figure 7: Group Mean Log10 Blood Viral Load

Virus shedding (Throat swab samples)

MPXV was detected in throat swab material from all control animals and Group 2 and 3 animals three days post-challenge; by 6 and 9 days post-challenge the throat swabs of remaining Group 2 and 3 animals were also virus-positive. A significant difference between the mean viral load in throat swabs of non-vaccinated animals (Group 1) and both vaccinated groups that received either liquid-frozen MVA-BN (Group 2) or freeze-dried MVA-BN (Group 3) was seen starting 6 days post challenge (Study Day 69) until the end of the observation period. Mean viral loads in throat swabs of Group 3 were lower than those of Group 2 at all post-challenge time points; on post-challenge days 15 to 24 the difference was significant.



Viral load was measured in throat swab samples collected on the day of challenge and every three days thereafter until Study Day 87 and Study Day 91. Mean viral loads (log10 genomes/mL +/- SEM) for each group are shown. The LOQ was 167 genome copies/mL, i.e. on 2.22 log10 scale. For calculation purposes for samples with signals below the quantification limit a value of 83.5 genome copies/mL, i.e. 1.92 log10 was used. Mean terminal values (+/- SEM) are shown for animals that succumbed prior to scheduled euthanasia (Group 1: five animals were euthanized, one animal was found dead).

Figure 8: Group Mean Log10 Throat Swab Viral Load

2. Comparison of the efficacy and immunogenicity of liquid-frozen and freeze-dried formulations of IMVAMUNE in the aerosol Monkeypox challenge model in Cynomolgus Macaques [BN-PRE-12-028]

The objective of this GLP-compliant study was to compare the survival and morbidity of non-vaccinated and liquid-frozen or freeze-dried MVA-BN (indicated as IMVAMUNE in the study report) vaccinated NHP after inhalation/aerosol challenge with MPXV. In addition to efficacy, the immunogenicity of the liquid-frozen and freeze-dried MVA-BN formulations were evaluated.

Groups of NHP received SC prime-boost vaccinations with $1x10^8$ TCID50 of either liquid-frozen or freeze-dried MVA-BN, or were inoculated with TBS as controls on Study Days 0 and 28.

Table 3: Study design (BN-PRE-12-028)

Group	N	Test/Reference Item Administration				Challenge Virus Administration	
		Vaccination	Dose[1] per Administration	Route[2]	Schedule (Study Day)[3]	Target Dose (PFU)	Schedule (Study Day)[4]
1	10	Vehicle Control (TBS)	N/A	SC	0 and 28	~$3x10^5$	63
2	12	Liquid-frozen MVA-BN	$1x10^8$ $TCID_{50}$				
3	13	Freeze-dried MVA-BN	$1x10^8$ $TCID_{50}$				

1 = Dose volume 0.5mL per vehicle control or MVA-BN vaccination; 2 = Subcutaneous (SC); 3 = First vaccination on Study Day 0, second vaccination on Study Day 28; 4 = All animals received an inhalation/aerosol challenge with monkeypox Zaire strain V79-I-005 BEI Resources NR-21738 of a target of 3 x 105 plaque forming units on Study Day 63. Abbreviations: N = Number; TCID50 = Median Tissue Culture Infectious Dose; PFU = Plaque Forming Units

Blood samples collected at different time-points prior to challenge were analysed for total vaccinia-specific antibody titres by ELISA and for neutralising antibody titres by PRNT at Bavarian Nordic.

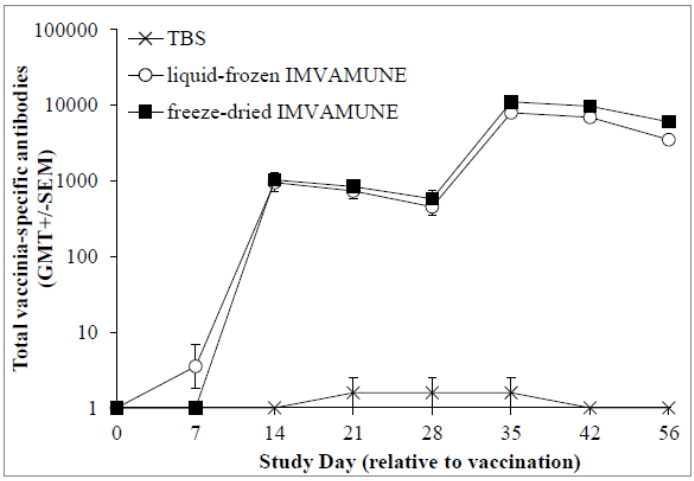
On Study Day 63, animals were challenged by the inhalation/aerosol route with a target MPXV dose of 3.0 $x10^5$ Plaque Forming Units (PFU).

The planned clinical observations and measurements of this study are almost the same as the above study.

Results

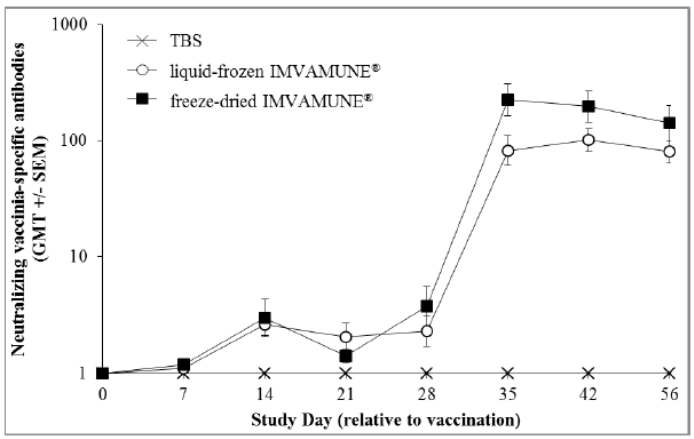
Vaccinia-specific total and neutralising antibody responses

Prime-boost vaccination with 1x10^8 TCID50 of liquid-frozen MVA-BN (Group 2) or freeze-dried MVA-BN (Group 3) induced 100% seroconversion by ELISA and by PRNT with comparable GMTs between the groups. Statistical analysis of the peak response for ELISA on Study Day 35 and for PRNT on Study Day 35 for Group 3 and Study Day 42 for Group 2, revealed no significant difference between the two different formulations comparing Log10 titers measured either by ELISA or by PRNT. Further, vaccinia-specific total and neutralising antibody responses did significantly correlate. It was noted that one animal in Group 1 on Study Days 21 through 35 had low levels of antibodies recorded but these were considered false positive results due to matrix effect.



NHPs were vaccinated with liquid-frozen or freeze-dried MVA-BN on Study Day 0 and 28, or received TBS. At various time-points sera were collected and analyzed by ELISA. Results are presented as the GMT together with the SEM.

Figure 9: Total Vaccinia-Specific Antibody Responses Quantified by ELISA



NHPs were vaccinated with liquid-frozen or freeze-dried MVA-BN on Study Day 0 and 28, or received TBS. At various time-points sera were collected and analyzed by PRNT. Results are presented as the GMT together with SEM

Figure 10: Neutralising Vaccinia-Specific Antibody Responses Quantified by PRNT

Appearance post-challenge

A summary of survival following challenge is shown below. All ten animals in the control group died or were euthanized (six were found dead and four met criteria for immediate euthanasia). All vaccinated animals survived the challenge irrespective of the formulation. The difference between the survival rate after challenge with MPXV of the control group (Group 1: 0% survival) and both vaccinated groups (Groups 2 and 3: 100% survival) was statistically significant. In the control group, the first fatalities occurred eight days after challenge, and the last fatality occurred 11 days after challenge.

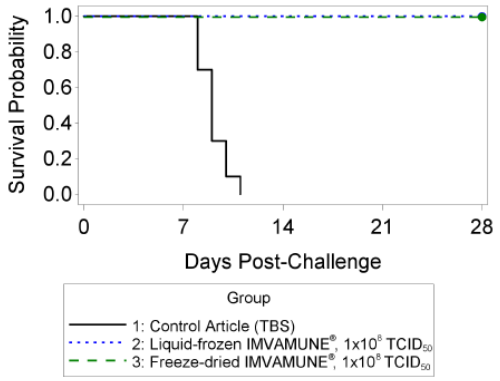
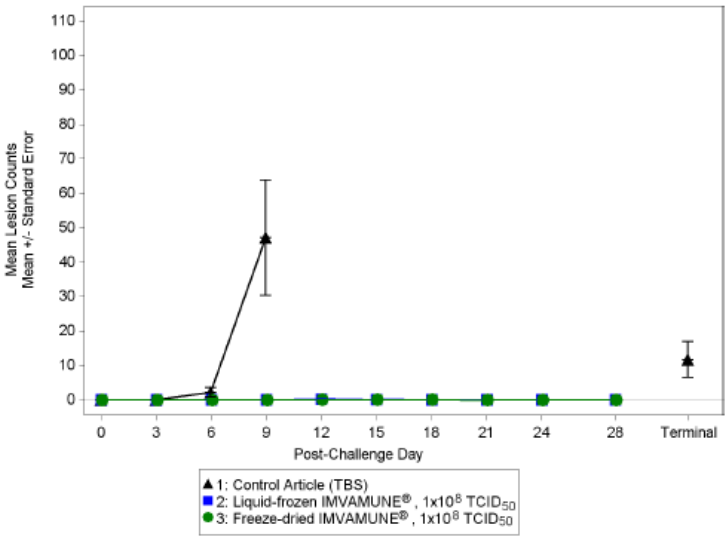


Figure 11: Kaplan-Meier Plot of Survival

Adverse clinical signs post-challenge in the non-vaccinated animals included hunched posture (weakness), dehydration, inappetence, cough and less frequently dyspnoea, nasal and ocular discharge and oedema. In both liquid-frozen and freeze-dried MVA-BN vaccinated groups most of these clinical signs, except dyspnoea, also occurred, but with reduced incidence and severity compared to control animals. Clinical scores were significantly higher in the control group compared to either vaccinated group from Day 6 to Day 9 post-challenge. All adverse clinical signs resolved in surviving animals by the end of the study observation period. The protective effect of vaccination was also apparent with regard to pock lesions, in which vaccinated animals exhibited a significantly lower number of pock lesions compared to non-vaccinated controls on Day 9 post-challenge.

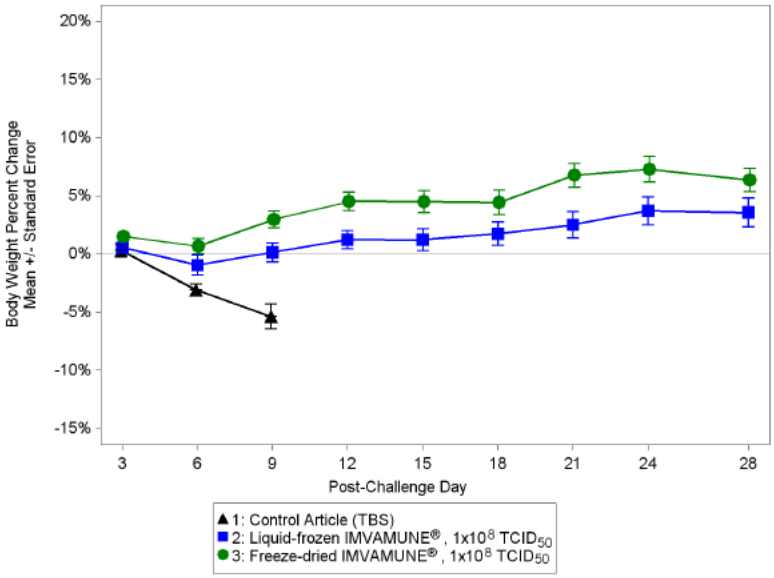


Skin lesions were counted every three days post challenge through Study Day 87 and Study Day 91. Group means (+/- SEM) are shown. Mean terminal values (+/- SEM) are shown for animals that succumbed prior to scheduled euthanasia (Group 1: four animals were euthanized, six animals were found dead).

Figure 12: Group Mean Lesion Counts

Body weight changes and body temperature changes post-challenge

Following MPXV challenge, the mean body temperature and body weight of non-vaccinated animals continued to decline until all non-vaccinated animals had succumbed. Body temperature change was also used as a criterion for euthanasia since it indicates when the animal loses the ability to regulate its body temperature. Statistical analysis of body weight changes detected significant differences between the control and the two vaccinated groups. In addition, freeze-died MVA-BN vaccinated animals tended to have a greater weight gain post challenge than animals vaccinated with the liquid-frozen formulation. However, no significant differences between the two vaccinated groups were detected for other clinical parameters (viral load, clinical scores, skin lesion counts) in the current study. Thus, differences between liquid-frozen (Group 2) and freeze-dried MVA-BN (Group 3) vaccinated groups in terms of body weights were most likely due to variations in the biological system and do not indicate a tendency for increased efficacy for one of the vaccines.

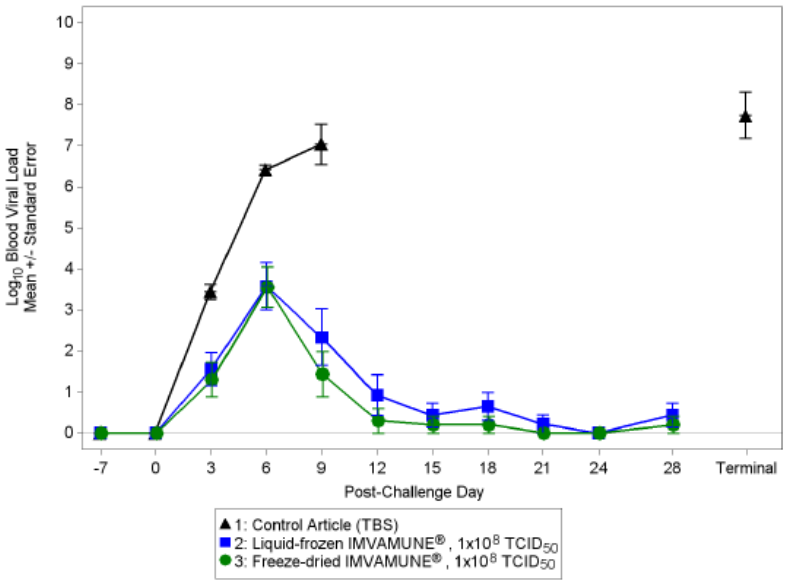


Body weight (in kg) was measured on the day of challenge (baseline prior to challenge) and every three days thereafter until Study Day 87 and Study Day 91. Body weight change (in %) from baseline was calculated and is shown as group mean (+/- SEM).

Figure 13: Group Mean Body Weight Change

Viremia (Whole Blood)

MPXV levels in the blood of vaccinated animals were significantly reduced compared to controls, and virus levels were undetectable in most vaccinated animals by the end of the study. However, genome numbers consistently decreased from Day 9 post challenge onwards and likely would have been below detectable limits and eliminated had the post challenge observation period been greater than 28 days. There was no significant difference between blood viral loads of the two vaccinated groups.

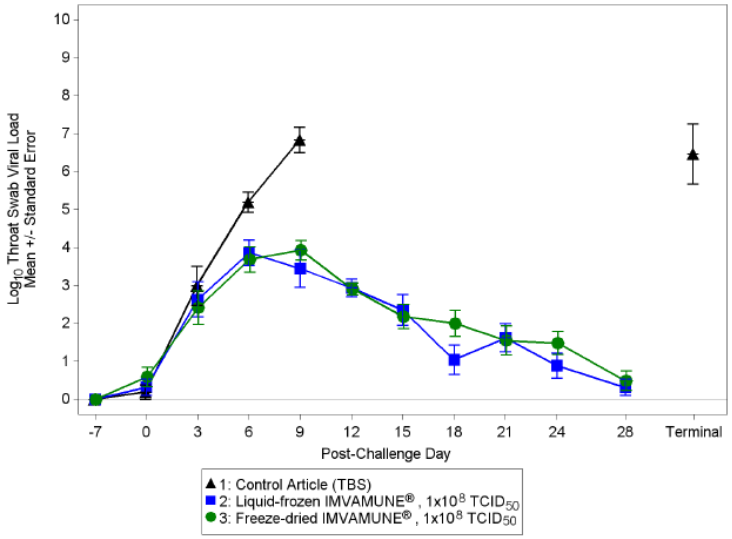


Viral load was measured in blood samples collected prior to challenge and on the day of challenge and every three days thereafter until Study Day 87 and Study Day 91. Mean viral loads (log10 copies/mL +/- SEM) for each group are shown. The LOQ was 800 genome copies/mL, i.e. 2.9 log10 scale. For calculation purposes for samples with signals below the quantification limit a value of 400 genomes/mL, i.e. 2.6 log10 was used. Mean terminal values (+/- SEM) are shown for animals that succumbed prior to scheduled euthanasia.

Figure 14: Group Mean Log10 Blood Viral Load

Virus shedding (Throat swab samples)

As illustrated below, MPXV was detected in throat swab material from most control Group 1 animals and most Group 2 and 3 animals at three days post-challenge; by 6 days post-challenge the throat swabs of remaining animals were also virus positive as well as the animals that were positive on Day 3 post-challenge. In throat swabs of vaccinated groups, the mean level of virus was significantly reduced compared to peak values in non-vaccinated controls. Vaccinations did not completely eliminate virus shedding in the oral cavity, and virus was longer detectable in throat swabs than in blood. There was no significant difference between throat swab viral loads of the two vaccinated groups based on quantitative PCR.



Viral load was measured in throat swab samples collected prior to challenge and on the day of challenge and every three days thereafter until Study Day 87 and Study Day 91. Mean viral loads (log10 copies/mL +/- SEM) for each group are shown. The LOQ was 167 genome copies/mL, i.e. 2.22 log10 scale. For calculation purposes for samples with signals below the quantification limit a value of 83.5 genome copies/mL, i.e. 1.92 log10 was used. Mean terminal values (+/- SEM) are shown for animals that succumbed prior to scheduled euthanasia.

Figure 15: Group Mean Log10 Throat Swab Viral Load

2.2.3. Discussion on non-clinical aspects

Submission strategy

The non-clinical aspects are exclusively restricted to the non-clinical pharmacology, involving the non-clinical overview addendum and non-clinical summary, making a cross-reference to the existing non-clinical dossier. In addition, two additional animal efficacy studies were included as a confirmation of the existing non-clinical dossier.

Non-clinical pharmacology studies

From existing non-clinical dossier, a total of 4 animal efficacy studies in NHPs using 3 challenge models (intravenous, intratracheal or aerosol routes) were summarised to assess the ability of IMVANEX to protect against lethal challenges with MPXV. In each challenge model, two subcutaneous injections with IMVANEX 28 days apart, at doses ranging from 10^6 to 10^8 TCID50, induced 60–100% protection from the death of MPXV-challenged animals. Single vaccination with $1x10^8$ TCID50 of IMVANEX also provided 88-100% protection in the intravenous (IV), intratracheal (i.t.) or aerosol routes challenge models.

Two additional animal studies submitted in this variation contribute to enlarged evidence for efficacy of IMVANEX in preventing severe MPX disease and death of the MPXV-challenged NHPs in IV and aerosol challenge models. Data across different outcomes (survival, clinical, disease/lesions, and virology/virus load) are consistent.

These animal efficacy data in different NHP challenge studies are important and lead to reasonable expectation that IMVANEX could induce protection against monkeypox in humans. Additionally, a post-authorisation efficacy study is imposed as part of the marketing authorisation to be able to obtain effectiveness data against monkeypox in humans in the case of an outbreak (refer to the clinical section).

Whenever measured in the protected animals that were vaccinated with IMVANEX, anti-vaccinia humoral and cellular immune responses, including binding and neutralising antibodies in the blood, were evidenced.

From existing non-clinical dossier, several animal efficacy studies in mice demonstrated that 2 doses (10^8 TCID50) of IMVANEX at 28 day interval induced significant systemic immunity and protected mice from a lethal intranasal challenge of other orthopoxviruses: replicating vaccinia virus (WR-VV strain) and the Ectromelia virus (ECTM, mousepox). This mouse efficacy data against WR-VV generated for IMVANEX is considered of good quality and is relevant to this variation, and thus reflected in the product information.

Lastly, the notified literature data that show protection of IMVANEX against MPX after post-exposure prophylaxis (PEP) use in prairie dogs is interesting. Nevertheless, outside of the scope of this extension of indication.

Based on the non-clinical data assessed, there is no cross-neutralisation data for cowpox. Upon request, the MAH withdrew during the procedure the indication for active immunisation against "related orthopoxvirus", keeping it limited to the addition of monkeypox and vaccinia virus in view of the data submitted.

2.2.4. Conclusion on the non-clinical aspects

The submitted non-clinical data are of adequate quantity and quality and considered pivotal to infer efficacy of IMVANEX in this variation for the active immunisation against monkeypox and vaccinia virus, especially in the absence of human efficacy data.

Considering the above data, smallpox and monkeypox vaccine (live modified vaccinia virus Ankara) is not expected to pose a risk to the environment.

2.3. Clinical aspects

GCP

Reference is made two three studies:

The submitted protocol of US CDC open-label prospective cohort study in DRC was approved by CDC Institutional Review Board (IRB) and the KSPH IRB. No CSR including a GCP-compliance statement has been submitted.

The submitted protocol of UK cohort surveillance study was said to be conducted in compliance with the principles set out in the Declaration of Helsinki and where applicable, the principles of GCP. No CSR including a GCP-compliance statement has been submitted.

The study POX-MVA-006, assessed in the context of EMEA/H/C/002596/II/0036, used to support this extension of indication was claimed to be conducted in compliance with the principles set out in the Declaration of Helsinki and where applicable, the principles of GCP.

2.3.1. Introduction

The MAH has not performed any clinical trials with the objective of assessing clinical efficacy against monkeypox.

Additional studies (protocols, preliminary results, without final CSR) are submitted:

- US CDC surveillance clinical trial in DRC: An open-label prospective cohort study of IMVAMUNE Smallpox vaccine in adult healthcare personnel at risk for Monkeypox in the DRC.

- Public Health England surveillance trial in the UK: A cohort study of serological responses to MVA-BN Smallpox Vaccine (Imvanex) administered during a Monkeypox outbreak in the UK.

The MAH provided up-to-date overview of IMVANEX efficacy and safety.

2.3.2. Clinical efficacy

Clinical data supporting the monkeypox indication

The MAH has not performed any clinical trials with the objective of assessing either immunogenicity or clinical efficacy against monkeypox.

US CDC surveillance clinical trial in DRC

This is a single-arm, open-label designed study without a formal, statistical testing for efficacy.

Eligible subjects (male and non-pregnant female adults aged 18 years and older, health care personnel at risk, regardless of history of prior smallpox vaccination) receive two doses of IMVANEX (licensed liquid-frozen formulation, or unlicensed freeze-dried formulation) administered on days 0 and 28 via subcutaneous injection.

The primary outcome measures include the proportion of subjects who develop suspected or confirmed monkeypox infection, as well as the proportion of subjects who experience exposure to MPXV, both in a 2-year time frame after initial vaccination.

Secondary objectives are to evaluate immunogenicity of IMVAMUNE in adult participants following receipt of one and two doses of the vaccine and to evaluate the safety, including SAEs and pregnancies.

The available exposure and safety data from this trial have continuously been reported in the routine, 6-monthly PSURs.

The numbers of enrolled, vaccinated and analyzed:

Information on the overall enrollment and data collected and analyzed on the study participants through 6-Jul-2021 (latest annual report), is presented in the below Table.

998 eligible participants received at least one dose of the liquid frozen formulation of IMVANEX in 2017 (Cohort 1), and 600 additional participants (Cohort 2) received at least one dose of a newly developed freeze-dried formulation of the vaccine.

In cohort 1, >97% received both scheduled doses and >88% completed all trial procedures up to the end of the 2-year follow-up period. In cohort 2, >95% received both scheduled doses and >85% completed all trial procedures up to the 1.5-year follow-up timepoint.

Table 4: Overall enrollment, vaccination and follow-up as of July 6, 2021

Study Enrollment, Vaccination and Follow-up Status	Cohort 1 - Liquid Frozen [n (%)]	Cohort 2- Lyophilized [n (%)]
Number of Participants Enrolled	1000	600
Number of Participants Administered 1st Dose	998 (99.8)	600 (100.0)
Number of Participants Administered 2 Doses	973 (97.3)	573 (95.5)
Number of Early Terminations (%)	0 (0)	0 (0)
Number of Participants Completed Follow-up	883 (88.3)*	514 (85.7)**

* For Cohort 1, through last follow-up on day 730
** For Cohort 2, day 365 follow-up was cancelled due to COVID-19 related prohibition on large gatherings and limitations on research activities. Cohort 2 participants returned in February 2021 for day 545 follow-up study visits.

Number of cases of monkeypox:

Across all ~1600 trial participants, no cases of monkeypox disease were observed in the 2-year follow-up period as per trial protocol. However, one participant of the Cohort 1 developed Monkeypox in November 2019, 2.5 years after the second dose of trial vaccine.

The participant who developed Monkeypox in November 2019 was a 45-year-old male (42-year-old at the time of vaccination) and completed the two-year study monitoring period in June 2019. The participant was previously vaccinated with Smallpox vaccine. Lesion samples were collected as part of routine surveillance and laboratory testing confirmed the presence of an orthopoxvirus infection (presumably Monkeypox given local epidemiology). Serology data from this participant showed a weak anti-orthopoxvirus IgG response which peaked at day 42 and was undetectable at day 730.

Table 5: IgG and IgM response for single vaccinia-experience participant who developed monkeypox 2.5 years after MVA-BN vaccination.

	D0	D14	D28	D42	D180	D365	D545	D730
IgG	-0.04	0.07	0.07	0.87	0.17	0.19	-0.07	-0.07
IgM	-0.22	-0.21	-0.21	-0.15	-0.19	-0.21	-0.24	-0.24

The MAH noticed that the previously described annual incidence of monkeypox infections in healthcare workers of this region was 17.4/10000. In a population of 1600 observed over a 2-year period, the expected number of monkeypox cases would therefore be approximately between 5 and 6.

Preliminary results of immunogenicity:

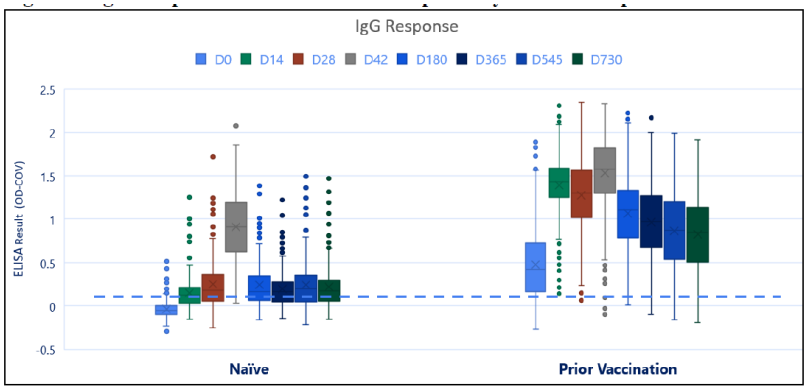
During this reporting period, CDC conducted additional immunogenicity analyses based on samples collected from participants in Cohort 1. Additional immunogenicity analyses continued throughout the next reporting period.

Immune response was assessed using a validated ELISA (vaccinia assay specificities). Updated results of preliminary analyses of IgG immune response and seroconversion by prior smallpox vaccination status and follow-up day are shown below. Participants who received smallpox vaccination during childhood (vaccinia-experienced) had higher IgG concentrations compared to vaccinia-naïve participants.

Table 6: IgG response and seroconversion for Cohort 1 participants

Samples*	D14	D28	D42	D180	D365	D545	D730
All Samples (n=999)	92%	89%	98%	88%	83%	80%	77%
Vaccinia-Naïve (n=294)	78%	75%	99%	76%	73%	74%	71%
Vaccinia-experienced (n=579)	99%	96%	97%	94%	89%	83%	81%

*Previous vaccination status could not be determined for some participants with incomplete vaccine history information.



*Seroconversion defined based on a rise in OD signal of 0.1 from baseline (Day 0). For all samples, median, mean, lower quartile (25%), upper quartile (75%), and outliers are shown.

Figure 16: IgG response for Cohort 1 participants by prior Smallpox Vaccination status

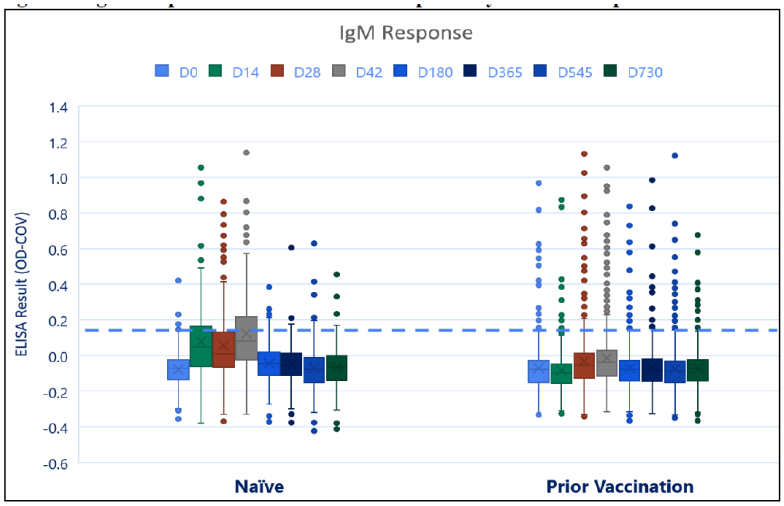
Persistence of IgG antibodies waned over the follow-up period.

Results of IgM immune responses are shown below.

Table 7: IgM response and seroconversion for Cohort 1 participants

Samples*	% Seroconverted (any timepoint)	% Seroconverted			
		D14	D28	D42	D180
All Samples (n=999)	24%	–	–	–	–
Vaccinia-Naïve (n=294)	50%	47%	30%	46%	6%
Vaccinia-experienced (n=579)	11%	6%	6%	9%	2%

*Previous vaccination status could not be determined for some participants with incomplete vaccine history information.



*Seroconversion defined based on a rise in OD signal of 0.15 from baseline (Day 0). For all samples, median, mean, lower quartile (25%), upper quartile (75%), and outliers are shown.

Figure 17: IgM response for Cohort 1 participants by prior Smallpox vaccination status

Data showed that IgM response is higher in vaccinia-naïve than in vaccinia-experienced, presumably due to residual immunity to orthopoxviruses in the latter cohort.

IgG response peaked 2 weeks post dose 2 of the vaccine in vaccinia-naïve cohort, pointing to a need for 2-dose series primary vaccination in this cohort. Overall, the IgG response (GMT, and to some extent SCR) is lower at month 6 and afterwards, in vaccinia-naïve than vaccinia-experienced subjects.

PRNT for vaccinia virus (Western Reserve strain) and monkeypox virus (West African strain) was conducted on a limited set of 73 samples at key timepoints: Day 0 (pre-vaccination), Day 42 (peak response after vaccination), and Day 730 (end of study to assess longevity of responses). Results are shown in below.

Table 8: Geometric mean titres and seroconversion rates (PRNT) in cohort 1 by prior smallpox vaccination status

	Vaccinia-naïve (n=30)		Vaccinia-experienced (n=43)	
	VACV-PRNT*	MPXV-PRNT*	VACV-PRNT*	MPXV-PRNT*
Geometric Mean Titers (95% CI)				
Day 0	43 (24 – 74)	11	233 (129 – 421)	>48
Day 42	264 (156 – 445)	>206	2863 (1583 – 5175)	>438
Day 730	57 (32 – 103)	22	484 (290 – 809)	>195
% Seroconversion (2-fold rise)**				
Day 0	–	–	–	–
Day 42	77%	–	84%	100%
Day 730	30%	–	51%	64%

* VACV-PRNT Vaccinia Virus (Western Reserve Strain) specific PRNT; MPXV-PRNT: Monkeypox virus (West African Strain) specific PRNT

** Seroconversion rate estimates for MPXV-PRNT included for samples with available data.

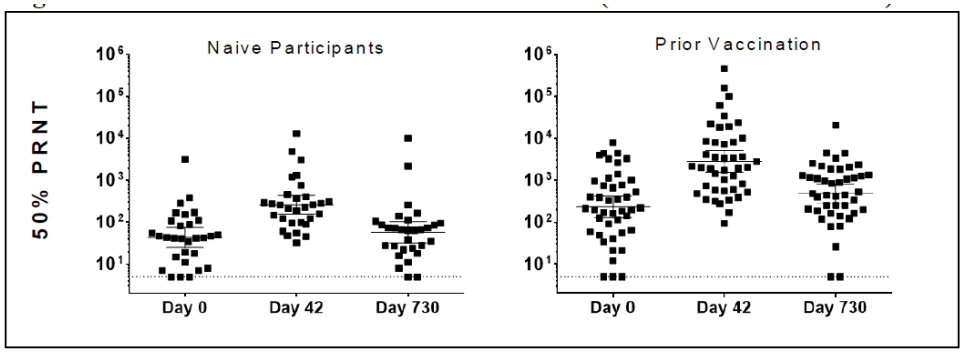


Figure 18: Serum neutralization of vaccinia virus (western reserve strain) for cohort 1

The vaccinia-specific PRNT data resembled those in the existing clinical dossier (also see POX-MVA-006 below), although Day 42 peak VACV-PRNT titers were relatively higher in this CDC study than that in the previous experience. More interesting are results of monkeypox-specific PRNT response, which peaked at day 42, similar to the previous experience with vaccinia specific PRNT. The durability of monkeypox-neutralization response was similar to the vaccinia one, with responses declining but still detectable up to year 2 post vaccination in vaccinia-experienced subjects. Based on these very limited data (N=73 in total), the Day 42 peak monkeypox-specific PRNT titers were overall lower in vaccinia-naïve than in vaccinia-experienced subjects. It should be noted that the PRNT assay for monkeypox is qualified and not fully validated.

No further information is available about seroconversion rates in vaccinia-naïve subjects nor the 95% confidence interval values, and it is unclear whether data were also accrued at early time points, e.g. day 7/day 14.

Public Health England surveillance trial in the UK

This is an observational prospective cohort study without a formal, statistical testing for efficacy.

Eligible subjects (adult healthcare workers that have received Imvanex for pre-exposure or post-exposure prophylaxis against monkeypox during the 2018 UK monkeypox outbreak) were tested for anti-orthopoxvirus serological responses.

The primary outcome measure in this surveillance project was antibody responses (GMT, SCR) to vaccinia virus at a single time point between days 28 and 56 following first dose of Imvanex.

The secondary outcome measures included antibody response (GMT, SCR) that neutralizes the specific monkeypox viruses involved in the UK outbreak, and also reference monkeypox viruses, and anti-vaccinia GMT and SCR at day 14 following the second dose of Imvanex in a subset of individuals, and safety.

Despite the primary objective of the study, no serological data were submitted and no CSR is available.

Reporting cases of monkeypox:

The MAH provided a descriptive summary based on an interim publication (Vaughan, 2018).It was reported that 89 subjects had received IMVANEX as post exposure prophylaxis (at least one single shot of no less than $5x10^7$ Inf.U), thereof 84 considered of intermediate risk and 5 considered as high-risk contacts. One case of monkeypox infection in a vaccinated subject was reported.

This healthcare worker was involved in the changing of potentially contaminated bedding from a patient with multiple skin lesions (before the monkeypox diagnosis was considered in this patient). The healthcare worker received post-exposure vaccination only after 5 days after the most recent exposure, and 6 to 7 days after the earliest exposure therefore missing the optimal timing. This subject then developed skin lesions consistent with monkeypox, with onset 8 days after vaccination, finally confirmed by PCR. The subject later recovered from this infection.

The target vaccination window was set for less than 4 days and up to maximum 14 days from exposure. The patient was vaccinia-naïve and received first dose of IMVANEX before symptom onset, vaccination was >4 days after the most recent exposure, which may be too late to prevent monkeypox. Nevertheless, post-exposure prophylaxis (PEP) use indication has not been regulatorily approved, and the optimal timing for post-exposure vaccination with Imvanex remains unknown.

The history of previous smallpox vaccination was not reported for these 89 exposed subjects.

Additional expected surveillances in the context of the current outbreak

The MAH has actively searched interaction with public health agencies of countries who are starting vaccine implementation programs.

The MAH informed that so far from all public health agencies contacted, registries of vaccinees are kept, although it is unknown about what details to be captured in registries. The MAH noted that several agencies have decided to perform active surveillance, safety or effectiveness analysis, with protocols still under development. Further details of the planned study will be described in the updated IMVANEX Risk Management Plan (RMP).

The MAH envisions to have a reasonable number of data share agreements with various registry owners across EU, UK, Canada and US, as well as other rest of world countries, in place, in order to present any of this data adding on to the overall benefit risk assessment of IMVANEX as soon as available, in respective aggregate reports.

Clinical data supporting prophylaxis against related orthopoxviruses

To support the indication extension to related orthopoxviruses infection and disease in adults 18 years and older, the MAH presented data of an existing clinical trial POX-MVA-006 assessed in variation with procedure number EMEA/H/C/002596/II/0036. According to the MAH, the attenuation of the take can be considered as a useful outcome measure, as it is a direct vaccine efficacy measure against replicating vaccinia virus strains as used in the traditional smallpox vaccines.

The study was set up in collaboration with the USAMRIID and conducted in a US military population stationed in the Yongsan Garrison in South Korea. The study enrolled exclusively healthy, vaccinia-naïve subjects, as they are considered the population most vulnerable to smallpox infection and preferred to demonstrate the protective efficacy of a new smallpox vaccine due to their vaccinia-naïve immune status.

Details about the design are provided in the following Table.

Table 9: Design of pivotal phase III trial POX-MVA-006

Group	Health Status Vaccinia Status	MVA-BN/ACAM2000 Dose/Route	Regimen Number of Vaccinations/ Day of Vaccination
Group 1 N=220	Healthy Vaccinia-naïve	MVA-BN Nominal titer 1 x 10^8 $TCID_{50}$/SC	2 / 1 each on Days 0 and 28
		ACAM2000 2.5–12.5 x 10^5 pfu/Scarification	1 / on Day 56
Group 2 N=220	Healthy Vaccinia-naïve	ACAM2000 2.5–12.5 x 10^5 pfu/Scarification	1 / on Day 0

The co-primary objectives were to demonstrate efficacy of IMVANEX by:

- Demonstrating non-inferiority of IMVANEX compared to ACAM2000, in terms of vaccinia specific PRNT antibody response at Day 42 for IMVANEX and Day 28 for ACAM2000; non-inferiority was met if 2-sided 95% CI of GMTs ratio (Group 1/Group 2) is entirely above 0.5.
- Showing that vaccination with IMVANEX prior to scarification with ACAM2000 results in an attenuation of the take; the endpoint was met if 95% CI of the Area Attenuation Ratio (AAR), reflecting the reduction in the Maximum Lesion Area (MLA), was significantly above 40%.

Results of immunogenicity first-primary endpoint

The first primary endpoint of the trial was met. At the Peak Visits (Day 42/Week 6 for Group 1 and Day 28/Week 4 for Group 2), GMTs were 153.5 and 79.3 for Groups 1 and 2, respectively, with a Group 1/Group 2 ratio of 1.935 (95% CI: 1.562, 2.397), demonstrating non-inferiority of IMVANEX to ACAM2000.

Since the 95% CI of the Group 1/Group 2 ratio at the Peak Visit is entirely above 1, meeting the criterion for superiority of IMVANEX over ACAM2000 as well. The individual Peak GMTs were 201.5 and 117.8 for Groups 1 and 2, respectively, with a Group 1/Group 2 ratio of 1.710 (95% CI: 1.421, 2.059), confirming the results obtained for the Peak Visit, see Table 3.

Table 10: PRNT non-inferiority at peak visit in POX-MVA-006 (PP set for immunogenicity, N=371)

Visit Week	Group 1 IMVANEX plus ACAM2000 (N* = 185)	Group 2 ACAM2000 (N* = 186)	Ratio of GMTs Group 1 / Group 2	Non-inferiority Met (Yes/No)
	GMT (95% CI)	GMT (95% CI)	Ratio (95% CI)	
Peak Visit	153.5 (134.3, 175.6)	79.3 (67.1, 93.8)	1.935 (1.562, 2.397)	Yes
Individual Peak	201.5 (178.5, 227.5)	117.8 (102.3, 135.7)	1.710 (1.421, 2.059)	Yes

Group 1 = 0.5 mL IMVANEX, 2 vaccinations of 1 × 10^8 $TCID_{50}$, administered SC, 1 each at Weeks 0 and 4; followed by ACAM2000, 1 vaccination of 2.5–12.5 × 10^5 pfu, administered via scarification, 4 weeks later (Week 8).

Group 2 = ACAM2000, 1 vaccination of 2.5–12.5 × 10^5 pfu, administered via scarification, at Week 0.

Abbreviations: CI = confidence interval; CSR = clinical study report; GMT = geometric mean titer; N = total number of subjects; N* = number of subjects in specified trial group; pfu = plaque forming units; PP = per protocol; PRNT = plaque reduction neutralization test; SC = subcutaneous; $TCID_{50}$ = tissue culture infectious dose $_{50}$.

The post-hoc analysis on GMT data obtained after the 1 dose of IMVANEX, applying same non-inferiority margin, revealed that PRNT GMT in Group 1 (IMVANEX) was non-inferior to Group 2 (ACAM2000) already

at Week 2 (GMTs were 16.2 for both Groups 1 and 2; GMT ratio: 0.997, 95% CI: 0.738, 1.348). This aspect may have implication for potential post-event emergency settings.

The kinetics of neutralising antibody responses of Group 1 (IMVANEX) versus Group 2 (ACAM2000) are displayed below.

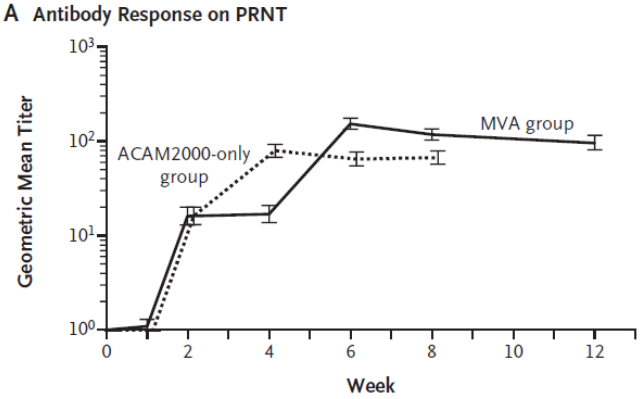


Figure 19: Neutralising Antibody Responses (PRNT using the vaccinia virus Western Reserve strain) among Participants in the Per-Protocol Population for Immunogenicity. Source: Pittman et al., 2019

Results of efficacy (lesion area) co-primary endpoint

The co-primary endpoint of the trial was met. The observed Maximum Lesion Area (MLA) reduction (take attenuation) of 97.9% (95% CI: 96.6%, 98.3%) was significantly greater than the pre-specified threshold of 40% agreed to by the FDA as a clinically relevant reduction of the take. Results of this trial are already reflected in the current SmPC.

Table 11: Digital camera lesion area statistics after ACAM2000 Vaccination in POX-MVA-006 (PP set, N=326)

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

Group 1 = 0.5 mL IMVAMUNE, 2 vaccinations of 1×10^8 $TCID_{50}$, administered SC, 1 each at Weeks 0 and 4; followed by ACAM2000, 1 vaccination of $2.5–12.5 \times 10^5$ pfu, administered via scarification, 4 weeks later (Week 8).

Group 2 = ACAM2000, 1 vaccination of $2.5–12.5 \times 10^5$ pfu, administered via scarification, at Week 0.

2.3.2.1. Discussion on clinical efficacy

IMVANEX was authorised under exceptional circumstances in the EU in 2013 for active immunisation against smallpox in adults. In response to the current monkeypox outbreak, the MAH submitted this variation to the EU to extend the current indication to monkeypox and related orthopoxvirus infection and disease in adults.

Clinical data in support of extension to Monkeypox indication

Clinical studies to assess efficacy and immunogenicity of IMVANEX against monkeypox disease are very limited. The MAH did not conduct any such trials designed to generate informative data.

The MAH provided limited results of two cohort clinical studies sponsored by US CDC and UK.

In the CDC study conducted in DRC, approximately 1600 healthy adult healthcare workers received primary series of IMVANEX and then monitored for occurrence of monkeypox disease. No case of monkeypox disease was observed in the 2-year follow-up period as per trial protocol, whereas one participant developed monkeypox at 2.5 years after the second dose of trial vaccine. According to the previously described annual incidence of human monkeypox infections in healthcare workers of this region (17.4/10000), the expected number of human monkeypox cases, in a population of 1600 observed over a 2-year period, would be approximately between 5 and 6. This information must be interpreted with caution, given serious limitations of design of this CDC study, such as use of single-arm and historical control and without a formal statistical testing for efficacy.

Based on the information and the study design, there is not a clear conclusion on efficacy of the study vaccine. There is uncertainty regarding if the confounding factors, including pre-existing immunity to Monkeypox were sufficiently controlled between the studied population and the population of healthcare workers of this region.

The CDC study also included some preliminary immunogenicity data as regards IMVANEX-induced antibody response, including monkeypox neutralising antibodies in 73 IMVANEX recipients (30 vaccinia-naïve, 43 vaccinia-experienced). This assay was not fully validated but qualified, which can be acceptable as this study is considered supportive. The results of monkeypox-specific PRNT response, which peaked at day 42, was similar to the previous experience with vaccinia specific PRNT. The durability of monkeypox-neutralization response was also similar to the vaccinia one, with responses declining but still detectable up to year 2 post vaccination in vaccinia-experienced subjects. It is acknowledged that interpretation of this type of data may be challenging in the absence of an established immune correlate of protection.

In UK study (interim publication), 89 adults received IMVANEX as PEP, one case of monkeypox infection was reported. The study has no concurrent control arm nor a formal statistical testing for efficacy. Therefore, this study is not conclusive either. Despite the primary objective of the study, no serological data were submitted.

Therefore, the ability of IMVANEX to prevent monkeypox in humans is presently inferred primarily (if not exclusively) from the animal efficacy data (see non-clinical discussion), in view of the lack of feasibility for conducting clinical efficacy studies. Due to the complexities and challenges to run a large-scale study, and to avoid any unnecessary delay in approval of the monkeypox indication, it is acceptable the generation of effectiveness data as a post-marketing commitment imposed in the marketing authorisation.

Clinical data submitted to support the extension of indication to related orthopoxvirus infection and disease

The initial MAA dossier included several clinical trials that have demonstrated the ability of IMVANEX to induce serum antibodies neutralising different vaccinia strains (WR-VV, IHD-J) in the vaccinia-naïve and vaccinia-experienced adults.

In this variation, the MAH presented key results of a pivotal phase 3 clinical trial (POX-MVA-006) which data are already reflected in the SmPC.

This trial demonstrated non-inferior immunogenicity of IMVANEX to ACAM2000 (2^{nd} generation replicating smallpox vaccine, derivative of NYCBH vaccinia strain), in 18-42 year old healthy vaccinia-naïve subjects. The peak vaccinia-specific PRNT titre (WR-VV strain) was 153.5 (95%CI: 134.3; 175.6) 2-week post-dose 2 in PP population (N=185) of IMVANEX recipients (2 doses 28 days apart, $1x10^8$ TCID50/SC), whereas it was 79.3 (95%CI: 67.1, 93.8) in PP population (N=186) of ACAM2000 vaccine recipients (single dose, $2.5\text{-}12.5x10^5$ pfu/scarification). Also of interest is that a single dose of IMVANEX induced comparable

vaccinia-neutralising antibody response, as did ACAM2000, at 2-week time point, a time when replicating smallpox vaccines are considered protective based on the traditional readout of take formation.

More importantly, this trial demonstrated that vaccination with IMVANEX, ahead of scarification with ACAM2000 (2.5-12.5x10^5 pfu/scarification), prevented the growth of the replicating vaccinia virus of ACAM2000 vaccine in the vast majority of subjects, corresponding to an efficacy of 97.9% (95% CI: 96.6%, 98.3%). This convincing data supports the prophylaxis use of IMVANEX against vaccinia virus disease, particularly in the occupational setting for laboratory employees working with replicating vaccinia virus.

Based on the clinical data assessed, the effect of IMVANEX on preventing cowpox has not been specifically investigated. The notable rarity or sporadic nature of reported human cowpox disease makes it infeasible to conduct human efficacy trial with IMVANEX, either pre-licensure or in a post-marketing setting. It might be of value to accrue data on cowpox-neutralising antibody response in IMVANEX recipients during deployment of the vaccine (post-marketing), to ascertain immunogenicity of IMVANEX in humans. Lack of any data, including animal data, specific for cowpox raised concerns. Upon request, the MAH withdrew the indication for active immunisation against "related orthopoxvirus", keeping it limited to the addition of monkeypox and vaccinia virus in view of the data submitted.

The data assessed could not conclude on the confirmation of prevention of infection against related orthopoxvirus. Upon request, the MAH withdrew the indication for prevention of infection against related orthopoxvirus.

2.3.2.2. Conclusions on the clinical efficacy

The submitted clinical data as well as existing clinical data in initial Marketing Authorisation Application (MAA) dossier, together with robust non-clinical data available, are of adequate quantity and quality to infer IMVANEX efficacy against monkeypox and vaccinia virus.

The MAH is committed to engage in collaboration with the national health authorities where the IMVANEX vaccine is deployed, to perform an effectiveness study with IMVANEX so as to generate confirmatory data.

The following measures (SOB) is considered necessary to address issues related to efficacy:

To ensure adequate monitoring of safety and effectiveness, the applicant should perform the following study to collect data where IMVANEX is used as a prophylactic vaccine and/or use in case of (re)-emergence of circulating Monkeypox:

- Non-interventional post-authorisation efficacy study (PAES): An observational, non-interventional post-authorisation safety and efficacy study for the prophylactic vaccination with IMVANEX following (re)-emergence of circulating Monkeypox infections. The study should start as soon as possible after the start of the outbreak.

2.3.3. Clinical safety

The MAH provided an overview of safety of IMVANEX in the clinical overview addendum. The overall safety profile of IMVANEX has previously been included in the dossier and has been updated with routine PSURs in 6-monthly intervals. The size of database consists of total >10,700 subjects to date, including both formulations (liquid frozen and freeze-dried formulation) from clinical trials.

Very commonly reported adverse events in the currently approved liquid frozen formulation (according to Section 4.8 of the EU SmPC) are local and systemic reactions, such as injection site pain, erythema, swelling, induration and pruritus, or headache, fatigue, myalgia and nausea.

In this variation, safety information is provided specifically for the two clinical studies mentioned in the efficacy section above.

CDC surveillance trial in DRC

Below described safety information is from submitted 2 annual reports. The MAH stated that a summary of SAEs and pregnancies from this trial was presented in routine PSURs and there were no SAEs related to study vaccine.

Non-serious Adverse Events (AEs) through 24-Jul-2020:

Analysis of immediate vaccine reactions among Cohort 1 showed that arthralgia, headache, dizziness, chills, and pruritis were reported by six study participants 30 minutes following vaccine administration. However, none were reported as SAEs and most reported these symptoms prior to vaccine administration. Furthermore, these expected AEs occurred in ≤0.1% of the total population receiving the study vaccine and this rate is lower than that seen in previous clinical trials.

Similarly, the frequency of mild-moderate adverse events reported to occur within 7 days of receiving the study vaccine was compared to previously published clinical trial data. With the exception of fever, all such adverse events were found to occur at significantly lower frequencies in the current study compared to previous MVA-BN clinical trial data. For ease of reference, adverse event data for Cohort 1 previously reported in last year's Annual Report are included below .

Safety data from Cohort 2 is currently being finalized in the database so that similar analyses can be performed and comparisons made between the two cohorts. No SAEs occurred within 30 minutes of vaccine administration of study participants in both cohorts.

Table 12: reported frequencies of symptoms prior to and 30 minutes after administration

	Cohort 1 (Liquid-Frozen)	
	Prior to Vaccine Administration # (%)	**30 Minutes After Vaccine Administration # (%)**
Any	48/1970 (2.44)*	6/1965 (0.31)*
Pruritis (itching) at the Vaccination Site	N/A	2/1961 (0.10)
Chills	6/1970 (0.30)	1/1961 (0.05)
Arthralgia/Arthritis	6/1969 (0.30)	1/1961 (0.05)
Headache	16/1970 (0.81)	1/1961 (0.05)
Dizziness	6/1970 (0.30)	1/1959 (0.05)
Sweating	1/1970 (0.05)	0
Fever	3/1969 (0.15)	0
Nausea/Vomiting	2/1970 (0.10)	0
Fatigue/Malaise	6/1970 (0.30)	0
Myalgia/Body Aches	8/1970 (0.41)	0
Chest Pain	8/1968 (0.41)	0
Difficulty Breathing	4/1968 (0.20)	0
Pain in the Arm(s)	4/1967 (0.20)	0
Underarm Swelling	1/1961 (0.05)	0
Pain at the Vaccination Site	N/A	0
Tenderness at the Vaccination Site	N/A	0
Erythema (redness) at the Vaccination Site	N/A	0
Induration (swelling) at the Vaccination Site	N/A	0

*Totals calculated based on those with "No" or "Yes" on at least 1 symptom. On all other totals, missing responses were excluded.
**Only 1 participant reported "Yes" both before and after vaccination. The symptom the participant reported for both was arthralgia.

Table 13: Frequency of solicited adverse events 7 days post-vaccination among cohort 1 participants (solicited adverse event, frequency/denominator(%))

	10-14%	6-9%	3-5%	0-2%
Local Site Reactions	Pain, 275/1927 (14)	Tenderness, 135/1926 (7) Induration, 114/1926 (6) Edema, 136/1927 (7) Pruritis, 148/1927 (8)	Erythema, 89/1927 (5)	-
General Systemic Systems	-	-	Fever, 81/1911 (4) Sweating, 78/1913 (4) Fatigue/Malaise, 84/1911 (4)	Chills, 45/1913 (2) Pain in the Arm, 44/1912 (2)
Lymphatic	-	-	-	Underarm Swelling, 33/1911 (2)
Gastrointestinal	-	-	-	Nausea/Vomiting, 36/ 1911 (2)
Cardiac and Respiratory	-	-	-	Chest Pain, 41/1912 (2) Difficulty Breathing, 14/1912 (0.7)
Nervous System	-	Headache, 141/1912 (7)	-	Dizziness, 46/1911 (2)
Musculoskeletal	-	-	Myalgia, 78/1912 (4) Arthralgia, 58/1912 (3)	-

Table 14: Participant-based frequency and percentage of vaccine adverse events by previous vaccination status with Odds Ratios and p-values for Cohort 1 participants (frequency/denominator (%))

	Previously Vaccinated	Vaccinia naïve	Odds Ratio	P-Value
Any Adverse Event	353/766 (45%)	128/221 (58%)	0.61 (0.49, 0.77)	<0.0001
Local Vaccination Site Reactions				
Pain	161/765 (21%)	78/221 (37%)	0.49 (0.35, 0.68)	<0.0001
Tenderness	75/765 (10%)	39/220 (18%)	0.50 (0.33, 0.77)	0.0014
Erythema (redness)	53/765 (7%)	24/221 (11%)	0.61 (0.37, 1.01)	0.0570
Induration (hard lump)	66/765 (9%)	31/220 (14%)	0.58 (0.36, 0.91)	0.0176
Edema (swelling)	88/765 (12%)	33/221 (15%)	0.74 (0.48, 1.14)	0.1724
Pruritis (itching)	95/765 (12%)	35/221 (16%)	0.75 (0.50, 1.15)	0.1868
General Systemic Symptoms				
Fever	51/765 (7%)	24/220 (11%)	0.58 (0.35, 0.97)	0.0384
Chills	22/765 (3%)	20/220 (9%)	0.30 (0.16, 0.55)	0.0001
Sweating	51/766 (7%)	20/220 (9%)	0.71 (0.72, 1.22)	0.2204
Nausea/Vomiting	19/765 (2%)	11/220 (5%)	0.48 (0.23, 1.03)	0.0606
Fatigue/Malaise	49/765 (6%)	28/220 (13%)	0.47 (0.29, 0.77)	0.0025
Myalgia (Muscle Pain)	49/766 (6%)	23/220 (10%)	0.59 (0.35, 0.98)	0.0435
Arthralgia (Joint Pain)	37/765 (5%)	18/220 (8%)	0.57 (0.32, 1.02)	0.0597
Headache	85/765 (11%)	40/219 (18%)	0.56 (0.37, 0.84)	0.0055
Dizziness	38/764 (5%)	6/220 (3%)	1.87 (0.78, 4.48)	0.1617
Chest Pain	23/765 (0.3%)	14/220 (6%)	0.46 (0.23, 0.90)	0.0241
Difficulty breathing	12/765 (2%)	2/220 (1%)	1.74 (0.39, 7.82)	0.4719
Pain in the arm(s)	24/765 (3%)	16/220 (7%)	0.41 (0.22, 0.79)	0.0078
Underarm swelling	23/765 (3%)	9/220 (4%)	0.73 (0.33, 1.59)	0.4258
Other				
Limit Activity	26/765 (3%)	9/221 (4%)	0.83 (0.38, 1.80)	0.6340
Medical Intervention	40/765 (5%)	19/221 (9%)	0.59 (0.33, 1.04)	0.0656

*Previously vaccinated vs vaccinia naïve analysis: age-based with age ≥37 years classified as vaccinated – 771 people classified as previously vaccinated, 221 vaccinia naïve, and 7 missing.

Serious adverse events

As of 6 July 2021, no SAEs have been determined to be related to study vaccine nor meeting the requirements (i.e., serious, unexpected, suspected adverse reaction) for the submission of Investigation New Drug (IND) safety reports.

Deaths

A cumulative total of 16 study participant deaths have been reported through 6-Jul-2021. 12 deaths among Cohort 1 that received liquid-frozen formulation of the study vaccine and 4 deaths among Cohort 2 that received lyophilized formulation of the study vaccine. No deaths have been deemed related to study vaccine by the local study physician or safety monitors as they occurred temporally distant from vaccine administration and/or alternate aetiologies were present to explain each death. Of the 16 deaths investigated by the local study physician, the following causes of death were identified: acute hepatitis and severe anaemia; skin infection of the leg (distant from the vaccine site injection); cerebral vascular accident secondary to hypertension; alcohol intoxication (n=2); cerebral vascular accident secondary to HIV infection and cryptococcal meningitis; traumatic head injury; acute gastroenteritis associated with severe malaria; opportunistic infections/AIDS; hepatic cirrhosis; suspected complications of tuberculosis; hepatic cancer and hepatitis B virus infection; suspect myocardial infarction; stroke in the context of acquired immunodeficiency (HIV/AIDS); hypertensive cardiopathy; and scrotal hernia complicated by septic shock.

According to the United Nations Department of Economic and Social Affairs the annual death rate in DRC is 9.6 deaths/1,000 population based on estimates from 2017. By comparison, the current annual death rate among the study participant population is 2.9 deaths/1,000 (16 deaths/1600 study participants / 3.5 years x 1,000 population). For this reason, the number of deaths seen in participants to date is not unexpected for this population.

From the 16 reported deaths, 4 deaths included neurologic or thrombotic/thromboembotic events: stroke in the context of acquired immunodeficiency (HIV/AIDS); hypertensive cardiopathy; cerebral vascular accident secondary to hypertension; cerebral vascular accident secondary to HIV infection and cryptococcal meningitis. Narratives of these 4 events were provided:

Stroke in the context of acquired immunodeficiency (HIV/AIDS): An adult patient of unknown gender and age was vaccinated with two doses of Jynneos (IMVANEX vaccine name in the United States) on day 0 and day 28, and on an unspecified date, an unknown amount of time after vaccination with Jynneos, the patient experienced reportedly "stroke in the context of acquired immunodeficiency". The patient's further relevant medical history and concomitant medications were not provided. Stroke has often been reported as a complication of AIDS. Given the alternative explanation provided the company follows the reporter's assessment – not related to vaccine.

Hypertensive cardiopathy: An adult patient of unknown gender and age was vaccinated with two doses of Jynneos on day 0 and day 28. An unknown amount of time after vaccination with Jynneos, the patient experienced hypertensive cardiopathy. The patient's relevant medical history and concomitant medications were not provided. Given the unknown comorbidities, unspecified temporal relationship, and lack of information on any further circumstances surrounding the event, the company follows the reporter's assessment as not related to vaccine.

Cerebral vascular accident secondary to hypertension: An adult patient of unknown gender and age experienced a serious event of cerebral vascular accident secondary to hypertension an unknown amount of time after the vaccination with 2 doses of Jynneos. The patient's relevant medical history and concomitant medications as per initial report includes "secondary to hypertension". Hypertension is known as a potential risk factor for cerebrovascular accident. Given the very limited information available the company follows the reporter's assessment – not related to vaccine.

Cerebral vascular accident secondary to HIV infection and cryptococcal meningitis: An adult patient (44-year-old), received the first dose of Jynneos on an unknown date and the second dose on 28-Aug-2017. On 19-Oct-2017, 52 days after vaccine, the subject experienced reportedly a cerebral vascular accident secondary to HIV infection and cryptococcal meningitis. On the same day the patient died. Given the limited information available, the company follows the reporter's assessment – not related to vaccine but other comorbidities. The cerebral vascular accident occurred 52 days after the second vaccination, which does not appear to point to a temporal relationship. Considering the presence of HIV infection and cryptococcal meningitis diagnosis, it can be agreed that death of this patient is unrelated to IMVANEX vaccine.

For the previous first three cases of death, very limited information was available making challenging to conduct a causality assessment. First of all, a temporal relationship cannot be; secondly, alternative explanation exists which suggests that the occurrence of the death may not necessarily be associated with the study vaccine.

In summary, taking into account the reported country-specific death background incidences, as well as comorbidities likely attributing to all fatal outcomes, the MAH agreed with the CDC assessment of unrelated to vaccine and there are no safety signals from this trial, as per the current information available.

In addition, in the CDC study, there was one suspect myocardial infarction assessed as unrelated by the local study physician, which contains only limited information, with unspecified temporal relationship, unknown comorbidities, and lack of information on any further circumstances surrounding the event. Given the unknown comorbidities, unspecified temporal relationship, and lack of information on any

further circumstances surrounding the event, the company follows the reporter's assessment as not related to vaccine.

Participant pregnancies

As of 6 July 2021, a total of 14 female study participants became pregnant within 6 months of receiving the study vaccine, 4 among Cohort 1 that received liquid-frozen formulation of the study vaccine and 10 among Cohort 2 that received lyophilized formulation of the study vaccine.

All pregnant study participants delivered healthy babies with the exception of one participant, who experienced a stillbirth at an estimated 37 week gestation based on her last menstrual period. According to the United Nations Department of Economic and Social Affairs, the annual infant death rate in DRC is 65 infant deaths per 1,000 live births based on estimates from 2017. This rate is likely higher in the Tshuapa Province compared to the national average given that this is one of the poorest provinces in DRC and access to quality medical care and prenatal care in particular is extremely limited. For this reason, the occurrence of a stillbirth was not unexpected for this population and is not believed to be related to the study vaccine.

PHE surveillance study in UK

The study was planned to recruit 120 participants. To MAH's latest information, 89 participants received IMVANEX in total. No SAEs pertaining to this study were received from health authorities (as of last PSUR DLP which as 31-Jan-2022).

Final data on non-serious AE from this study is not yet available to the MAH, as no CSR has been received yet.

2.3.3.1. Discussion on clinical safety

The safety profile of IMVANEX has been well characterized in clinical trials involving in total >10,700 subjects to date, including both liquid frozen and freeze-dried formulations, and supported by routine PSURs in 6-monthly intervals.

Very commonly reported AEs in the currently approved liquid frozen formulation (according to section 4.8 of the SmPC) are local and systemic reactions, such as injection site pain, erythema, swelling, induration and pruritus, or headache, fatigue, myalgia and nausea.

Safety information is provided specifically for the two clinical studies mentioned in the efficacy section above.

In the CDC monkeypox cohort study, the most frequently reported AEs were local vaccination site reactions with frequencies up to 37% (injection site pain in vaccinia naïve participants) and general, systemic symptoms with frequencies up to 18% (headache in vaccinia naïve participants). These frequencies are well in line or even below those reported in the previous cumulative experience with IMVANEX.

As of 6 July 2021, there have not been SAEs that have been determined to be related to study vaccine nor meeting the requirements (i.e., serious, unexpected, suspected adverse reaction) for the submission of IND safety reports, according to the MAH. A total of 16 deaths assessed as unrelated by the local study physician were reported in the CDC study. Four of them were neurovascular or thrombotic/ thromboembotic events, including stroke in the context of acquired immunodeficiency (HIV/AIDS); hypertensive cardiopathy; cerebral vascular accident secondary to hypertension; cerebral vascular accident secondary to HIV infection and cryptococcal meningitis**.** For the case of cerebral vascular secondary to HIV infection and cryptococcal meningitis, it occurred 52 days after the second vaccination,

which does not appear to point to a temporal relationship. Considering the presence of HIV infection and cryptococcal meningitis diagnosis, it can be agreed that death of this patient is unrelated to IMVANEX vaccine. For the reminding three cases of death, very limited information available makes it very challenging to conduct a causality assessment. The MAH committed to provide the follow-up information to the EMA upon availability.

In addition, in the CDC study, there was one suspect myocardial infarction assessed as unrelated by the local study physician. Very limited information is included in the submitted case narrative, precluding causality assessment. The MAH committed to consolidate, and update all follow up information and include it in the next PSUR (DLP 31-Jul-2022).

In the CDC study, 14 female study participants became pregnant within 6 months of receiving the study vaccine, and one out of them experienced a stillbirth at an estimated 37-week gestation. The occurrence of a stillbirth was not unexpected for this population and is unlikely to be related to the study vaccine, when taking into account the reported country-specific background infant death rate in DRC.

In the PHE surveillance study in UK, no SAEs pertaining to this study were received by the MAH.

Taken together, there are no important identified risks to date based on the currently available database. However, the size of database is not sufficient to characterise very rare adverse events. As per Risk Management Plan version 8.0 (approved on 02 September 2021 in the EU), there are no important identified risks; important potential risks are myo-/pericarditis and postvaccinal encephalitis.

2.3.3.2. Conclusions on clinical safety

The reactogenicity and safety of IMVANEX has been characterised in clinical trials included in the existing clinical dossier.

Safety data from the CDC and the UK cohort studies did not raise safety signal of major concern.

2.3.4. PSUR cycle

Based on the current circumstances with the monkeypox outbreak, the CHMP is of the opinion that the already existing entry in the EURD list for smallpox and monkeypox vaccine (live modified vaccinia virus Ankara) needs to be amended as follows: the PSUR cycle for the medicinal product should follow a half-yearly cycle. The next data lock point will be 31-Jul-2022.

2.4. Risk management plan

The MAH submitted an updated RMP version 9.0 with this application.

The CHMP received the following PRAC Advice on the submitted RMP:

The PRAC considered that the RMP version 9.0 is not acceptable and requested the MAH to submit and updated RMP within 2 months of the conclusion of this variation. RMP version 8.0 remains as the latest approved.

The CHMP endorsed this advice without changes.

2.5. Update of the Product information

The CHMP adopted a new indication (section 4.1) as follows:

"Active immunisation against smallpox, monkeypox and disease caused by vaccinia virus in adults (see sections 4.4 and 5.1)

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

As a consequence of this new indication, sections 1, 4.2, 4.4, 4.6 and 5.1 of the SmPC have also been updated. The Package Leaflet and Labelling are updated in accordance.

Annex II is updated to refer to the newly imposed post-authorisation efficacy study as a specific obligation.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

2.5.1. User consultation

No justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH. However, the changes to the package leaflet do not require user consultation with target patient groups.

2.5.2. Labelling and package leaflet exemptions

A request of translation exemption of the labelling as per Art.63.1 of Directive 2001/83/EC has been submitted by the MAH proposing that the details listed in Article 54 appear in only one official language English (EN) on all packaging components (vial and outer carton), as well as EN package leaflet. The main grounds of the justification were that IMVANEX doses are potentially used for stockpiling, vaccinating laboratory, healthcare workers, military forces and in case of any monkeypox outbreak, and the fact that the medicinal product will not be delivered directly to the patient for self-administration but by a healthcare professional.

a) Outer and immediate labelling in English only

The QRD* Group has temporarily accepted the proposed labelling exemption to provide outer and immediate packaging in EN as per art 63(3) for one year, until the end of July 2023.

*Germany would accept English only vial label but request a multilingual outer carton.

b) Printed package leaflet in English only

The QRD* Group has temporarily accepted the proposed labelling exemption to provide printed package leaflet in English only within the outer carton as per art 63(3) for one year, until the end of July 2023. However, the MAH shall provide printed package leaflets in local languages alongside the supplies of the vaccine.

*Germany would require multilingual printed package leaflet to be provided within the outer carton.

The labelling subject to translation exemption as per the QRD Group decision above will however be translated in all languages in the Annexes published with the EPAR on EMA website, but the printed materials will only be translated in the language(s) as agreed by the QRD Group.

In addition, the Applicant has requested an exemption for omission to include any blue box information on the outer carton for unlimited period of time. The main grounds of the justification were: IMVANEX doses used for stockpiling or in case of emergency outbreak situations, therefore, unpredictable orders from each MS. Moreover, this exemption was justified on the deep-frozen storage/shipping requirements

and the necessity to label batches ahead of time before allocation to specific countries. One batch will be delivered to several countries.

c) Request to omit Blue Box

The QRD Group* has temporarily accepted the proposed labelling exemption for the omission of blue box information for Imvanex for one year, until the end of July 2023.

*Germany has not accepted this translation exemption and would require the blue box information to be displayed on the carton.

*For Denmark, the omission of the blue box on the outer pack would be acceptable. However, the blue box information "Nordic v.nr." is needed e.g., as a sticker on the box.

The MAH shall contact separately the Croatian, Slovenian and Slovak national authority to formalise the above outcome.

2.5.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Imvanex (smallpox and monkeypox vaccine (live modified vaccinia virus Ankara)) is included in the additional monitoring list as it is approved under exceptional circumstances.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

After smallpox has been eradicated, monkeypox has become the most significant orthopoxvirus that causes infection and disease in humans. The clinical course of monkeypox is similar to smallpox, although milder and with a significantly lower case fatality rate. Monkeypox is endemic in tropical rainforests of Western and Central Africa with a yet unknown host species. Human-to-animal contact is suspected to be a source of human infections in endemic Western and Central African countries. In 2020, more than 6,000 cases of human monkeypox, with >200 deaths, have been reported in the DRC.

Most recently, a multi-country monkeypox outbreak is spreading to previously non-endemic countries, mostly in the European region. According to the WHO situation report on Monkeypox on 7 July 2022, 6,027 laboratory-confirmed cases of monkeypox and 3 deaths have been reported to the WHO from 59 countries from the period of 1 January 2022 to 4 July 2022. Approximately 82% of the cases are in Europe, and 15% in the Americas, including more than 1000 confirmed cases in UK (1,351), Spain (1,256) and Germany (1,242), and 300 or more confirmed cases in Canada (300) and the United States (460). Based on the gender data available on 4,406 cases, men made up 99.5% of the cases, and men aged 18 to 44 years accounted for 79% of the cases.

Other related orthopoxviruses that are known to cause human infection and disease include cowpox and replicating vaccinia virus strains. The orthopoxviruses as such are generally less virulent, relative to

smallpox and monkeypox viruses, and disease (pox lesions) caused by such orthopoxviruses may be less frequent and shows fewer spread across the body. Of note, human cowpox and vaccinia infection and disease is generally associated with occupational risk and thereby only rare or sporadic events. Occurring of such events is primarily among the laboratory personnel who works with cowpox or vaccinia virus, and those healthcare personnel who administer replicating smallpox (vaccinia) vaccine or care for patients infected with such orthopoxviruses.

3.1.2. Available therapies and unmet medical need

In the EU, there is no vaccine specifically licensed for active immunisation for prevention of orthopoxviruses other than smallpox. IMVANEX was approved in 2013 in the EU for prevention of smallpox in adults.

In relation to specific treatment, tecovirimat the only medicinal product currently approved in the European Union for the treatment of smallpox, monkeypox and cowpox in adults and children with body weight at least 13 kg. Tecovirimat is inhibitor of a viral protein relevant for release of virus particles from host cells and has recently been approved in the EU for the treatment of smallpox, monkeypox and cowpox. It has been authorised based on testing in animal models using other orthopoxviruses than smallpox only.

3.1.3. Main clinical studies

No new clinical trials sponsored by the MAH have been submitted.

The MAH provided key results of animal efficacy studies already included in initial MAA dossier and two additional confirmatory NHP challenge studies, along with relevant but limited information derived from two clinical cohort studies sponsored by US CDC (completed) or by UK (ongoing), to support IMVANEX use in monkeypox indication.

The MAH summarized results of a pivotal phase 3 clinical trial (POX-MVA-006), coupled with animal efficacy data, to support the extension of indication to related orthopoxviruses.

3.2. Favourable effects

IMVANEX has shown pronounced protective effect consistently in a variety of animal challenge models using the intravenous, intratracheal and aerosol routes of administration of monkeypox virus in NHPs, as well as the intranasal route in prairie dogs. Dose-dependent efficacy, i.e., 60-100% against lethal challenge with monkeypox virus, was observed, following two subcutaneous injections of the vaccine 4-week apart, at doses ranging from $1x10^6$ to $1x10^8$ TCID50 in NHPs. Whenever measured in the protected animals that were vaccinated with IMVANEX, anti-vaccinia humoral and cellular immune responses, including binding and neutralising antibodies in the blood of the vaccinated animals, could be evidenced. Interestingly, single vaccination with $1x10^8$ TCID50 of IMVANEX also conferred 88-100% protection of monkeypox in NHPs in the intravenous and intratracheal route challenge models, which is relevant for emergency settings.

Beyond key animal data, limited information is available. No cases of monkeypox disease were reported in approximately 1600 healthy adults that live in a geographic region where monkeypox is endemic after they had received a primary series of IMVANEX and followed for up to 2 years period post vaccination. This CDC-sponsored study was uncontrolled and without a formal statistical testing for efficacy. Very preliminary data were also derived from UK surveillance study that reported 1 case of monkeypox among 89 subjects who received post-exposure prophylaxis with IMVANEX.

The CDC-sponsored cohort study produced preliminary immunogenicity data as regards IMVANEX-induced antibody response, including monkeypox-neutralising antibodies in 73 IMVANEX recipients (30 vaccinia-naïve, 43 vaccinia-experienced). The results of monkeypox-specific PRNT response were similar to the previous experience with vaccinia specific PRNT. The durability of monkeypox-neutralization response was also similar to the vaccinia one, with responses declining but still detectable up to year 2 post vaccination in vaccinia-experienced subjects.

Concerning prophylaxis use of IMVANEX to prevent vaccinia virus disease, the data provided was linked to clinical trial POX-MVA-006, where an efficacy of 97.9% (95% CI: 96.6%, 98.3%) in preventing the growth of replicating vaccinia virus of ACAM2000 vaccine (a derivative of NYCBH strain) was demonstrated in healthy vaccinia-naïve adults when vaccination with IMVANEX ($1x10^8$ TCID50/SC, 28 days apart) was implemented ahead of scarification with ACAM2000 ($2.5\text{-}12.5x10^5$ pfu/scarification) in study participants. In addition, this study demonstrated that two doses of IMVANEX was at least as immunogenic as single dose ($2.5\text{-}12.5x10^5$ pfu/scarification) of ACAM2000 replicating vaccinia vaccine, at peak response visit. Vaccinia-specific PRNT titre (WR-VV strain) in IMVANEX recipients was 153.5 (95%CI: 134.3; 175.6) 2-week post dose 2 in the per-protocol population (N=185), whereas it was 79.3 (95%CI: 67.1, 93.8) in ACAM2000 vaccine recipients in the per-protocol population (N=186). Also of interest is that a single dose of IMVANEX induced comparable vaccinia-neutralising antibody response, as did ACAM2000, at 2-week time point, a time when replicating smallpox vaccines are considered protective based on the traditional readout of take formation.

3.3. Uncertainties and limitations about favourable effects

No clinical efficacy trial or effectiveness study in the field that would allow to generate confirmatory data has been conducted with IMVANEX. The submitted 2 cohort studies suffer from serious limitations in study designs, including use of single-arm and historical control, lack of a formal statistical testing for efficacy, etc. The very limited immunogenicity data on monkeypox-neutralising antibody derived from CDC study is hard to interpret, due to the non-validated analytic method, and also the fact of gap of knowledge about an immune correlate of protection against monkeypox.

Furthermore, a direct translation of animal efficacy data to humans carries an obvious uncertainty.

Therefore, although protection against disease in humans is expected, it is still unknown whether IMVANEX prophylactic use can confer reasonable level of protection in humans under the conditions of natural monkeypox disease transmission. The activity of current monkeypox outbreak makes it likely that it is feasible to perform an effectiveness study with IMVANEX so as to generate confirmatory data. Hence, the CHMP has added a new specific obligation within this extension of indication application with the request for a PAES to be conducted. The MAH proposed a prospective non-interventional multicentre cohort study to investigate safety and effectiveness of IMVANEX against monkeypox.

3.4. Unfavourable effects

The safety profile of IMVANEX has been well characterized in clinical trials involving in total >10,700 subjects to date, including both liquid frozen and freeze-dried formulations, and supported by routine PSURs in 6-monthly intervals.

Very commonly reported AEs in the currently approved liquid frozen formulation (according to section 4.8 of the SmPC) are local and systemic reactions, such as injection site pain, erythema, swelling, induration and pruritus, or headache, fatigue, myalgia and nausea.

In the CDC monkeypox cohort study provided in this application, the most frequently reported adverse events were local vaccination site reactions with frequencies up to 37% (injection site pain in vaccinia

naïve participants) and general, systemic symptoms with frequencies up to 18% (headache in vaccinia naïve participants). These frequencies are well in line or even below those reported in the previous cumulative experience with IMVANEX.

As of 6 July 2021, there have not been SAEs that have been determined to be related to study vaccine nor meeting the requirements (i.e., serious, unexpected, suspected adverse reaction) for the submission of IND safety reports, according to the MAH.

In the PHE surveillance study in UK, no SAEs pertaining to this study were received by the MAH.

Taken together, there are no important identified risks to date, based on the existing database.

3.5. Uncertainties and limitations about unfavourable effects

In the CDC monkeypox cohort study, 16 deaths were reported as of 6 July 2021, and were assessed as unrelated by the local study physicians. Four of them were neurovascular or thrombotic/thromboembotic events, including stroke in the context of acquired immunodeficiency (HIV/AIDS); hypertensive cardiopathy; cerebral vascular accident secondary to hypertension; cerebral vascular accident secondary to HIV infection and cryptococcal meningitis. Very limited information was available for the first three cases of deaths.

In the CDC study, there was one suspect myocardial infarction. Only limited information was available.

3.6. Effects Table

Table 1. Effects Table for Imvanex for active immunisation against monkeypox and vaccinia virus

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Protection For Monkeypox and vaccinia virus	Animal models, MPX challenge in NHP Vaccinia WR-VV challenge in mice ECTM challenge in mice		IMVANEX	yes	Moderate strength due to robustness of animal efficacy data	Existing Non-clinical dossier 2 additional NHP/MPX models
Protection For vaccinia virus	Clinical trials, ACAM2000 scarification/challenge		IMVANEX	yes	High strength due to efficacy outcome as co-primary in vaccinia-naïve, for vaccinia (related orthopoxvirus)	POX-MVA-006
Human immunogenicity For related vaccinia virus	Vaccinia WR-VV Vaccinia IHD-J		IMVANEX	yes	Moderate strength due to use of validated assay and surrogate endpoint rather than efficacy endpoint, for vaccinia (related orthopoxvirus)	Existing clinical dossier
Protection For MPX	US CDC surveillance clinical study: An open-label		IMVANEX	no	Low strength due to serious deficiency of trial design (historical control, no formal	CDC study

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
	prospective cohort study				statistical testing for efficacy)	
Human immunogenicity For MPX	US CDC surveillance clinical study: An open-label prospective cohort study		IMVANEX	no	Low strength due to lack of info on PRNT assay validation, insufficient info provided	CDC study
Unfavourable Effects						
Reactogenicity profile	In vaccinia-naïve In vaccinia-experienced		IMVANEX	yes	High strength due to consistency of finding across multiple clinical trials, based on sufficient assessment	Existing clinical dossier CDC study
Safety profile	In vaccinia-naïve In vaccinia-experienced		IMVANEX	yes	High strength due to consistent finding pre- and post-licensure, based on reasonable size of database	Existing clinical dossier, routine PSURs, and 2 additional clinical studies in this application

Abbreviations: WR-VV: Western Reserve vaccinia virus, ECTM: Ectromelia virus (mousepox), MPX: monkeypox.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Considering the conduct of human efficacy clinical trials against monkeypox is infeasible. Animal efficacy data regarding prevention of monkeypox generated from different NHP challenge models are considered most pertinent to inferring efficacy of IMVANEX against monkeypox in humans. The cross-neutralization data generated from clinical trials (WR-VV, IHD-J, ACAM2000 vaccine strain, derivative of NYCBH strain) and cross-protectivity from mice (WR-VV, Ectromelia, monkeypox) are also relevant to monkeypox indication.

Clinical efficacy of IMVANEX in preventing growth of replicating vaccinia virus is most relevant to supporting IMVANEX prophylaxis use in preventing vaccinia disease.

Regarding unfavourable effects, IMVANEX is found well-tolerated in healthy adults, with mild to moderate and transient local and systemic reactions, including injection site pain, erythema, swelling, induration and pruritus, or headache, fatigue, myalgia and nausea. With a size of total >10,700 subjects to date, from clinical trials, the safety profile of IMVANEX remains to be favorable. There are no important identified risks. Provided information from the CDC study and UK surveillance project do not raise safety signals of major concern.

3.7.2. Balance of benefits and risks

Taking into account the favourable safety profile, with only mild to moderate and transient adverse events, and the consistent signs towards protective efficacy based on animal challenge models and

corresponding human immunogenicity data, the benefit risk profile of IMVANEX for prevention of monkeypox and disease caused by vaccinia virus, is considered favourable.

Therefore, approval of IMVANEX extension of indication to monkeypox and disease caused by vaccinia virus is recommended.

3.8. Conclusions

The overall benefit risk balance of IMVANEX is positive.

4. Recommendations

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends, by consensus, the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II, IIIA and IIIB

Extension of indication to include active immunisation against monkeypox and disease caused by vaccinia virus in adults for Imvanex; as a consequence, sections 1, 4.1, 4.2, 4.4, 4.6 and 5.1 of the SmPC are updated. The Package Leaflet and Labelling are updated in accordance. Furthermore, the PI is brought in line with the latest QRD template version 10.2.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I, II, IIIA and IIIB are recommended.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion IMVANEX-EMEA/H/C/002596/II/0076.