Summary Report of Benefit-Risk Assessment

JYNNEOS SUSPENSION FOR INJECTION

NEW DRUG APPLICATION

Active Ingredient(s)	Modified Vaccinia Ankara - Bavarian Nordic (MVA-BN, live, non-replicating)
Product Registrant	Aenon Pharmaceuticals Sea Pte. Ltd.
Product Registration Number	SIN17067P
Application Route	Abridged evaluation
Date of Approval	23 August 2024

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A INTRODUCTION

Jynneos is a vaccine indicated for prevention of smallpox and mpox disease in adults 18 years of age and older determined to be at high risk for smallpox or mpox infection.

The active substance, Modified Vaccinia Ankara - Bavarian Nordic (MVA-BN), is an attenuated, non-replicating orthopoxvirus that elicits humoral and cellular immune responses to orthopoxviruses.

Jynneos is available as suspension for injection containing 0.5 mL with 0.5×10^8 to 3.95×10^8 Infectious Units (Inf. U) of MVA-BN. Other ingredients are Tris, Sodium Chloride and Water for Injection.

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, live, non-replicating MVA-BN, is manufactured at Bavarian Nordic A/S (BN-K), Denmark. The drug product, Jynneos Suspension for Injection, is manufactured at Bavarian Nordic A/S (BN-K), Denmark and Grand River Aseptic Manufacturing (GRAM), USA.

Drug substance:

Adequate controls have been presented for the reagents, cell banks and seed lots. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate. The drug substance manufacturer is compliant with Good Manufacturing Practice (GMP). Process validation was conducted on five consecutive batches.

The characterisation of the drug substance and its impurities has been appropriately performed. Potential and actual impurities are adequately controlled in the specifications.

The drug substance specifications were established in accordance with ICH Q6B guideline, and the impurity limits were appropriately qualified. The analytical methods used were adequately described and non-compendial methods have been validated in accordance with ICH Q2 guideline, with information on the reference standards used for identity, assay and impurities testing presented.

The stability data presented was adequate to support the storage of the drug substance at -40°C to -60°C with a shelf life of 82 months. The packaging is Celsius® Flexible Freeze-Thaw (FFT) containers.

Drug product:

The manufacturing process involves pooling and mixing of DS and formulation of DS with sterile filtered formulation buffer to final bulk and aseptic filling. This is considered a standard manufacturing process.

Both manufacturing sites are compliant with GMP. Proper development and validation studies were conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

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The specifications are established in accordance with ICH Q6B guideline and impurity limits were adequately qualified. The analytical methods used are adequately described and non-compendial methods have been validated in accordance with ICH Q2 guideline, with information on the reference standards used for identity, assay and impurities testing presented.

The stability data submitted was adequate to support the approved shelf-life of 3 years at -15°C to -25°C, 5 years at -40°C to -60°C or 9 years at -70°C to -90°C. The container closure system is a Type 1 clear borosilicate glass vial.

C ASSESSMENT OF CLINICAL EFFICACY

The efficacy of the vaccine for prevention of smallpox and mpox disease was inferred from data from animal challenge studies, as well as clinical immunogenicity data from one pivotal Phase 3 study (POX-MVA-006) and two key secondary supportive studies (POX-MVA-013 and POX-MVA-023). In addition, immunogenicity data against mpox virus (MPXV) from the US Centers for Disease Control and Prevention (CDC) surveillance clinical study conducted in the Democratic Republic of Congo (DRC) provided further supportive data. The data requirements and approach are internationally aligned and accepted considering the use of the vaccine in exceptional circumstances during smallpox and mpox outbreaks.

In the animal challenge studies and clinical pivotal study, MVA-BN was compared against ACAM2000. ACAM2000 is a live replicating vaccinia virus-based vaccine currently registered for active immunisation against smallpox disease. Based on the established genetic similarity (96.3% identical for the nucleotide sequence encoding essential enzymes and structural proteins) between the smallpox and mpox viruses which suggests a potential for cross-neutralisation with ACAM2000, ACAM2000 was deemed an appropriate comparator for evaluating the protective efficacy against both smallpox and mpox.

Animal challenge studies

The protective efficacy of MVA-BN in animals was investigated through challenge studies with several virus strains in mice and non-human primates (NHPs) using various routes of administration. These included:

- Intranasal (IN) challenge with Vaccinia Virus Western Reserve (VV-WR) in BALB/c mice
- IN challenge with ectromelia virus (ECTV) in BALB/c mice
- Respiratory (intratracheal [IT] and aerosol) challenge with MPXV in cynomolgus macaques
- Intravenous (IV) challenge with MPXV in cynomolgus macaques

The efficacy of MVA-BN was compared with ACAM2000. Across the studies, MVA-BN at the proposed clinical dose (i.e., $1x10^8$ Inf. U / dose) was able to afford 100% protection in mice against lethal challenge with 50x murine lethal dose 50 (MLD_{50}) VV-WR and 58x MLD_{50} ECTV, and 89 to 100% protection in NHPs against lethal challenge with $5x10^7$ plaque forming units (pfu) MPXV (IV challenge), $1x10^6$-$5x10^6$ pfu MPXV (IT challenge), and $3x10^5$ pfu MPXV (aerosol challenge). The protection rates in the MVA-BN arms were comparable to those observed in the ACAM2000 arms.

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Overall survival in animal challenge studies

Vaccination	% Survival (survivor animal/total animal)				
	Mice model		NHP model		
	VV-WR (IN) (50x MLD_{50})	ECTV (IN) (58x MLD_{50})	MPXV (IV) ($5x10^7$ pfu)	MPXV (IT) ($1x10^6$-$5x10^6$ pfu)	MPXV (aerosol) ($3x10^5$ pfu)
MVA-BN	100% (282/282)	100% (132/132)	100% (19/19)	89% (24/27)	100% (18/18)
ACAM2000	97% (34/35)	100% (8/8)	100% (6/6)	100% (28/28)	-
Control (across studies)	0%	0-10%	0-40%	0%	0-17%

Clinical immunogenicity study

The immunogenicity of Jynneos was based primarily on one pivotal Phase 3 study, POX-MVA-006), which was a randomised, open-label, non-inferiority study comparing the two-dose regimen of MVA-BN with ACAM2000 given alone or after MVA-BN priming to healthy, smallpox vaccine-naïve subjects aged 18 to 42 years. This study was conducted in a military-only environment in South Korea, as the use of the comparator ACAM2000 has been limited to military personnel due to its safety risks.

Subjects in the study were randomised in a 1:1 ratio to two groups:

- Group 1: subjects received two 0.5 mL (1×10^8 Inf. U) doses of MVA-BN administered 28 days apart (Days 0 and 28) via subcutaneous injection in the non-dominant upper arm, followed by a single dose of ACAM2000 ($2.5\text{-}12.5 \times 10^5$ pfu) via scarification four weeks (Day 56) after the second MVA-BN vaccination.
- Group 2: subjects received one dose of ACAM2000 ($2.5\text{-}12.5 \times 10^5$ pfu) via the percutaneous route (scarification), in accordance with the USA military smallpox vaccine program.

The co-primary endpoints were vaccinia-specific neutralising antibody titre determined by plaque reduction neutralisation test (PRNT) at Peak Visit and maximum lesion area (MLA) after scarification with ACAM2000. Peak Visit was defined as the time points when the highest expected antibody titres would be observed. Based on the results obtained during the MVA-BN development program and clinical studies conducted with ACAM2000, the Peak Visit was identified as two weeks after the second dose of MVA-BN in Group 1 and four weeks after ACAM2000 single dose in Group 2. MLA was defined as the maximum of two measurements: the lesion area measured on Day 6-8 (after scarification) or the lesion area measured on Day 13-15 (after scarification).

The key secondary immunogenicity endpoints included PRNT geometric mean titres (GMTs) at the individual peak and at all sampling time points, as well as PRNT seroconversion (SC) rates, defined as the percentage of initially seronegative subjects with appearance of antibody titres equal or greater than the assay cut-off value (ACV) in a vaccinia-specific PRNT. The key secondary take attenuation endpoints, which represent control of injection site vaccine virus replication conferred by the immune response to previous vaccination, included investigator-measured maximum lesion diameter (MLD) after ACAM2000 scarification and take assessment by blinded Independent Take Review Committee (ITRC). MLD was defined as the largest diameter measured across the lesion on Day 6-8 or Day 13-15 post ACAM2000 scarification.

The study tested two co-hypotheses:

- Immunogenicity hypothesis: The immunogenicity co-primary endpoint was to assess non-inferiority of MVA-BN compared to ACAM2000 in terms of PRNT GMTs at Peak Visits. The

non-inferiority margin (Δ) was pre-specified at 0.301 on the $\log_{10}$ scale (equivalent to a doubling on the original titre scale for the GMTs). The non-inferiority of MVA-BN to ACAM2000 would be demonstrated if the lower bound of the 95% confidence interval (CI) of the difference between the two log-transformed peak PRNT GMT values was above -0.301 (equivalent to 0.5 on the original titre scale for the GMTs).

- Take attenuation hypothesis: The take attenuation co-primary hypothesis was to assess if the median of the MLA following ACAM2000 vaccination was significantly reduced for subjects in Group 1 who received prior MVA-BN vaccinations compared to those in Group 2 who received no prior MVA-BN vaccinations. This analysis assessed if the area attenuation ratio (AAR) based on the MLA was significantly above λ=40% (defined based on literature). AAR was calculated as 1 minus the ratio of median MLA in Group 1 (M1) over the median MLA in Group 2 (M2), i.e., 1-M1/M2.

A total of 433 subjects were vaccinated (220 in Group 1 and 213 in Group 2). Baseline characteristics and demographics were balanced between groups. The median age was 22 years (range: 18 to 42 years). The majority of subjects were males (84.3%) and Whites (60.5%). Among the 443 subjects vaccinated, 371 subjects were included in the per protocol set (PPS) for immunogenicity, and 326 were included in the PPS for take attenuation.

PRNT GMTs at Peak Visit were 153.5 (95% CI: 134.3, 175.6) for Group 1 and 79.3 (95% CI: 67.1, 93.8) for Group 2. The ratio of PRNT GMTs (Group 1/Group 2) was 1.935 (95% CI: 1.562, 2.397), demonstrating non-inferiority of MVA-BN compared to ACAM2000 as the pre-specified non-inferiority margin was met. The MLA was 0.0 mm^2 (95% CI: 0.0, 2.0) in Group 1 and 76.0 mm^2 (95% CI: 70.0, 87.0) in Group 2. The AAR for MLA was 97.9% (95% CI: 96.6%, 98.3%), which met the pre-specified margin of lower bound of 95% CI greater than 40%, showing that prior MVA-BN vaccination resulted in an attenuation of take in terms of MLA, i.e., a reduction in skin lesion areas.

The results also showed that one dose of MVA-BN elicited modest vaccinia-specific antibody response as measured at 2 and 4 weeks after the first dose, and the antibody titres increased significantly after the second dose of MVA-BN. Both MVA-BN and ACAM2000 vaccination resulted in high and comparable PRNT SC rates at Peak Visits (>90%).

PRNT GMTs and SC rates at all sampling points

Visit week	MVA-BN (2 doses at Weeks 0 and 4) (N=185)		ACAM2000 (1 dose at Week 0) (N=186)	
	GMT (95% CI)	SC (95% CI) (%)	GMT (95% CI)	SC (95% CI) (%)
Week 0	1.0 (1.0, 1.1)	-	1.0 (1.0, 1.0)	-
Week 1	1.1 (1.0, 1.3)	8.7 (5.1, 13.8)	1.0 (1.0, 1.0)	1.6 (0.3, 4.7)
Week 2	16.2 (13.0, 20.1)	90.8 (85.6, 94.5)	16.2 (13.0, 20.0)	91.8 (86.9, 95.4)
Week 4	16.9 (13.7, 20.8)	94.1 (89.6, 97.0)	79.3 (67.1, 93.8)	97.3 (93.8, 99.1)
Week 6	153.5 (134.3, 175.6)	100.0 (98.0, 100.0)	64.7 (54.9, 76.2)	97.2 (93.7, 99.1)
Week 8	118.2 (102.9, 135.8)	100.0 (98.0, 100.0)	67.1 (56.9, 79.0)	96.7 (93.0, 98.8)
Week 12	96.5 (80.1, 116.2)	99.4 (96.8, 100.0)	-	-

With regard to the secondary take attenuation endpoints, a significant relative reduction in investigator-measured MLD in subjects receiving MVA-BN was observed as compared to those receiving ACAM2000. The median MLD was 0.0 mm for Group 1 and 11.0 mm for Group 2. According to the blinded ITRC take assessment, the majority of the subjects who received MVA-BN prior to ACAM2000 vaccination had absent takes (53.9%), while the remainder had partial or full takes (23.0% each). In contrast, the majority of Group 2 subjects had full takes (92.5%).

Lot-to-lot consistency study

Lot-to-lot consistency was assessed in a Phase 3, randomised, double-blind, placebo-controlled study POX-MVA-013. A total of 4005 vaccinia-naïve adult subjects were randomised in a 1:1:1:1 ratio to receive two doses of MVA-BN at 4-week intervals from 1 of 3 consecutive lots or placebo. Across the treatment groups, the ratio of PRNT GMTs at 2 weeks after the second MVA-BN dose ranged from 0.8577 to 1.1012, with the 95% CIs for the ratios falling within the pre-defined equivalence range of 0.5-2.0. Hence, statistical equivalence among the three consecutive lots was demonstrated. Consistent results were also observed for vaccinia-specific antibodies as determined by ELISA.

Long-term clinical immunogenicity data

Long-term immunogenicity data up to 2 years post-vaccination was assessed in Study POX-MVA-023. In vaccinia-naïve subjects, the PRNT GMTs against vaccinia declined to assay cut-off levels by 6 months and undetectable by 2 years post-vaccination. The durability of MVA-BN-induced neutralising antibody response appeared to be short in vaccinia-naïve subjects. Given that there was no established correlation of protection for both smallpox and mpox, the long-term efficacy of MVA-BN could not be concluded. Notwithstanding the limitation of the available data, the severity of the disease and the high infection risk in the target vaccination population outweighed concerns on the lack of long-term efficacy data.

US CDC surveillance clinical study

Immunogenicity data of MVA-BN against MPXV was reported in a published US CDC surveillance clinical study[1] conducted in the DRC. This was an ongoing, single-arm, open-label clinical study which investigated approximately 1,600 health care workers in a health zone affected by frequent human mpox cases in the DRC. Immunogenicity of MVA-BN against MPXV in terms of PRNT GMTs was assessed in a subset of subjects (n=999) who received MVA-BN. The results showed that mpox-specific (West African strain) neutralising antibodies were induced following MVA-BN vaccination, regardless of prior vaccination status. The antibody responses against MPXV peaked at Day 42 and declined between Day 42 and Day 730. The antibody titres against MPXV were numerically lower than that seen against vaccinia virus, which was expected as MVA-BN is a vaccinia virus-based vaccine. However, the range of GMTs against both MPXV and vaccinia virus overlapped, suggesting comparable immune responses.

Conclusion on efficacy

The efficacy of vaccinia virus-based vaccines for the prevention of smallpox was evident predicated on the eradication of smallpox disease. Protective efficacy of 80-100% after challenge via IN, IT, IV and aerosol routes with lethal doses of VV-WR, ECTV and MPXV in relevant animal models (mice and NHPs) was considered supportive of vaccine effectiveness against smallpox and mpox. The clinical immunogenicity study POX-MVA-006 demonstrated non-inferiority in respect of PRNT GMTs against vaccinia virus with two doses of MVA-BN versus one dose of ACAM2000. In addition, significant attenuation of take in terms of MLA was observed in subjects who received MVA-BN prior to ACAM2000. These were further supported by results observed the DRC study which reported antibody response against MPXV comparable to that seen against vaccinia virus. Taken together, MVA-BN is expected to confer

[1] Priyamvada L, et al. Serological responses to the MVA-based JYNNEOS monkeypox vaccine in a cohort of participants from the Democratic Republic of Congo. Vaccine. 2022 Nov 28;40(50):7321-7327.

protection against both smallpox and mpox infections based on the animal challenge and clinical immunogenicity data.

The approval for Jynneos is subject to the condition attached to the product registration for the company to submit a systematic literature review assessing the real-world effectiveness of Jynneos against mpox.

D ASSESSMENT OF CLINICAL SAFETY

The safety data of MVA-BN was primarily derived from the Main integrated summary of safety (ISS) population, consisting of a total of 5,110 vaccinia-naïve subjects (including 350 subjects with atopic dermatitis [AD] and 379 HIV subjects) who were exposed to the standard dose and regimen of MVA-BN in the proposed liquid-frozen (LF) formulation, and 409 vaccinia-experienced subjects who received one dose of MVA-BN. In addition, supporting data was provided for the ISS population (n=7,860) consisting of all subjects who received at least one dose of MVA-BN regardless of formulation, administration route, dose, and regimen.

Summary of adverse events (AEs) – Main ISS population

	Vaccinia-naïve subjects (N=5,110)	**Vaccinia-experienced subjects (N=409)**
Any solicited AE	88.8%	95.6%
Solicited local AE	86.8%	93.4%
Solicited general AE	58.0%	51.1%
Unsolicited AEs		
Vaccination period Grade 3 or higher AEs	37.9% 2.5%	41.6% 2.7%
Related AEs Grade 3 or higher related AEs	15.9% 0.4%	17.8% 0.5%
Follow-up period	2.0%	2.7%
Serious AEs		
Vaccination period	0.6%	0.2%
Follow-up period	0.6%	1.0%
Deaths	0.0% (1 event)	0.0%
AEs leading to discontinuation	0.4%	0.0%

The majority of the subjects in the Main ISS population (88.8% of vaccinia-naïve and 95.6% of vaccinia-experienced subjects) experienced at least one solicited AE. Solicited local AEs, including injection site pain, erythema, swelling, induration and pruritus, were reported in 86.8% of vaccinia-naïve subjects and 93.4% of vaccinia-experienced subjects. Solicited general AEs were reported in 58.0% of vaccinia-naïve and 51.1% of vaccinia-experienced subjects. The most frequently reported solicited general AEs were myalgia (36.4%), headache (34.8%), and fatigue (31.3%). Most of the solicited AEs were mild or moderate in severity and the proportion of subjects with Grade 3 or higher solicited AEs were low (10.7% with Grade 3 or higher solicited local AEs and 5.9% with Grade 3 or higher solicited general AEs). The most frequently reported Grade 3 or higher solicited local AEs included injection site pain (6.8%) and injection site erythema (3.5%). The most frequently reported Grade 3 and higher solicited general AEs were headache (2.6%), fatigue (2.8%), and myalgia (2.2%).

When compared with ACAM2000, the incidences of solicited local and general AEs were similar between subjects receiving MVA-BN and those receiving ACAM2000 (86.6% vs 92.0% and 57.2% vs 57.7%, respectively), but subjects receiving MVA-BN reported less Grade 3 or higher solicited AEs (12.1% vs 27.2%).

Unsolicited AEs were reported in 38.2% of subjects who received MVA-BN during the vaccination period, of which the majority were mild or moderate in severity. The most frequently reported unsolicited AEs were viral upper respiratory tract infection (3.2%), upper respiratory tract infection (2.7%), and troponin I increased (2.4%). The incidence of unsolicited AEs with MVA-BN was less than half of that reported for ACAM2000, where 97.7% of subjects reported at least one unsolicited AEs during the vaccination period.

Across the subpopulations, AD subjects appeared to have more Grade 3 or higher solicited local AEs (15.4% vs 11.2% for vaccinia-naïve healthy subjects) whereas at-risk subjects (AD subjects and HIV subjects) reported higher incidences of unsolicited AEs (59.1% for AD subjects and 60.2% for HIV subjects vs 34.3% for vaccinia-naïve healthy subjects).

In all studies, subjects were monitored for cardiac symptoms, electrocardiogram (ECG) changes and troponin I levels. In the Main ISS population, the proportion of subjects with AEs of special interest (AESIs) was low (1.3%). The most frequently reported AESIs were elevated troponin I (0.5%), palpitations (0.2%), and tachycardia (0.2%). The majority of AESIs were mild in severity. Across the studies, treatment-related AESIs were reported in 81 (1.0%) subjects, of which 65 (0.8%) subjects experienced troponin I elevation. All of these 65 subjects were from two studies in which a more sensitive troponin assay was used; and no clinically meaningful cardiac abnormalities were identified among these subjects. The majority of the treatment-related AESIs were mild or moderate in intensity, and all the AESIs resolved. In the ACAM2000 arm, 1 (0.5%) subject reported cardiac AESI. Based on available data on ACAM2000, suspected cases of myocarditis and/or pericarditis have been observed in healthy adult primary vaccinees receiving ACAM2000 at an approximate rate of 5.7 per 1,000 (95% CI: 1.9, 13.3). In this regard, MVA-BN was not considered to pose significant cardiac safety risks.

The incidence of SAEs was low in the Main ISS population: 0.6% during vaccination period and 0.7% during the follow-up period. There were no particular trends with regard to the nature of the pooled SAEs and most SAEs occurred in single subjects only. There were 7 SAEs assessed by the investigator as at least possibly related to MVA-BN. Further assessment showed that 3 events (cardiomyopathy, pneumonia, non-ST segment elevation myocardial infarction without epicardial coronary artery disease) were unlikely to be related to MVA-BN, 3 events (sarcoidosis, Crohn's disease, extraocular muscle paresis) appeared to be unlikely related to MVA-BN but a causal relationship could not be completely ruled out, while 1 event (throat tightness) was probably related to MVA-BN. The latter four events (sarcoidosis, Crohn's disease, extraocular muscle paresis, and throat tightness) have been reflected in the package insert.

The incidence of AEs leading to discontinuation was low (<1%) and comparable to that observed in the placebo group. There were 2 deaths reported but none was considered to be related to the vaccine.

Overall, MVA-BN was well-tolerated in the target population. No major safety concerns were identified in the submitted studies.

E ASSESSMENT OF BENEFIT-RISK PROFILE

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Smallpox is a serious acute contagious disease associated with a fatality rate of 30-40%. After the eradication of smallpox in 1980 and cessation of smallpox vaccination, the majority of the current population has no immunity to smallpox and therefore are susceptible in the event of a smallpox outbreak. Currently registered smallpox vaccine contains live, replication-competent vaccinia virus and is associated with severe adverse events. Mpox is a rare viral zoonotic disease caused by MPXV, which is genetically similar to smallpox. Mpox shares similar but less severe clinical features compared to smallpox, with a mortality rate of 1-10%. There was no mpox vaccine registered in Singapore, hence there was an unmet medical need for this vaccine.

In the pivotal study POX-MVA-006 conducted in vaccinia-naïve healthy subjects, two doses of MVA-BN administered at 4 weeks apart induced higher PRNT GMTs at Peak Visit when compared with the active comparator vaccine ACAM2000 (153.5 [95% CI: 134.3, 175.6] vs 79.3 [95% CI: 67.1, 93.8]), demonstrating that MVA-BN was not only non-inferior but superior to ACAM2000 in eliciting neutralising antibodies against vaccinia virus. The co-primary take attenuation endpoint showed that prior MVA-BN vaccination resulted in an attenuation of take in terms of MLA following ACAM2000 scarification (AAR of 97.9% [95% CI: 96.6%, 98.3%]). The study results were supported by the secondary immunogenicity and take attenuation endpoints, as well as similar trend of antibody response observed against MPXV in the DRC study.

In the animal challenge studies, two doses of MVA-BN administered at 4 weeks apart were able to confer comparable protections with ACAM2000 in BALB/c mice against lethal intranasal challenge with vaccinia virus and ECTV, as well as in cynomolgus monkeys against lethal intratracheal or aerosol or intravenous challenge with MPXV.

The data from the animal challenge studies, together with the immunogenicity data from the pivotal study, gave reasonable assurance that vaccination with MVA-BN confers reasonable protection against smallpox and mpox infections, similar to the comparator vaccine ACAM2000.

In terms of safety, the most frequently reported AEs with MVA-BN were injection site reactions, followed by solicited general AEs including myalgia, headache, and fatigue. The most frequently reported unsolicited AEs were viral upper respiratory tract infection, upper respiratory tract infection, and troponin I increased. The majority of the solicited and unsolicited AEs were mild and moderate in severity. The proportion of subjects with AESIs was low (≤1.3%). Most of the treatment-related AESIs were troponin I elevation without clinically meaningful cardiac abnormalities. The majority of the treatment-related AESIs were mild or moderate in intensity, and all the AESIs resolved. The incidences of SAEs and AEs leading to discontinuation were low with no trends or patterns detected and there were no treatment-related deaths reported. Overall, MVA-BN was well tolerated with no major safety concerns identified.

In conclusion, the efficacy of MVA-BN was inferred based on animal challenge studies and human immunogenicity data. The totality of evidence based on the submitted data was considered reasonably sufficient to support its use under exceptional circumstances. The systematic literature review of the real-world effectiveness data would be required to substantiate the vaccine effectiveness. In addition, as part of the considerations for use in exceptional circumstances, the supply of vaccine should be in accordance with Ministry of Health (MOH)’s instructions.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefit-risk balance of Jynneos for prevention of smallpox and mpox disease in adults 18 years of age and older determined to be at high risk for smallpox or mpox infection was deemed favourable and approval of the product registration was granted on 23 August 2024.

The approval of this application is subject to the submission of the systematic literature review assessing the real-world effectiveness of Jynneos against mpox to confirm the vaccine effectiveness, and the supply of the vaccine would be in accordance with MOH's instructions.

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JYNNEOS SUSPENSION FOR INJECTION
Smallpox and mpox vaccine, Live, Non-replicating

1 INDICATIONS AND USAGE

JYNNEOS is a vaccine indicated for prevention of smallpox and mpox disease in adults 18 years of age and older determined to be at high risk for smallpox or mpox infection.

2 DOSAGE AND ADMINISTRATION

For subcutaneous injection only.

2.1 Dose and Schedule

Administer two doses (0.5 mL each) of JYNNEOS 4 weeks apart.

2.2 Preparation and Administration

Allow the vaccine to thaw and reach room temperature before use.
Once thawed, the vaccine may be kept at +2°C to +8°C for 4 weeks. Do not refreeze.

When thawed, JYNNEOS is a milky, light yellow to pale white colored suspension.
Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.
If either of these conditions exists, the vaccine should not be administered.

Swirl the vial gently before use for at least 30 seconds. Withdraw a dose of 0.5 mL into a sterile syringe for injection.

Administer JYNNEOS by subcutaneous injection, preferably into the upper arm.

3 DOSAGE FORMS AND STRENGTHS

JYNNEOS is a suspension for injection. Each dose (0.5 mL) is supplied in a single-dose vial.

4 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients *[see Description (8)]* or trace residues (chicken protein, benzonase, gentamicin and ciprofloxacin).

5 WARNINGS AND PRECAUTIONS

5.1 Severe Allergic Reactions

Appropriate medical treatment must be available to manage possible anaphylactic reactions following administration of JYNNEOS.

Persons who experienced a severe allergic reaction following a previous dose of JYNNEOS or following exposure to any component of JYNNEOS may be at increased risk for severe allergic reactions after JYNNEOS. The risk for a severe allergic reaction should be weighed against the risk for disease due to smallpox or mpox.

5.2 Altered Immunocompetence

Immunocompromised persons, including those receiving immunosuppressive therapy, may have a diminished immune response to JYNNEOS.

5.3 Limitations of Vaccine Effectiveness

Vaccination with JYNNEOS may not protect all recipients.

5.4 Interaction with other medicinal products and other forms of interaction

No interaction studies with other vaccines or medicinal products have been performed. Therefore, concomitant administration of JYNNEOS with other vaccines should be avoided.
The concomitant administration of the vaccine with any immunoglobulin including Vaccinia Immune Globulin (VIG) has not been studied and should be avoided.

5.5 Syncope

Syncope (fainting) has been reported following vaccination with JYNNEOS. Procedures should be in place to avoid injury from fainting.

5.6 Traceability

In order to improve the traceability of vaccines, the name and the batch number of the administered product should be clearly recorded.

5.7 Concurrent illness

Immunisation should be postponed in individuals suffering from an acute severe febrile illness or acute infection. The presence of a minor infection and/or low-grade fever should not result in the deferral of vaccination.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared with rates in the clinical trials of another vaccine and may not reflect the rates observed in practice. There is the possibility that broad use of JYNNEOS could reveal adverse reactions not observed in clinical trials.

The overall clinical trial program included 23 studies and a total of 8,992 individuals 18 through 80 years of age who received at least 1 dose of JYNNEOS (8,264 smallpox vaccine-naïve and 728 smallpox vaccine-experienced individuals).

Table 1:

Adverse Reactions Reported in Completed Clinical Trials[a] with MVA-BN (N = 8992[b] subjects)

MedDRA System Organ Class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)
Infections and infestations	-	-	Nasopharyngitis, Upper respiratory tract infection	Sinusitis, Conjunctivitis, Gastroenteritis Influenza, Oral Herpes, Viral Infection
Blood and lymphatic system disorders	-	-	Lymphadenopathy	
Metabolism and nutrition disorders	-	Appetite disorder	-	
Psychiatric disorders	-	-	Sleep disorder	
Nervous system disorders	Headache	-	Dizziness, Paresthesia	Migraine, Disgeusia, Hypoaesthesia, Peripheral sensory neuropathy, Somnolence
Ear and labyrinth disorders	-	-		Vertigo, Ear pain
Cardiac disorders	-	-	-	Tachycardia
Respiratory, thoracic and mediastinal disorders	-	-	Pharyngolaryngeal pain, Rhinitis, Cough	Oropharyngeal pain
Gastrointestinal disorders	Nausea	-	Diarrhea, Vomiting, Dry mouth	Abdominal Pain, Aphthous stomatitis
Skin and subcutaneous tissue disorders	-	-	Rash, Pruritus, Dermatitis, Urticaria	Skin discolouration, Ecchymosis, Hyperhidrosis, Night sweats, Rash popular, Subcutaneous

MedDRA System Organ Class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)
				nodule, Angioedema
Musculoskeletal and connective tissue disorders	Myalgia	Pain in extremity, Arthralgia	Musculoskeletal stiffness, Neck pain	Back pain, Muscle spasms, Musculoskeletal pain, Muscular weakness
General disorders and administration site conditions	Injection site pain, Injection site erythema, Injection site swelling, Injection site induration, Injection site pruritus, Fatigue	Rigor/Chills, Injection site nodule, Injection site discolouration, Injection site haematoma, Injection site warmth, Axillary pain	Underarm swelling, Malaise, Injection site haemorrhage, Injection site irritation, Flushing, Chest pain, Injection site bruising, Injection site vesicles,	Injection site exfoliation, Injection site paraesthesia, Injection site rash, Injection site inflammation, Injection site reaction, Asthenia, Influenza like illness, Injection site dryness, Oedema, peripheral, Injection site anesthesia, Injection site movement impairment, Injection site papule
Investigations	-	Body temperature increased, Pyrexia	Troponin I increased, Hepatic enzyme increased, White blood cell count decreased, Mean platelet	White blood cell count increased, Blood bilirubin increased, Blood creatinine

MedDRA System Organ Class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)
			volume decreased	increased
Injury, poisoning and procedural complications	-	-	-	Contusion

Note: The frequency groups for adverse drug reactions, and the naming conventions for these groups, are based on the WHO guidance for reporting adverse events following immunization (AEFI).

a POX-MVA-001, -002, -004, -005, -006, -007, -008, -009, -010, -011, -013, -023, -024, -027, -028, -029, -030, -031, -036, -037, -03X, HIV-NEF-004 and HIV-POL-002

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

Solicited Adverse Reactions

Solicited Adverse Reactions in Smallpox Vaccine-Naïve Individuals:

The safety of JYNNEOS in smallpox vaccine-naïve individuals was evaluated in Study 1 [1], a randomized, double-blind, placebo-controlled study conducted in the US in which vaccinia-naïve adults ages 18 to 40 years received either two doses of JYNNEOS (N=3003), or two injections of Tris-Buffered Saline (placebo, N=1002) four weeks apart.

In the total study population, the mean age was 28 years; 47.9% of the subjects were men; 77.4% were white/Caucasian, 17.8% black/African American, 1.9% Asian, 0.5% American Indian/Alaska Native, 0.4% Native Hawaiian/Other Pacific, 1.9% other racial groups; and 11.4% of subjects were of Hispanic/Latino ethnicity. The demographic compositions of JYNNEOS and placebo groups were similar.

In Study 1, subjects were monitored for local and systemic adverse reactions using diary cards for an 8-day period starting on the day of each vaccination. The frequencies of solicited local and systemic adverse reactions following any dose of JYNNEOS are presented in Table 2.

Table 2: Percentages of Subjects with Solicited Local Injection Site Reactions and Systemic Adverse Reactions within 8 Days of Administration of Any Dose of JYNNEOS in Adults 18 to 40 Years of Age, Study 1[X]

Reaction	JYNNEOS N=2943 %	Placebo N=980 %
Local (Injection site)	--	--
Pain	84.9	19.1
Pain, Grade 3[a]	7.4	1.0
Redness	60.8	17.7
Redness ≥ 100 mm	1.5	0.0

Swelling	51.6	5.6
Swelling ≥ 100 mm	0.8	0.0
Induration	45.4	4.6
Induration ≥ 100 mm	0.3	0.0
Itching	43.1	11.7
Itching, Grade 3[b]	1.6	0.2
Systemic	--	--
Muscle Pain	42.8	17.6
Muscle Pain, Grade 3[b]	2.6	0.7
Headache	34.8	25.6
Headache, Grade 3[b]	2.4	2.1
Fatigue	30.4	20.5
Fatigue, Grade 3[b]	3.0	1.3
Nausea	17.3	13.1
Nausea, Grade 3[b]	1.5	1.2
Chills	10.4	5.8
Chills, Grade 3[b]	1.0	0.3
Fever[c]	1.7	0.9
Fever, Grade ≥ 3[c]	0.2	0.0

X NCT01144637

[a] Grade 3 pain defined as spontaneously painful

[b] Grade 3 itching, muscle pain, headache, fatigue, nausea and chills defined as preventing routine daily activities

[c] Fever defined as oral temperature ≥ 38°C, Grade ≥ 3 fever defined as ≥ 39.0°C

N: number of subjects

In Study 1, the majority of solicited local and systemic adverse reactions reported with JYNNEOS had a median duration of 1 to 6 days. In general, there were similar proportions of subjects reporting solicited local or systemic reactions of any severity after Dose 2 of JYNNEOS compared with Dose 1, with the exception of injection site pain, which was more commonly reported following Dose 1 (79.3%) than Dose 2 (69.9%).

Solicited Adverse Reactions in Persons Previously Vaccinated with a Smallpox Vaccine:

Three studies (Study 2, Study 3, and Study 4, [2-4]) conducted in the US and Germany evaluated the safety of JYNNEOS in 409 persons previously vaccinated with a smallpox vaccine who received one or two doses of JYNNEOS (mean age 39 years, range 20-80 years; 59% women; 98.8% white/Caucasian; 0.7% Asian; 0.5% black/African American). Subjects were monitored for local and systemic adverse reactions using diary cards for an 8-day period starting on the day of each vaccination. Across all three studies, solicited local adverse reactions reported following any dose of JYNNEOS were redness (80.9%), pain (79.5%), induration (70.4%), swelling (67.2%), and itching (32.0%) at the injection site; solicited systemic adverse reactions reported following any dose of JYNNEOS were fatigue (33.5%), headache (27.6%), muscle pain (21.5%), nausea (9.8%), chills (0.7%), and fever (0.5%).

Solicited Adverse Reactions in HIV-infected Individuals:

The safety of JYNNEOS in HIV-infected individuals was evaluated in Study 5 [5], an open label trial conducted in the US that included 351 HIV-infected smallpox vaccine-naïve subjects,
131 HIV-infected subjects who previously received smallpox vaccine, 88 non-HIV-infected smallpox vaccine-naïve subjects and 9 non-HIV-infected subjects who had previously received a smallpox vaccine. The racial/ethnic and gender compositions of HIV-infected smallpox vaccine-naïve subjects

and those who had previously received smallpox vaccine were similar and overall were 17.0% women; 45.8% white/Caucasian; 0.4% Asian; 33.2% black/African American; 19.0% Hispanic/Latino ethnicity; the HIV-infected smallpox vaccine-naïve group tended to be younger (mean age 37 years) compared to those who had previously received a smallpox vaccine (mean age 45 years). Subjects had CD4 counts ≥ 200 and ≤ 750 cells/μL at study entry.

Solicited local and systemic adverse reactions were reported at similar or lower frequencies in HIV-infected smallpox vaccine-naïve subjects as compared to those seen in non-HIV-infected smallpox vaccine-naive individuals in this study.

In HIV-infected subjects with previous smallpox vaccine exposure, fever and chills were reported in 1.5% and 8.4% of subjects respectively. Frequencies of other solicited local and general adverse reactions in this population were similar to those reported in Studies 2-4 in non-HIV-infected subjects who had previously received smallpox vaccination.

Solicited Adverse Reactions in Individuals with Atopic Dermatitis:

The safety of JYNNEOS in smallpox vaccine-naïve subjects with currently active or a history of atopic dermatitis (AD) was evaluated in a multicenter, open-label clinical study (Study 6 [6]) conducted in the US and Mexico that included 350 subjects with AD and 282 subjects without AD. In the overall study the mean age of subjects was 27 years (range 18-42 years), and subjects were 59.0% women, 39.4% white/Caucasian, 10.9% Asian, 9.0% black/African American, 2.2% Other, and 38.4% Hispanic/Latino ethnicity. Demographic compositions were similar between subjects with and without AD. In subjects with AD, solicited local and systemic adverse reactions were reported at similar frequencies as those in subjects without AD in this study, with the exception of redness (61.2% with AD vs. 49.3% without AD), swelling (52.2% with AD vs. 40.8% without AD), chills (15.9% with AD vs. 7.8% without AD) and headache (47.2% with AD vs. 34.8% without AD).

Serious Adverse Events

The integrated analyses of serious adverse events (SAEs) pooled safety data across 22 studies, which included a total of 7,093 smallpox vaccine-naïve subjects and 766 smallpox vaccine- experienced subjects who received at least 1 dose of JYNNEOS and 1,206 smallpox vaccine-naïve subjects who received placebo only. SAEs were monitored from the day of the first study vaccination through at least 6 months after the last study vaccination.

Among the smallpox vaccine-naïve subjects, SAEs were reported for 1.5% of JYNNEOS recipients and 1.1% of placebo recipients. Among the smallpox vaccine-experienced subjects enrolled in studies without a placebo comparator, SAEs were reported for 2.3% of JYNNEOS recipients. Across all studies, a causal relationship to JYNNEOS could not be excluded for 4 SAEs, all non-fatal, which included Crohn's disease, sarcoidosis, extraocular muscle paresis and throat tightness.

Cardiac Adverse Events of Special Interest

Evaluation of cardiac adverse events of special interest (AESIs) included any cardiac signs or symptoms, ECG changes determined to be clinically significant, or troponin-I elevated above 2 times the upper limit of normal. In the 22 studies, subjects were monitored for cardiac-related signs or symptoms through at least 6 months after the last vaccination.

The numbers of JYNNEOS and placebo recipients, respectively, with troponin-I data were: baseline level (6,376 and 1,203); level two weeks after first dose (6,279 and 1,166); level two weeks after second

dose (1,683 and 193); unscheduled visit, including for clinical evaluation of suspected cardiac adverse events (500 and 60).

Cardiac AESIs were reported to occur in 1.3% (95/7,093) of JYNNEOS recipients and 0.2% (3/1,206) of placebo recipients who were smallpox vaccine-naïve. Cardiac AESIs were reported to occur in 2.1% (16/766) of JYNNEOS recipients who were smallpox vaccine-experienced. The higher proportion of JYNNEOS recipients who experienced cardiac AESIs was driven by 28 cases of asymptomatic post-vaccination elevation of troponin-I in two studies: Study 5, which enrolled 482 HIV-infected subjects and 97 healthy subjects, and Study 6, which enrolled 350 subjects with atopic dermatitis and 282 healthy subjects. An additional 127 cases of asymptomatic post-vaccination elevation of troponin-I above the upper limit of normal but not above 2 times the upper limit of normal were documented in JYNNEOS recipients throughout the clinical development program, 124 of which occurred in Study 5 and Study 6. Proportions of subjects with troponin-I elevations were similar between healthy and HIV-infected subjects in Study 5 and between healthy and atopic dermatitis subjects in Study 6. A different troponin assay was used in these two studies compared to the other studies, and these two studies had no placebo controls. The clinical significance of these asymptomatic post-vaccination elevations of troponin-I is unknown.

Among the cardiac AESIs reported, 6 cases (0.08%) were considered to be causally related to JYNNEOS vaccination and included tachycardia, electrocardiogram T wave inversion, electrocardiogram abnormal, electrocardiogram ST segment elevation, electrocardiogram T wave abnormal, and palpitations.

None of the cardiac AESIs considered causally related to study vaccination were considered serious.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postmarketing use of JYNNEOS. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure.

Cardiac Disorders: myocarditis, pericarditis

Immune System Disorders: hypersensitivity reactions, including angioedema, rash, and urticaria

Nervous System Disorders: dizziness, syncope

6.3 Overdose

No case of overdose has been reported.

7 USE IN SPECIFIC POPULATIONS

7.1 Pregnancy

Risk Summary

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. Available human data on

JYNNEOS administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy.

The effect of JYNNEOS on embryo-fetal and post-natal development was evaluated in four developmental toxicity studies conducted in female rats and rabbits. In two studies, rats were administered a single human dose of JYNNEOS (0.5 mL) once prior to mating and on one or two occasions during gestation. In the third study, rats were administered a single human dose of JYNNEOS (0.5 mL) on two occasions during gestation. In the fourth study, rabbits were administered a single human dose of JYNNEOS (0.5 mL) once prior to mating and on two occasions during gestation. These animal studies revealed no evidence of harm to the fetus *[see Data]*.

Data

Animal Data
Developmental toxicity studies were conducted in female rats and rabbits. In one study, female rabbits were administered a single human dose of JYNNEOS (0.5 mL) by the subcutaneous route on three occasions: prior to mating, and on gestation days 0 and 14. Three studies were conducted in female rats administered a single human dose of JYNNEOS (0.5 mL) by the subcutaneous route on two or three occasions: prior to mating, and on gestation days 0 and 14; or prior to mating, and on gestation day 0; or on gestation days 0 and 6. No vaccine-related fetal malformations or variations and adverse effects on female fertility or pre-weaning development were reported in these studies.

7.2 Lactation

Risk Summary

It is not known whether JYNNEOS is excreted in human milk. Data are not available to assess the effects of JYNNEOS in the breastfed infant or on milk production/excretion.

The development and health benefits of breastfeeding should be considered along with the mother's clinical need for JYNNEOS and any potential adverse effects on the breastfed child from JYNNEOS or from the underlying maternal condition. For preventive vaccines, the underlying condition is susceptibility to disease prevented by the vaccine.

7.3 Pediatric Use

Safety and effectiveness of JYNNEOS have not been established in individuals less than 18 years of age.

7.4 Geriatric Use

Forty-two smallpox vaccine-experienced adults 65 to 80 years of age received at least one dose of JYNNEOS (Study 4).

Clinical studies of JYNNEOS did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

8 DESCRIPTION

When thawed, JYNNEOS (Smallpox and mpox vaccine, Live, Non-replicating) is a milky, light yellow

to pale white colored suspension for subcutaneous injection.

JYNNEOS is a live vaccine produced from the strain Modified Vaccinia Ankara-Bavarian Nordic (MVA-BN), an attenuated, non-replicating orthopoxvirus. MVA-BN is grown in primary Chicken Embryo Fibroblast (CEF) cells suspended in a serum-free medium containing no material of direct animal origin, harvested from the CEF cells, purified and concentrated by several Tangential Flow Filtration (TFF) steps including benzonase digestion. Each 0.5 mL dose is formulated to contain 0.5 x 10^8 to 3.95 x 10^8 infectious units of MVA-BN live virus in 10 mM Tris (tromethamine), 140 mM sodium chloride at pH 7.7. Each 0.5 mL dose may contain residual amounts of host-cell DNA (≤ 20 mcg), protein (≤ 500 mcg), benzonase (≤ 0.0025 mcg), gentamicin (≤ 0.400 mcg) and ciprofloxacin (≤ 0.005 mcg).

JYNNEOS is a sterile vaccine formulated without preservatives. The vial stoppers are not made with natural rubber latex.

9 CLINICAL PHARMACOLOGY

9.1 Mechanism of Action

Pharmacotherapeutic group: Vaccines, other viral vaccines, ATC code: J07BX01

JYNNEOS is an attenuated, live, non-replicating smallpox and mpox vaccine that elicits humoral and cellular immune responses to orthopoxviruses. Vaccinia neutralizing antibody responses in humans were evaluated to establish the effectiveness of JYNNEOS for prevention of smallpox and mpox.

10 NONCLINICAL TOXICOLOGY

10.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

JYNNEOS has not been evaluated for carcinogenic or mutagenic potential, or for impairment of male fertility in animals. Developmental toxicity studies conducted in rats and rabbits vaccinated with JYNNEOS revealed no evidence of impaired female fertility *[see Use in Specific Populations (7.1)]*.

10.2 Animal Toxicology and/or Pharmacology

The efficacy of JYNNEOS to protect cynomolgus macaques (*Macaca fascicularis*) against a mpox virus (MPXV) challenge was evaluated in several studies. Animals were administered Tris-Buffered Saline (placebo) or JYNNEOS (1 x 10^8 TCID50) sub-cutaneously on day 0 and day 28. On day 63, animals were challenged with MPXV delivered by aerosol (3 x 10^5 pfu), intravenous (5 x 10^7 pfu) or intratracheal (5 x 10^6 pfu) route. Across all studies, 80-100% of JYNNEOS-vaccinated animals survived compared to 0-40% of control animals.

11 CLINICAL STUDIES

11.1 Vaccine Effectiveness

Vaccine effectiveness against smallpox was inferred by comparing the immunogenicity of JYNNEOS to a registered smallpox vaccine (ACAM2000) based on a Plaque Reduction Neutralization Test

(PRNT) using the Western Reserve strain of vaccinia virus and was supported by efficacy data from animal challenge studies. *[see Nonclinical Toxicology (10.2)]*

Vaccine effectiveness against mpox was inferred from the immunogenicity of JYNNEOS against vaccinia virus in a clinical study and from efficacy data from animal challenge studies. *[see Nonclinical Toxicology (10.2)]*

11.2 Immunogenicity

Study 7 [7] (N=433) was a randomized, open-label study conducted at US military facilities in South Korea to compare the immunogenicity of JYNNEOS to ACAM2000 in healthy smallpox vaccine-naïve adults 18 through 42 years of age. Subjects were randomized to receive either two doses of JYNNEOS (N=220) administered 28 days apart or one dose of ACAM2000 (N=213). In the total study population, the mean age was 24 years and 23 years in subjects receiving JYNNEOS and ACAM2000, respectively; 82.3% and 86.4% of the subjects were men; 57.3% and 63.8% were white/Caucasian, 21.8% and 18.8% black/African American, 6.4% and 5.6% Asian, 3.6% and 2.8% American Indian/Alaska Native, 2.3% and 1.4% Native Hawaiian/Other Pacific, 8.6% and 7.5% other racial groups, and 24.5% and 18.8% of Hispanic/Latino ethnicity (JYNNEOS and ACAM2000, respectively).

The primary immunogenicity endpoint was geometric mean titer (GMT) of vaccinia neutralizing antibodies assessed by PRNT at "peak visits" defined as two weeks after the second dose of JYNNEOS and four weeks after the single dose of ACAM2000. Analyses of antibody responses were performed in the per-protocol immunogenicity (PPI) population, consisting of individuals who received all vaccinations and completed all visits up until the peak visit without major protocol violations pertaining to immunogenicity assessments. Table 3 presents the pre-vaccination and "peak visit" PRNT GMTs from Study 7.

Table 3: Comparison of Vaccinia-Neutralizing Antibody Responses Following Vaccination with JYNNEOS or ACAM2000 in Healthy Smallpox Vaccine-Naïve Adults 18 through 42 Years of Age, Study 7[x], Per Protocol Set for Immunogenicity[y]

Time Point	JYNNEOS[a] (N=185) GMT[b] [95% CI]	ACAM2000[a] (N=186) GMT[b] [95% CI]
Pre-Vaccination	10.1 [9.9, 10.2]	10.0 [10.0, 10.0]
Post-Vaccination "Peak Visit"[y]	152.8[c] [133.3, 175.0]	84.4[c] [73.4, 97.0]

x NCT01913353

y Per Protocol Set for Immunogenicity included subjects who received all vaccinations, completed all visits up until the specified "peak visits" (two weeks after the second dose of JYNNEOS or 4 weeks after the single dose of ACAM2000) without major protocol violations pertaining to immunogenicity assessments.

a JYNNEOS was administered as a series of two doses given 28 days apart, and ACAM2000 was administered as a single dose.

b GMT of vaccinia-neutralizing antibody titers assessed by plaque reduction neutralization test (PRNT) using the Western Reserve vaccinia strain. Values below the assay lower limit of quantitation (LLOQ) of 20 were imputed to a titer of 10; the proportions of subjects with pre-vaccination titers less than the assay lower limit of detection were 98.9% among subjects randomized to JYNNEOS and 97.8% among subjects randomized to ACAM2000, respectively.

c Non-inferiority of the "peak visit" PRNT GMT for JYNNEOS compared to ACAM2000 was demonstrated as the lower bound of the 1-sided 97.5% CI for the GMT ratio (JYNNEOS/ACAM2000) was > 0.5.

N: Number of subjects in the specified treatment group; GMT: Geometric Mean Titer; 95% CI: 95% confidence interval, lower limit and upper limit.

PRNT GMTs were also evaluated at pre-specified time points post-vaccination and prior to the "peak visits". The PRNT GMTs at two and four weeks after the first dose of JYNNEOS (prior to the second dose), were 23.4 (95% CI: 20.5, 26.7) and 23.5 (95% CI: 20.6, 26.9), respectively. The PRNT GMT at two weeks after the single dose of ACAM2000 was 23.7 (95% CI: 20.9, 26.8).

Study 3 (NCT00686582) showed that the titers of vaccinia-specific neutralizing antibodies decreased significantly within two years after vaccination. However, the clinical implications of this decline and the duration of protective immunity remain uncertain, as no established serological correlation for protection against both smallpox and mpox exists.

12 REFERENCES

1. Study 1: NCT01144637
2. Study 2: NCT00316524
3. Study 3: NCT00686582
4. Study 4: NCT00857493
5. Study 5: NCT00316589
6. Study 6: NCT00316602
7. Study 7: NCT01913353

13 HOW SUPPLIED/STORAGE AND HANDLING

13.1 How Supplied

13.1.1 Package of 10 single-dose vials

13.1.2 Package of 20 single-dose vials

Not all pack sizes may be marketed.

13.2 Storage Conditions

Keep frozen at -25°C +/-5°C or -50°C +/-10°C or -80°C +/-10°C. Expiry date depends on storage temperature *[see Shelf-life (13.3)]*.
Store in the original package to protect from light.
Once thawed, the vaccine may be kept at +2°C to +8°C for 4 weeks.
Do not re-freeze a vial once it has been thawed.
Do not use the vaccine after the expiration date shown on the vial and carton label.

13.3 Shelf life

3 years at -20°C +/-5°C
5 years at -50°C +/-10°C
9 years at -80°C +/-10°C

13.4 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal

products.

Product Owner:
Bavarian Nordic
A/S Philip Heymans Alle 3
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Date of Revision: 08/2024