EMADOC-1700519818-2751582
Committee for Medicinal Products for Human Use (CHMP)

Type II group of variations assessment report

Procedure No. EMA/VR/0000316261

Invented name: IMVANEX

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

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

This application is in the area of: (Non-)Clinical RMP

Note

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

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Status of this report and steps taken for the assessment			
Current step	**Description**	**Planned date**	**Actual Date**
☐	Submission deadline	28 Nov 2025	28 Nov 2025
☐	Validation	28 Dec 2025	11 Dec 2025
☐	Start date	29 Dec 2025	29 Dec 2025
☐	CHMP Rapporteur AR	27 Jan 2026	30 Jan 2026
☐	PRAC Rapporteur AR	30 Jan 2026	30 Jan 2026
☐	PRAC comments	4 Feb 2026	4 Feb 2026
☐	Updated PRAC Rapporteur AR	5 Feb 2026	9 Feb 2026
☐	PRAC outcome	12 Feb 2026	12 Feb 2026
☐	CHMP comments	16 Feb 2026	16 Feb 2026
☐	Updated CHMP Rapporteur AR	19 Feb 2026	19 Feb 2026
☒	CHMP Outcome	26 Feb 2026	26 Feb 2026

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1. Background information on the procedure

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Bavarian Nordic A/S submitted to the European Medicines Agency on 28 November 2025 an application for group of variations.

The following changes were proposed:

Variation(s) requested		**Type**
C.I.4	C.I.4 Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet due to new quality, preclinical, clinical or pharmacovigilance data	Variation type II
A.6	A.6 Change in ATC Code / ATC Vet Code	Variation type IA

A grouped application as follows: Type II (C.I.4): Update of sections 4.8 and 5.1 in order to update clinical information based on the final clinical study report of study DMID 22-0020 stage 2, listed as a Specific Obligation in the Annex II. This is a Phase 2 randomized open label multisite trial to inform Public Health strategies involving the use of MVA-BN vaccine for Mpox. The Annex II and Package Leaflet are updated in accordance. The RMP version 11.1 has also been submitted. In addition, the MAH took the opportunity to introduce minor changes to the PI. Type IA (A.6): To change the ATC Code from 'other viral vaccines, ATC code: J07BX' to 'smallpox and monkeypox vaccines, ATC code: J07BX01'

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

2. Overall conclusion and impact on the benefit/risk balance

The extension of indication to adolescents from 12 to 17 years of age (procedure EMEA-H-C-002596-II-0108) was granted in September 2024 based on the interim analysis report of study DMID 22-0020 stage 2. This submission was done based in the interest of public health to contain the mpox outbreak at that time. As consequence of this procedure, a new specific obligation (SOB-004) was added to the Annex II Section E of Imvanex Product Information (PI) requesting the MAH to submit the final clinical study report (CSR) of the study to further characterise the safety information of Imvanex in adolescents. The current submission is intended to fulfil the SOB-004.

The interim analysis submitted in the procedure EMEA-H-C-002596-II-0108 was performed based on data up to cut-off date, 22 February 2024, which included safety data reported through Study Day 210 (180 days Post Dose 2) and immunogenicity data up to Study Day 43 (14 days Post Dose 2). Data up to Study Day 57 were considered clean. The study was fully enrolled with a total of 526 participants: 315 adolescents from Stage 2 [Arm 5] 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.

Efficacy

The plaque reduction neutralization test (PRNT) response of anti-vaccinia neutralizing antibodies induced by Modified Vaccinia Ankara – Bavarian Nordic (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 neutralizing antibodies in adults versus adolescents in order to infer effectiveness is acceptable.

The vaccinia virus-specific PRNT geometric mean titres (GMT) in adolescents from 12 to 17 years of age 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]). Therefore, non-inferiority of vaccination with MVA-BN in adolescents versus adults was demonstrated. Vaccinia virus-specific PRNT GMTs in the adolescent sub-groups from 12 to 14 years of age and from 15 to 17 years of age were similar with a trend to be higher in the 12 to 14 years of age sub-group.

For both adults and adolescents, a waning of humoral immunity was demonstrated to a similar extend, with a vaccinia virus-specific PRNT half-life of 166 day and 167 days in adolescents and adults, respectively.

Anti-MVA binding antibody analysis supports the vaccinia virus-specific PRNT analysis.

Safety

The overall summary of adverse events (AEs) presents a similar safety profile in a comparison of the adults and adolescents age groups.

During the follow-up phase after the interim analysis, 3 serious adverse events (SAEs) were reported in arm 5 adolescents, major depressive disorder (study day 231), pyelonephritis (study day 365), and infective myositis (study day 330). Two SAEs were reported in arm 4 adults, pyelonephritis (study day 319) and suicide ideation (study day 182). The SAEs were not considered related to the study product. This is agreed. No deaths were reported from clinical trial DMID 22-0020 (stage 2).

There were no cardiac AEs considered related to study vaccination, and in particular no reported cases of myocarditis / pericarditis which are classified as adverse events of special interest (AESIs) in this study. Two participants, one adolescent and one adult, reported mild AEs of tachycardia. However, the available subject-number (315 adolescents) is too low for addressing rare risks such as cardiovascular risks as identified with other smallpox-vaccines in the past.

There were two pregnancies in adolescent participants during the study that resulted in live births without congenital anomalies.

The majority of AEs refer to local and systemic solicited events. The presented comparison of respective AEs in adolescents and adults is similar with no major differences and occurred at similar frequencies after dose 1 and dose 2.

Within the adolescent sub-groups there is a slight trend of higher incidences of AEs in the 12 to 14 years age group.

Results from the clinical study demonstrated that MVA-BN was overall well-tolerated in adolescents aged 12 to 17 years of age with a safety and reactogenicity profile comparable to adults. No new or unexpected safety concerns were identified. Overall, the findings support the favourable safety profile of MVA-BN administration in the adolescent population.

Updates to SmPC sections 4.8 and 5.1. have been agreed to reflect the final study results of study DMID 22-0020 stage 2. The PL is updated accordingly. In addition, the deletion of the SOB-004 from the Annex II.E is agreed. The RMP has been updated accordingly.

The benefit-risk balance of IMVANEX remains positive.

3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation(s) requested		Type
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☒is recommended for approval.

Amendments to the marketing authorisation

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

4. EPAR changes

The table in the 'Steps after' module of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above

Summary

SmPC section 4.8.

Pharyngitis and presyncope are added with frequency rare to the adverse reactions table.

Adolescents 12-17 years

Data from Stage 2 of study DMID 22-0020 show a similar safety profile in adolescents as in adults. Stage 2 of the study enrolled 315 adolescents aged 12 to 17 years and 135 adults aged 18 to 50 years. The most frequent local adverse reaction was injection site pain (> 70%), and the most frequent systemic adverse reactions were fatigue (> 50%) and headache (50%). The reactogenicity was similar between younger (12 to 14 years of age) and older (15 to 17 years of age) adolescents.

SmPC section Section 5.1.

Study in adolescents 12-17 years

DMID 22-0020 was a phase 2, open-label, multisite trial in the US with a 2-fold purpose:

- To evaluate intradermal dose-sparing strategies in adults to extend the limited supply during the global public health crisis (DMID 22-0020 stage 1 - randomized)
- To evaluate the vaccine safety and immunogenicity among adolescents of 12 to 17 years of age to extend vaccination eligibility to the adolescent population (DMID 22-0020 stage 2).

The primary objective of stage 2 of DMID 22-0020 was to determine if peak humoral immune response in adolescents 12 to 17 years of age following SC administration of two 0.5 mL doses of MVA-BN 28 days apart is non-inferior to the response in adults 18 to 50 years of age who received two 0.5 mL doses of MVA-BN 28 days apart administered SC.

For the primary analysis, samples from adult participants from stage 1 (arm 3) and stage 2 were analysed together (211 participants) and compared to samples from adolescents from stage 2 (315 participants).

The majority of participants in the mITT population were seroconverted at day 43 (99.0% in adolescents and 97.7% in adults). The long-term seroconversion rates at day 210 were 82.9% in adolescents and 54.6% in adults and at day 394 were 81.5% in adolescents and 46% in adults.

For more information, please refer to the Summary of Product Characteristics.

Annex: Rapporteur’s assessment comments on the type II variation

5. Introduction

Bavarian Nordic A/S (BN) has developed a proprietary strain of vaccinia virus (MVA-BN) as a live, highly attenuated, non-replicating viral vaccine. MVA-BN is grown in chicken embryo fibroblast cells, harvested, concentrated, and purified.

MVA-BN is registered under the trade names IMVAMUNE in Canada, IMVANEX in the EU and UK, and JYNNEOS in Mexico, Singapore, Switzerland, and the US for use in adults as a vaccine for prevention of smallpox and mpox, as well as disease caused by vaccinia virus (VV) (in EU, UK, and Switzerland) or by other orthopoxviruses (in Canada and Mexico). MVA-BN is also approved for use in adolescents from 12 to 17 years of age in the EU.

The extension of indication to adolescents (procedure EMEA-H-C-002596-II-0108) was granted in September 2024 based on the interim analysis report. As consequence of this procedure, a new specific obligation (SOB-004) was added to the Annex II.E of the PI.

This submission is intended to fulfill the following IMVANEX specific obligation (SOB-004): "In order to further characterize the safety information of IMVANEX in adolescents 12 to 17 years of age, the MAH shall submit 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."

In addition, the company is taking this opportunity to update the ATC code from 'other viral vaccines, ATC code: J07BX' to 'smallpox and monkeypox vaccines, ATC code: J07BX01' (variation category A.6).

Stage 2 of clinical trial DMID 22-0020, sponsored by the US Division of Microbiology and Infectious Diseases (DMID) of the National Institutes of Health (NIH), was an open-label, comparative, multicenter immunogenicity and safety study of MVABN vaccine in adolescents 12 to 17 years of age (stage 2, arm 5) in comparison with adults 18 to 50 years of age (stage 1, arm 3 and stage 2, arm 4) in this study conducted in the US. The clinical efficacy data presented include only the subcutaneous (SC) administration of MVA-BN, therefore the results from the stage 1 intradermal (ID) administration (arms 1 and 2) are not included.

Stage 2 of clinical trial DMID 22-0020 was conducted from March 2023 to August 2024 in the US.

6. Clinical Efficacy aspects

6.1. Methods – analysis of data submitted

Overview of Clinical Trial DMID 22-0020

Study Design

This was a phase 2, open-label multi-site platform trial to evaluate strategies to inform public health decisions regarding the use of MVA-BN for mpox prevention and mitigation of outbreaks. As MVA-BN is also used for smallpox prophylaxis, this trial aimed to inform public health decisions on the use of the vaccine for smallpox. The trial was divided into stages according to public health needs and scientific

priorities. Public health strategies were evaluated in separate stages of the trial and included ID dose-sparing strategies and SC dosing in adults (stage 1) and extension of the target population for MVA BN to include adolescents (stage 2, SC administration), the focus of the information provided herein.

Stage 2 enrolled a population that was representative of the US population to ensure broad applicability of the study findings for use of MVA BN in adolescents. For this stage, the study recruited 315 healthy adolescents (161 adolescents aged 12 to 14 years and 154 adolescents aged 15 to 17 years) and 135 healthy adults aged 18 to 50 years between 22 Mar 2023 and 20 Jul 2023. All participants were smallpox or mpox vaccine naïve (licensed or investigational vaccines), and did not have a history of mpox, cowpox or vaccinia virus infections. The comparator group of adults for the non-inferiority testing of the primary immunogenicity endpoint in stage 2 included the 135 adults from stage 2 (arm 4) and an additional 76 adults from stage 1 (arm 3), totaling 211 adults. All participants included in stage 2 and stage 1 arm 3 analyses were assigned the same dose regimen. The study design for stages 1 and 2 is shown in Table 1.

Participants who received SC doses of MVA-BN received 2 injections of 0.5 mL on study days 1 and 29 (28 days apart) and were followed for a total of 365 days after the last dose in stage 2. There were 9 study visits (plus an optional screening visit) with the last visit approximately 1 year after the second study vaccination. Participants reporting a laboratory-confirmed case of mpox were seen at a sick visit.

Table 1: Stage 1 and 2 study design

Stage	Arm	Age in years	N	Dose of MVA-BN [a]	Route of Administration [b]
1 (Adult)	1	18 to 50	76	2×10^7 $TCID_{50}$ (0.1 mL)	Intradermal
	2		77	1×10^7 $TCID_{50}$ (0.05 mL)	Intradermal
	3		76	1×10^8 $TCID_{50}$ (0.5 mL)	Subcutaneous
2 (Adult and Adolescent)	4	18 to 50	135	1×10^8 $TCID_{50}$ (0.5 mL)	Subcutaneous
	5	12 to 17	315	1×10^8 $TCID_{50}$ (0.5 mL)	Subcutaneous

Abbreviations: Inf.U = infectious units; N = number of participants per group; $TCID_{50}$ = tissue culture infectious dose of virus required to infect 50% of host cells.

[a] The virus titer assay was changed from the $TCID_{50}$-based assay to the flow cytometry Infectious unit (Inf.U)-based assay. Equivalency of the 2 methods has been demonstrated, and thus the units can be used interchangeably. That is, the nominal titer of 1×10^8 $TCID_{50}$ MVA-BN per 0.5 mL corresponds to the licensed MVA-BN standard dose containing no less than 5×10^7 Inf.U per 0.5 mL dose.

[b] Subcutaneous administration in the upper arm on day 1 and 29. Intradermal administration in the volar aspect (inner side) of the forearm on day 1 and day 29.

Immunogenicity

Analysis Populations

Modified Intention-to-Treat (mITT) Population

The primary analysis population for immunogenicity summaries include all enrolled participants who received at least 1 dose of vaccine and contributed both pre- and at least 1 post-vaccination venous blood sample for immunogenicity testing for which valid results were reported.

Stage 1 arm 3 adults that received the same vaccination sequence were pooled with stage 2 arm 4 adults for the primary endpoint analysis only. Stage 2 arm 4 adults-only were analyzed in comparison

to stage 2 arm 5 adolescents as an additional sensitivity analysis to assess the impact of the inclusion of stage 1 adults on the primary non-inferiority analysis.

Per Protocol (PP) Population

Immunogenicity data from all or select visits for participants in the mITT population were excluded from sensitivity analysis in the PP population according to the following criteria:

- Data from all available visits for participants that were found to have been ineligible at baseline.
- Data from all visits on and after a protocol deviation that was considered to affect the science (as determined by the sponsor at an ad hoc meeting). Major protocol deviations included but were not limited to:
    - Did not receive second study vaccination,
    - Did not receive full dose or received incorrect dose,
    - Received any non-study vaccination within 7 days of study vaccination.
- Data from any visit, including dosing visit, that occurred substantially out of window. Substantially out of window was defined as a visit occurring more than three days before or more than seven days after the visit window. Visit windows for visits after dose 2 are adjusted to reflect the actual date of receipt of dose 2, not based on days after dose 1.

Immunogenicity Measurements

The BN vaccinia virus-Western Reserve strain (VV-WR) PRNT assay was used to assess the primary immunogenicity objective. Serum samples from baseline (day 1, pre-vaccination), day 29, and day 43 were tested, as available, by BN in duplicate; samples from day 210 and day 394 were also analyzed. The lower limit of detection (LLOD) for this assay was NT50 (50% neutralization titer) titer of 20, and there was no reported lower limit of quantification (LLOQ) or upper limit of quantification (ULOQ). Results below the LLOD were imputed as one-half the LLOD. This assay was performed as previously described (Pittman, 2019) and is the assay used in the marketing authorizations of MVA BN.

Humoral immunity to anti-MVA binding antibodies using an enzyme-linked immunosorbent assay (ELISA), at baseline (day 1), day 29, day 43, day 210, and day 394. The LLOD for this assay was a titer of 50, and the LLOQ was 100, while no ULOQ was reported. Results below the LLOD were imputed as one-half the LLOD, and results between the LLOD and the LLOQ were imputed as the midpoint of the two. A sensitivity analysis was conducted where all results below LLOQ were imputed as one-half the LLOQ.

Serum samples collected prior to receiving the first vaccination on day 1 and on day 43 were also assessed for neutralizing antibody responses using a monkeypox virus specific PRNT. This assay was conducted by Battelle Biomedical Research Center under contract to the National Institute of Allergy and Infectious Disease (NIAID) using Batelle's MPXV hMPXV/USA/MA001/2022 (Lineage B.1, Clade IIb) strain-specific PRNT. The LLOD for this assay was an NT50 titer of 19, and the LLOQ was 26, while no ULOQ was reported. Results below the LLOD were imputed as one-half the LLOD, and results between the LLOD and the LLOQ were imputed as the midpoint of the two. The assay was considered optimized but not fully validated. Because this assay was still in development, it was only included as an exploratory endpoint.

Primary Immunogenicity Endpoints

The primary immunogenicity objective was to determine if expected peak (day 43) humoral immune responses in adolescents 12 to 17 years old are non-inferior to adults after receipt of a 2 dose SC regimen of 1 × 108 TCID50 MVA-BN. The primary immunogenicity endpoint was vaccinia virus specific PRNT GMT at day 43.

Secondary Immunogenicity Endpoints

The secondary immunogenicity objectives and endpoints were as follows:

- To evaluate humoral immune responses at baseline, prior to the second vaccination, and following receipt of the 2-dose SC regimen of 1 × 108 TCID50 MVA-BN in adolescents compared to adults on each study day.
  - Vaccinia virus specific PRNT GMT at study days 1, 29, 43, 210, and 394.
- To evaluate the kinetics of the humoral immune responses to the 2-dose SC regimen of 1 × 108 TCID50 MVA BN in adolescents and adults through day 365 after the second dose is administered.
  - Vaccinia virus specific PRNT half-life (t ½).
- To evaluate seroconversion between adolescent and adult study arms.
  - Vaccinia virus specific PRNT GMT at study days 29, 43, 210, and 394.

Exploratory Immunogenicity Endpoints

The exploratory immunogenicity objectives and endpoints were as follows:

- To evaluate other measures of the humoral immune responses for each regimen.
  - Results from additional immunologic assays (ELISA) for vaccinia and other related viruses.
- To evaluate humoral immune responses of the 2-dose SC regimen of 1×10^8 $TCID_{50}$ MVA-BN to monkeypox virus in adolescents compared to adults.
  - Monkeypox virus specific PRNT GMT at day 1 and 43.

Geometric mean titers of antibodies, GMT ratios (GMTRs, defined as ratio of GMT in adolescents to GMT in adults), and geometric mean fold-rises (GMFRs), and percentage of participants achieving seroconversion were calculated to assess the humoral immune response in adolescents compared to adults. For this analysis, seroconversion was defined depending on baseline measurements at day 1 (pre-vaccination). If baseline was positive (i.e., ≥ lower limit of detection [LLOD]), a ≥2-fold rise from baseline indicated a positive seroconversion result. If baseline was negative (ie, < LLOD), a subsequent measurement ≥ LLOD indicated a positive seroconversion result. Corresponding 95% confidence intervals (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 non-inferiority 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 (after dose 1). Non-inferiority (NI) was defined by a significant *p* value and a GMTR 95% CI lower bound ≥0.67 (ie, the lower bound of the 95% CI for the difference of the log10 titer means ≥-0.174).

6.2. Results

A tabular overview containing number of trial sites, trial start and end date, enrollment targets, design features, drugs, and objectives for clinical trial DMID 22-0020 is presented in Table 2.

A tabular overview of trial duration, inclusion criteria, efficacy parameters, subject disposition, and demographic characteristics for clinical trial DMID 22-0020 is presented in Table 3.

Table 1: Clinical Trial Design – Study DMID 22-0020

Study ID	Number of Study Centers/ Location	Study Start/ Study End Total Enrollment	Design Control Type	Study Drug Dose[a], Route & Regimen	Study Objectives
DMID 22-0020	18/ United States	20-Mar-2023/28-Aug-2024 Stage 1/arm 3: 76 Stage 2/arm 4: 135 Stage 2/arm 5: 315	Non-inferiority, open-label, non-placebo-controlled phase 2 trial	2 doses of 1×10^8 $TCID_{50}$ MVA-BN (SC), on days 1 and 29	To determine if peak humoral immune responses in adolescents ages 12 to 17 years following administration of a 2-dose 1×10^8 $TCID_{50}$ 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 1×10^8 $TCID_{50}$ MVA-BN. To describe safety of a 2-dose 1×10^8 $TCID_{50}$ MVA-BN regimen administered SC in adolescents ages 12 to 17 years.

Abbreviations: ID = identifier; SC = subcutaneous, $TCID_{50}$ = tissue culture infectious dose of virus required to infect 50% of host cells.

[a] The virus titer assay was changed from the $TCID_{50}$-based assay to the flow cytometry infectious unit (Inf.U)-based assay. Equivalency of the 2 methods has been demonstrated, and thus the units can be used interchangeably. The nominal titer of 1×10^8 $TCID_{50}$ MVA-BN per 0.5 mL corresponds to the licensed MVA-BN standard dose containing no less than 5×10^7 Inf.U per 0.5 mL dose.

Table 2: Study DMID 22-0020 - Duration, Inclusion Criteria, Immunogenicity/Efficacy Parameters, Subject Disposition and Demographics Characteristics

Trial Identification Vaccine Formulation	No. of Subjects	Duration	Sex at Birth (No. M/F)	Race: (Adults/Adolescents)	Inclusion Criteria/Exclusion Criteria	Primary Efficacy (or Immunogenicity)
DMID 22-0020 MVA-BN	Stage 1/arm 3: 76 adults Stage 2: Planned: 450 (arm 4 135; arm 5: 315) Analyzed: 450 (arm 4:	18 months Vaccinations on day 1 and day 29, FU visits on days 8, 29, 36, 43,	94 M adults 160 M adolescents 117 F adults	White: 361 (145 /216) Black: 62 (31/31) Multi-racial: 74 (17/57) Unknown: 8 (5/3)	Included were Healthy non-pregnant, non-breastfeeding adults 18 to 50 years old. Excluded were adults with a history of	VV-WR-specific neutralizing antibodies (PRNT) prior to receiving the first vaccination on day 1, and on

Trial Identification Vaccine Formulation	No. of Subjects	Duration	Sex at Birth (No. M/F)	Race: (Adults/Adolescents)	Inclusion Criteria/Exclusion Criteria	Primary Efficacy (or Immunogenicity)
	135; arm 5: 315) 161 (12 to 14 years) 154 (15 to 17 years) 211 (18 to 50 years)	210, and 394[a].	155 F adolescents		receiving smallpox or mpox vaccine (licensed or investigational) or Any history of monkeypox, cowpox, or vaccinia infection	days 29, 43, 210, and 394

Abbreviations: F = female; FU = follow-up; M = male; No. = number; PRNT = plaque reduction neutralization test; VV-WR = vaccinia virus-western reserve strain.

[a] Immunogenicity serum sampling at certain FU visits (days 1, 29, 43,210 and 394).

Narrative Description of Clinical Trial DMID 22-0020

Clinical trial DMID 22-0020 was a phase 2 open-label, non-placebo controlled, multi-site clinical trial that evaluated the safety and immunogenicity of 2 doses of 1×10^8 TCID50 MVA-BN vaccine, given SC 4 weeks apart among adolescents ages 12 to 17 years compared to adults ages 18 to 50 years. The virus titer assay was changed from the TCID50-based assay to the flow cytometry infectious unit (Inf.U)-based assay. Equivalency of the 2 methods has been demonstrated, and thus the units can be used interchangeably. The 1×10^8 TCID50 per 0.5 mL MVA BN vaccine dose corresponds to the standard dose of MVA-BN (0.5×10^8 to 3.95×10^8 Inf.U per 0.5 mL). The primary efficacy objective was to determine peak humoral immune responses in adolescents ages 12 to 17 years were non-inferior to the response in adults ages 18 to 50 years. The primary safety objective was to describe the safety of a 2-dose 1×10^8 TCID50 MVA-BN regimen administered SC in adolescents 12 to 17 years old, in terms of frequency and severity of AEs, AESIs, medically attended adverse events (MAAEs) and SAEs.

The MVA-BN vaccine administered in adolescents 12 to 17 years old was non-inferior to the immunogenicity observed in healthy adults, and the primary immunogenicity endpoint of non-inferiority for peak vaccinia-virus specific PRNT at day 43 was met. Three hundred thirteen adolescents and all 211 adults satisfied the criteria for inclusion in the modified intention-to-treat (mITT) population. Of these participants, 304 adolescents and 208 adults completed the day 43 visit and contributed a venous blood sample. Immunogenicity data summaries and analyses were presented for the mITT population and, if there were protocol deviations determined to potentially impact the analysis, the PP population.

The secondary endpoints of PRNT GMTs, GMTR, and non-inferiority test results for day 210, day 394, and peak response at any time also met non-inferiority compared with adults, with adolescents having higher GMT than adults at the same time points. Adolescents also had a greater GMFR than arm 4 adults at both time points and for peak responses. Importantly, there were no differences in the half-life of vaccinia-virus specific PRNT between adults and adolescents, with medians of 167 and 166 days, respectively. Finally, assessments of exploratory endpoints of anti-MVA binding antibody GMTs and GMTRs showed that adolescents generated higher antibody levels at all time points. Therefore, these data confirm that adolescents mount a robust antibody response to MVA-BN vaccine, in the standard dose regimen.

The exploratory endpoints of monkeypox virus-specific PRNT GMTs and seroconversion rates at days 1 and 43 in adolescents compared with adults were similar. However, the immune responses were too low to draw any conclusions, and the assays require further optimization and validation.

Primary and Secondary Immunogenicity Results – Vaccinia-specific PRNT

Summary statistics and hypothesis testing results corresponding to the primary and secondary hypotheses are displayed in Table 5 and Table 6, respectively. Immunogenicity data summaries and analysis were presented for the mITT population. The results for the mITT population are similar to the PP population. The PP population results and not provided in this overview but complete details are available in the DMID 22-0020 Stage 2 Final Integrated CSR (dated 19 Nov 2025). Adolescents had a consistently higher GMT against VV than adults after dose 1. As assessed by the VV-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). The sensitivity analysis excluding arm 3 (stage 1) adult participants yielded similar GMTR results (day 43: 1.59 [95% CI: 1.26, 2.00. Based on non-overlapping 95% CIs, the adolescents' GMT was greater than the adults' GMT on day 43 (adolescent GMT: 470.3 [95% CI: 422.3, 523.8]; adult GMT: 293.2 [95% CI: 249.8, 344.2]).

Responses for arm 5 adolescents were considered non-inferior to the arm 4 adults at day 210 (GMTR [95% CI]: 1.66 [1.34, 2.06]; p <0.001), day 394 (1.94 [1.57, 2.39]; p <0.001), and for peak responses (1.59 [1.26, 2.02]; p <0.001). While superiority testing was not formally planned, arm 5 adolescents generally had higher titer responses than arm 4 adults on day 210, day 394, and for peak responses (Table 6).

Vaccinia-specific PRNT GMTs are displayed in Figure 2 and Table 7. Arm 5 adolescents had similar responses to arm 4 adults on both study days, as evident in the GMTRs (ratio of adolescents' GMT to adults' GMT): GMTR (95% CI) at day 1: 0.93 (0.85, 1.01) and at day 29: 1.12 (0.88, 1.43). The majority of participants in the mITT population remained seroconverted after day 29 until day 210, however the seroconversion rate for arm 4 adults dropped to 46% by day 394. Arm 5 adolescents had a greater GMFR than arm 4 adults at both time points as well as for peak responses. Although no formal superiority test was performed, 12- to 14-year-olds had a greater VV- specific PRNT GMT than arm 4 participants on day 43. Both 12- to 14-year-olds and 15- to 17-year-olds had higher VV specific PRNT GMTs than arm 4 participants on days 210, 394, and for peak response. Corresponding GMTRs at days 43, 210, 394, and peak response for both 12 to 14-year-olds and 15 to 17-year-olds indicate greater VV- specific PRNT GMTs than the arm 4 adults starting at all time points after dose 2.

Table 8 displays the vaccinia virus specific PRNT GMFRs and seroconversion rates and the corresponding 95% CIs. For VV, 99.0% of adolescents (95% CI: 97.1, 99.8) seroconverted on day 43 with a GMFR of 46.9 (95% CI: 42.1, 52.3). Adults had a similar percentage of seroconversions when including and excluding arm 3 (stage 1) for all study days. On day 43, 97.7% of adults (95% CI: 93.5%, 99.5%) seroconverted, with a GMFR of 27.3 (95% CI: 22.4, 33.3). The majority of participants in the mITT population remained seroconverted at day 210, however the seroconversion rate for arm 4 adults dropped to 46% by day 394 (81.5% of adolescents at day 394). Arm 5 adolescents had a greater GMFR than arm 4 adults at both time points as well as for peak responses.

The humoral immune responses as assessed by VV-specific PRNT half-life showed that there were no differences in the half-life of VV-specific PRNT between adults and adolescents, with medians of 167 and 166 days, respectively (Table 9).

Reverse cumulative distribution curves, displaying on the y-axis the cumulative proportion of responses at least as high as the corresponding titer on the x-axis, are presented for VV-specific PRNT for the mITT population in Figure 3. The overall distribution of titers was similar in each age group for

day 1 through day 43, however at days 210 and 394 the arm 5 adolescents had a greater proportion at higher titers than the arm 4 adults.

Table 5: Vaccinia Virus Specific PRNT Primary Hypothesis Testing at Day 43, mITT Population

Time Point	Statistic	Adolescents (Arm 5) (N=313)	Adults (Arm 4) (N=135)	Pooled Adults (Arm 3 + Arm 4)[c] (N=211)
Study Day 43, Post Dose 2	n	304	132	208
	GMT (95% CI)	470.3 (422.3, 523.8)	295.7 (240.8, 363.2)	293.2 (249.8, 344.2)
	GMTR (95% CI)	N/A	1.59 (1.26, 2.00)	1.60 (1.32, 1.95)
	p-value[a]	N/A	<0.001	<0.001
	Non-inferiority result[b]	N/A	Yes	Yes

Abbreviations: CI = Confidence Interval, calculated using Student's t-distribution for GMT and Welch-Satterthwaite t-test for GMTR; GMT = Geometric mean titer; GMTR = Geometric mean titer ratio of adolescents to adults; mITT = Modified Intention-to-Treat Population; N = Number of participants in the mITT Population; n = Number of participants with data at time point; N/A = not applicable; PRNT = plaque reduction neutralization test.
[a] Two-sample t-test with unequal variance, non-inferiority (NI) margin of 0.67 and 2-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 at the given time point as assessed by vaccinia virus specific PRNT GMT.
[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] Stage 1 arm 3 adults were combined with stage 2 arm 4 adults as a comparator group for the primary analysis. Arm 3 participants were excluded for a sensitivity analysis (adults [arm 4]).

Table 3: Vaccinia Virus Specific PRNT and Secondary Hypothesis Testing, mITT Population

Time Point	Statistic	Adolescents (Arm 5) (N=313)	Adults – Arm 4 Only (N=135)
Study Day 1, Pre-Dose 1	n	313	135
	GMT (95% CI)	10.0 (10.0, 10.1)	10.8 (9.9, 11.8)
	GMTR (95% CI)	N/A	0.93 (0.85, 1.01)
Study Day 29, Pre-Dose 2	n	310	134
	GMT (95% CI)	51.1 (45.6, 57.4)	45.7 (36.9, 56.7)
	GMTR (95% CI)	N/A	1.12 (0.88, 1.43)
Study Day 210, Post Dose 2	n	310	130
	GMT (95% CI)	43.9 (39.7, 48.5)	26.4 (21.8, 32.0)
	GMTR (95% CI)	N/A	1.66 (1.34, 2.06)
	p-value[a]	N/A	<0.001
	Non-inferiority result[b]	N/A	Yes
Study Day 394, Post Dose 2	n	303	124
	GMT (95% CI)	44.8 (40.3, 49.7)	23.1 (19.2, 27.8)
	GMTR (95% CI)	N/A	1.94 (1.57, 2.39)
	p-value[a]	N/A	<0.001
	Non-inferiority result[b]	N/A	Yes
Peak Anytime Post Dose 1	n	313	135
	GMT (95% CI)	456.6 (410.5, 507.9)	286.7 (231.6, 354.9)

Time Point	Statistic	Adolescents (Arm 5) (N=313)	Adults – Arm 4 Only (N=135)
	GMTR (95% CI)	N/A	1.59 (1.26, 2.02)
	p-value[a]	N/A	<0.001
	Non-inferiority result[b]	N/A	Yes

Abbreviations: CI = confidence iterval, calculated using Student's t-distribution for GMT and Welch-Satterthwaite t-test for GMTR; GMT = geometric mean titer; GMTR = geometric mean titer ratio of adolescents to adults; mITT = modified intention-to-treat population; N = number of participants in the mITT population; n = number of participants with data at time point; N/A = not applicable; PRNT = plaque reduction neutralization test.
[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".

Table 4: Vaccinia Virus Specific PRNT Geometric Mean Titer Results and Geometric Mean Titer Ratio to Adolescents Results with 95% Confidence Intervals by Adolescent Age Subgroup, mITT Population

		Adolescents (Arm 5)		Adults (Arm 4)
Time Point	Statistic	12 to 14 years old (N=159)	15 to 17 years old (N=154)	≥ 18 years old (N=135)
Study Day 1, Pre-Dose 1	n	159	154	135
	GMT (95% CI)	10.0 (NC[a])	10.0 (10.0, 10.1)	10.8 (9.9, 11.8)
	GMTR (95% CI)	0.92 (0.85, 1.01)	0.93 (0.85, 1.01)	N/A
Study Day 29, Pre-Dose 2	n	158	152	134
	GMT (95% CI)	49.7 (42.8, 57.7)	52.6 (44.0, 63.0)	45.7 (36.9, 56.7)
	GMTR (95% CI)	1.09 (0.84, 1.41)	1.15 (0.87, 1.52)	N/A
Study Day 43, Post Dose 2	n	154	150	132
	GMT (95% CI)	522.8 (452.0, 604.7)	421.9 (359.9, 494.6)	295.7 (240.8, 363.2)
	GMTR (95% CI)	1.77 (1.38, 2.27)	1.43 (1.10, 1.85)	N/A
Study Day 210, Post Dose 2	n	158	152	130
	GMT (95% CI)	52.7 (46.1, 60.2)	36.3 (31.3, 42.0)	26.4 (21.8, 32.0)
	GMTR (95% CI)	2.00 (1.58, 2.52)	1.37 (1.08, 1.75)	N/A
Study Day 394, Post Dose 2	n	155	148	124
	GMT (95% CI)	54.9 (47.8, 63.0)	36.1 (31.1, 42.0)	23.1 (19.2, 27.8)
	GMTR (95% CI)	2.38 (1.89, 2.99)	1.56 (1.23, 1.98)	N/A
Peak Anytime Post Dose 1	n	159	154	135
	GMT (95% CI)	500.5 (432.6, 579.0)	415.3 (355.5, 485.2)	286.7 (231.6, 354.9)
	GMTR (95% CI)	1.75 (1.35, 2.26)	1.45 (1.11, 1.88)	N/A

Abbreviations: CI = confidence interval, calculated using Student's t-distribution for GMT and Welch-Satterthwaite t-test for GMTR; GMT = geometric mean titer; GMTR = geometric mean titer ratio of adolescents to adults; mITT = modified intention-to-treat population; N = number of participants in the mITT population; n = number of participants with data at time point; N/A = not applicable; NC = not calculable; PRNT = plaque reduction neutralization test.
[a] Not calculable due to insufficient variation

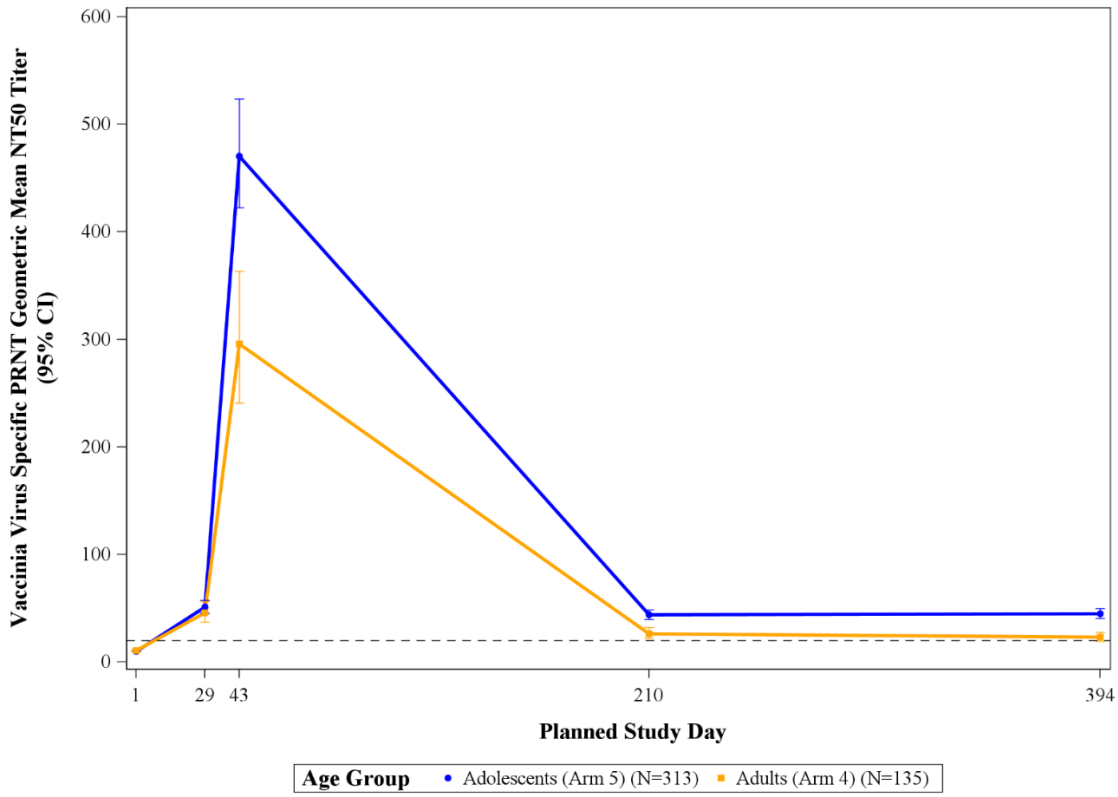
Table 5: Vaccinia Virus Specific PRNT Geometric Mean Fold Rise and Seroconversion by Time Point and Age Group, mITT Population

Time Point	Statistic	Adolescents (Arm 5) (N=313)	Adults (Arm 4) (N=135)
Study Day 29, Pre-Dose 2	n	310	134
	GMFR[a] (95% CI)	5.1 (4.5, 5.7)	4.2 (3.5, 5.1)

Time Point	Statistic	Adolescents (Arm 5) (N=313)	Adults (Arm 4) (N=135)
	% with Seroconversion[b] (95% CI)	82.6 (77.9, 86.6)	76.9 (68.8, 83.7)
Study Day 43, Post Dose 2	n	304	132
	GMFR[a] (95% CI)	46.9 (42.1, 52.3)	27.3 (22.4, 33.3)
	% with Seroconversion[b] (95% CI)	99.0 (97.1, 99.8)	97.7 (93.5, 99.5)
Study Day 210, Post Dose 2	n	310	130
	GMFR[a] (95% CI)	4.4 (4.0, 4.8)	2.4 (2.1, 2.9)
	% with Seroconversion[b] (95% CI)	82.9 (78.2, 86.9)	54.6 (45.7, 63.4)
Study Day 394, Post Dose 2	n	303	124
	GMFR[a] (95% CI)	4.5 (4.0, 5.0)	2.1 (1.8, 2.5)
	% with Seroconversion[b] (95% CI)	81.5 (76.7, 85.7)	46.0 (37.0, 55.1)
Peak Anytime, Post Dose 1	n	313	135
	GMFR[a] (95% CI)	45.6 (41.0, 50.7)	26.5 (21.6, 32.5)
	% with Seroconversion[b] (95% CI)	99.4 (97.7, 99.9)	97.0 (92.6, 99.2)

Abbreviations: CI = confidence interval, calculated using student's t-distribution for GMFR and Clopper-Pearson methodology for seroconversion; GMFR = geometric mean fold rise; LLOD = lower limit of detection; mITT = modified intention-to-treat population; N = number of participants in the mITT population; n = number of participants with data at time point; PRNT = plaque reduction neutralization test.
Notes: Peak humoral response is the maximum titer response for each participant across all study visits, including supplemental visits.
[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 titer compared to pre-dose 1 if any detectable result at pre-dose 1, or any detectable result if result < lower limit of detection (LLOD) at pre-dose 1.

Figure 1: Geometric Mean Titer of Vaccinia Virus Specific PRNT by Time Point and Age Group, mITT Population



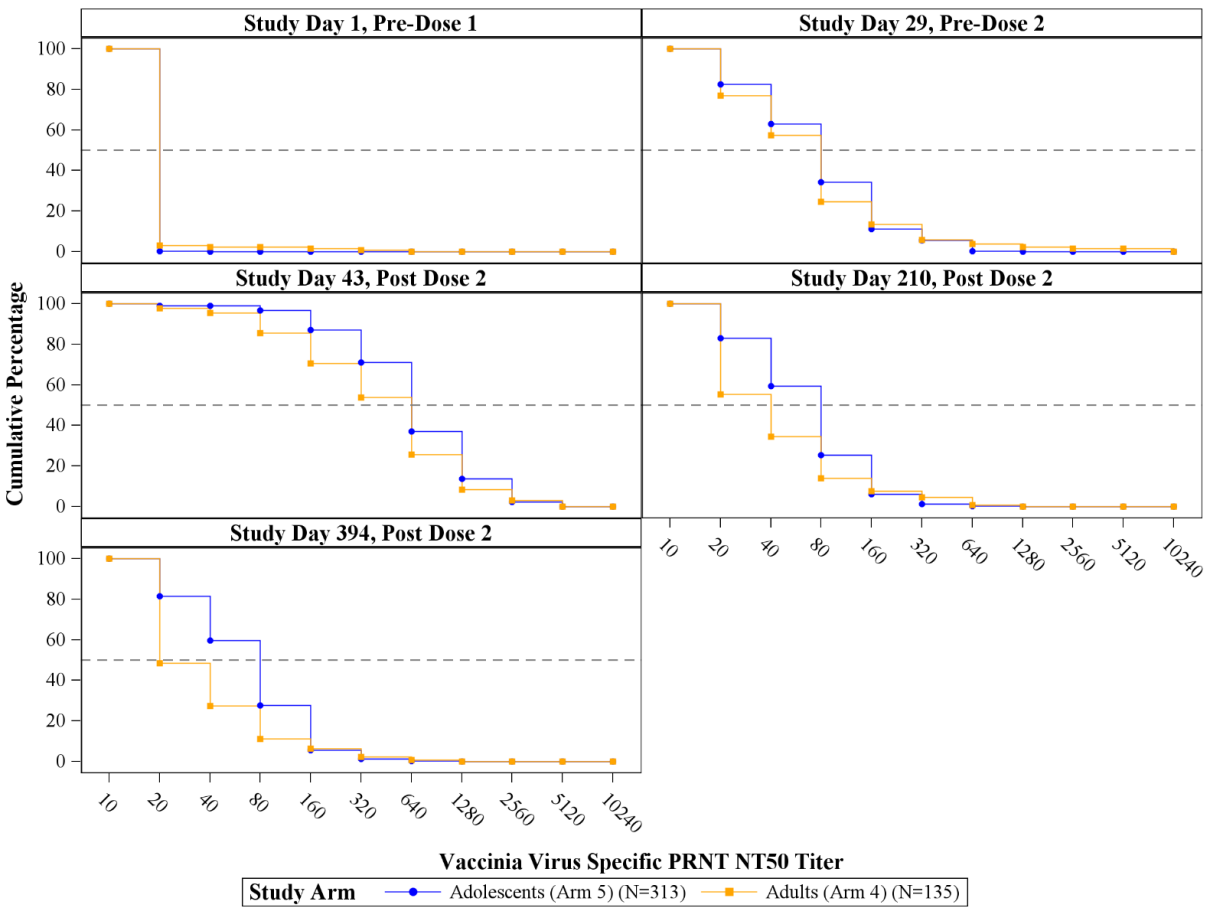
Abbreviations: CI = confidence interval; GMT = geometric mean titer; mITT = modified intention-to-treat population; N = number of participants in the mITT population; NT_{50} = 50% neutralization titer; PRNT = plaque reduction neutralization test.
Dashed line represents the lower limit of detection of assay.

Table 6: Vaccinia Virus Specific PRNT Half-Life Secondary Hypothesis Testing, mITT Population

Hypothesis	Statistic	Adolescents (Arm 5) (N=313)	Adults (Arm 4) (N=135)
Humoral immune responses in adolescents as assessed by Vaccinia-specific PRNT half-life similar to adults	n	304	130
	Median (Minimum, Maximum)	166 (136, 370)	167 (156, 362)
	Mean (95% CI)	170.2 (167.0, 173.5)	179.7 (171.4, 188.0)
	p-value[a]	N/A	0.763

Abbreviations: CI = confidence interval, calculated using Student's t-distribution; mITT = modified intention-to-treat population; N = number of participants in the per protocol population; n = number of participants with data at day 43 and post-day 43; N/A = not applicable; PRNT = plaque reduction neutralization test; VV-WR = vaccinia virus-Western Reserve strain.
Participants whose VV-WR PRNT did not fall below ½ the day 43 result at any post-day 43 visit were imputed as the last study day with VV-WR PRNT results.
[a] Wilcoxon Mann Whitney test.

Figure 2: Reverse Cumulative Distribution of Vaccinia Virus Specific PRNT by Time Point and Age Group, mITT Population



Abbreviations: mITT = modified intention-to-treat population; N = number of participants in the mITT population; NT_{50}= 50% neutralization titer; PRNT = plaque reduction neutralization test.

Exploratory Immunogenicity Results

Anti-MVA Binding Antibody ELISA

Using ELISA, anti-MVA binding antibody GMTs and GMTRs are presented for day 1, day 29, day 43, day 210, day 394, and for peak response after dose 1 in Table 10. Assessment of anti-MVA binding antibody GMTs and GMTRs showed that adolescents generated higher antibody levels at all time points.

GMTs are presented graphically for day 1 through day 394 for the mITT population in Figure 4.

Table 7: Anti-MVA Binding Antibody Geometric Mean Titer Results and Geometric Mean Titer Ratio to Adolescents Results with 95% Confidence Intervals by Age Group, mITT Population

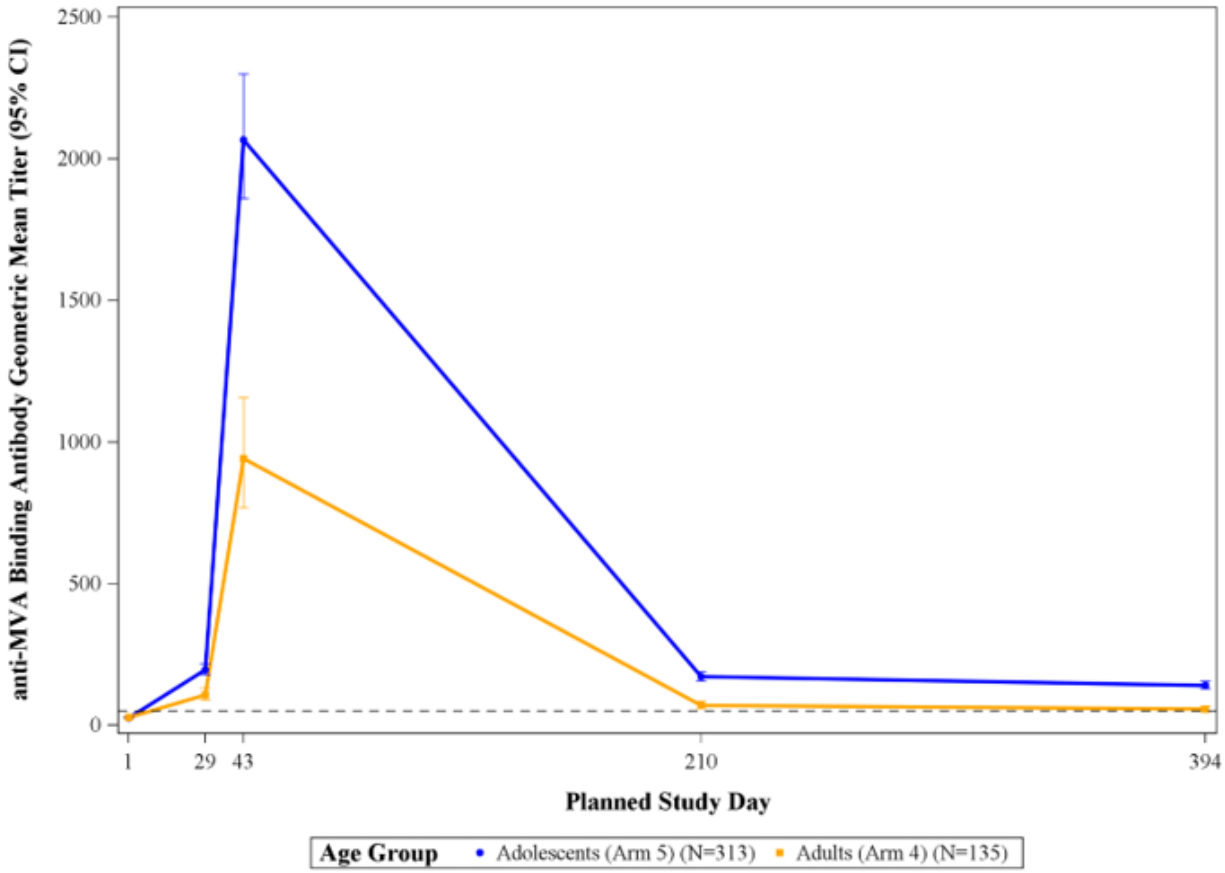
Time Point	Statistic	Adolescents (Arm 5) (N=313)	Adults (Arm 4) (N=135)
Study Day 1, Pre-Dose 1	n	313	135
	GMT (95% CI)	27.0 (25.9, 28.1)	28.0 (25.3, 31.0)
	GMTR (95% CI)	N/A	0.96 (0.86, 1.07)
Study Day 29, Pre-Dose 2	n	310	134
	GMT (95% CI)	197.1 (179.0, 217.1)	108.3 (89.4, 131.1)
	GMTR (95% CI)	N/A	1.82 (1.47, 2.26)
Study Day 43, Post Dose 2	n	304	132
	GMT (95% CI)	2067.7 (1859.4, 2299.4)	942.1 (767.5, 1156.5)
	GMTR (95% CI)	N/A	2.19 (1.74, 2.76)
Study Day 210, Post Dose 2	n	310	130
	GMT (95% CI)	172.6 (157.4, 189.3)	71.4 (59.8, 85.3)
	GMTR (95% CI)	N/A	2.42 (1.98, 2.95)
Study Day 394, Post Dose 2	n	303	124
	GMT (95% CI)	141.6 (129.1, 155.3)	57.6 (49.0, 67.6)
	GMTR (95% CI)	N/A	2.46 (2.04, 2.96)
Peak Anytime Post Dose 1	n	313	135
	GMT (95% CI)	1982.9 (1785.6, 2202.0)	899.9 (730.6, 1108.5)
	GMTR (95% CI)	N/A	2.20 (1.75, 2.78)

Abbreviations: CI = confidence interval, calculated using student's t-distribution for GMT and Welch-Satterthwaite t-test for GMTR; GMT = geometric mean titer; GMTR = geometric mean titer ratio of adolescents to adults; LLOD = lower limit of detection; LLOQ = lower limit of quantification; mITT = modified intention-to-treat population; N = number of participants in the mITT population; n = number of participants with data at timepoint; N/A = not applicable.

Notes: Peak humoral response is the maximum titer response for each participant across all study visits, including supplemental visits.

Results below the assay lower limit of detection are imputed as LLOD/2. Results below the assay lower limit of quantitation but at or above the lower limit of detection are imputed as (LLOD+LLOQ)/2.

Figure 3: Geometric Mean Titer of Anti-MVA Binding Antibody by Time Point and Age Group, mITT Population



Abbreviations: CI = confidence interval; mITT = modified intention-to-treat population; N = number of participants in the mITT population.
Dashed line represents the lower limit of quantitation (LLOQ) of assay

Monkeypox-specific PRNT

Summary statistics and hypothesis testing results corresponding to exploratory hypotheses are displayed in Table 11 and Table 12. These results are exploratory; monkeypox virus-specific assays are not validated and require further optimization. Monkeypox virus-specific PRNT GMTs are displayed in Figure 5. Adolescents (day 43 GMT: 9.8 [95% CI: 9.6, 10.0]) had similar immune responses to adults (day 43 GMT: 10.0 [95% CI: 9.5, 10.6]) for monkeypox virus. However, the majority of immune responses were below LLOD.

Table 13 displays the GMFR, percentage of participants with seroconversion, and the corresponding 95% CIs for and monkeypox virus-specific PRNT. Only 3% of adolescents (95% CI: 1.4, 5.6) and 3.0% of adults (95% CI: 0.8, 7.6) seroconverted for monkeypox virus. GMFR was 1.0 for both adolescents and adults (95% CI: 1.0, 1.0).

Table 8: Monkeypox Virus Specific PRNT Hypothesis Testing, mITT Population

Time Point	Statistic	Adolescents (Arm 5) (N=313)	Adults (Arm 4) (N=135)
Study Day 1, Pre-Dose 1	n	313	135
	GMT (95% CI)	9.5 (NC[c])	9.8 (9.5, 10.1)
	GMTR (95% CI)	N/A	0.97 (0.94, 1.00)
Study Day 43, Post Dose 2	n	303	132

Time Point	Statistic	Adolescents (Arm 5) (N=313)	Adults (Arm 4) (N=135)
	GMT (95% CI)	9.8 (9.6, 10.0)	10.0 (9.5, 10.6)
	GMTR (95% CI)	N/A	0.98 (0.92, 1.03)
	p-value[a]	N/A	<0.001
	Non-inferiority result[b]	N/A	Yes

Abbreviations: CI = confidence interval, calculated using student's t-distribution for GMT and Welch-Satterthwaite t-test for GMTR; GMT = geometric mean titer; GMTR = geometric mean titer ratio of adolescents to adults; mITT = modified intention-to-treat population; N = number of participants in the mITT population; n = number of participants with data at time point; N/A = not applicable; NC = not calculable; PRNT = plaque reduction neutralization test.

[a] Two-sample t-test with unequal variance, non-inferiority (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] NC = Not calculable due to insufficient variation.

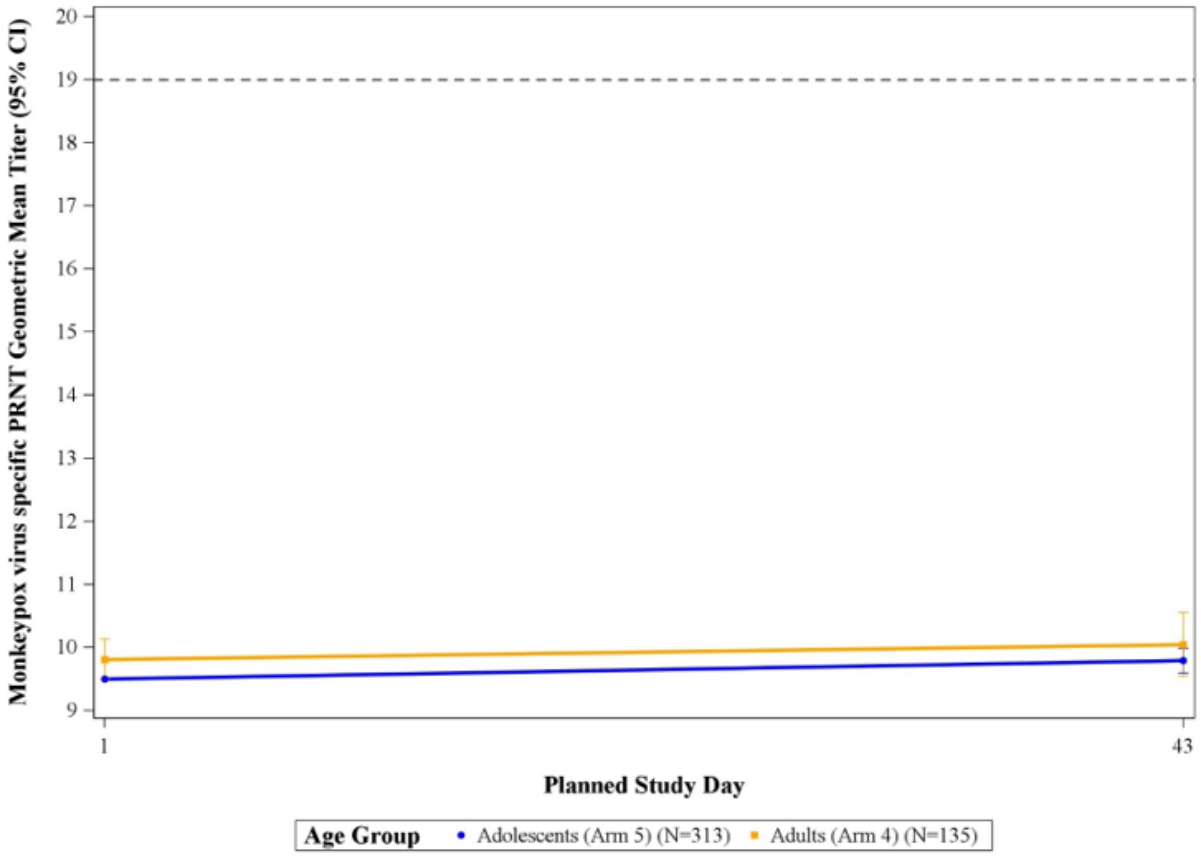
Table 9: Monkeypox Virus Specific PRNT Geometric Mean Titer Results and Geometric Mean Titer Ratio to Adolescents Results with 95% Confidence Intervals by Adolescent Age Subgroup, mITT Population

		Adolescents (Arm 5)		Adults (Arm 4)
Time Point	Statistic	12-14 years old (N=159)	15-17 years old (N=154)	≥18 years old (N=135)
Study Day 1, Pre-Dose 1	n	159	154	135
	GMT (95% CI)	9.5 (NC[a])	9.5 (NC[a])	9.8 (9.5, 10.1)
	GMTR (95% CI)	0.97 (0.94, 1.00)	0.97 (0.94, 1.00)	N/A
Study Day 43, Post Dose 2	n	154	149	132
	GMT (95% CI)	9.9 (9.6, 10.3)	9.6 (9.4, 9.8)	10.0 (9.5, 10.6)
	GMTR (95% CI)	0.99 (0.93, 1.05)	0.96 (0.91, 1.01)	N/A

Abbreviations: CI = confidence interval, calculated using student's t-distribution for GMT and Welch-Satterthwaite t-test for GMTR; GMT = geometric mean titer; GMTR = geometric mean titer ratio of adolescents to adults; mITT = modified intention-to-treat population; N = number of participants in the mITT population; n = number of participants with data at time point; N/A = not applicable; NC = not calculable; PRNT = plaque reduction neutralization test.

[a] Not calculable due to insufficient variation.

Figure 4: Geometric Mean Titer of Monkeypox Virus Specific PRNT by Time Point and Age Group, mITT Population



Abbreviations: CI = confidence interval; mITT = modified intention-to-treat population; N = number of participants in the mITT population; PRNT = plaque reduction neutralization test.
Dashed Line represents the lower limit of detection of assay.

Table 10: Monkeypox Virus Specific PRNT Geometric Mean Fold Rise (GMFR) and Seroconversion by Time Point and Age Group, mITT Population

Time Point	Statistic	Adolescents (Arm 5) (N=313)	Adults (Arm 4) (N=135)
Study Day 43, Post Dose 2	n	303	132
	GMFR[a] (95% CI)	1.0 (1.0, 1.1)	1.0 (1.0, 1.1)
	% with Seroconversion[b] (95% CI)	3.0 (1.4, 5.6)	3.0 (0.8, 7.6)

Abbreviations: CI = confidence interval, calculated using student's t-distribution for GMFR and Clopper-Pearson methodology for seroconversion. GMFR = geometric mean fold rise; N = number of participants in the mITT population; n = number of participants with data at time point.
[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 titer compared to pre-dose 1 if any detectable result at pre-dose 1, or any detectable result if result < lower limit of detection (LLOD) at pre-dose 1.

Comparison of Results of Subpopulations

Age Subgroups – Adolescents

Arm 5 adolescents were divided into 12 to 14-year-old and 15 to 17-year-old subgroups to see if there were any differences in response between the 2 age subgroups. The mean age and age ranges were similar across study sites within each adolescent age subgroup. For vaccinia virus-specific PRNT, GMT results were similar between younger (12 to 14-year-olds) and older (15 to 17-year-olds) adolescents on day 29, but only younger adolescents had a generally higher immune response than adults at day 43. The GMTs and GMTRs were higher across all time points for 12 to 14-year-olds compared to 15 to 17-year-olds.

6.3. Discussion

Within procedure No. EMEA/H/C/002596/II/0108 an interim analysis of the Study DMID Protocol 22-0020, Stage 2 was performed based on data up to cut-off date, 22 February 2024, which included safety data reported through Study Day 210 (180 days Post Dose 2) and immunogenicity data up to Study Day 43 (14 days Post Dose 2). Data up to Study Day 57 were considered clean.

As of the data cutoff date, 22 February 2024, 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.

Three hundred and four (97%) adolescents and 208 (99%) adults contributed a venous blood sample for the primary endpoint at Day 43.

The overall demographics was found to be adequate for the purpose of the study.

The PRNT response of anti-vaccinia neutralizing 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 neutralizing antibodies in adults vs. adolescents in order to infer effectiveness is acceptable in this procedure.

The primary objective of this Study DMID Protocol 22-0020 was to determine if peak humoral immune responses in adolescents aged 12 to 17 years following administration of a 2-dose 1×10^8 TCID50 MVA-BN regimen administered SC are non-inferior to the response in adults aged 18 to 50 years who received the licensed 2-dose SC regimen of 1×10^8 TCID50 MVA-BN. For the primary analysis samples from adult participants from stage 1 arm 3 and stage 2 arm 4 were analysed together (211 samples) and compared to samples from adolescents from stage 2 arm 5 (315 samples).

As already presented with the interim analysis the vaccinia virus-specific PRNT GMT in adolescents 12 – 17 years of age 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]). The pre-planned analysis of non-inferiority successfully demonstrated non-inferiority of vaccination with MVA-BN in adolescents vs. adults. Vaccinia virus-specific PRNT GMTs in the adolescent sub-groups 12 – 14 years of age and 15 – 17 years of age were similar with a trend to be higher in the 12 – 14 years of age sub-group.

For both adults and adolescents a waning of humoral immunity was demonstrated to a similar extend, with a vaccinia virus-specific PRNT half-life of 166 day and 167 days in adolescents and adults, respectively.

Anti-MVA binding antibody analysis support the vaccinia virus-specific PRNT analysis.

The monkeypox-specific PRNT did not reveal substantial titres in both adults and adolescent groups. The PRNT assay that was used was not fully validated and results should be interpreted with caution. 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 (Type II Procedure EMEA/H/C/002596/II/0100, positive CHMP Opinion 25 July 2024).

7. Clinical Safety aspects

7.1. Methods – analysis of data submitted

Overall Extent of Exposure

MVA-BN has been evaluated in adolescents in stage 2 of 1 phase 2 clinical trial DMID 22 0020, conducted in the US. The dose and dosing schedule used for adults, 0.5 mL 1×10^8 TCID50 MVA BN administered subcutaneously, was used for adolescents and administered on days 1 and 29. The virus titer assay was changed from the TCID50-based assay to the flow cytometry infectious unit (Inf.U)-based assay. Equivalency of the 2 methods has been demonstrated, and thus the units can be used interchangeably. The 1×10^8 TCID50 per 0.5 mL MVA BN vaccine dose corresponds to the standard dose of MVA BN (0.5×10^8 to 3.95×10^8 Inf.U per 0.5 mL). All enrolled participants received study vaccination and were included in the Safety Population. Of the 315 enrolled arm 5 adolescents, 312 (>99%) received 2 doses of MVA BN. Of the 315 arm 5 adolescents enrolled in this study, 303 (96%) completed the final blood draw on day 394. One hundred twenty-four (92%) of the 135 arm 4 adults enrolled completed the final blood draw (Table 14).

Table 14: Participant Disposition by Age Group

Participant Disposition	Adolescents (Arm 5) (N=315)		Adults (Arm 4) (N=135)		Adults (Arm 3)[d] (N=76)		All Stage 2 Participants[e] (N=450)		All Participants (N=526)	
	n	%	n	%	n	%	n	%	n	%
Screened	-	-	-	-	-	-	471	-	-	-
Enrolled	315	100	135	100	76	100	450	100	526	100
Received Dose 1	315	100	135	100	76	100	450	100	526	100
Received Dose 2[a]	312	>99	131	97	76	100	443	98	519	99
Completed Primary Endpoint (Study Day 43)	304	97	132	98	76	100	436	97	512	97
Completed Study Day 210[b]	312	>99	130	96	N/A	N/A	442	98	N/A	N/A
Completed Final Blood Draw (Study Day 394)	303	96	124	92	N/A	N/A	427	95	N/A	N/A
Completed Follow-up (Study Day 394)	308	98	125	93	N/A	N/A	433	96	N/A	N/A
Completed Study Day 394 Per Protocol[c]	307	97	125	93	N/A	N/A	432	96	N/A	N/A

Abbreviations: N = number of participants enrolled; n = number of participants meeting the row criteria; N/A = not available.

[a] Refer to early terminations or discontinued participants listing for reasons participants discontinued or terminated early.

[b] Safety data cut-off for the interim Clinical Study Report.

[C] Refer to participants excluded from analysis populations listing for reasons participants are excluded from the Analysis populations.

[d] Stage 1 arm 3 adults were combined with stage 2 arm 4 adults as a comparator group for the primary immunogenicity analysis.
[e] Stage 2 participants consist of arm 4 (adults) and arm 5 (adolescents).

Demographic and Other Characteristics of Study Population

Demographic Characteristics

Demographic and baseline characteristics are summarized in Table 15.

Approximately half of enrolled arm 5 adolescents (155/315 adolescents, 49%) were female, while a higher proportion of arm 4 adults (80/135 adults, 59%) were female. The majority of enrolled participants were white (arm 5: 216/315 adolescents, 69%; arm 4: 98/135 adults, 73%; arm 3: 47/76 adults, 62%) and not Hispanic or Latino (arm 5: 251/315 adolescents, 80%; arm 4: 95/135 adults, 70%; arm 3: 54/76 adults, 71%). One arm 5 adolescent (<1%), 2 arm 4 adults (1%), and 3 arm 3 adults (4%) were HIV-positive at baseline. University of Alabama Birmingham predominantly enrolled Black or African American females (8/9 adolescents, 89%). Ponce Medical School Foundation, Inc., CAIMED Center only enrolled Hispanic or Latinos (57/57 participants [30 adolescents and 27 adults], 100%). Otherwise, differences between study sites were minimal and not expected to be confounding.

Of the 315 arm 5 adolescents, 161 (51%) were ages 12 to 14 years old and 154 (49%) were ages 15 to 17 years old at enrollment. The mean age of enrolled adolescents (arm 5) was 14.4 years old. The mean age of adults was 36.1 years old (arm 4). The mean age and age ranges were similar across study sites within each study arm.

Table 15: Summary of Categorical Demographic and Baseline Characteristics by Age Group, All Enrolled Participants

		Adolescents (Arm 5) (N=315)		Adults (Arm 4) (N=135)	
Variable	**Characteristic**	**n**	**%**	**n**	**%**
Sex at Birth	Male	160	51	55	41
	Female	155	49	80	59
Ethnicity	Not Hispanic or Latino	251	80	95	70
	Hispanic or Latino	63	20	40	30
	Not Reported	1	<1		
Race	American Indian or Alaska Native	-	-	-	-
	Asian	8	3	5	4
	Native Hawaiian or Other Pacific Islander	-	-	-	-
	Black or African American	31	10	17	13
	White	216	69	98	73
	Multi-Racial	57	18	13	10
	Unknown	3	<1	2	1
Age Group	12 to 14 years old	161	51	N/A	N/A
	15 to 17 years old	154	49	N/A	N/A
	≥18 years old	N/A	N/A	135	100
HIV Status	Negative	314	>99	133	99
	Positive	1	<1	2	1

Abbreviations: HIV = human immunodeficiency virus; N = number of participants enrolled; n = number of participants meeting the row criteria; N/A = not applicable.

7.2. Results

Adverse Events

Analysis of Adverse Events

Safety analyses are based on data from stage 2 of clinical trial DMID 22-0020. The dataset includes 315 adolescents and 135 adults who received MVA-BN. AEs and medical history were coded according to the MedDRA dictionary version 25.1 or higher.

This study used the following toxicity grading scale: "FDA Guidance for Industry, Toxicity Grading Scale for Healthy Adults and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" as a reference.

Solicited local (injection site) reactogenicity was assessed from the time of each vaccination through 7 days afterward. Participants recorded both local and systemic reactions on a memory aid during this period. Any events still ongoing at follow-up visits on days 8 or 36 were monitored at subsequent visits until their resolution.

Unsolicited AEs were assessed from day 1 through day 57 and SAEs were assessed through day 394. Protocol specified AESIs and related MAAEs were collected from day 1 through day 210. For stage 2, a protocol specified AESI was defined as a case of myocarditis or pericarditis. All AEs, related MAAEs, protocol specified AESIs, and SAEs were followed through resolution or until the site investigator deemed the event to be chronic or the participant was stable.

Common Adverse Events

An overall summary (adolescents and adults) of AEs reported in this trial is presented in Table 16. Out of 450 participants enrolled in stage 2, 400 participants (89%) experienced at least 1 local solicited AE, and 326 participants (72%) experienced at least 1 systemic solicited AE. Three hundred two participants (67%) experienced at least 1 unsolicited AE, and 243 participants (54%) experienced at least 1 unsolicited AE deemed related to the study product, including 20 (4%) reporting event(s) of moderate severity.

No related SAEs were reported. Five participants (1%) experienced unsolicited AEs leading to discontinuation of study product. There were no unsolicited AEs reported that lead to study withdrawal. Fifty-one (51) participants (11%) reported at least 1 MAAE; 36 of which were arm 5 adolescents (11%) and 15 of which were arm 4 adults (11%). No AESIs were reported.

Arm 5 adolescent subgroups are reported separately in Table 17.

At least 1 local solicited AE was reported for 91% of adolescents in the 12- to 14-year-old subgroup and 85% in the 15- to 17-year-old subgroup. At least 1 systemic solicited AE was reported in 81% of adolescents in the 12- to 14-year-old subgroup and 67% in the 15- to 17-year-old subgroup. At least 1 unsolicited AE was experienced in 68% of adolescents in the 12- to 14-year-old subgroup and 59% of adolescents in the 15- to 17-year-old subgroup. At least 1 related unsolicited AE was experienced in 52% of adolescents in the 12- to 14-year-old subgroup and 46% of adolescents in the 15- to 17-year-old subgroup. Moderate, related unsolicited AEs were experienced by 5% of adolescents in the 12- to 14-year-old subgroup and 1% of adolescents in the 15- to 17-year-old subgroup, and all other related AEs in the adolescents were mild in severity.

In the 12- to 14-year-old subgroup, 1% experienced at least 1 SAE, neither of which were related to study product, and 1% experienced an unsolicited AE leading to discontinuation of study product. In the 15- to 17-year-old subgroup, 1 adolescent (<1%) experienced at least 1 SAE, which was not related to study product. No adolescents in this subgroup experienced unsolicited AEs leading to discontinuation of study product. No adolescents in either subgroup experienced an unsolicited AE leading to study withdrawal. MAAEs were reported by 16% of 12- to 14-year-old adolescents and 7% of 15- to 17-year-old adolescents.

Adverse events occurring in ≥5% of participants in any study cohort are listed by MedDRA system organ class (SOC) and PT in Table 18 for all stage 2 participants and by age subgroup for arm 5 adolescents. The majority of commonly reported AEs were solicited events.

Solicited Adverse Events

Table 11 lists the number and percentage of participants experiencing solicited AEs with 95% CI for adolescents (arm 5) and adults (arm 4) by symptom and dose. Solicited systemic and local AEs were similar between adolescents and adults for each dose and occurred at similar frequencies after dose 1 (through day 8) and dose 2 (through day 36).

Overall, 74% of adolescents and 68% of adults experienced a solicited systemic AE after at least 1 of the doses. Among arm 5 adolescents, the most common solicited systemic AEs after either dose were fatigue (52%), headache (50%), and myalgia (40%). Among arm 4 adults, the most common solicited systemic AEs after either dose were fatigue (49%) and headache (44%).

Solicited local AEs also occurred at similar frequencies in adolescents and adults after dose 1 and dose 2, with 88% of adolescents and 91% of adults experiencing a local AE after at least 1 of the doses. Most solicited AEs were classed as mild or moderate in severity. In adolescents, the most common solicited local AEs after either dose were pain at the injection site (74%) and erythema/redness (61%). In adults, the most common solicited local AEs after either dose were same as for adolescents, pain at the injection site (76%) and erythema/redness (74%). Solicited AEs for arm 5 adolescent subgroups are reported separately in Table 21.

When comparing reactions after each dose, a greater number of adolescents in the 12- to 14-year-old subgroup experienced systemic AEs after each dose compared to the 15- to 17-year-old subgroup. In the 12 to 14- year-old subgroup 72% of adolescents compared to 55% of adolescents in the 15- to 17-year-old subgroup experienced solicited systemic AEs after dose 1 and 58% of 12- to 14-year-olds and 47% of 15- to 17-year-olds experienced them after dose 2. Headache and fatigue were the most common after each dose in both subgroups.

Similarly, when comparing reactions after each dose, a slightly greater number of adolescents in the 12- to 14-year-old subgroup experienced local AEs compared to the 15- to 17-year-old subgroup, with pain at the injection site reported most frequently after each dose. For the 12- to 14-year-olds, 65% and 62% reported injection site pain after dose 1 and dose 2, respectively. For the 15- to 17-year-olds, 57% and 58% reported injection site pain after dose 1 and dose 2, respectively.

Proportion of Participants with a Solicited AE

Table 22 presents a comparison of the proportions of participants in each age group experiencing solicited events after either dose 1 or 2. The proportion of participants per age group who reported at least 1 solicited AE was the same for arm 5 adolescents and for arm 4 adults, 93%. Solicited systemic AE were reported in 74% of adolescents and 68% of adults. Solicited local AEs were experienced in 88% of adolescents and 91% of adults. The proportion of adolescents for each solicited AE was also comparable to adults.

Severity of Solicited Adverse Events

The type and severity of solicited AEs were comparable between adolescents and adults.

Table 23 presents the number and percentage of participants experiencing severe solicited events by symptom, dose, and age group. Severe solicited AEs were reported in 25 adolescents (8%) and 27 adults (20%).

Severity of Solicited Adverse Events in Adolescents

For adolescents, after dose 1, most solicited AEs were graded as mild (55%). Moderate solicited AEs were reported in 30% of adolescents, and 2% reported severe solicited AEs. The severe AEs reported were fatigue, fever, myalgia, and induration/swelling (<1%). The most common moderate AEs were fatigue (12%), headache, and pain at the injection site (10%). The most common mild AEs were pain at the injection site (51%), erythema/redness (33%), headache (29%) and fatigue (29%).

Three adolescents (<1%) reported severe fatigue, 1 each (<1%) reported severe fever, severe myalgia, and severe induration/swelling (Table 23).

After dose 2, the most solicited AEs were graded as moderate (42%). Severe solicited AEs were reported in 6% of adolescents, and 36% of adolescents reported mild solicited AEs. The severe AEs reported were erythema/redness (5%), induration/swelling (4%), fatigue (1%), nausea, chills, and headache, fever, and change in appetite (<1%). The most common moderate AEs were fatigue (11%) and headache (10%). The most common mild AEs were pain at the injection site (49%), headache (20%), fatigue (20%), and myalgia (18%).

Fifteen adolescents (5%) reported severe erythema/redness, 11 (4%) reported severe induration/swelling, 4 (1%) experienced severe fatigue, 2 each (<1%) experienced severe nausea, chills, and headache and 1 each (<1%) experienced severe fever and change in appetite (Table 23).

Severity of Solicited Adverse Events in Adults

For adults, after dose 1, most solicited AEs were graded as mild (50%). Moderate solicited AEs were reported in 31% of adults, and 3% of adults reported severe solicited AEs. The severe AEs reported were fatigue, arthralgia, erythema/redness, and induration/swelling (<1%). The most common moderate AEs were erythema/redness (19%) and fatigue (12%). The most common mild AEs were pain at the injection site (61%), headache (30%), and fatigue (28%).

Two adults each (1%) experienced severe fatigue, severe erythema/redness, and severe induration/swelling. One adult (<1%) experienced severe arthralgia (Table 23).

After dose 2, the most solicited AEs were graded as moderate (37%) or mild (35%). Severe solicited AEs were reported in 19% of adults. The severe AEs reported were erythema/redness (17%), induration/swelling (9%), chills and fatigue (2%) and change in appetite, myalgia, and arthralgia (<1%). The most common moderate AEs were erythema/redness (31%), induration/swelling (24%), headache (7%), and fatigue (6%). The most common mild AEs were pain at the injection site (62%), pruritis at the injection site (50%), fatigue (27%), myalgia (20%), and headache (18%).

Twenty-two adults (17%) experienced severe erythema/redness, 12 (9%) experienced severe induration/swelling, 2 adults each (2%) experienced severe chills and fatigue, and 1 (<1%) experienced severe change in appetite, myalgia, and arthralgia (Table 23).

Duration of Injection Site Adverse Events

A summary of the duration of injection site AEs is presented in Table 24. The duration of solicited systemic AEs was not collected. For participants with ongoing events at study completion or early termination, duration is censored at the date of study completion or early termination. For participants with ongoing events during follow-up, duration is censored at the planned last visit. Details on the duration of solicited local injection site AEs are provided in Table 24. Duration and onset of each injection site AE were also comparable between adolescent and adult groups after dose 1 and dose 2. Injection site reactions reported ranged from 3 to 26 days in adolescents compared to 3 to 28 days in adults.

Adolescents

After dose 1, local reactions for pain at the injection site, erythema/redness, induration/swelling, and pruritis reported in adolescents had median durations of 4, 3, 3, and 3 days respectively. Injection site pain was reported in 61% of adolescents and the median study day of onset was day 2. For moderate pain, the median duration was greater at 7 days; however, the median study day of onset was earlier at 1.5 days. Injection site erythema was reported in 38% of adolescents and the median study day of onset was day 2. In adolescents after dose 1, the shortest duration reported was injection site erythema, induration and pruritus, a median duration of 3 days. The longest median duration was 26 days for injection site discoloration.

After dose 2, local reactions for pain at the injection site, erythema/redness, induration/swelling, and pruritis reported in adolescents had median durations of 3 days each. Injection site pain was reported in 60% of adolescents and the median study day of onset was day 1. Erythema at the injection site was reported in 52% of adolescents and the median study day of onset was day 2. For both moderate and severe erythema, the median duration increased to 3 days and 5 days, respectively. The shortest duration of 3 days was comparable to after dose 1 (injection site erythema, induration, and pruritus) and also included injection site pain. The longest was also injection site discoloration, but the median duration of 16 days was less than reported after dose 1.

Adults

After dose 1, local reactions for pain at the injection site, erythema/redness, induration/swelling, and pruritis reported in adults had median durations of 4, 4, 5, and 3 days respectively.

Pain at the injection site was reported in 64% of adults and the median study day of onset was day 2. Injection site nodules were reported by 56% adults and median study day of onset was day 8, and the median duration was 28 days. The shortest duration reported was injection site pruritus, median duration of 3 days. The longest median duration was 28 days for injection site nodule.

After dose 2, local reactions for pain at the injection site, erythema/redness, induration/swelling, and pruritis reported in adolescents had median durations of 3, 4, 4 and 3 days respectively. Pain at the injection site was reported in 66% of adults and the median study day of onset was day 2. For moderate injection site pain, the median duration was 5 days. Erythema at the injection site was reported by 66% of adults and the median study day of onset was day 2. For moderate and severe erythema, the median duration was 4 days and 5 days, respectively. The shortest duration was still 3 days and reported for injection site pain and pruritus. The longest duration of injection site adverse events was injection site discoloration, a median of 13 days.

Unsolicited Adverse Events

Unsolicited AEs were reported by 63% of adolescents and 75% of adults within 28 days of receiving either dose 1 or 2. The most common AEs for both adolescents and adults were injection site nodule and injection site discoloration and were experienced at a lower incidence in adolescents. For adolescents, injection site nodule and injection site discoloration were reported in 37% and 17% of adolescents, respectively. For adults, injection site nodule and injection site discoloration were reported in 58% and 28% of participants respectively.

The most common AEs considered related to study vaccination in adolescents were injection site nodule (29% after dose 1 and 10% after dose 2) and injection site discoloration 17% (11% after dose 1 and 8% after dose 2). For adults, the most common AEs considered related to study vaccination were injection site nodule, (50% after dose 1 and 32% after dose 2) and injection site discoloration (18% after dose 1 and 19% after dose 2). The AE of dizziness was reported within 28 days of either vaccination in 3% (8/315) of adolescents and was considered related to study vaccination. No arm 4 adults reported dizziness within 28 days after either dose.

No life-threatening (grade 4) AEs were reported and there were no severe (grade ≥3) related AEs, however 8 participants (2%) experienced severe unrelated AEs. Five of these participants were arm 5 adolescents (2%) and 3 were arm 4 adults (2%). There were 20 participants (4%) with moderate related AEs and 39 participants (9%) with moderate unrelated AEs. Ten of the participants experiencing moderate related AEs were arm 5 adolescents (3%) and 10 of the participants experiencing moderate related AEs were arm 4 adults (7%).

Table 25 details unsolicited AEs for the adolescent subgroups (with severity and considered relationship to study vaccination). Younger adolescents (aged 12 to 14 years) experienced related AEs in similar frequencies to older adolescents (aged 15 to 17 years), most of which were mild in severity. Eighty-three adolescents (52%) in the 12- to 14-year-old subgroup experienced at least 1 related unsolicited AE, and 60 adolescents (37%) in this subgroup experienced an unrelated unsolicited AE. In the 15- to 17-year-old subgroup, 71 adolescents (46%) experienced at least 1 related unsolicited AE, and 40 adolescents (26%) experienced at least 1 unrelated unsolicited AE. Of the related AEs experienced by the 12- to 14-year-olds, 75 adolescents (47%) experienced mild AEs, and 8 adolescents (5%) experienced moderate AEs. Of the related AEs experienced by the 15- to 17-year-olds, 69 adolescents (45%) experienced mild AEs, and 2 adolescents (1%) experienced moderate AEs.

In the 12- to 14-year-old subgroup, 2 adolescents (1%) experienced at least 1 SAE, and 2 adolescents (1%) experienced an unsolicited AE leading to discontinuation of study product. No adolescents in this subgroup experienced unsolicited AEs leading to study withdrawal. One adolescent in the 15- to 17-year-old subgroup experienced at least 1 SAE; however, no unsolicited AEs led to discontinuation of study product or study withdrawal (Table 17).

Table 16: Overall Summary of Adverse Events by Age Group

		Adolescents (Arm 5) (N=315)		Adults (Arm 4) (N=135)		All Participants (N=450)	
Event Category[a]	**Subcategory**	**n**	**%**	**n**	**%**	**n**	**%**
At least one local solicited adverse event	Any Severity	277	88	123	91	400	89
At least one systemic solicited adverse event	Any Severity	234	74	92	68	326	72
At least one unsolicited adverse event	Any Severity	201	64	101	75	302	67
At least one related unsolicited adverse event	Any Severity	154	49	89	66	243	54
	Mild (grade 1)	146	46	85	63	231	51
	Moderate (grade 2)	10	3	10	7	20	4
	Severe (grade 3)	-	-	-	-	-	-
At least one severe (grade 3) or higher unsolicited adverse event	Any Relatedness	5	2	3	2	8	2
	Related	-	-	-	-	-	-
	Not Related	5	2	3	2	8	2
At least one serious adverse event[b]	Any Severity	3	<1	2	1	5	<1
At least one related, serious adverse event	Any Severity	-	-	-	-	-	-
At least one unsolicited adverse event leading to study withdrawal[c]	Any Severity	-	-	-	-	-	-
At least one adverse event leading to discontinuation of study product	Any Severity	2	<1	3	2	5	1
At least one medically attended adverse event (MAAE)	Any Severity	36	11	15	11	51	11
At least one unanticipated problem (UP)	Any Severity	-	-	-	-	-	-
At least one suspected unexpected serious adverse reaction (SUSAR)	Any Severity	-	-	-	-	-	-

Abbreviations: eCRF = electronic case report form; MAAE = medically attended adverse event; N = number of participants in the safety population; n = number of participants meeting the row criteria; SUSAR = suspected unexpected serious adverse reaction; UP = unanticipated problem.
No life-threatening (grade 4) events were observed.
[a] Participants are counted once for each category regardless of the number of events.
[b] A listing of serious adverse events is included in the listing of serious adverse events.
[c] As reported on the adverse event eCRF.
No life-threatening (grade 4) events were observed.

Table 17: Overall Summary of Adverse Events by Adolescent Age Subgroup

		Adolescents (arm 5) 12 to 14 years old (N=161)		Adolescents (arm 5) 15 to 17 years old (N=154)	
Event Category[a]	**Subcategory**	**n**	**%**	**n**	**%**
At least one local solicited adverse event	Any Severity	146	91	131	85
At least one systemic solicited adverse event	Any Severity	131	81	103	67
At least one unsolicited adverse event	Any Severity	110	68	91	59
At least one related unsolicited adverse event	Any Severity	83	52	71	46
	Mild (grade 1)	76	47	70	45
	Moderate (grade 2)	8	5	2	1
	Severe (grade 3)	-	-	-	-
At least one severe (grade 3) or higher unsolicited adverse event	Any Relatedness	5	3	-	-
	Related	-	-	-	-
	Not Related	5	3	-	-
At least one serious adverse event	Any Severity	2	1	1	<1
At least one related, serious adverse event	Any Severity	-	-	-	-
At least one unsolicited adverse event leading to study withdrawal[c]	Any Severity	-	-	-	-
At least one adverse event leading to discontinuation of study product[b]	Any Severity	2	1	-	-
At least one medically attended adverse event (MAAE)	Any Severity	25	16	11	7
At least one unanticipated problem	Any Severity	-	-	-	-
At least one suspected unexpected serious adverse reaction (SUSAR)	Any Severity	-	-	-	-

Abbreviations: eCRF = electronic case report form; MAAE = medically attended adverse event; N = number of participants in the safety population; n = number of participants meeting the row criteria; SUSAR = suspected unexpected serious adverse reaction;.
No life-threatening (grade 4) events were observed.
[a] Participants are counted once for each category regardless of the number of events.
[b] A listing of serious adverse events is included in the listing of serious adverse events.
[c] As reported on the adverse event eCRF.

Table 18: Solicited and Unsolicited Adverse Events Occurring in 5% of Participants in Any Age Group by MedDRA System Organ Class and Preferred Term, and Age Group, Safety Population

		Adolescents (Arm 5) (N=315)			Adults (Arm 4) (N=135)			All Participants (N=450)		
MedDRA System Organ Class	**MedDRA Preferred Term**	**n**	**%**	**Events**	**n**	**%**	**Events**	**n**	**%**	**Events**
Serious Adverse Events										
All	All	-	-	-	-	-	-	-	-	-
Other (Non-serious) Adverse Events										
All	All	301	96	2256	128	95	1100	429	95	3356

		Adolescents (Arm 5) (N=315)			Adults (Arm 4) (N=135)			All Participants (N=450)		
MedDRA System Organ Class	**MedDRA Preferred Term**	**n**	**%**	**Events**	**n**	**%**	**Events**	**n**	**%**	**Events**
Gastrointestinal disorders	Nausea	75	24	96	20	15	24	95	21	120
General disorders and administration site conditions	Chills	44	14	53	22	16	27	66	15	80
	Fatigue	164	52	230	66	49	102	230	51	332
	Injection site bruising	18	6	20	3	2	4	21	5	24
	Injection site discoloration	53	17	57	38	28	51	91	20	108
	Injection site erythema	192	61	281	100	74	156	292	65	437
	Injection site induration	175	56	238	90	67	137	265	59	375
	Injection site nodule	117	37	128	79	59	110	196	44	238
	Injection site pain	232	74	380	103	76	172	335	74	552
	Injection site pruritus	158	50	223	81	60	119	239	53	342
	Pyrexia	13	4	13	7	5	7	20	4	20
Infections and infestations	Upper respiratory tract infection	17	5	17	6	4	6	23	5	23
Metabolism and nutrition disorders	Appetite disorder	55	17	67	17	13	20	72	16	87
Musculoskeletal and connective tissue disorders	Arthralgia	52	17	62	23	17	28	75	17	90
	Myalgia	129	41	171	47	35	59	176	39	230
Nervous system disorders	Headache	157	50	220	60	44	78	217	48	298

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; N = number of participants in the safety population (number of participants at risk); n = number of participants reporting event.
Events = Total frequency of events reported. Solicited events are only counted once per associated dose.
There were no serious adverse events that occurred in at least 5% of participants.

Table 19: Solicited and Unsolicited Adverse Events Occurring in 5% of Participants in Any Age Subgroup by MedDRA System Organ Class and Preferred Term, and Adolescent Age Subgroup, Safety Population

		Adolescents (Arm 5) 12 to 14 years old (N=161)			Adolescents (Arm 5) 15 to 17 years old (N=154)		
MedDRA System Organ Class	**MedDRA Preferred Term**	**n**	**%**	**Events**	**n**	**%**	**Events**
Serious Adverse Events							
All	All	-	-	-	-	-	-
Other (Non-serious) Adverse Events							
All	All	158	98	1227	143	93	1029
Gastrointestinal disorders	Nausea	42	26	53	33	21	43
General disorders and administration site conditions	Chills	26	16	32	18	12	21
	Fatigue	92	57	129	72	47	101
	Injection site bruising	12	7	13	6	4	7
	Injection site discolouration	26	16	29	27	18	28
	Injection site erythema	95	59	146	97	63	135
	Injection site induration	93	58	129	82	53	109
	Injection site nodule	64	40	70	53	34	58

		Adolescents (Arm 5) 12 to 14 years old (N=161)			Adolescents (Arm 5) 15 to 17 years old (N=154)		
MedDRA System Organ Class	**MedDRA Preferred Term**	**n**	**%**	**Events**	**n**	**%**	**Events**
	Injection site pain	124	77	203	108	70	177
	Injection site pruritus	75	47	107	83	54	116
	Pyrexia	10	6	10	3	2	3
Infections and infestations	Upper respiratory tract infection	12	7	12	5	3	5
Metabolism and nutrition disorders	Appetite disorder	37	23	42	18	12	25
Musculoskeletal and connective tissue disorders	Arthralgia	29	18	34	23	15	28
	Myalgia	77	48	101	52	34	70
Nervous system disorders	Headache	85	53	117	72	47	103

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; N = number of participants in the safety population (number of participants at risk); n = number of participants reporting event; Events = total frequency of events reported.
Solicited events are only counted once per associated dose.
There were no serious adverse events that occurred in at least 5% of participants.

Table 20: Number and Percentage of Participants Experiencing Solicited Events with 95% Confidence Intervals by Symptom, Dose, and Age Group

	Post Dose 1 Adolescents (Arm 5) (N=315)			Post Dose 1 Adults (Arm 4) (N=135)			Post Dose 2 Adolescents (Arm 5) (N=312)			Post Dose 2 Adults (Arm 4) (N=131)			Post Either Dose Adolescents (Arm 5) (N=315)			Post Either Dose Adults (Arm 4) (N=135)		
Symptom	**n**	**%**	**95 % CI**	**n**	**%**	**95 % CI**	**n**	**%**	**95 % CI**	**n**	**%**	**95 % CI**	**n**	**%**	**95 % CI**	**n**	**%**	**95 % CI**
Any Symptom	274	87	83, 90	114	84	77, 90	263	84	80, 88	119	91	85, 95	294	93	90, 96	126	93	88, 97
Systemic Symptoms																		
Any Systemic Symptom	201	64	58, 69	79	59	50, 67	165	53	47, 59	66	50	42, 59	234	74	69, 79	92	68	60, 76
Fever	7	2	<1, 5	3	2	<1, 6	6	2	<1, 4	4	3	<1, 8	13	4	2, 7	7	5	2, 10
Chills	25	8	5, 11	15	11	6, 18	28	9	6, 13	12	9	5, 15	44	14	10, 18	22	16	11, 24
Nausea	49	16	12, 20	11	8	4, 14	47	15	11, 20	13	10	5, 16	75	24	19, 29	20	15	9, 22
Headache	122	39	33, 44	46	34	26, 43	97	31	26, 37	32	24	17, 33	156	50	44, 55	60	44	36, 53
Fatigue	132	42	36, 48	56	41	33, 50	98	31	26, 37	46	35	27, 44	164	52	46, 58	66	49	40, 58
Change in Appetite	41	13	10, 17	9	7	3, 12	26	8	6, 12	11	8	4, 15	55	17	13, 22	17	13	8, 19
Myalgia	90	29	24, 34	27	20	14, 28	79	25	21, 31	32	24	17, 33	127	40	35, 46	47	35	27, 43
Arthralgia	34	11	8, 15	15	11	6, 18	27	9	6, 12	13	10	5, 16	51	16	12, 21	23	17	11, 24

	Post Dose 1 Adolescents (Arm 5) (N=315)			Post Dose 1 Adults (Arm 4) (N=135)			Post Dose 2 Adolescents (Arm 5) (N=312)			Post Dose 2 Adults (Arm 4) (N=131)			Post Either Dose Adolescents (Arm 5) (N=315)			Post Either Dose Adults (Arm 4) (N=135)		
Symptom	**n**	**%**	**95 % CI**	**n**	**%**	**95 % CI**	**n**	**%**	**95 % CI**	**n**	**%**	**95 % CI**	**n**	**%**	**95 % CI**	**n**	**%**	**95 % CI**
Local Symptoms																		
Any Local Symptom	243	77	72, 82	105	78	70, 84	248	79	75, 84	116	89	82, 93	277	88	84, 91	123	91	85, 95
Pain at injection site	193	61	56, 67	86	64	55, 72	187	60	54, 65	86	66	57, 74	232	74	68, 78	103	76	68, 83
Erythema/redness	119	38	32, 43	68	50	42, 59	162	52	46, 58	86	66	57, 74	192	61	55, 66	100	74	66, 81
Induration/swelling[a]	93	30	25, 35	60	44	36, 53	144	46	41, 52	76	58	49, 67	174	55	50, 61	90	67	58, 75
Pruritus at injection site	96	30	25, 36	48	36	28, 44	127	41	35, 46	71	54	45, 63	158	50	44, 56	81	60	51, 68

Abbreviations: CI = confidence interval, calculated using Clopper-Pearson methodology; N = number of participants in the safety population who received the specified dose; n = number of participants meeting the row criteria
Notes: Only events that occurred within the reactogenicity period (7 days after dose) were considered.
[a] Graded according to the induration grading scale.

Table 21: Number and Percentage of Participants Experiencing Solicited Events with 95% Confidence Intervals by Symptom, Dose, and Adolescent Age Subgroup

	Post Dose 1 Adolescents (Arm 5) 12 to 14 years old (N=161)			Post Dose 1 Adolescents (Arm 5) 15 to 17 years old (N=154)			Post Dose 2 Adolescents (Arm 5) 12 to 14 years old (N=158)			Post Dose 2 Adolescents (Arm 5) 15 to 17 years old (N=154)		
Symptom	**N**	**%**	**95% CI**	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**
Any Symptom	146	91	85, 95	128	83	76, 89	138	87	81, 92	125	81	74, 87
Systemic Symptoms												
Any Systemic Symptom	116	72	64, 79	85	55	47, 63	92	58	50, 66	73	47	39, 56
Fever	4	2	<1, 6	3	2	<1, 6	6	4	1, 8	-	-	-
Chills	17	11	6, 16	8	5	2, 10	15	9	5, 15	13	8	5, 14
Nausea	28	17	12, 24	21	14	9, 20	25	16	11, 22	22	14	9, 21
Headache	66	41	33, 49	56	36	29, 44	50	32	24, 40	47	31	23, 38
Fatigue	75	47	39, 55	57	37	29, 45	54	34	27, 42	44	29	22, 36
Change in Appetite	26	16	11, 23	15	10	6, 16	16	10	6, 16	10	6	3, 12
Myalgia	53	33	26, 41	37	24	18, 32	46	29	22, 37	33	21	15, 29

	Post Dose 1 Adolescents (Arm 5) 12 to 14 years old (N=161)			Post Dose 1 Adolescents (Arm 5) 15 to 17 years old (N=154)			Post Dose 2 Adolescents (Arm 5) 12 to 14 years old (N=158)			Post Dose 2 Adolescents (Arm 5) 15 to 17 years old (N=154)		
Symptom	**N**	**%**	**95% CI**	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**
Arthralgia	19	12	7, 18	15	10	6, 16	14	9	5, 14	13	8	5, 14
Local Symptoms												
Any Local Symptom	127	79	72, 85	116	75	68, 82	132	84	77, 89	116	75	68, 82
Pain at injection site	105	65	57, 73	88	57	49, 65	98	62	54, 70	89	58	50, 66
Erythema/redness	63	39	32, 47	56	36	29, 44	83	53	44, 61	79	51	43, 59
Induration/swelling[a]	49	30	23, 38	44	29	22, 36	79	50	42, 58	65	42	34, 50
Pruritus at injection site	44	27	21, 35	52	34	26, 42	63	40	32, 48	64	42	34, 50

Abbreviations: CI = confidence interval, calculated using Clopper-Pearson methodology; N = number of participants in the safety population who received the specified dose; n = number of participants meeting the row criteria
Notes: Only events that occurred within the reactogenicity period (7 days after dose) were considered.
[a] Graded according to the induration grading scale.

Table 22: Comparison of the Proportion of Participants Experiencing Solicited Events by Age Group – Post Either Dose

Symptom	Adolescents (Arm 5) (N=315) Proportion (95% CI)	Adults (Arm 4) (N=135) Proportion (95% CI)	Difference (Adults – Adolescents) and 95% CI
Any Symptom	0.93 (0.90, 0.96)	0.93 (0.88, 0.97)	0.000 (-0.050, 0.050)
Systemic Symptoms			
Any Systemic Symptom	0.74 (0.69, 0.79)	0.68 (0.60, 0.76)	-0.061 (-0.154, 0.031)
Fever	0.04 (0.02, 0.07)	0.05 (0.02, 0.10)	0.011 (-0.033, 0.054)
Chills	0.14 (0.10, 0.18)	0.16 (0.11, 0.24)	0.023 (-0.050, 0.096)
Nausea	0.24 (0.19, 0.29)	0.15 (0.09, 0.22)	-0.090 (-0.166, -0.014)
Headache	0.50 (0.44, 0.55)	0.44 (0.36, 0.53)	-0.051 (-0.151, 0.050)
Fatigue	0.52 (0.46, 0.58)	0.49 (0.40, 0.58)	-0.032 (-0.133, 0.069)
Change in Appetite	0.17 (0.13, 0.22)	0.13 (0.08, 0.19)	-0.049 (-0.119, 0.021)
Myalgia	0.40 (0.35, 0.46)	0.35 (0.27, 0.43)	-0.055 (-0.152, 0.042)
Arthralgia	0.16 (0.12, 0.21)	0.17 (0.11, 0.24)	0.008 (-0.067, 0.084)
Local Symptoms			
Any Local Symptom	0.88 (0.84, 0.91)	0.91 (0.85, 0.95)	0.032 (-0.028, 0.092)
Pain at injection site	0.74 (0.68, 0.78)	0.76 (0.68, 0.83)	0.026 (-0.060, 0.113)
Erythema/redness	0.61 (0.55, 0.66)	0.74 (0.66, 0.81)	0.131 (0.040, 0.223)
Induration/swelling[a]	0.55 (0.50, 0.61)	0.67 (0.58, 0.75)	0.114 (0.018, 0.211)
Pruritus at injection site	0.50 (0.44, 0.56)	0.60 (0.51, 0.68)	0.098 (-0.001, 0.198)

Abbreviations: CI = confidence interval, calculated using Clopper-Pearson methodology for proportions and Wald methodology for the difference; N = number of participants in the safety population; n = number of participants meeting the row criteria; Proportion = n divided by N.
[a] Graded according to the induration grading scale.

Table 23: Number and Percentage of Participants Experiencing Severe Solicited Events by Symptom, Dose, and Age Group

	Post Dose 1 Adolescents (Arm 5) (N=315)			Post Dose 1 Adults (Arm 4) (N=135)			Post Dose 2 Adolescents (Arm 5) (N=312)			Post Dose 2 Adults (Arm 4) (N=131)			Post Either Dose Adolescents (Arm 5) (N=315)			Post Either Dose Adults (Arm 4) (N=135)		
Symptom	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**
Any Symptom	6	2	<1, 4	4	3	<1, 7	20	6	4, 10	25	19	13, 27	25	8	5, 11	27	20	14, 28
Systemic																		
Any Symptom	5	2	<1, 4	2	1	<1, 5	6	2	<1, 4	3	2	<1, 7	10	3	2, 6	4	3	1, 7
Fever	1	< 1	<1, 2				1	< 1	<1, 2				2	< 1	<1, 2			
Chills							2	< 1	<1, 2	2	2	<1, 5	2	< 1	<1, 2	2	1	<1, 5
Nausea							2	< 1	<1, 2				2	< 1	<1, 2			
Headache							2	< 1	<1, 2				2	< 1	<1, 2			
Fatigue	3	< 1	<1, 3	2	1	<1, 5	4	1	<1, 3	2	2	<1, 5	6	2	<1, 4	3	2	<1, 6
Chage in Appetite							1	< 1	<1, 2	1	< 1	<1, 4	1	< 1	<1, 2	1	< 1	<1, 4
Myalgia	1	< 1	<1, 2							1	< 1	<1, 4	1	< 1	<1, 2	1	< 1	<1, 4
Arthralgia				1	< 1	<1, 4				1	< 1	<1, 4				2	1	<1, 5
Local Symptoms																		
Any Local Symptom	1	< 1	<1, 2	2	1	<1, 5	16	5	3, 8	23	18	11, 25	17	5	3, 9	24	18	12, 25
Pain at injection site																		
Erythema/redness				2	1	<1, 5	15	5	3, 8	22	17	11, 24	15	5	3, 8	23	17	11, 24
Induration/swelling[a]	1	< 1	<1, 2	2	1	<1, 5	11	4	2, 6	12	9	5, 15	12	4	2, 7	13	10	5, 16
Pruritus at injection site																		

Abbreviations: CI = confidence interval, calculated using Clopper-Pearson methodology; N = number of participants in the safety population who received the specified dose; n = number of participants meeting the row criteria.
Notes: Severity is the maximum severity reported during the reactogenicity period (7 days post dose) for each participant.
No life-threatening (grade 4) events were observed.
[a] Graded according to the induration grading scale.

Table 24: Duration of Injection Site Adverse Events

	Injection Site Bruising	Injection Site Discolouration	Injection Site Erythema	Injection Site Induration	Injection Site Nodule	Injection Site Pain	Injection Site Pruritus
Adolescents (Arm 5) Post-Dose 1 (N=315)							
Any Severity (n [%])	17 [5]	47 [15]	119 [38]	94 [30]	110 [35]	193 [61]	96 [30]

	Injection Site Bruising	Injection Site Discolouration	Injection Site Erythema	Injection Site Induration	Injection Site Nodule	Injection Site Pain	Injection Site Pruritus
Median Onset Day Post-Dose [Minimum, Maximum]	7.0 [1, 9]	9.0 [4, 36]	2.0 [1, 8]	2.5 [1, 9]	9.0 [2, 36]	2.0 [1, 8]	3.0 [1, 8]
Median Days Duration [Minimum, Maximum]	6.0 [2, 27]	26.0 [4, 372]	3.0 [1, 18]	3.0 [1, 20]	22.0 [2, 54]	4.0 [1, 18]	3.0 [1, 11]
Adolescents (Arm 5) Post-Dose 2 (N=312)							
Any Severity (n [%])	3 [<1]	10 [3]	162 [52]	144 [46]	18 [6]	187 [60]	127 [41]
Median Onset Day Post-Dose [Minimum, Maximum]	7.0 [4, 8]	10.0 [6, 22]	2.0 [1, 5]	2.0 [1, 6]	9.0 [2, 15]	1.0 [1, 5]	2.0 [1, 8]
Median Days Duration [Minimum, Maximum]	6.0 [1, 12]	16.0 [3, 410]	3.0 [1, 21]	3.0 [1, 11]	11.5 [3, 170]	3.0 [1, 11]	3.0 [1, 9]
Adults (Arm 4) Post-Dose 1 (N=135)							
Any Severity (n [%])	3 [2]	31 [23]	70 [52]	61 [45]	76 [56]	86 [64]	48 [36]
Median Onset Day Post-Dose [Minimum, Maximum]	8.0 [8, 28]	9.0 [4, 37]	3.0 [1, 9]	3.0 [1, 9]	8.0 [1, 35]	2.0 [1, 8]	3.0 [1, 8]
Median Days Duration [Minimum, Maximum]	23.0 [8, 23]	26.0 [3, 382]	4.0 [1, 23]	5.0 [1, 28]	28.0 [2, 200]	4.0 [1, 28]	3.0 [1, 27]
Adults (Arm 4) Post-Dose 2 (N=131)							
Any Severity (n [%])	1 [<1]	20 [15]	86 [66]	76 [58]	34 [26]	86 [66]	71 [54]
Median Onset Day Post-Dose [Minimum, Maximum]	7.0 [7, 7]	8.0 [4, 16]	2.0 [1, 4]	2.0 [1, 3]	8.0 [4, 16]	2.0 [1, 5]	2.0 [1, 6]
Median Days Duration [Minimum, Maximum]	10.0 [10, 10]	13.0 [4, 351]	4.0 [1, 20]	4.0 [1, 18]	8.0 [3, 114]	3.0 [1, 8]	3.0 [1, 9]

Abbreviations: N = number of participants in the safety population who received the specified dose; n = number of participants experiencing a given preferred term.
Duration is calculated as the total days from first non-zero grade to last non-zero grade. For participants with ongoing events at study completion or early termination, duration is censored at the date of study completion or early termination. Severity is categorized by maximum grade at any day post dose.
No life-threatening (grade 4) events were observed.

Table 25: Unsolicited Adverse Events by MedDRA System Organ Class and Preferred Term, Maximum Severity, Relationship, and Adolescent Age Subgroup Reported in More Than 1 Participant

			Adolescents (Arm 5) 12 to 14 years old (N=161)				Adolescents (Arm 5) 15 to 17 years old (N=154)			
			Related		Not Related		Related		Not Related	
MedDRA System Organ Class	Preferred Term	Severity	n	%	n	%	n	%	n	%
Any SOC	Any PT	Any Severity	83	52	60	37	71	46	40	26
		Mild	75	47	36	22	69	45	30	19
		Moderate	8	5	19	12	2	1	10	6
		Severe	-	-	5	3	-	-	-	-
Blood and lymphatic system disorders	Lymphadenopathy	Any Severity	2	1	1	<1	2	1	-	-
		Mild	2	1	1	<1	2	1	-	-
Eye Disorders	Any PT	Any Severity	-	-	1	<1	-	-	2	1

			Adolescents (Arm 5) 12 to 14 years old (N=161)				Adolescents (Arm 5) 15 to 17 years old (N=154)			
			Related		Not Related		Related		Not Related	
MedDRA System Organ Class	**Preferred Term**	**Severity**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
		Mild	-	-	1	<1	-	-	2	1
Gastrointestinal disorders	Any PT	Any Severity	1	<1	3	2	1	<1	3	2
		Mild	1	<1	2	1	-	-	3	1
		Moderate	-	-	1	<1	1	<1	1	<1
	Dyspepsia	Any Severity	-	-	2	1	-	-	-	-
		Mild	-	-	1	<1	-	-	-	-
		Moderate	-	-	1	<1	-	-	-	-
General disorders and administration site conditions	Any PT	Any Severity	74	46	16	10	67	44	6	4
		Mild	71	44	16	10	67	44	6	4
		Moderate	3	2	-	-	-	-	-	-
	Injection site bruising	Any Severity	-	-	12	7	-	-	6	4
		Mild	-	-	12	7	-	-	6	4
	Injection site discoloration	Any Severity	26	16	-	-	27	18	-	-
		Mild	26	16	-	-	27	18	-	-
	Injection site haemorrhage	Any Severity	3	2	1	<1	1	<1	-	-
		Mild	3	2	1	<1	1	<1	-	-
	Injection site nodule	Any Severity	64	40	-	-	53	34	-	-
		Mild	61	38	-	-	53	34	-	-
		Moderate	3	2	-	-	-	-	-	-
Immune system disorders	Any PT	Any Severity	-	-	2	1	-	-	-	-
		Mild	-	-	2	1	-	-	-	-
Infections and infestations	Any PT	Any Severity	1	<1	29	18	2	1	19	12
		Mild	1	<1	15	9	2	1	13	8
		Moderate	-	-	11	7	-	-	6	4
		Severe	-	-	3	2	-	-	-	-
	COVID-19	Any Severity	-	-	4	2	-	-	1	<1
		Mild	-	-	4	2	-	-	1	<1
	Folliculitis	Any Severity	-	-	-	-	-	-	2	1
		Mild	-	-	-	-	-	-	2	1
	Gastroenteritis	Any Severity	-	-	3	2	-	-	2	1
		Mild	-	-	1	<1	-	-	-	-
		Moderate	-	-	2	1	-	-	2	1
	Influenza	Any Severity	-	-	2	1	-	-	-	-
		Moderate	-	-	2	1	-	-	-	-
	Nasopharyngitis	Any Severity	-	-	1	<1	-	-	3	2
		Mild	-	-	1	<1	-	-	3	2
	Pharyngitis	Any Severity	-	-	-	-	2	1	1	<1

			Adolescents (Arm 5) 12 to 14 years old (N=161)				Adolescents (Arm 5) 15 to 17 years old (N=154)			
			Related		Not Related		Related		Not Related	
MedDRA System Organ Class	**Preferred Term**	**Severity**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
		Mild	-	-	-	-	2	1	1	<1
	Pharyngitis streptococcal	Any Severity	-	-	3	2	-	-	2	1
		Mild	-	-	2	1	-	-	1	<1
		Moderate	-	-	-	-	-	-	1	<1
		Severe	-	-	1	<1	-	-	-	-
	Upper respiratory tract infection	Any Severity	-	-	12	7	-	-	5	3
		Mild	-	-	8	5	-	-	3	2
		Moderate	-	-	3	2	-	-	2	1
		Severe	-	-	1	<1	-	-	-	-
Injury, poisoning and procedural complications	Any PT	Any Severity	-	-	10	6	-	-	5	3
		Mild	-	-	7	4	-	-	3	2
		Moderate	-	-	3	2	-	-	2	1
	Skin abrasion	Any Severity	-	-	2	1	-	-	-	-
		Mild	-	-	2	1	-	-	-	-
	Skin laceration	Any Severity	-	-	2	1	-	-	-	-
		Mild	-	-	2	1	-	-	-	-
Musculoskeletal and connective tissue disorders	Any PT	Any Severity	1	<1	3	2	-	-	1	<1
		Mild	1	<1	3	2	-	-	1	<1
	Myalgia	Any Severity	1	<1	2	1	-	-	-	-
		Mild	1	<1	2	1	-	-	-	-
Nervous system disorders	Any PT	Any Severity	8	5	4	2	3	2	3	2
		Mild	3	2	3	2	1	<1	2	1
		Moderate	5	3	1	<1	2	1	1	<1
	Dizziness	Any Severity	6	4	2	1	2	1	1	<1
		Mild	3	2	2	1	1	<1	1	<1
		Moderate	3	2	-	-	1	<1	-	-
Reproductive system and breast disorders	Any PT	Any Severity	-	-	2	1	-	-	1	<1
		Mild	-	-	1	<1	-	-	1	<1
		Severe			1	<1				
Respiratory, thoracic and mediastinal disorders	Any PT	Any Severity	-	-	2	1	1	<1	3	2
		Mild	-	-	2	1	1	<1	2	1
		Moderate	-	-	-	-	-	-	1	<1
Skin and subcutaneous tissue disorders	Any PT	Any Severity	-	-	3	2	-	-	7	5
		Mild	-	-	-	-	-	-	7	5
		Moderate	-	-	3	2	-	-	-	-

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; N = number of participants in the safety population; n = number of participants meeting the row criteria; PT = preferred term; SOC = system organ class.

Notes: Maximum severity is taken for each relationship status. A participant may be counted in 'Related' and 'Not Related' for the same PT.

No grade 4 events were observed.

Deaths

No deaths were reported from clinical trial DMID 22-0020 (stage 2).

Other Serious Adverse Events

Serious adverse events are listed in Table 26.

During the follow-up phase, 3 SAEs were reported in arm 5 adolescents, major depressive disorder (study day 231), pyelonephritis (study day 365), and infective myositis (study day 330). Two SAEs were reported in arm 4 adults, pyelonephritis (study day 319) and suicide ideation (study day 182). The SAEs were not considered related to the study product nor were they considered a suspected unexpected serious adverse reaction (SUSAR), unanticipated problem (UP), or AESI.

Table 26: Listing of Serious Adverse Events

Adverse Event	Associated with Dose No.	No. of Days Post Associated Dose (Duration)	No. of Days Post Dose the Event Became Serious	Reason Reported as an SAE	SUSAR/ UP/ AESI?	Severity	Relationship to Study Vaccination	If Not Related, Alternative Etiology	Action Taken with Study Vaccination	Participant Discontinued Due to AE	Outcome	MedDRA System Organ Class	MedDRA Preferred Term
Age Group: Adolescents (Arm 5**AE Number:** 010													
Major depressive episode	2	231 (Ongoing)	231	Hospitalization /Prolonged Hospitalization	No	Severe	Not Related	Other medical condition or illness: major depressive disorder	Not applicable	No	Recovering /Resolving	Psychiatric disorders	Major depression
Comments: Participant diagnosed with Major Depressive Disorder on 06-Jun-2023 and Generalized Anxiety Disorder on 29-Jun-2023. Participant had 3 separate admissions to a psychiatric hospital. Per PVG's guidance, these 3 Major Depressive Episodes were combined to 1 SAE and the outcome was updated to recovering. Participant was hospitalized for the third major depressive episode from 01-May-2024 to 16-May-2024.													
Age Group: Adolescents (Arm 5), **AE Number:** 002													
Pyelonephritis	2	365 (4)	365	Hospitalization /Prolonged Hospitalization	No	Moderate	Not Related	Other medical condition or illness: kidney infection	Not applicable	No	Recovered /Resolved	Infections and infestations	Pyelonephritis
Comments: Patient was prescribed Macrobid to be taken once Bactrim was finished. Participant wss on this medication as a preventative measure until 2 weeks postpartum.													
Age Group: Adolescents (Arm 5), **AE Number:** 005													

Adverse Event	Associated with Dose No.	No. of Days Post Associated Dose (Duration)	No. of Days Post Dose the Event Became Serious	Reason Reported as an SAE	SUSAR/ UP/ AESI?	Severity	Relationship to Study Vaccination	If Not Related, Alternative Etiology	Action Taken with Study Vaccination	Participant Discontinued Due to AE	Outcome	MedDRA System Organ Class	MedDRA Preferred Term
Infective myositis	2	330 (16)	330	Hospitalization /Prolonged Hospitalization	No	Severe	Not Related	Other medical condition or illness: bacterial infection	Not applicable	No	Recovered /Resolved	Infections and infestations	Infective myositis
Comments: None													
Age Group: Adults (Arm 4), **AE Number:** 004													
Pyelonephritis	2	319 (9)	324	Hospitalization /Prolonged Hospitalization	No	Severe	Not Related	Other medical condition or illness: bacterial upper urine tract infection	Not applicable	No	Recovered /Resolved	Infections and infestations	Pyelonephritis
Comments: 27-Mar-2024: Per PI, severity is graded life-threatening (grade 4) due to the hospitalization, otherwise, this event is graded severe (grade 3). 28-JUN-2024: Severity updated to grade 3 per the emmes query and after discussion with PI.													
Age Group: Adults (Arm 4), **AE Number:** 003													
Suicide ideation	2	182 (6)	182	Hospitalization /Prolonged Hospitalization	No	Moderate	Not Related	Other: domestic violence	Not applicable	No	Recovered /Resolved	Psychiatric disorders	Suicidal ideation
Comments: Hospitalized													

Abbreviations: AE = adverse event; AESI = adverse event of special interest; ID = participant identifier; MedDRA = Medical Dictionary for Regulatory Activities; No. = number; PI = primary investigator; PVG = pharmacovigilance; SAE = serious adverse event; SUSAR = suspected unexpected serious adverse reaction; UP = unanticipated problem.

Other Significant Adverse Events

Ten arm 5 adolescents (3%) and 10 arm 4 adults (7%) experienced at least 1 related moderate AE. None of these AEs resulted in study withdrawal.

Two related MAAEs were reported in arm 4 adults, 1 moderate event of psoriasis 15 days after dose 2 and 1 mild event of irregular menstrual bleeding 2 days after dose 1. None of the MAAEs resulted in study withdrawal, and there were no reported UPs or AESIs.

Cardiac adverse events of special interest

There were no cardiac AEs considered related to study vaccination. Two participants, 1 adolescent and 1 adult, reported mild AEs of tachycardia.

Analysis of Adverse Events by Organ System or Syndrome

The most commonly reported AEs were solicited events. The majority of AEs that occurred were reported as general disorders and administration site conditions. The most frequent AE reported was injection site pain, 74% of adolescents and 76% of adults experiencing the AE. The next most common were injection site erythema reported in 61% of adolescents and 74% of adults, followed by injection site induration/swelling reported in 56% of adolescents and 67% of adults. The incidences reported for these were lower in adolescents than in adults.

Clinical Laboratory Evaluations

No safety clinical laboratory evaluations were performed in clinical trial DMID 22-0020 (stage 2), other than pregnancy tests.

Abnormal vital signs

Vital sign measurements included systolic blood pressure, diastolic blood pressure, pulse, and oral temperature. Vital signs were assessed at days 1 and 29 prior to vaccination and as needed at other study visits if interim change in medical status reported by participant. Vital signs were tabulated by visit and treatment group.

No abnormal diastolic BP were reported for arm 5 adolescents. However, of the 285 arm 5 adolescents with after baseline measurements, 3 (1%) reported low systolic BP and 2 (<1%) reported elevated systolic BP. Of the 132 arm 4 adults with after baseline measurements, 6 (5%) reported elevated diastolic BP, 2 of which were severe, and 10 (8%) reported elevated systolic BP, 2 of which were severe.

Of the 285 arm 5 adolescents with after baseline results, 8 (3%) reported a decreased pulse rate and 5 (2%) reported an increased pulse rate. Of the 132 arm 4 adults with post baseline measurements, 6 (5%) reported a decreased pulse rate and 2 (2%) reported an increased pulse rate.

No trends in vital signs abnormalities were noted.

Physical Examinations

Physical examinations were performed on days 1, 8, 29, 36, 43, and as needed at other study visits if interim change in medical status was reported by the participant. The skin was assessed as part of the physical exam and other body systems were assessed if indicated.

The abnormal physical examination findings were reported as AEs. Additionally, hyperpigmentation (injection site discoloration) and injection site nodule measurements were monitored and measured regardless of AE status.

No trends in physical examination abnormalities were noted.

Withdrawals and Discontinuation

Arm 5 adolescents had fewer early withdrawals from the study than arm 4 adults (7/315 adolescents, 2% vs. 10/135 adults, 7%; $p = 0.013$).

Of the 315 enrolled arm 5 adolescents, 3 (<1%) did not receive the second vaccination due to an AE (solicited or unsolicited), 1 of which (solicited reactogenicity: arm pain) led to early withdrawal from the study on day 11. All 3 of these adolescents belonged to the younger (12- to 14-year-old) age

group. In addition to the participant terminating early due to a solicited AE, 6 arm 5 adolescents terminated early. One was lost to follow-up on day 33, 1 was lost to follow-up on day 459, 1 was withdrawn from the study by their parent on day 45, and the other 3 were unreachable after day 394.

Of the 135 enrolled arm 4 adults, 4 (3%) did not receive the second vaccination, of which 3 were due to an AE and 1 no longer met inclusion criteria #4 (Females of reproductive potential who have sexual intercourse with male partners must be using highly effective contraception for at least 1 month prior to signing ICF and agrees to use acceptable method of contraception through day 57). Eight adults were lost to follow-up, of which many only had the last study visit left to complete. One arm 4 adult voluntarily withdrew on day 45. One arm 4 adult also terminated early and became unreachable at day 394.

Pregnancies

Two pregnancies were reported in arm 5 adolescents. Both pregnancies resulted in live births with no congenital abnormalities reported.

Safety in Special Groups and Situations

Intrinsic Factors

Age

Secondary safety outcomes are analyzed in Table 27 to compare arm 5 adolescents to arm 4 adults and in Table 28 to compare arm 5 adolescent age subgroups to arm 4 adults.

Adolescents had fewer severe solicited events and fewer mild related unsolicited AEs than arm 4 adults. Arm 5 adolescents experienced fewer more moderate related unsolicited AEs than arm 4 adults.

- Arm 5 adolescents (n [%]) vs. arm 4 adults (n [%])
  - Severe solicited AEs: 25 (8%) adolescents vs. 27 (20%) adults
  - Mild related unsolicited AEs: 146 (46%) adolescents vs. 85 (63%) adults
  - Moderate related unsolicited AEs: 10 (3%) adolescents vs. 10 (7%) adults

Similar conclusions are made when comparing each arm 5 adolescent age subgroup to arm 4 adults. Additionally, 15- to 17-year-olds had fewer moderate unsolicited AEs than adults 18 years and older.

- 12 to 14 years old (n [%]) vs. ≥18 years old (n [%])
  - Severe solicited AEs: 18 (11%) vs. 27 (20%) adults
  - Mild related unsolicited AEs: 76 (47%) adolescents vs. 85 (63%) adults
  - Moderate related unsolicited AEs: 8 (5%) adolescents vs. 10 (7%) adults
- 15 to 17 years old (n [%]) vs. ≥18 years old (n [%])
  - Severe solicited AEs: 7 (5%) vs. 27 (20%) adults
  - Mild related unsolicited AEs: 70 (45%) adolescents vs. 85 (63%) adults
  - Moderate related unsolicited AEs: 2 (1%) adolescents vs. 10 (7%) adults

No life-threatening (grade 4) AEs were reported. Two arm 4 adults (1%) experienced at least 1 related MAAE. Seven arm 5 adolescents (2%) and 10 arm 4 adults (7%) withdrew from the study. Three arm 5 adolescents (<1%) and 4 arm 4 adults (3%) discontinued vaccination. Significant differences were observed in the proportion of participants in arm 5 vs arm 4 that experienced withdrawals ($p = 0.013$),

however the differences in proportions of adolescents and adults experiencing related MAAEs (p = 0.090) and discontinuing treatment (p = 0.205) were not significant (p = 0.205).

Of the 7 adolescents withdrawn from the study, 4 (2%) were in the 12- to 14-year-old subgroup and 3 (2%) were in the 15- to 17-year-old subgroup. All 3 discontinuations of vaccination occurred in the 12- to 14-year-old subgroup.

When the proportion of participants experiencing related MAAEs, withdrawals, and discontinuation of vaccination for each arm 5 adolescent age subgroup was compared to the arm 4 adults there were no significant differences in MAAEs for either subgroup. There were significant differences in withdrawals between the 15- to 17-year-old subgroup and adults (p = 0.043), however there were no significant differences for the 12- to 14-year-olds (p = 0.057). When comparing proportions of participants experiencing discontinuation, there was a significant difference between the 15- to 17-year-olds vs. adults (p = 0.046) but not between the 12- to 14-year-olds vs. adults (p = 0.706).

Table 27: Summary of Secondary Safety Outcomes by Age Group

			Adolescents (Arm 5) (N=315)		Adults (Arm 4) (N=135)		All Participants (N=450)		
Participants with[a]	**Relatedness**	**Severity**	**n**	**%**	**n**	**%**	**n**	**%**	**Adolescents vs. Adults p-value[c]**
At least one solicited systemic or local AE	Any Relatedness	Mild (Grade 1)	292	93	125	93	417	93	-
		Moderate (Grade 2)	182	58	82	61	264	59	-
		Severe (Grade 3)	25	8	27	20	52	12	-
At least one unsolicited AE	Related	Mild (Grade 1)	146	46	85	63	231	51	-
		Moderate (Grade 2)	10	3	10	7	20	4	-
		Severe (Grade 3)	-	-	-	-	-	-	-
	Not Related	Mild (Grade 1)	74	23	36	27	110	24	-
		Moderate (Grade 2)	31	10	11	8	42	9	-
		Severe (Grade 3)	5	2	3	2	8	2	-
At least one unsolicited SAE[b]	Related	Any Severity	-	-	-	-	-	-	-
	Not Related	Any Severity	3	<1	2	1	5	1	-
At least one AESI	Any Relatedness	Any Severity	-	-	-	-	-	-	-
At least one MAAE	Related	Any Severity	-	-	2	1	2	<1	0.090
Withdrawal of Study	N/A	N/A	7	2	10	7	17	4	0.013
Discontinuation of Vaccination	N/A	N/A	3	<1	4	3	7	2	0.205

Abbreviations: AE = adverse event; AESI = adverse event of special interest; MAAE = medically attended adverse event; N = number of participants in the Safety Population; n = number of participants meeting the row criteria; N/A = not applicable; SAE = serious adverse event.

[a] Participants are counted once for each category regardless of the number of events.

[b] Refer to the Listing of Serious Adverse Events for more details.

[C] Fisher's exact-test.

No life-threatening (grade 4) events were observed.

Table 28: Summary of Secondary Safety Outcomes by Adolescent Age Subgroup

			Adolescents (Arm 5) 12 to 14 years old (N=161)		Adolescents (Arm 5) 15 to 17 years old (N=154)		Adults (Arm 4) ≥ 18 years old (N=135)			
Participants with[a]	**Relatedness**	**Severity**	**n**	**%**	**n**	**%**	**n**	**%**	**Adolescents 12 to 14 years old vs. Adults ≥ 18 years old p-value[c]**	**Adolescents 15 to 17 years old vs. Adults ≥ 18 years old p-value[c]**
At least one solicited systemic or local AE	Any Relatedness	Mild (Grade 1)	154	96	138	90	125	93	-	-
		Moderate (Grade 2)	98	61	84	55	82	61	-	-
		Severe (Grade 3)	18	11	7	5	27	20	-	-
At least one unsolicited AE	Related	Mild (Grade 1)	76	47	70	45	85	63	-	-
		Moderate (Grade 2)	8	5	2	1	10	7	-	-
		Severe (Grade 3)	-	-	-	-	-	-	-	-
	Not Related	Mild (Grade 1)	42	26	32	21	36	27	-	-
		Moderate (Grade 2)	21	13	10	6	11	8	-	-
		Severe (Grade 3)	5	3	-	-	3	2	-	-
At least one unsolicited SAE[b]	Related	Any Severity	-	-	-	-	-	-	-	-
	Not Related	Any Severity	2	1	1	<1	2	1	-	-
At least one AESI	Any Relatedness	Any Severity	-	-	-	-	-	-	-	-
At least one MAAE	Related	Any Severity	-	-	-	-	2	1	0.207	0.217
Withdrawal of Study	N/A	N/A	4	2	3	2	10	7	0.057	0.043
Discontinuation of Vaccination	N/A	N/A	3	2	-	-	4	3	0.706	0.046

Abbreviations: AE = adverse event; AESI = adverse event of special interest; MAAE = medically attended adverse event; N = number of participants in the safety population; n = number of participants meeting the row criteria; N/A = not applicable; SAE = serious adverse event.
[a] Participants are counted once for each category regardless of the number of events.
[b] Refer to the listing of serious adverse events for more details.
[c] Fisher's exact-test.
No life-threatening (grade 4) events were observed.

7.3. Discussion

This study provides data on the safety of MVA-BN vaccine administered SC in a 2-dose series, 28 days apart, in adolescents aged 12 to 17 years. The overall summary of Adverse Events (Table 18) presents a similar safety profile in a comparison of the adults and adolescents age groups.

During the follow-up phase after the interim analysis, 3 SAEs were reported in arm 5 adolescents, major depressive disorder (study day 231), pyelonephritis (study day 365), and infective myositis (study day 330). Two SAEs were reported in arm 4 adults, pyelonephritis (study day 319) and suicide ideation (study day 182). The SAEs were not considered related to the study product which can be agreed.

No deaths were reported from clinical trial DMID 22-0020 (stage 2).

There were no cardiac AEs considered related to study vaccination, and in particular no reported cases of myocarditis / pericarditis which are classified as AESIs in this study. Two participants, 1 adolescent and 1 adult, reported mild AEs of tachycardia. However, the available subject-number (315 adolescents) is too low for addressing rare risks such as cardiovascular risks as identified with other smallpox-vaccines in the past.

There were two pregnancies in adolescent participants during the study that resulted in live births without congenital anomalies.

The majority of Adverse Events refers to local and systemic solicited Events. The presented comparison of respective AEs in adolescents and adults appears similar with no major differences and occurred at similar frequencies after dose 1 and dose 2. The only AE seen more frequently in adolescents is dizziness which is explained by the MAH with the association with phlebotomy.

Within the adolescent sub-groups there is a slight trend of higher incidences of adverse events in the 12 – 14 years age group.

Results from the clinical study demonstrated that MVA BN was overall well-tolerated in adolescents ages 12 to 17 years with a safety and reactogenicity profile comparable to adults. No new or unexpected safety concerns have been identified. Overall, the findings support the favorable safety profile of MVA-BN administration in the adolescent population.

8. PRAC advice

Not applicable.

9. Risk management plan

The MAH submitted an updated RMP version 12.0 with this application. The main proposed RMP changes were the following (additions are highlighted in blue and deletions are highlighted in ~~red~~):

9.1. Safety Specification

Epidemiology of the indications and target population

The indication for IMVANEX is active immunisation against smallpox, mpox and disease caused by vaccinia virus (VV) in individuals 12 years of age and older.

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

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

The target population of IMVANEX includes adults (general population) and adolescents (12-17 years) who are indicated for vaccination against smallpox/monkeypox. In addition, due to the non-replicating properties, IMVANEX is expected to be used in individuals not eligible for vaccination with replicating smallpox vaccines like immunocompromised individuals and individuals with atopic dermatitis (AD).

Table 9: Indication epidemiology: Paediatric population

Indication/target population	Mpox vaccination in Adolescents (12-17 years) at risk of exposure to monkeypox virus
Incidence of target indication	Unknown/evolving (highly dependent on being part of at-risk groups)
Prevalence of target indication	Unknown/evolving
Mortality in target indication	<0.1% for monkeypox
Potential health risk	Severe disease, potentially fatal
Demographic profile of target population	Adolescents, 12-17 years

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

[…]

In the European region, since the start of outbreak in May 2022 and up to 28-Jul-2025, 29 EU/EEA countries have reported a total of 24 995 confirmed mpox cases (ECDC, 2025a), including 10 deaths mostly in people living with HIV (PLWH) (Vaughan, 2024). After a peak in 2022, the outbreak continues at a low level of transmission in this region, as well as in the Americas, the South-East Asia Region, and the Western Pacific. Standing mpox recommendations were issued by the WHO Director-General in August 2023 that remained valid for 1 year until 20-Aug-2024 (WHO, 2023).

Since late 2023, an epidemic of MPXV clade I has been affecting the Democratic Republic of the Congo (DRC) and has spread to several other African countries, including Burundi, Rwanda, Uganda, Kenya, Ethiopia, Malawi, Mozambique, Republic of Congo, Central African Republic, South Sudan, Tanzania, Zambia. This outbreak is characterized by human to human transmission through close physical contact, both sexual and non-sexual. The outbreak in Africa has led to a significant number of cases and deaths, with the DRC reporting the highest number of cases. The rapid rise and geographical spread of MPXV clade Ia and Ib have raised global concerns. The Africa Centres for Disease Control and Prevention (Africa CDC) reported over 17 000 suspected and confirmed cases in 2024, with a CFR

of 3%. The outbreak has been declared a Public Health Emergency of Continental Security by Africa CDC on 13-Aug-2024, and a Public PHEIC by the WHO on 14-Aug-2024 (WHO, 2024b).

Since the beginning of 2022 and as of 01-Aug-2024, Africa CDC reported 42 260 mpox cases and 1537 deaths across 18 African Union Member States (Africa CDC, 2024). The outbreak has been declared a PHECS by Africa CDC on 13-Aug-2024 (Ndembi, 2024) and a Public PHEIC by the WHO on 14-Aug-2024 (WHO, 2024b). WHO has ended the mpox PHEIC as of 05-Sep-2025 (WHO, 2025a). However, the Africa CDC's PHECS for mpox remains in effect (Africa CDC, 2025). Getting laboratory confirmation of cases is challenging, but from 01-Jan-2025 to 19-Oct-2025, WHO reported an additional 39 799 confirmed mpox cases and 178 deaths in 27 African countries (WHO, 2025b).

Of note, as of 24 Jun 2024 and referring to the EMA evaluation of the vaccine, the DRC issued a temporary use authorisation for MVA-BN, for immunisation of persons presenting a high risk of exposure to mpox.

[…]

Important co-morbidities:

Table 11: Important co-morbidity in different target populations

Indication/target population	**Important co-morbidity**
General population	As per general population, e.g. cardiovascular and malignancies
HIV individuals	Hepatitis, malignancies, opportunistic infections, hyperlipidemia, atherosclerosis, coronary artery disease, cardiomyopathy
Atopic individuals	Asthma, rhinitis, conjunctivitis
Military personnel	None
First-line responders	None
Laboratory personnel	None
Paediatric population (adolescents, 12-17 years)	Same as adults, malnutrition-

PRAC Rapporteur assessment comment:

The epidemiology part of the RMP was updated to include data on the paediatric population. This is accepted.

Clinical trial exposure

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

Open completed trials referred to in the following tables are: POX-MVA-007, POX-MVA-008, POX-MVA-010, POX-MVA-011, POX-MVA-023, POX-MVA-03X, DMID 22-0020 stage 2.

Table 18: Total Clinical Exposure to IMVANEX by Number of Doses

Doses	Persons (randomized trials)	Persons (open trials)	Total
1	1002	~~314~~321	~~1316~~1323
2	6337	~~1282~~1725	~~7619~~8062
3	65	0	65

Table 19: Clinical Exposure to IMVANEX by Dose Strength

Strength	Persons (randomized trials)	Persons (open trials)	Total
10^6 $TCID_{50}$	18	0	18
10^7 $TCID_{50}$	358	0	358
10^8 $TCID_{50}$	6954	2046	9000
2×10^8 $TCID_{50}$	29	0	29
5×10^8 $TCID_{50}$	45	0	45

Table 20: Clinical exposure to IMVANEX (by Age Group and Sex)

Age group	Male			Female		
	rand. trials	open trials	total	rand. trials	open trials	total
Adult (age range 18-55 years)	3598	~~888~~943	~~4486~~4541	3680	~~706~~786	~~4386~~4466
Adolescents (age range 12-17 years)	0	160	160	0	155	155
Elderly (age range 56-80 years)	49	2	51	77	0	77
Total	3647	~~890~~1103	~~4537~~4752	3757	~~706~~941	~~4463~~4698

Table 21: Clinical Exposure to IMVANEX by Ethnic Origin and Age Group

Ethnic group	Persons (randomized trials)	Persons (open trials)
Adult (age range 18-55 years)		
Caucasians (incl. others)	6091	1333

Black	1096	301
Asian	183	97
Adolescents (age range 12-17 years)		
Caucasians (incl. others)	0	276
Black	0	31
Asian	0	8

Table 22: Clinical Exposure to IMVANEX by past Vaccinia Exposure (all age groups)

Vaccinia	Persons (randomized trials)	Persons (open trials)
Naïve	7029	~~1209~~1659
Experienced	375	387

Table 23: Clinical Exposure to IMVANEX - Special populations (by Study Design)

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

In addition, 34 female vaccinees became pregnant after vaccination.

PRAC Rapporteur assessment comment:

The clinical trial exposure was updated with data from study DMID 22-0020. The information is acknowledged.

Populations not studied in clinical trials

Table 26: Exclusion criteria which are NOT proposed to remain as contraindications

Exclusion criteria which are NOT proposed to remain as contraindications		
Criteria	**Reason for being an exclusion criterion**	**Justification for not being a contraindication**
Malignancy or history of malignancy	only healthy subjects to be included in trial	
History or clinical manifestation of clinically significant and severe hematological, renal, hepatic, pulmonary, central nervous, cardiovascular or gastrointestinal disorders	Only healthy subjects to be included in trial	
History and risk of coronary heart diseases	Only healthy subjects to be included in trial	No confirmed case of myo-/pericarditis in completed clinical trials (N=~~8992~~9442)

History of alcohol abuse/intravenous drug abuse	Risk of poor compliance during trial	Compliance not relevant for vaccination setting outside a clinical trial
History or clinical manifestation of immune modifying conditions / diseases or immune modifying therapies	Risk of decreased immune response in vaccinee; Only healthy subjects to be included in trial	Additional trial in immunocompromised population completed with favorable safety and immunogenicity results

Limitations in respect to populations typically under-represented in clinical trial development programmes (abbreviated)

No studies have been undertaken in

- Children and adolescents (<12 years)
- Pregnant and breastfeeding women
- Individuals with relevant co-morbidity such as clinically significant renal, hepatic or cardiac impairment

Limited data are available in

- Geriatric subjects (age 65+) (N=120)
- Immunocompromised patients (HIV infected subjects N=696)
- Adolescents 12-17 yrs (N=315)

Post-authorisation experience

Table 28: Worldwide Shipments of IMVANEX

No of doses shipped	**Cumulative 31-Jul-2013 to 31-Jul-2025**
US	~~15 533 000~~15 941 130
EU/EEA	~~3 067 460~~5 470 689
Canada	~~4 615 000~~5 916 500
UK	~~154 280~~309 400
Others[b]	~~1 428 300~~1 869 630
Africa	1 011 700
Total	~~24 798 040~~30 519 049

Actual post-authorisation usage data (abbreviated)

[…]

In addition to this, in order to obtain actual exposure data, the MAH actively screens local health authority webpages for data concerning the use of the product, including information of doses administered, first versus second dose, stratified by region (by country within the EU), gender and age groups and age groups where available. During the peak of the vaccination campaign following the mpox outbreak in May 2022, public health agencies in major Western world countries have published actual administration data of mpox vaccine (ie. MVA-BN) administration. In summary, by July 2024, more than 1.8 million doses had been administered in the US, UK, EU/EEA, Canada and Australia. In 2024, no further systematic reporting of administration data from these countries was available. In a report, published on 28-Aug-2025 with a cutoff date of 31-Jul-2025, the WHO shared that more than 986 000 MVA-BN doses have been administered in African countries. This results in an estimate of >2.8 million doses of MVA-BN administered. However, this is likely an underestimate of the true exposure as countries other than the aforementioned, have not published administration data.

Post-Authorisation Use in Special Populations

Paediatric Populations:

- In August 2022, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for MVA-BN for persons aged <18 years. In the US, the peak of MVA-BN administrations in response to the 2022 mpox outbreak occurred between May 2022 and January 2023. The CDC reported the following MVA-BN administration numbers in persons <18 years during that period:

Age Group (Years)	Number of First Doses	Number of Second Doses
0–4	302	66
5–11	406	130
12–17	586	216

A limited number of adverse event reports in 22 adolescent individuals were received from the US under the EUA use granted since August 2022, with most cases coded as administration errors, primarily due to intradermal administration or off-label use. No safety concerns emerged from this use.

- In addition, 13 Emergency Use Authorisations (EUAs) have been published in African countries. These EUA have been granted:
  - in individuals 1 year of age and older in 1 country,
  - in individuals 12 years of age and older in 6 countries,
  - in adults in 2 countries,
  - no age indication has been mentioned in 4 countries.

BN has been unable to identify age-related exposure data in these countries.

PRAC Rapporteur assessment comment:

With regard to post-authorisation experience of MVA-BN, the number of shipped doses was updated. This is endorsed. In addition, a section about post-authorisation use in special populations was added.

However, a large part of this section provides information about the clinical trial DMID 22-0020 and is not considered relevant for inclusion in this section. The MAH was therefore requested to remove this part from the RMP (**OC**). In a revised version of the risk management plan version 11.1, information about the clinical trial DMID 22-0020 was removed in the section about post-authorisation use in special populations.

9.2. Pharmacovigilance plan

Safety concerns and overview of previous pharmacovigilance actions

- Since May 2022, a multinational mpox outbreak (primarily clade IIb) spread outside historically endemic regions, with most early transmission occurring within sexual networks of gay and bisexual men. Transmission continues at low levels in many countries. Separately, during 2024–2025 the Democratic Republic of the Congo experienced a large clade I outbreak with higher severity and deaths, and in October 2025 clade Ib mpox with local transmission was detected in parts of the EU/EEA, prompting renewed vigilance. Overall, risk to the general public remains low, but children, pregnant people, and those with weakened immunity (including advanced or untreated HIV) face greater risk of severe disease. Mpox during pregnancy can lead to fetal or neonatal infection and adverse outcomes such as pregnancy loss, stillbirth, preterm birth, and neonatal mpox. Note: WHO declared a PHEIC for the clade I upsurge on 14-Aug-2024 and lifted it in September 2025; mpox remains a public-health concern requiring sustained surveillance and targeted prevention. There is no single up-to-date global figure for all paediatric mpox cases beyond aggregate percentages and regional reports. For the 2022–2023 multinational outbreak, children and adolescents <18 years accounted for ~1.3% of confirmed cases. In the DRC in 2024, ~39% of reported cases were in children <5 years, with substantial mortality in this group. In endemic African settings overall, children constitute a much larger share of cases than in the 2022–2023 global outbreak outside Africa (Hoxha, 2023; WHO, 2025a).
- Severe and life-threatening adverse reactions such as inadvertent inoculation, eczema vaccinatum, progressive vaccinia, generalized vaccinia, and postvaccinal encephalitis that have been observed after the administration of conventional smallpox vaccines are due to the replication of the vaccinia strains. IMVANEX is replication incompetent in human cells and consequently has a better safety and tolerability profile. It is essentially impossible that IMVANEX could induce the severe side effects listed above associated with replication competent vaccinia viruses. Furthermore, with an overall rate (all age groups; data historically reported for Dryvax) of 529.2 cases/million vaccinations for inadvertent inoculation, 38.5 cases/million vaccinations for eczema vaccinatum, 241.5 cases/million vaccinations for generalized vaccinia, 1.5 cases/million vaccinations for progressive vaccinia and 12.3 cases/million vaccinations for postvaccinal encephalitis in primary (vaccinia-naïve) vaccinees, these rare events are highly unlikely to be captured in a clinical trial and true monitoring may therefore only be possible during a post-market surveillance. Nevertheless, all these events would constitute an SAE and thus be captured via the routine AE reporting procedure within the clinical trials.
- Early clinical trials of IMVANEX enrolled adults and generally excluded pregnant or lactating individuals and those <18 years and often excluded recent recipients of immunoglobulins or other vaccines for methodological reasons. However, subsequent adolescent studies have been conducted, pregnancy/lactation studies are currently underway, and public-health guidance allows offering IMVANEX during pregnancy or breastfeeding with shared decision-making. In contrast, replicating vaccinia vaccines (e.g., Dryvax/ACAM2000) have contraindications in

pregnancy, many immunocompromised states, and certain dermatologic/cardiac conditions. Nevertheless, pregnancies exposed to the Investigational Medicinal Product (IMP) cannot be excluded with certainty and would have been followed up until delivery.

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

PRAC Rapporteur assessment comment:
Information related to the use of MVA-BN in children and adolescents was added. This is acknowledged. No changes to the pharmacovigilance activities are proposed.

Overall conclusions on the PhV Plan

The proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product. The study in the post-authorisation development plan is sufficient to monitor the effectiveness of the risk minimisation measures.

9.3. Risk minimisation measures

PRAC Rapporteur assessment comment:
No changes to the risk minimisation measures are proposed. This is endorsed.

9.4. Elements for a public summary of the RMP

The elements for a public summary of the RMP do not require revision following the conclusion of the procedure.

9.5. Annexes

The annexes have been updated appropriately.

9.6. Overall conclusion on the RMP

☒ The changes to the RMP version 12.0 and the changes to the conditions and obligations of MA are acceptable.

10. Changes to the Product Information

As a result of this variation, sections 4.8 and 5.1 of the SmPC are being updated to reflect the final study results of study DMID 22-0020 stage 2. The Package Leaflet (PL) is updated accordingly.

Changes are made to the Opinion Annex II conditions as detailed in the recommendations section above.

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

11. Request for supplementary information

11.1. Major objections

Not applicable.

11.2. Other concerns

Clinical aspects

Not applicable.

RMP aspects

In RMP part II, module SV Post-authorisation experience, a section about post-authorisation use in special populations was added. However, a large part of this section provides information about the clinical trial DMID 22-0020 and is not considered relevant for inclusion in this section. The MAH is therefore requested to remove this part (highlighted in yellow in the AR) from the RMP.

12. Assessment of the responses to the request for supplementary information

12.1. Major objections

Not applicable.

12.2. Other concerns

RMP aspects

Question 1

In RMP part II, module SV Post-authorisation experience, a section about post-authorisation use in special populations was added. However, a large part of this section provides information about the clinical trial DMID 22-0020 and is not considered relevant for inclusion in this section. The MAH is therefore requested to remove this part (highlighted in yellow in the AR) from the RMP.

Summary of the MAH's response

A revised risk management plan version 12.0 was submitted.

Assessment of the MAH's response

The MAH provided a revised version of the risk management plan version 12.0. In the updated RMP,

the information related to the clinical trial DMID 22-0020 was removed in the section about post-authorisation use in special populations. The issue is considered resolved.

Conclusion

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly