19 September 2024
EMA/484428/2024
Committee for Medicinal Products for Human Use (CHMP)

Extension of indication variation assessment report

Imvanex

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

Procedure No. EMEA/H/C/002596/II/0108

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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Table of contents

List of abbreviations

AE	adverse event
AESI	adverse event of special interest
BN	Bavarian Nordic
CI	confidence interval
CSR	Clinical study report
DMID	Division of Microbiology and Infectious Disease
DNA	Deoxyribonucleic acid
DRC	Democratic Republic of the Congo
GCP	Good clinical practice
GMT	geometric mean titres
GMTR	geometric mean titres ratio: ratio of GMT in adolescents to GMT in adults
GMFR	geometric mean fold rise
HIV	Human immunodeficiency virus
Inf.U.	infectious units
LLOD	Lowe limit of detection
MAA	Marketing authorisation application
mAAE	medically attended adverse event
mITT	modified intention-to-treat
MVA-BN	Modified Vaccinia Ankara – Bavarian Nordic
MPXV	monkeypox virus
NI	Non-inferiority
NIH	National Institute of Health
PHEIC	Public Health Emergency of International Concern
PI	Product information
PK	pharmacokinetics
PRNT	plaque reduction neutralization test
PT	preferred term
REC	Recommendation
RMP	risk management plan
SAE	serious adverse event
SAP	Statistical analysis plan
SC	subcutaneous
SmPC	Summary of Product Characteristics
SOB	Specific obligation
UP	unanticipated problem
VV	vaccinia virus
WHO	World Health Organization
WR	Western Reserve

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 9 August 2024 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 and IIIB

Extension of indication to include treatment of adolescents from 12 to 17 years of age for Imvanex based on interim results from study DMID 22-0020. This is a Phase 2 randomized open label multisite trial to inform Public Health strategies involving the use of MVA-BN vaccine for mpox. As a consequence, sections 4.1, 4.2, 4.8, and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Furthermore, the PI is brought in line with the latest QRD template version 10.4.

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

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0284/2023 on the agreement of a Paediatric Investigation Plan (PIP).

At the time of submission of the application, the PIP P/0284/2023 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 and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Jan Mueller-Berghaus Co-Rapporteur: Not applicable

Timetable	Actual dates
Submission date	9 August 2024
Start of procedure:	21 August 2024
CHMP Rapporteur Assessment Report	4 September 2024
CHMP members comments	9 September 2024
ETF meeting	10 September 2024
Updated CHMP Rapporteur Assessment Report	12 September 2024
CHMP Opinion	19 September 2024

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Smallpox

Smallpox virus (Variola virus) is a member of the family Poxviridae belonging to the subfamily *Chordopoxviridae* and genus *Orthopoxvirus*. Vaccinia virus contains a large linear double-stranded DNA genome amounting to approximately 190,000 base pairs and encoding more than 200 proteins. Viral particles are typically brick shaped and measure ~300 x 230 nm. Virions released through the cell membrane are enveloped but most virions remain cell-associated and are released by cellular disruption that leaves them without an envelope. Both enveloped and non-enveloped viruses are infectious.

Smallpox was eradicated (declaration 1981; last known case in 1977) as a result of the WHO global campaign.

Monkeypox (Mpox)

Mpox is a viral zoonosis caused by the mpox virus, a member of the orthopoxvirus family. It was first identified in 1958 and the first cases of mpox in humans were reported in the 1970s in the Central African region. Since then, mpox in humans has been reported repeatedly throughout Sub-Saharan Africa, including West Africa and Central Africa, with rising frequency in recent years.

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

In May-2022, a multi-country mpox clade II outbreak spread to previously non-endemic countries, following reports of a number of cases across several Member States not linked to countries where the disease is endemic. The outbreak widened globally, and WHO declared mpox a PHEIC for the first time, in July 2022. Less than a year later, in May 2023, noting significant progress having been made in

controlling the outbreak, the WHO removed the PHEIC status; but urged governments, health authorities and impacted communities to remain vigilant.

On 15 August 2024, Sweden became the first country outside the African continent to confirm mpox clade Ib in an individual with travel history to central Africa. The confirmation of the case came just one day after WHO declared mpox a PHEIC for the second time in 2 years, following an upsurge in new and concerning cases in the DRC and several neighbouring countries, including the emergence of a new strain, clade Ib, which appears to be more severe than clade II.

The clinical course of mpox 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 mpox is associated with milder disease, fewer deaths, and limited human-to-human transmission. Human infections with the Central African mpox 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 mpox virus.

People who live with or have close contact (including sexual contact) with someone who has mpox, 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.

State the claimed therapeutic indication

In the context of the currently ongoing mpox outbreak and in view of the need to prevent mpox in paediatric age groups, interim data have been presented to support an extension of the indication of Imvanex to individuals from 12 years of age.

Interim immunogenicity and safety data from a clinical study sponsored by the US DMID of the NIH evaluating the immunogenicity and safety of MVA-BN in adolescents 12-17 years of age have become available and support the administration of MVA-BN in this age group.

Following the finalisation of the study in Oct-2024, the MAH will submit by 30-May-2025 the final CSR together with the updated RMP to further characterise the safety information of Imvanex in adolescents 12 to 17 years of age.

Management

Control of the 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 EU for the treatment of smallpox, mpox 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.

In the EU, Imvanex is currently approved for active immunisation against smallpox, mpox and disease caused by vaccinia virus in adults.

2.1.2. About the product

Imvanex is a live, highly attenuated, non-replicating viral vaccine for protection against smallpox, mpox and disease caused by vaccinia virus in adults. The vaccine is suspension for injection. One dose (0.5 mL) contains MVA-BN live virus no less than 5 x 107 infectious unit.

Imvanex is manufactured based on the manufacturer's proprietary strain of the orthopoxvirus MVA-BN that is grown in chicken embryo fibroblast cells, harvested, concentrated, and purified.

Imvanex was approved under exceptional circumstances in the EU on 31 July 2013 for active immunisation against smallpox in adults. On 22 July 2022, an extension of indication to include active immunisation against mpox and disease caused by vaccinia virus in adults was approved.

The primary vaccination schedule consists of two 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

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

2.4. Clinical efficacy

Methods

Study DMID 22-0020, is an open label, comparative, multicentre immunogenicity and safety study of MVA-BN vaccine in adolescents 12-17 years of age (Arm 5) in comparison with adults 18-50 years of age (Arm 3 and Arm 4) in the Stage 2 of this study conducted in the US (see table 1). An interim analysis of the Study Stage 2 was performed based on data up to cut-off date, 22 February 2024, which includes immunogenicity data up to Study Day 43 (14 days Post Dose 2) and safety data reported through Study Day 210 (180 days Post Dose 2).
Data up to Study Day 57 are clean. Data after Study Day 57 are as reported. This interim examination of the data was noted in the protocol and undertaken as described in the SAP.

Table 1:DMID Protocol Number 22-0020-Study Design

Arm	Dose of JYNNEOS (MVA-BN)[b]	Route of Administration[a]	Vaccination Day	
			Day 1	Day 29
Stage 1				
3 (Adults 18-50) N=76	Standard dose 1x 10^8 Inf. U.	Subcutaneous	X	X
Stage 2				
4 (Adults 18-50) N=135	Standard dose	Subcutaneous	X	X
5 (Adolescents 12-17) N=315	Standard dose	Subcutaneous	X	X

[a] Subcutaneous is administered in the fatty subcutaneous tissue of the upper arm.
[b] 0.5 x 10^8 to 3.95 x 10^8 infectious units
[c] corresponding to no less than 5 x 10^7 Inf.U as authorised in the EU

Study participants

As of the data cut-off date the study was fully enrolled with a total of 526 participants: 315 adolescents and 211 adults (76 adults from Stage 1 [Arm 3] and 135 adults from Stage 2 [Arm 4]). All enrolled participants completed their first dose and 99% completed their second dose (see table 2). 304 (97%) adolescents and 208 (99%) adults contributed a venous blood sample for the primary endpoint at Day 43 (Table 2).

Table 2: Participant Disposition by Age Group

	Adolescents (N=315)		Adults[a] (N=211)		All Participants (N=526)	
Participant Disposition	**n**	**%**	**n**	**%**	**n**	**%**
Screened	--	--	--	--	558	--
Enrolled	315	100	211	100	526	100
Received Dose 1	315	100	211	100	526	100
Received Dose 2	312	>99	207	98	519	99
Completed Primary Endpoint (Study Day 43)	304	97	208	99	512	97

Abbreviations: N=Number of participants enrolled; n=number of participants meeting the row criteria.
[a] Arms 3 and 4 were combined as a comparator group in the analysis.

Demographics

Of the 315 adolescents enrolled, 160 (51%) were male, 216 (69%) are white, and 251 (80%) are not Hispanic or Latino (see table 3). No adolescents were HIV-positive. Of the 211 adults enrolled in Arm 3 in Stage 1 and Arm 4 in Stage 2, 94 (45%) are male, 149 (71%) are not Hispanic or Latino, and 145 (69%) are white. Five (2%) adults were HIV-positive at baseline (see table 3).
The median age of enrolled adolescents is 14.0 years with 161 (51%) of adolescent participants being in the age group of 12 to 14 years. The median age of enrolled adults (Arm 3 and Arm 4) is 36.0 years.

Table 3: Summary of Categorical Demographic and Baseline Characteristics by Age Group, All Enrolled Subjects

		Adolescents (N=315)		Adults[a] (N=211)		All Participants (N=526)	
Variable	**Characteristic**	**n**	**%**	**n**	**%**	**n**	**%**
Sex at Birth	Male	160	51	94	45	254	48
	Female	155	49	117	55	272	52
Ethnicity	Not Hispanic or Latino	251	80	149	71	400	76
	Hispanic or Latino	63	20	62	29	125	24
	Not Reported	1	<1	-	-	1	<1
Race	American Indian or Alaska Native	-	-	1	<1	1	<1
	Asian	8	3	12	6	20	4
	Native Hawaiian or Other Pacific Islander	-	-	-	-	-	-
	Black or African American	31	10	31	15	62	12
	White	216	69	145	69	361	69

		Adolescents (N=315)		Adults[a] (N=211)		All Participants (N=526)	
Variable	**Characteristic**	**n**	**%**	**n**	**%**	**n**	**%**
	Multi-Racial	57	18	17	8	74	14
	Unknown	3	<1	5	2	8	2
Age Group	12-14 years old	161	51	N/A	N/A	161	31
	15-17 years old	154	49	N/A	N/A	154	29
	18-50 years old	N/A	N/A	211	100	211	40
HIV Status	Negative	309	98	206	98	515	98
	Positive	-	-	5	2	5	<1
	Not Reported	6	2	-	-	6	1

Abbreviations: N=Number of participants enrolled.
n=Number of participants meeting the row criteria.
N/A=Not applicable.
[a] Arms 3 and 4 were combined as a comparator group in the analysis.

Methods to evaluate immunogenicity

In view of their demonstrated role in protection against a lethal mpox challenge in animals immunised with a live attenuated vaccinia vaccine, anti-vaccinia neutralising antibodies were proposed as a correlate of protection (Edghill-Smith, 2005). The measured clinical response in terms of anti-vaccinia neutralising antibodies by a validated PRNT, together with animal studies, formed the basis for the approval of MVA-BN as smallpox and mpox vaccine.

Therefore, the assessment of MVA-BN for immunisation of adolescents was based on the direct comparison of the PRNT response induced by the vaccine in this population with the immune response measured in adults, using the same PRNT as in the initial MAA.

Blood is collected for the evaluation of immunogenicity at Day 1, Day 29, Day 43, Day 210 and Day 394. The interim analysis includes immunogenicity data at Study Day 1, Day 29 (28 days Post Dose 1) and Day 43 (14 days Post Dose 2).

Objectives/endpoints

The primary immunogenicity objective of study Stage 2 was:

- To determine if peak humoral immune responses in adolescents ages 12 to 17 years following administration of a 2-dose 1 x 10^8 Inf.U. (corresponding to no less than 5 x 107 Inf.U.) MVA-BN regimen administered SC are non-inferior to the response in adults ages 18 to 50 years who received the licensed 2-dose SC regimen of 1 x 10^8 Inf.U. MVA-BN. The associated endpoint was vaccinia virus specific PRNT GMT at Day 43.

The main secondary immunogenicity objectives of study Stage 2 were:

- To evaluate humoral immune responses following receipt of the 2-dose SC regimen of 1 x 10^8 Inf.U MVA-BN in adolescents compared to adults on each study day. The associated endpoint for the interim analysis was vaccinia virus specific PRNT GMT at Day 29 and Day 43.

- To evaluate seroconversion between adolescent and adult study arms. The associated endpoint for the interim analysis was vaccinia virus specific seroconversion rate by PRNT at Day 29 and Day 43.

The humoral response in terms of Monkeypox virus neutralizing antibodies was assessed under an exploratory objective:

- To evaluate humoral immune responses of the 2-dose SC regimen of 1 x 10^8 Inf.U. MVA-BN to monkeypox virus in adolescents compared to adults. The associated endpoint was Monkeypox virus specific PRNT GMT at Day 43.

Immunogenicity assays

Serum samples for assessment of neutralising antibody responses after vaccination with MVA-BN as measured by the BN VV-WR strain PRNT were collected prior to receiving the first vaccination on Day 1, and on Days 29, 43, 210, and 394. This assay was performed as previously described (Pittman, 2019) and is the assay used in the initial MAA of MVA-BN. This assay is validated.
Serum samples collected prior to receiving the first vaccination on Day 1 and on Day 43 were assessed for neutralising antibody responses using a mpox virus specific PRNT. This assay was conducted by Battelle Biomedical Research Center and uses an mpox clade 2b virus (hMPXV/USA/MA001/2022, ATCC/BEI Resources) and should be considered optimized but not fully validated. Since this assay is still in development, it was only included as an exploratory endpoint.

Immunogenicity analysis cohort

For this interim analysis, the analysis of immunogenicity was based on the mITT population, which includes all enrolled participants who received at least one dose of vaccine and contributed pre- and at least one post-vaccination venous blood sample for immunogenicity testing for which results were reported. Two (<1%) adolescents did not contribute any post-vaccination blood samples with immunogenicity results and were excluded from the mITT population. Overall, 313 adolescents and all 211 adults satisfied the criteria for inclusion in the mITT population. Of these participants, 304 adolescents and 208 adults completed the Day 43 visit and contributed a venous blood sample.

Statistical methods

The following hypotheses relating to antibody responses were assessed in the interim analysis:

- Primary Hypothesis: At Day 43 the humoral immune response of the MVA-BN SC (standard dose regimen) in adolescents will be non-inferior to the standard MVA-BN SC regimen in adults, as assessed by PRNT GMT.
- Secondary Hypothesis: The humoral immune response of the MVA-BN SC regimen in adolescents, as assessed by PRNT GMT, will be similar to the MVA-BN SC regimen in adults at all study days.
- Exploratory Hypothesis: The humoral immune response of the MVA-BN SC regimen in adolescents, as assessed by monkeypox virus specific PRNT GMT, will be similar to the MVA-BN SC regimen in adults at Day 1 and 43.

Seroconversion was defined depending on baseline measurements at Day 1 (pre-vaccination). If baseline was positive, i.e. ≥ LLOD, a ≥ 2-fold rise from baseline indicated a positive seroconversion result. If baseline was negative, i.e. < LLOD, a subsequent measurement ≥ LLOD indicated a positive seroconversion result.
GMTs of antibodies, GMT ratios (GMTRs, defined as ratio of GMT in adolescents to GMT in adults), GMFRs, and percentage of participants achieving seroconversion were calculated to help assess the humoral immune response in adolescents compared to adults. Corresponding 95% CIs for each assessment were also calculated. The 95% CIs for GMTs and GMFRs were calculated using Student's t-distribution, the 95% CIs for GMTRs were calculated using Welch-Satterthwaite t-test, and the 95% CIs for seroconversion rates were calculated using Clopper-Pearson methodology.
Additionally, a NI test with an unequal variance and two-sample t-test statistic was performed to obtain a p-value for Day 43 (expected peak antibody response) and actual participant peak response day (Post Dose 1). NI was defined by a significant p-value and a GMTR 95% CI lower bound ≥ 0.67 (i.e., the lower bound of the 95% CI for the difference of the log10 titer means ≥ -0.174).
Arm 3 from Stage 1 and Arm 4 from Stage 2 were combined as the comparator group for the primary analyses. Arm 3 participants were then excluded for sensitivity analyses, to qualitatively assess whether there were any substantial differences between adult participants enrolled in each stage; however, it was not anticipated for the inclusion/exclusion of Arm 3 to affect the results.

Results

Vaccinia virus specific response at Day 43

As assessed by the vaccinia virus-specific PRNT, adolescents were found to have a humoral immune response that was non-inferior to adults on Day 43, the expected peak response day (GMTR: 1.60 (95% CI: 1.32, 1.95); p<0.001) (see table 4).
Based on non-overlapping 95% CIs, the GMT in adolescents was greater than the GMT in adults on Day 43 (Adolescent GMT: 470.3 [95% CI: 422.3, 523.8]; Adult GMT: 293.2 [95% CI: 249.8, 344.2]).

Table 4: Vaccinia Virus Specific PRNT Primary Hypothesis Testing, mITT Population

Hypothesis	Statistic	Adolescents (N=313)	Adults[c] (N=211)	Adults - Arm 4 Only (N=135)
At Day 43 the humoral immune response in adolescents is non-inferior to adults, as assessed by Vaccinia specific PRNT GMT	n	304	208	132
	GMT (95% CI)	470.3 (422.3, 523.8)	293.2 (249.8, 344.2)	295.7 (240.8, 363.2)
	GMTR (95% CI)	N/A	1.60 (1.32, 1.95)	1.59 (1.26, 2.00)
	p-value[a]	N/A	<0.001	<0.001
	Non-inferiority result[b]	N/A	Yes	Yes

Abbreviations: N = Number of participants in the mITT Population. n = Number of participants with data at time point. CI = Confidence Interval, calculated using Student's t distribution for GMT and Welch-Satterthwaite t test for GMTR.
[a] Two-sample t-test with unequal variance, NI margin of 0.67 and two-sided type I error rate of 0.05 to test the null hypothesis that humoral immune response in adolescents will be noninferior to adults.
[b] If the lower bound of the GMTR 95% CI is greater than or equal to 0.67 (NI=0.174 log10 scale) prior to rounding, the result is "Yes".
[c] Arms 3 and 4 were combined as a comparator group in the primary analysis. Arm 3 participants were excluded for a s ensitivity analysis.

Vaccinia virus specific response at all timepoints

As assessed by the vaccinia virus-specific PRNT, adolescents had similar baseline antibody titers at Day 1 and a similar humoral immune response on Day 29 compared to adults. The GMTR at Day 29 was 1.15 versus adults with 95%CI including 1 (0.93, 1.42) (see table 5).

When considering the day of peak response (i.e. time of highest GMT at any time point after Dose 1) the immune response in adolescents was also non-inferior to that of adults (GMTR: 1.53 (1.25, 1.86); p<0.001) (see Table 5). The GMTR at peak Day (1.53) was similar to the GMTR at Day 43 (1.60) (see Table 4).

Table 5: Vaccinia Virus Specific PRNT Secondary Hypothesis Testing, mITT Population

Hypothesis	Statistic	Adolescents (N=313)	Adults[c] (N=211)	Adults - Arm 4 Only (N=135)
At Day 1 humoral immune baseline in adolescents is similar to adults, as assessed by Vaccinia specific PRNT GMT	n	313	211	135
	GMT (95% CI)	10.0 (10.0, 10.1)	10.9 (10.2, 11.8)	10.8 (9.9, 11.8)
	GMTR (95% CI)	N/A	0.92 (0.85, 0.98)	0.93 (0.85, 1.01)
At Day 29 humoral immune response in adolescents is non-inferior to adults, as assessed by Vaccinia specific PRNT GMT	n	310	210	134
	GMT (95% CI)	51.1 (45.6, 57.4)	44.4 (37.3, 53.0)	45.7 (36.9, 56.7)
	GMTR (95% CI)	N/A	1.15 (0.93, 1.42)	1.12 (0.88, 1.43)
At peak (any day post-dose 1) humoral immune response in adolescents is non-inferior to adults, as assessed by Vaccinia specific PRNT GMT	n	313	211	135
	GMT (95% CI)	450.6 (404.1, 502.4)	295.0 (249.8, 348.3)	285.8 (230.8, 353.8)
	GMTR (95% CI)	N/A	1.53 (1.25, 1.86)	1.58 (1.24, 2.00)
	p-value[a]	N/A	<0.001	<0.001
	Non-inferiority result[b]	N/A	Yes	Yes

Abbreviations: N = Number of participants in the mITT Population.
n = Number of participants with data at time point.
CI , calculated using Student's t distribution for GMT and Welch Satterthwaite t test for GMTR.
a Two-sample t-test with unequal variance, noninferiority (NI) margin of 0.67 and two-sided type I error rate of 0.05 to test the null hypothesis that humoral immune response in adolescents will be non-inferior to adults.
b If the lower bound of the GMTR 95% CI is greater than or equal to 0.67 (NI=0.174 log10 scale) prior to rounding, the result is "Yes".
[c] Arms 3 and 4 were combined as a comparator group in the primary analysis. Arm 3 participants were excluded for a s ensitivity analysis.

Most adolescents (82.6%) had already shown seroconversion in terms of vaccinia virus-specific neutralizing antibodies compared to 75.2% of adults 28 days post Dose 1. At Day 43, 14 days after Dose 2, seroconversion rates were similar in adolescents (99%) and adults (97.6%) (see Table 6).

Table 6: Vaccinia Virus Specific PRNT Geometric Mean Fold Rise (GMFR) and Seroconversion Results by Time Point and Age Group, mITT Population

Time Point	Statistic	Adolescents (N=315)	Adults[c] (N=211)	Adults - Arm 4 Only (N=135)
Study Day 29 (Pre-Dose 2)	n	310	210	134
	GMFR[a] (95% CI)	5.1 (4.5, 5.7)	4.1 (3.5, 4.7)	4.2 (3.5, 5.1)
	% with Seroconversion[b] (95% CI)	82.6 (77.9, 86.6)	75.2 (68.8, 80.9)	76.9 (68.8, 83.7)
Study Day 43 (Post Dose 2)	n	304	208	132
	GMFR[a] (95% CI)	46.9 (42.1, 52.3	26.7 (22.9, 31.3)	27.3 (22.4, 33.3)
	% with Seroconversion[b] (95% CI)	99.0 (97.1, 99.8)	97.6 (94.5, 99.2)	97.7 (93.5, 99.5
Peak Anytime Post Dose 1	n	313	211	135
	GMFR[a] (95% CI)	45.0 (40.3, 50.1	26.9 (23.0, 31.6)	26.4 (21.6, 32.4)
	% with Seroconversion[b] (95% CI)	99.4 (97.7, 99.9)	97.2 (93.9, 98.9)	97.0 (92.6, 99.2)

Abbreviations: N=Number of participants in the mITT Population.
n= Number of participants with data at time point.
CI, calculated using Student's t distribution for GMFR and Clopper-Pearson methodology for Seroconversion.
[a]GMFR represents the geometric mean fold rise in antibody for the corresponding time point compared to pre-dose 1.
[b]Seroconversion represents the percentage of participants with at least a 2-fold rise in antibody titre compared to pre-dose 1 if any detectable result at pre-dose 1 or any detectable result if result < LLOD at pre-dose 1.
[c]Arms 3 and 4 were combined as a comparator group in the primary analysis. Arm 3 participants were excluded for a sensitivity analysis.

Mpox virus specific response

At Day 43, 14, days after Dose 2, adolescents (GMT: 9.8 [95% CI: 9.6, 10.0]) had similar immune responses to adults (GMT: 10.0 [95% CI: 9.6, 10.4]) for mpox virus PRNT (see table 7).

However, the majority of immune responses were below the LLOD of the assay, and most study participants did not show seroconversion for mpox-specific PRNT (see table 8). The PRNT assay used to measure mpox-specific neutralizing antibodies, although optimized, is not considered fully validated.

Table 7: Monkeypox Virus Specific PRNT Hypothesis Testing, mITT Population

Hypothesis	Statistic	Adolescents (N=313)	Adults[c] (N=211)	Adults - Arm 4 Only (N=135)
At Day 1 humoral immune baseline in adolescents is similar to adults, as assessed by Monkeypox specific PRNT GM	n	313	211	135
	GMT (95% CI)	9.5 (-)	9.7 (9.5, 9.9)	9.8 (9.5, 10.1)
	GMTR (95% CI)	N/A	0.98 (0.96, 1.00)	0.97 (0.94, 1.00)
At Day 43 humoral immune response in adolescents is non-inferior to adults, as assessed by Monkeypox specific PRNT GMT	n	303	208	132
	GMT (95% CI	9.8 (9.6, 10.)	10.0 (9.6, 10.4)	10.0 (9.5, 10.6)
	GMTR (95% CI)	N/A	0.98 (0.94, 1.02)	0.97 (0.92, 1.03)
	p-value[a]	N/A	<0.001	<0.001
	Non-inferiority result[b]	N/A	Yes	Yes

Abbreviations: N=Number of participants in the mITT Population.
n=Number of participants with data at time point.
CI=Confidence Interval, calculated using Student's t distribution for GMT and Welch-Satterthwaite t test for GMTR.
[a]Two-sample t-test with unequal variance, NI margin of 0.67 and two-sided type I error rate of 0.05 to test the null hypothesis that humoral immune response in adolescents will be non-inferior to adults.
[b]If the lower bound of the GMTR 95% CI is greater than or equal to 0.67 (NI=0.174 log10 scale) prior to rounding, the result is "Yes".
[c]Arms 3 and 4 were combined as a comparator group in the primary analysis. Arm 3 participants were excluded for a sensitivity analysis

Table 8: Monkeypox Virus Specific PRNT GMFR and Seroconversion Results by Time Point and Age Group, mITT Population

Time Point	Statistic	Adolescents (N=315)	Adults[c] (N=211)	Adults - Arm 4 Only (N=135)
Study Day 43 (Post Dose 2)	n	303	208	132
	GMFR[a] (95% CI)	1.0 (1.0, 1.0)	1.0 (1.0, 1.1)	1.0 (1.0, 1.1)
	% with Seroconversion[b] (95% CI)	3.0 (1.4, 5.6)	3.4 (1.4, 6.8)	3.0 (0.8, 7.6)

Abbreviations: N=Number of participants in the mITT Population.
n=Number of participants with data at time point.
CI, calculated using Student's t distribution for GMFR and Clopper-Pearson methodology for Seroconversion.
[a]GMFR represents the geometric mean fold rise in antibody for the corresponding time point compared to pre-dose 1.
[b]Seroconversion represents the percentage of participants with at least a 2-fold rise in antibody titre Compared to pre-dose 1 if any detectable result at pre-dose 1, or any detectable result if result < LLOD at pre-dose 1.
[c]Arms 3 and 4 were combined as a comparator group in the primary analysis. Arm 3 participants were excluded for a sensitivity analysis.

2.4.1. Discussion on clinical efficacy

The overall demographics for the purpose of the study is acceptable. The PRNT response of anti-vaccinia neutralising antibodies induced by MVA-BN in non-human primate animal models challenged with mpox formed the basis for the approval of MVA-BN as mpox vaccine. Therefore, direct comparison of anti-vaccinia neutralising antibodies in adults versus adolescents in order to infer effectiveness is acceptable in this procedure.

The seroconversion rates in terms of vaccinia virus-specific neutralizing antibodies observed in this study in adolescents and adults at 14 days post Dose 2 were in the range of those reported earlier at this timepoint in vaccinia-naïve healthy adults. Previously estimated seroconversion rates by PRNT in healthy adults, range 77.2- 99.8% 14 days post Dose 2 compared with 97.6% in adults and 99% in adolescents in the DMID study.

Although no response was detected in this study in terms of mpox-specific neutralizing antibodies, both in adolescent and in adults, the PRNT that was used is not fully validated. Of note, MVA-BN was shown protective against mpox in the 2022 mpox outbreak with effectiveness estimates ranging 66-90% for a 2-dose regimen, based on consistent data from several effectiveness studies in the systematic literature review conducted by BN (i.e. Payne et al. 2022; Bertran et al. 2023; Brousseau et al. 2023; Dalton et al. 2023; Deputy et al. 2023; Fontán-Vela et al. 2023; Montero Morales et al. 2023a; Ramchandani et al. 2023; Rosenberg et al. 2023; Schildhauer et al. 2023) as already reflected in the SmPC section 5.1.

2.4.2. Conclusions on the clinical efficacy

In adolescents, MVA-BN elicited a high vaccinia virus-specific neutralizing immune response that was non-inferior to that mounted by adults, with GMTs at Day 14 post Dose 2 that were higher than in adults. Given the correlation between the immune response and protective effectiveness, it may be inferred that MVA-BN will provide at least similar protection in adolescents than in adults against disease.

The vaccinia virus-specific PRNT GMT in adolescents was greater than the GMT in adults on Day 43 (Adolescent GMT: 470.3 [95% CI: 422.3, 523.8]; Adult GMT: 293.2 [95% CI: 249.8, 344.2]). Confidence intervals do not overlap. Non-inferiority of vaccination with MVA-BN in adolescents versus adults was demonstrated. GMP values and seroconversion rates at different timepoints after vaccination with MVA-BN are greater in the adolescent population than in the adult population.

Given the high and non-inferior result to adults' immune response mounted by adolescents in the validated vaccinia virus-specific PRNT assay, which is identical to that used for initial MAA, the protective efficacy of MVA-BN in adolescents may be inferred.

The following post-authorisation measure (REC) is considered necessary to address issues related to efficacy:

While PRNT values against vaccinia virus are acceptable for this procedure to infer effectiveness from a healthy adult population to other populations it is highly recommended to develop PRNT assays against mpox, both clade 1 and clade 2. Values from these assays could inform on potential differences in the cross-protection of MVA-BN against mpox viruses. Additionally, or alternatively other assays should be explored for their use, e.g. a binding assay.

2.5. Clinical safety

Introduction

Clinical safety has been presented in the clinical overview and in the interim report, comparing the safety profile of adolescents and adults. The submitted interim data package includes safety data reported through Study Day 210 (180 days Post Dose 2). At the time of the submission, study DMID 22-0020 is still ongoing. Data up to Study Day 57 are clean. Data after Study Day 57 are as reported. No raw data is available. Further, long-term data are yet open. However, no specific risk beyond the known safety-profile of similar vaccines has been identified based on the available safety data. The complete data package including the final CSR and the updated RMP is expected to be submitted by 30-May-2025.

Patient exposure

As of the data cut-off date, the study was fully enrolled with a total of 526 participants: 315 adolescents and 211 adults (76 adults from Stage 1 [Arm 3] and 135 adults from Stage 2 [Arm 4]). All enrolled participants completed their first dose and 99% completed their second dose.

Adverse events

Reactogenicity was measured from the time of each study vaccination through 7 days after each study vaccination by the occurrence of solicited AEs, including systemic and injection site (local) events. Systemic AEs included fever, chills, nausea, headache, fatigue, change in appetite, myalgia, and arthralgia. Local AEs included pain at the injection site, erythema/redness, induration/swelling, and pruritis at the injection site.

Unsolicited, non-serious AEs were collected from the time of each study vaccination through approximately 28 days after each study vaccination. MAAEs, UPs and AESIs were collected from the time of the first study vaccination through approximately 181 days after the last study vaccination.

In view of historical reports of cardiac AEs during the 2002-2004 smallpox vaccination campaign of military personnel and civilian first responders conducted in the US with 2 vaccines (Dryvax and ACAM2000) (Cassimatis, 2004), cardiac-related signs or symptoms were monitored as AESIs during the clinical development of MVA-BN. Based on MVA-BN Phase 3 safety results, there were no pre-specified AESIs in Stage 1 of the clinical study conducted in adults. In study Stage 2, which involves adolescent participants, monitoring for protocol specified AESI is part of the study as less is known about the safety profile in this population. In addition, an exclusion criterion for adolescents and adults with relevant cardiac history that could place them at risk was added in Stage 2. For study Stage 2, a protocol specified AESI is defined as a case of myocarditis or pericarditis; AESIs are to be collected from Day 1 through 210.
Cardiac AESIs were monitored for MVA-BN. In 22 studies, cardiac AESIs were reported to occur in 1.3% (95/7,093) of MVA-BN recipients and in 0.2% (3/1,206) of placebo recipients who were smallpox vaccine naïve. The higher proportion of MVA-BN recipients who experienced cardiac AESIs was driven by cases of asymptomatic postvaccination elevation of troponin I, the clinical significance of which is unknown.

SAEs are collected from time of first study vaccination through end of study. The MAAE, UP, AESI, and SAE reporting periods are still ongoing at the time of this interim analysis.

All AEs or SAEs were assessed for severity, according to the FDA toxicity grading scale (FDA, 2007). For AEs not included in the protocol-defined grading scale, specific scale used to assess severity is defined.

Results

Solicited Adverse Events

The overall frequency of solicited systemic AEs after either vaccination was similar in adolescents (74%) and adults (73%). Likewise, the overall frequency of solicited local AEs after either vaccination was similar in adolescents (88%) and adults (91%).

The most frequently reported systemic AE was fatigue (52% and 56% in adolescents and adults, respectively), followed by headache (50% and 49%) and myalgia (40% and 38%). The most frequently reported local AE was pain at injection site (74% and 81% in adolescents and adults, respectively), followed by erythema/redness (61% in adolescents and 66% in adults).

In both age groups, frequencies of individual solicited systemic and local AEs were similar after Dose 1 and after Dose 2.

Unsolicited Adverse Events

Among adolescents, 64% (201 out of 315) experienced at least one unsolicited AE, compared to 70% of adults (147 out of 211).

At least one related unsolicited AE was reported by 49 % of adolescents (154 out of 315) and 59% of adults (125 out of 315). The majority of related unsolicited AEs were mild (Grade 1) and there were no related, severe (Grade 3) unsolicited AEs.

In adolescents, within 28 days post either dose, the majority of reported unsolicited AEs judged as related to study vaccination were represented by injection site conditions (193 events in 140 out of 315 participants or 44%).

There were 17 events (in 17 participants) of injection site nodules and 13 events (in 13 participants) of injection site discoloration that were associated with Dose 1 but not observed until Post Dose 2. When considering either vaccination, there were 131 events injection site nodule in 117/315 participants or 37%, and 56 events injection site discoloration in 52/315 participants or 17%.

In adults, the most frequently reported unsolicited AEs judged as related to study vaccination were also injection site conditions (212 events in 122 out of 211 participants or 58%). The most common PT for both doses was injection site nodule (Post Dose 1: 96 events in 96/211 participants or 45%; Post Dose 2: 52 events in 50/211 participants or 24%). There were 10 events (in 10 participants) of injection site nodules and 11 events (in 11 participants) of injection site discoloration that were associated with Dose 1 but not observed until Post Dose 2. When considering either vaccination, there were 148 events of injection site nodule in 112/211 participants or 53% and 61 events of injection site discoloration in 46/122 participants or 22%.

Other related unsolicited AEs were reported by ≤1% of adolescents.

Adolescents reported AEs of dizziness judged as related to study vaccination more frequently than adults (9 events in 8 out of 315 or 3% of adolescent participants; no dizziness events reported from adult participants). Seven events were associated with Dose 1, and 2 events were associated with Dose 2. Seven of the nine events occurred on the day of vaccination or the following day. None of these events resulted in syncopal episodes, and none required medical intervention or lead to discontinuation of study product.

Table 9: Summary of AEs

		Adolescents (N=315)		Adults (N=211)		All Participants (N=526)	
Event Category[a]	**Subcategory**	**n**	**%**	**n**	**%**	**n**	**%**
At least one local solicited adverse event	Any Severity	277	88	193	91	470	89
At least one systemic solicited adverse event	Any Severity	234	74	154	73	388	74
At least one unsolicited adverse event	Any Severity	201	64	147	70	348	66
At least one related unsolicited adverse event	Any Severity	154	49	126	60	280	53
	Mild (Grade 1)	146	46	122	58	268	51
	Moderate (Grade 2)	10	3	10	5	20	4
	Severe (Grade 3)	-	-	-	-	-	-
At least one severe (Grade 3) unsolicited adverse event	Any Relatedness	3	<1	2	<1	5	<1
	Related	-	-	-	-	-	-
	Not Related	3	<1	2	<1	5	<1
At least one serious adverse event	Any Severity	-	-	2	<1	2	<1
At least one related, serious adverse event	Any Severity	-	-	-	-	-	-
At least one adverse event leading to study withdrawal[b]	Any Severity	-	-	-	-	-	-
At least one adverse event leading to discontinuation of study product[b]	Any Severity	2	<1	3	1	5	<1
At least one medically attended adverse event (MAAE)	Any Severity	34	11	19	9	53	10
At least one unanticipated problem (UP)	Any Severity	-	-	-	-	-	-
At least one suspected unexpected serious adverse reaction (SUSAR)	Any Severity	-	-	-	-	-	-

Abbreviations: N = Number of participants in the Safety Population.
n=Numberoof participants meeting the row criteria.
[a]Participants are counted once for each category regardless of the number of events.
[b]As reported on the Adverse Event eCRF

Number and Percentage of Participants Experiencing *Solicited Events* with 95% Confidence Intervals by Symptom, Dose, and Age Group are presented in the table 10.

Table 10: Number and Percentage of subjects experiencing solicited AEs

	Post Dose 1 Adolescents (N=315)			Post Dose 1 Adults (N=21			Post Dose 2 Adolescents (N=312			Post Dose 2 Adults (N=207)			Post Either Dose Adolescents (N=315)			Post Either Dose Adults (N=211)		
Symptom	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**
Any Symptom	275	87	83, 91	186	88	83, 92	263	84	80, 88	186	90	85, 94	294	93	90, 96	200	95	91, 97
Any Systemic Symptom	201	64	58, 69	134	64	57, 70	165	53	47, 59	110	53	46, 60	234	74	69, 79	154	73	66, 79
Fever	7	2	1, 5	4	2	1, 5	6	2	1, 4	5	2	1, 6	13	4	2, 7	9	4	2, 8
Chills	25	8	5, 11	23	11	7, 16	28	9	6, 13	19	9	6, 14	44	14	10, 18	35	17	12, 22
Nausea	49	16	12, 20	19	9	6, 14	47	15	11, 20	26	13	8, 18	75	24	19, 29	39	18	13, 24
Headache	122	39	33, 44	82	39	32, 46	97	31	26, 37	57	28	22, 34	156	50	44, 55	103	49	42, 56
Fatigue	132	42	36, 48	95	45	38, 52	98	31	26, 37	81	39	32, 46	164	52	46, 58	119	56	49, 63
Change in appetite	41	13	10, 17	20	9	6, 14	26	8	6, 12	19	9	6, 14	55	17	13, 22	30	14	10, 20
Myalgia	90	29	24, 34	51	24	19, 31	79	25	21, 31	55	27	21, 33	127	40	35, 46	80	38	31, 45
Arthralgia	34	11	8, 15	23	11	7, 16	27	9	6, 12	20	10	6, 15	51	16	12, 21	36	17	12, 23
Any Local Symptom	244	77	72, 82	172	82	76, 87	248	79	75, 84	177	86	80, 90	277	88	84, 91	193	91	87, 95
Erythema/redness	119	38	32, 43	92	44	37, 51	162	52	46, 58	121	58	51, 65	192	61	55, 66	140	66	60, 73
Induration/swelling[a]	101	32	27, 38	92	44	37, 51	144	46	41, 52	110	53	46, 60	178	57	51, 62	131	62	55, 69
Pruritus	96	30	25, 36	78	37	30, 44	127	41	35, 46	103	50	43, 57	158	50	44, 56	123	58	51, 65

Abbreviations N = Number of participants in the Safety Population for the given age group that received the specified dose.
n = Number of participants meeting the row criteria.
CI = Confidence interval, calculated using Clopper-Pearson methodology.
[a] Graded according to SAP v1.0 Table 6.

Unsolicited AEs are presented in the Table 11 and Table 12. Adolescents and adults are separated in two tables.

Table 11: Related unsolicited AEs within 28ds post dose, Adolescents

		Within 28 Days Post Dose 1			Within 28 Days Post Dose 2			Within 28 Days Post Either Dose		
MedDRA System Organ Class	**MedDRA Preferred Term**	**n**	**%**	**Events**	**n**	**%**	**Events**	**n**	**%**	**Events**
Any SOC	Any PT	120	38	141	57	18	76	154	49	217
Blood and lymphatic system disorders	Lymphadenopathy	2	<1	2	2	<1	2	4	1	4
Gastrointestinal disorders	Vomiting	-	-	-	1	<1	1	1	<1	1
General disorders and administration site conditions	Any PT	110	35	127	51	16	66	140	44	193
	Injection site discolouration	33	10	33	23	7	23	52	17	56
	Injection site haemorrhage	-	-	-	1	<1	1	1	<1	1
	Injection site macule	1	<1	1	1	<1	1	2	<1	2
	Injection site nodule	92	29	92	32	10	39	117	37	131
	Injection site rash	-	-	-	2	<1	2	2	<1	2
	Injection site warmth	1	<1	1	-	-	-	1	<1	1
Infections and infestations	Any PT	2	<1	2	1	<1	1	3	<1	3
	Herpes zoster reactivation	-	-	-	1	<1	1	1	<1	1
	Pharyngitis	2	<1	2	-	-	-	2	<1	2
Musculoskeletal and connective tissue disorders	Myalgia	-	-	-	1	<1	1	1	<1	1
Nervous system disorders	Any PT	8	3	8	4	1	5	11	3	13
	Dizziness	7	2	7	2	<1	2	8	3	9
	Headache	-	-	-	1	<1	1	1	<1	1
	Hypoaesthesia	-	-	-	1	<1	1	1	<1	1
	Paraesthesia	-	-	-	1	<1	1	1	<1	1
	Presyncope	1	<1	1	-	-	-	1	<1	1
Respiratory, thoracic and mediastinal disorders	Rhinorrhoea	1	<1	1	-	-	-	1	<1	1
Skin and subcutaneous tissue disorders	Petechiae	1	<1	1	-	-	-	1	<1	1

Abbreviations: N =Number of participants in the Safety Population.
n = number of participants who began to experience the given PT within 28 days of a given dose regardless of associated dose.
For each timepoint, a participant is only counted once per PT.
17 events n 17 participants with PT of Injection site nodule and 13 events in 13 participants with PT of Injection site discolouration associated with Dose 1 injection site were not observed until Post Dose 2 and are counted in Within 28 Days Post Dose 2' column

Table 12: Related unsolicited AEs within 28ds post dose, Adults

		Within 28 Days Post Dose 1			Within 28 Days Post Dose 2			Within 28 Days Post Either Dose		
MedDRA System Organ Class	**MedDRA Preferred Term**	**n**	**%**	**Events**	**n**	**%**	**Events**	**n**	**%**	**Events**
Any SOC	Any PT	104	49	131	70	33	96	125	59	227
Blood and lymphatic system disorders	Lymphadenopathy	2	<1	2	2	<1	2	4	2	4
Gastrointestinal disorders	Vomiting	1	<1	1	-	-	-	1	<1	1
General disorders and administration site conditions	Any PT	101	48	124	65	31	88	122	58	212
	Injection site discolouration	27	13	27	31	15	34	46	22	61
	Injection site haemorrhage	1	<1	1	-	-	-	1	<1	1
	Injection site nodule	96	45	96	50	24	52	112	53	148
	Injection site rash	-	-	-	1	<1	1	1	<1	1
	Oedema peripheral	-	-	-	1	<1	1	1	<1	1
Injury, poisoning and procedural complications	Immunisation reaction	1	<1	1	1	<1	1	2	<1	2
Musculoskeletal and connective tissue disorders	Muscle spasms	1	<1	1	-	-	-	1	<1	1
Nervous system disorders	Balance disorder	-	-	-	1	<1	1	1	<1	1
Reproductive system and breast disorders	Menstruation irregular	1	<1	1	-	-	-	1	<1	1
Respiratory, thoracic and mediastinal disorders	Any PT	-	-	-	2	<1	2	2	<1	2
	Asthma	-	-	-	1	<1	1	1	<1	1
	Throat irritation	-	-	-	1	<1	1	1	<1	1
Skin and subcutaneous tissue disorders	Any PT	1	<1	1	2	<1	2	3	1	3
	Night sweats	-	-	-	1	<1	1	1	<1	1
	Psoriasis	-	-	-	1	<1	1	1	<1	1
	Urticaria	1	<1	1	-	-	-	1	<1	1
.										

Abbreviations: N = Number of participants in the Safety Population.
n = Number of participants who began to experience the given PT within 28 days of a given dose regardless of associated dose.
For each time point, a participant is only counted once per PT.
11 events in 11 participants with PT of Injection site discolouration and 10 events in 10 participants with PT of Injection site nodule associated with Dose 1 injection site were not ob served until Post Dose 2 and are counted in 'Within 28 Days Post Dose 2' column

Serious adverse event/deaths/other significant events

No SAEs have been reported in the adolescent age-group (for comparison: 2 out of 211 in the adult age-group).

34 Adolescents (11%) experienced at least one medically attended AE compared to 19 (9%) adults.

Discontinuation due to adverse events

AEs in 2 adolescents were leading to discontinuation. No further information available.

2.5.1. Discussion on clinical safety

Inclusion and Exclusion Criteria meet current standards. Of note, for Stage 2, adolescent or adult participant who had a history of myocarditis/pericarditis or a history of structural congenital heart defect/cardiac dysrhythmia with increased risk to the participant, are excluded. Myocarditis

(Pericarditis and associated symptoms are reflected in the protocol as AESIs). Reason is an associated moderate risk of myo-/pericarditis for ACAM2000, a second-generation smallpox vaccine, derived from a clone of Dryvax, purified, and produced using modern cell culture technology, currently approved in several non-EU countries for active immunisation against smallpox disease. Further, for the first-generation smallpox-vaccine (Dryvax), being used during the 2002-2004 smallpox vaccination campaign to protect military personnel and civilian first-responders, there were high rates of pericarditis and myocarditis reported among those vaccinated with Dryvax. Similarly, high rates were detected after receipt of ACAM2000.

The available subject-number (315 adolescents) is too low for addressing rare risks, e.g. cardiovascular risks as identified with other smallpox-vaccines in the past. Cardiovascular risk is yet addressed in the RMP and will be followed, respectively.

The overall Summary of AEs (Table 9) presents a similar safety profile on a high level of comparison for adults and adolescents. Of note, no SAEs have been reported.

The majority of AEs refers to local and systemic *solicited* Events. The presented comparison of respective AEs in adolescents and adults is similar with no major differences. Regarding Injection site reactions, an overall high number of "any local symptom" (88/91% adolescents/adults) has been presented as expected. However, Table 11 "Related Unsolicited AEs" reflects even more administration site conditions (covering Injection site discolouration, haemorrhage, macule, nodule, rash, and warmth). These should be further analysed as soon as final CSR is available.

Safety profile will be further characterised when the final CSR is submitted since the study is still ongoing. Nervous system disorders, cardiac disorders and other relevant medical conditions are awaited to be addressed within the final CSR. Further, Gastrointestinal disorders should be presented, comparatively (adolescents versus adults) with the final CSR submission.

As a result, an additional SOB regarding the ongoing study DMID 22-0020 is requested. Final CSR should be provided by 30-May-2025.

2.5.2. Conclusions on clinical safety

The available clinical safety has been presented in the clinical overview, comparing the safety profile of adolescents and adults. Respective study DMID 22-0020 is still ongoing and the presented data are interim data. Data up to Study Day 57 are clean. Data after Study Day 57 are as reported. However, no specific risk beyond the known safety-profile of similar vaccines has been identified.

The following measure (SOB) is considered necessary to address issues related to safety:

In order to further characterise the safety information of Imvanex in adolescents 12 to 17 years of age, the applicant should submit by 30-May-2025 the final clinical study report of study DMID 22-0020:

- A Phase 2 Randomised, Open-Label, Multisite Trial to Inform Public Health Strategies Involving the Use of MVA-BN Vaccine for mpox.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Update of the Product information

The CHMP adopted a new indication (section 4.1) and the updated indication is now as follows:

> *"Active immunisation against smallpox, monkeypox and disease caused by vaccinia virus in individuals 12 years of age and older ~~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 4.2, 4.8 and 5.1 have also been updated. The Package Leaflet has been updated accordingly. Changes were also made to the PI to bring it in line with the current Agency/QRD template.

Annex II is updated to refer to the new specific obligation.

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

2.6.1. 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.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

After smallpox has been eradicated, mpox has become the most significant orthopoxvirus that causes infection and disease in humans. The clinical course of mpox is similar to smallpox, although milder and with a significantly lower-case fatality rate. Mpox is endemic in Western and Central Africa.

In May-2022, a multi-country mpox clade II outbreak spread to previously several non-endemic countries. The outbreak widened globally, and in July 2022, WHO declared mpox a PHEIC for the first time. In May 2023, significant progress was made in controlling the outbreak and the PHEIC status was removed.

On 15 August 2024, Sweden became the first country outside the African continent to confirm mpox clade I in an individual with travel history to central Africa. The confirmation of the case came just one day after WHO declared mpox a PHEIC for the second time in 2 years, following an upsurge in new and concerning cases in the DRC and several neighbouring countries, including the emergence of a new strain, clade Ib, which appears to be more severe than clade II.

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 mpox viruses, and disease (pox lesions) caused by such orthopoxviruses may be less frequent and shows less spread across the body.

3.1.2. Available therapies and unmet medical need

In the EU, Imvanex is a vaccine approved to protect against smallpox (2013) and mpox and disease caused by the vaccinia virus (2022) in adults. Currently, there is no vaccine licensed specifically for patients below 18 years of age.

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

3.1.3. Main clinical studies

To support the current EoI, the MAH submitted interim results of the ongoing Study DMID 22-0020. This study is an open label, comparative, multicentre immunogenicity and safety study conducted in the US. The primary immunogenicity objective of study Stage 2 was to determine if peak humoral immune responses in adolescents ages 12 to 17 years following MVA-BN regimen administered SC is non-inferior to the response in adults ages 18 to 50 years. The associated endpoint was vaccinia virus specific PRNT GMT at Day 43. This interim analysis was performed based on data up to cut-off date, 22 February 2024, which includes immunogenicity data up to Study Day 43 (14 days Post Dose 2) and safety data reported through Study Day 210 (180 days Post Dose 2).
Data up to Study Day 57 are clean. Data after Study Day 57 are as reported. The MAH is requested to submit by 30-May-2025 the final CSR of study DMID 22-0020.

3.2. Favourable effects

In adolescents 12-17 years of age, MVA-BN elicited a high vaccinia virus-specific neutralizing immune response that was non-inferior to that mounted by adults, with GMTs at Day 14 post Dose 2 that were higher than in adults. Given the correlation between the immune response and protective effectiveness, it is inferred that MVA-BN will provide at least similar protection in adolescents than in adults against disease.

The seroconversion rates in terms of vaccinia virus-specific neutralizing antibodies observed in this study in adolescents and adults at 14 days post Dose 2 were in the range of those reported earlier at this timepoint in vaccinia-naïve healthy adults. Previously estimated seroconversion rates by PRNT in healthy adults, range 77.2- 99.8% 14 days post Dose 2 compared with 97.6% in adults and 99% in adolescents in the DMID study.

Clinical safety has been presented in the clinical overview, comparing the safety profile of adolescents and adults. No specific risks beyond the known safety-profile of similar vaccines has been identified.

3.3. Uncertainties and limitations about favourable effects

While PRNT values against vaccinia virus are acceptable for this procedure to infer effectiveness from a healthy adult population to other populations it is highly recommended to better characterize mpox-specific response developing PRNT assays against mpox, both clade 1 and clade 2. Values from these assays could inform on potential differences in the cross-protection of MVA-BN against mpox viruses. Additionally, or alternatively other assays should be explored for their use, e.g. a binding assay.

Respective study DMID 22-0020 is still ongoing and the presented data are interim data. No specific risk beyond the known safety-profile of similar vaccines has been identified.

3.4. Unfavourable effects

The presented comparison of respective AEs in adolescents and adults appears similar with no major differences (see tables 9 and 10). Regarding Injection site reactions, an overall high number of "any local symptom" (88/91% adolescents/adults) has been presented as expected. However, there are more administration site reactions (covering skin discolouration, haemorrhage, macule, nodule, rash, and warmth). Taken together, there are no major risks identified to date.

3.5. Uncertainties and limitations about unfavourable effects

Regarding Injection site reactions, further analyses are expected as soon as final data are available. Safety profile of Imvanex in adolescents 12 to 17 years of age will be further characterised when the final CSR as well as the RMP are submitted by 30 May 2025 since the study is still ongoing and further data cleaning is expected. Nervous system disorders, cardiac disorders and other relevant medical conditions are awaited to be addressed within the final CSR. Further, gastrointestinal disorders should be presented, comparatively (adolescents versus adults) for further discussion as soon as final data are available.

3.6. Effects Table

Table 13: Effects Table for Imvanex for active immunisation against smallpox, monkeypox and disease caused by vaccinia virus in individuals 12 to 17 years of age

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Protection (Study Day 43)	The protective efficacy of MVA-BN in this age group is inferred from adults	-	Imvanex	Yes	MVA-BN elicited vaccinia virus-specific neutralizing immune response that was non-inferior to that mounted by adults	Study DMID 22-0020
Unfavourable Effects						
Safety profile	There are more administration site reactions (covering Injection site skin discolouration, haemorrhage, macule, nodule, rash, and warmth) than in adults.	-	Imvanex	Yes	Safety will be further characterised when the final CSR is submitted	Study DMID 22-0020

Abbreviations: MVA-BN: Modified Virus Ankara-Bavarian Nordics, AE: Adverse Events.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

In adolescents 12-17 years of age, MVA-BN elicited a vaccinia virus-specific neutralizing immune response that was non-inferior to that mounted by adults. Given the correlation between the immune response and protective effectiveness, it may be inferred that MVA-BN will provide at least similar protection in adolescents than in adults against disease.

Regarding unfavourable effects, Imvanex is found well-tolerated in healthy 12-17 years of age patients according to the interim data from the currently ongoing study DMID 22-0020 with a mainly similar safety-profile in adolescents as in adults. According to the current database, the most frequent injection site reaction was injection site pain (>70%), and the most frequent systemic adverse reactions were fatigue (> 50%) and headache (50%). However, data after Study Day 57 are as reported in the interim report. Since the study is still ongoing, safety profile will be further characterised when the final CSR is submitted.

Given the current PHEIC as declared by WHO, it is considered that the identified safety uncertainties of Imvanex in adolescents 12 to 17 years of age can be addressed post-authorisation, through the submission of the final CSR for the ongoing study DMID 22-0020 (SOB).

3.7.2. Balance of benefits and risks

Taking into account the neutralizing immune response that was non-inferior to that mounted by adults and that the overall safety profile of adolescents is comparable to the adults, the benefit risk profile of Imvanex for prevention of smallpox, mpox and disease caused by vaccinia virus in individuals 12 to 17 years of age, is considered favourable.

Therefore, approval of Imvanex extension of indication to adolescents from 12 to 17 years of age is recommended.

3.8. Conclusions

The overall benefit-risk of Imvanex is positive.

4. Recommendations

Outcome

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 and IIIB

Extension of indication to include active immunisation of adolescents from 12 to 17 years of age for

Imvanex based on interim results from study DMID 22-0020. This is a Phase 2 randomised open label multicentre trial to inform Public Health strategies involving the use of MVA-BN vaccine for mpox. As a consequence, sections 4.1, 4.2, 4.8, and 5.1 of the SmPC and Annex II.E are updated. The Package Leaflet is updated in accordance. Furthermore, the PI is brought in line with the latest QRD template version 10.4.

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

Amendments to the marketing authorisation

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

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan PIP P/0284/2023 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.