



## Review Memorandum

**Date:** August 9, 2022

**To:** The File

**From:** Peter Marks, MD, PhD (CBER/OD)

**Applicant name:** National Institute for Allergy and Infectious Diseases (NIAID)

**EUA Application Number:** 28801

**Product:** JYNNEOS (Smallpox and Monkeypox Vaccine, Live, Non-replicating)

**Subject:** **Assessment of two doses (each 0.1 mL dose containing  $2 \times 10^7$  TCID<sub>50</sub> of MVA-BN) of JYNNEOS via the intradermal (ID) route of administration for prevention of monkeypox disease in individuals 18 years of age and older determined to be at high risk for monkeypox infection and the use of two-doses (each 0.5 mL dose containing  $1 \times 10^8$  TCID<sub>50</sub> of MVA-BN) of JYNNEOS via the subcutaneous (SC) route of administration for prevention of monkeypox disease in individuals under 18 years of age determined to be at high risk for monkeypox infection**

This memorandum provides a summary, review, and recommendation for the emergency use authorization (EUA) of JYNNEOS (Smallpox and Monkeypox Vaccine, Live, Non-replicating) to authorize the administration of: (i) two doses (each 0.1 mL dose containing  $2 \times 10^7$  TCID<sub>50</sub> of MVA-BN, hereafter referred to as 0.1 mL) of JYNNEOS 4 weeks apart via the intradermal (ID) route of administration to individuals 18 years of age and older determined to be at high risk for monkeypox infection; and (ii) two doses (each 0.5 mL dose containing  $1 \times 10^8$  TCID<sub>50</sub> of MVA-BN, hereafter referred to as 0.5 mL) of JYNNEOS 4 weeks apart via the subcutaneous (SC) route of administration to individuals under 18 years of age determined to be at high risk for monkeypox infection.

### **Executive Summary**

Monkeypox is an orthopoxvirus that is related to smallpox. The first human case of monkeypox was recorded in 1970 and monkeypox has been associated with sporadic outbreaks over the past decades, often in international travelers who had visited the African continent. In the current outbreak, which to date has primarily affected men who have sex with men and their intimate contacts, the disease often manifests as painful lesions in the genital region that can take two to three weeks to completely heal.

JYNNEOS is an FDA-licensed vaccine in the United States (U.S.) that is approved for prevention of monkeypox and smallpox disease in individuals 18 years of age and older who are determined to be at high risk for smallpox or monkeypox infection. It is a live virus vaccine produced from the strain Modified Vaccinia Ankara-Bavarian Nordic (MVA-BN), an attenuated, non-replicating orthopoxvirus, that was



originally developed for use in the event of a smallpox bioterrorist attack in certain populations (e.g., immunocompromised individuals). JYNNEOS is approved for use as a 2-dose (0.5 mL each) regimen administered by subcutaneous injection with the doses given 4 weeks apart.

There is currently a limited supply of JYNNEOS available globally and in the U.S. Approximately 1.6 to 1.7 million people are currently estimated to be at elevated risk of monkeypox in the U.S. and may need vaccination, including those eligible for pre-exposure prophylaxis with medications to prevent human immunodeficiency virus (HIV). Therefore, 3.2 to 3.4 million doses of JYNNEOS would be required to immunize that population. However, only about half that number of doses are currently estimated to be available before the end 2022. In addition to the limitations on the supply of JYNNEOS, individuals under 18 years of age are increasingly potentially being exposed to monkeypox and are in need of post exposure prophylaxis.

Alternative approaches to use of the licensed regimen of JYNNEOS have been explored as potential options to make up the shortfall in doses including use of ACAM2000 and delaying second doses of JYNNEOS. The approaches were not considered acceptable. In contrast, data has been submitted as part of an EUA request from the Division of Microbiology and Infectious Diseases (DMID) at NIAID to allow the administration of JYNNEOS vaccine to be administered by the ID route for the prevention of monkeypox infection in individuals 18 years and older. The core of the submission is DMID Protocol 09-0002.

In this Phase 2 study, subjects were randomized 1:1:1 to receive two doses of vaccine 28 days apart. One group (n=167 subjects), “Liquid-SC” group, received JYNNEOS administered sub-cutaneously (each 0.5mL dose containing  $1 \times 10^8$  TCID<sub>50</sub> MVA-BN), a second group (n=191 subjects), “Liquid-ID” group, received JYNNEOS administered intradermally (each 0.1mL dose containing  $2 \times 10^7$  TCID<sub>50</sub> MVA-BN). A third group (n=165 subjects) received a different formulation of the vaccine administered subcutaneously “Lyophilized-SC” group. An approximately equal number of males and females were enrolled. The age range of enrolled subjects was 18-38 years. Most subjects were non-Hispanic and white, approximately 10% characterized their race as black and 4% as Asian. The study was performed at eight sites in the U.S. in accordance with good clinical practices. This review will focus on the data for the first two groups (Liquid-SC and Liquid-ID).

Safety data for the Liquid-SC and Liquid-ID groups includes information on systemic reactions, local reactions, and serious adverse events. Serious adverse events were uncommon overall (4 events) and were balanced on the different trial arms; all were considered not associated with vaccine. Feeling tired (fatigue) was the most prevalent systemic reaction reported and was similar between the two groups (49.7% for SC versus 51.3% for ID following either vaccine dose). Overall systemic reactions including elevated oral temperature, muscle aches, chills, headache, nausea, feeling tired, change in appetite, and joint pain taken together were similar following either dose of the vaccine and were also similar between the two groups (65.3% for SC versus 68.1% for ID following either vaccine dose).

In terms of local reactogenicity, pain at the injection site was more prevalent in the Liquid-SC group (91.0% for SC versus 65.4% for ID) and itching (pruritis) was more prevalent in the Liquid-ID group (48.5% for SC versus 89% for ID). Redness (erythema) at the injection site was very common in both SC (84.4%) and ID (100%) groups. In the SC arm this resolved within 14 days following the second vaccine dose in all individuals, whereas in the ID arm 44% still had erythema at the end of this period.



Additionally, a few patients receiving on the ID arm developed small nodules or discoloration at the injection site. The functional grade of local adverse events following either dose of the vaccine were generally similar in percentage.

Following vaccination with JYNNEOS SC and ID immunogenicity was evaluated using 4 different assays. These were plaque reduction neutralizing antibody titers (PRNT) obtained using assays performed at St. Louis University (SLU) and Bavarian-Nordic (BN), and Enzyme linked immunosorbent assay (ELISA) values obtained at SLU and BN. The development of the immune response over time following SC and ID administration was nearly identical, and the  $\log_2$  transformed peak titers obtained following ID administration were non-inferior to the SC route using results obtained using all four assays.

The available information provides evidence indicating that the immunogenicity of JYNNEOS administered by the SC and ID routes appears to be nearly identical. The systemic side effect profile with the two routes of administration is also very similar. The local side effect profile using the route of ID administration is associated with less local pain, but more local redness and itching. These data, together with the data supporting the licensure of JYNNEOS, support a positive benefit-risk profile for JYNNEOS when administered intradermally to prevent monkeypox disease in individuals determined to be at high risk of monkeypox infection. In the current setting of a monkeypox outbreak that is continuing to spread in the context of a limited number of vaccine doses, the additional doses of vaccine that will be made available may also help to benefit public health measurably by assisting in containment efforts.

In addition to the ID use, JYNNEOS administered by the SC route to individuals under 18 years of age determined to be at high risk for monkeypox infection is reasonable based on the available JYNNEOS safety and immunogenicity data in adults as well as the historical data with use of live vaccinia virus smallpox vaccine in pediatric populations.

Based on the totality of evidence available, including NIAID DMID Protocol 09-0002, the review team concludes that the known and potential benefits of administering two doses (0.1 mL) of JYNNEOS 4 weeks apart via the ID route of administration to individuals 18 years of age and older determined to be at high risk for monkeypox infection for prevention of monkeypox disease, outweigh the known and potential risks for those individuals. Additionally, based on the totality of evidence available, the review team concludes that the known and potential benefits of administering two doses (0.5 mL) of JYNNEOS 4 weeks apart via the SC route of administration to individuals younger than 18 years of age determined to be at high risk for monkeypox infection for prevention of monkeypox disease, outweigh the known and potential risks for those individuals. Therefore, the review team recommends authorizing the use of: (i) two doses (0.1 mL each) of JYNNEOS 4 weeks apart via the ID route of administration for prevention of monkeypox disease in individuals 18 years of age and older determined to be at high risk for monkeypox infection; and (ii) two doses (0.5 mL) of JYNNEOS 4 weeks apart via a SC route of administration for prevention of monkeypox disease in individuals younger than 18 years of age determined to be at high risk for monkeypox infection.

Safety surveillance under the oversight of FDA and CDC will actively and passively monitor for risks of local and systemic side effects and other known and unknown short-term and long-term risks of the authorized vaccine.



## **Review**

### **Disease Background**

Monkeypox is an orthopoxvirus that is related to smallpox.<sup>1</sup> Monkeypox was discovered in 1958 when two outbreaks of a pox-like disease occurred in colonies of monkeys kept for research. Despite being named “monkeypox,” the original source of the disease remains unknown. However, African rodents and non-human primates (like monkeys) might harbor the virus and infect people.

The first human case of monkeypox was recorded in 1970 and monkeypox has been associated with sporadic outbreaks over the past decades, often in international travelers who had visited the African continent. The most recent outbreak of monkeypox that began in early 2022 is associated with the less virulent West African clade of the virus. It has primarily affected men who have sex with men and their intimate contacts, and the disease often manifests as painful pustular lesions in the genital region that can take two to three weeks to completely heal. These lesions may have very high titers of infectious virus present, and until the lesions completely heal over these individuals can potentially spread the virus further.

Although endemic monkeypox is generally a self-limited illness, in some it can be a serious illness and is associated with a case fatality rate of 1 to 10%. Death appears to be more common in young children and immunocompromised individuals. In those with HIV, it is not clear whether or not antiretroviral therapy modifies the risk of death from monkeypox.<sup>2</sup>

On May 17, 2022, the first confirmed case of monkeypox was identified in the U.S. As of August 7, 2022, there are 7,510 cases in 48 states, the District of Columbia and Puerto Rico.<sup>3</sup> Worldwide, as of August 3, 2022, there has been over 28,000 confirmed cases in 88 countries.<sup>4</sup> On July 23, 2021, the World Health Organization declared the current monkeypox outbreak a Public Health Emergency of International Concern (PHEIC). On August 4, 2022, the U.S. Department of Health and Human Services (HHS) declared the ongoing spread of monkeypox virus in the U.S. a Public Health Emergency (PHE).

### **JYNNEOS for the Prevention of Monkeypox**

JYNNEOS is an FDA-licensed vaccine in the U.S. that is approved for prevention of smallpox and monkeypox disease in individuals 18 years of age and older who are determined to be at high risk for smallpox or monkeypox infection. It is a live, non-replicating vaccine using Modified Vaccinia Ankara

---

<sup>1</sup> See Moore MJ, Rathish B, Zahra F. Monkeypox.StatPearls, Last update July 16, 2022; <https://www.ncbi.nlm.nih.gov/books/NBK574519/>, last accessed August 7, 2022.

<sup>2</sup> Thornhill JP, Barkati S, Walmsley S et al. Monkeypox Virus Infection in Humans across 16 Countries — April–June 2022. *N Engl J Med*, July 21, 2022, <https://www.nejm.org/doi/full/10.1056/NEJMoa2207323>.

<sup>3</sup> See CDC website, Technical Report: Multi-National Monkeypox Outbreak, United States, 2022 at <https://www.cdc.gov/poxvirus/monkeypox/clinicians/technical-report.html#:~:text=July%2025%2C%202022-,Summary%3A%20U.S.%20Case%20Data,of%20Columbia%2C%20and%20Puerto%20Rico> (last accessed Aug. 7, 2022). The case counts include those who tested positive for either monkeypox virus or orthopoxvirus (OPX).

<sup>4</sup> See CDC website, 2022 Monkeypox Outbreak Global Map, available at <https://www.cdc.gov/poxvirus/monkeypox/response/2022/world-map.html> (last accessed Aug. 7, 2022).



(MVA) virus that was originally developed for use in the event of a smallpox bioterrorist attack in certain populations (e.g., immunocompromised individuals). JYNNEOS is approved for use as a 2-dose (0.5 mL each) regimen administered by SC injection with the doses given 4 weeks apart.

Data indicate that JYNNEOS given by SC injection on days 1 and 28 protects against monkeypox disease by day 42. These data do not come exclusively from clinical effectiveness studies conducted in humans. Instead, the data supporting human efficacy is inferential and comes from a combination of studies looking at the safety and immune response of the vaccine in humans in combination with a monkeypox virus challenge study that was conducted in non-human primates (*cynomolgus macaques*).<sup>5</sup>

There is currently a limited supply of JYNNEOS available globally and in the United States. Approximately 1.6 to 1.7 million people are currently estimated to be at elevated risk of monkeypox in the U.S. and may need vaccination, including those eligible for pre-exposure prophylaxis with medications to prevent HIV.<sup>6</sup> Therefore, 3.2 to 3.4 million doses of JYNNEOS would be required to immunize that population. However, only about half that number of doses are currently estimated to be available before the end 2022.

Alternative approaches to use of the licensed regimen of JYNNEOS have been explored as potential options to make up the shortfall in doses. ACAM2000 may be effective against monkeypox, but it is not currently licensed for this indication, and is contraindicated in individuals with severe immunodeficiency who are not expected to benefit from the vaccine. These individuals may include individuals who are undergoing bone marrow transplantation or individuals with primary or acquired immunodeficiency who require isolation. Additionally, ACAM2000 must be given by a multiple puncture technique with a bifurcated needle, and the live vaccine virus is shed from the vaccination site and can be spread to other parts of the body or to other individuals. Therefore, appropriate care of the vaccination site is required until it is completely healed, which may take four weeks or longer. This is particularly relevant if the individual receiving the vaccine comes into direct contact with immunocompromised individuals, who can be infected with vaccinia and experience serious complications related to the live virus vector. ACAM2000 is also associated myocarditis in approximately 1 in 175 recipients. Other serious adverse reactions associated with ACAM2000 include encephalitis, progressive vaccinia, severe vaccinia skin infections, and eczema vaccinatum.

Consideration has also been given to use of delayed second doses of the JYNNEOS vaccine. In this scenario, the existing supply of vaccine would be used to start the immunization process in twice as many individuals, and second doses would be delayed for 3 to 6 months. This is an approach that has been proposed by a number of state health authorities and is being implemented in several places outside of the U.S. Three issues strongly mitigate against proceeding with the delayed second dose strategy. First, there are no clinical studies of JYNNEOS available that indicate that a single dose of the vaccine will protect against high titer viral monkeypox exposures through several months following vaccination. Second, data

---

<sup>5</sup> Earl PL, Americo JL, Wyatt LS et al. Immunogenicity of a highly attenuated MVA smallpox vaccine and protection against monkeypox. *Nature* 2004; 428:182-5, <https://www.nature.com/articles/nature02331>.

<sup>6</sup> <https://www.cdc.gov/nchhstp/newsroom/fact-sheets/hiv/PrEP-for-hiv-prevention-in-the-US-factsheet.html#:~:text=Young%20people%20ages%2016%2D24,and%2035%2D44%2C%20respectively>, last accessed August 7, 2022.



indicate that a single dose of JYNNEOS is likely to provide a significantly lower geometric mean titer (GMT) than the licensed 2-dose regimen, 16.9 [13.7, 20.8] as compared to 153.5 [134.3, 175.6], respectively.<sup>7</sup> Third, use of all the available doses of JYNNEOS may not allow vaccination of the target population at risk in a timely manner, and will completely deplete the supply of JYNNEOS in the event that a larger population of individuals needs to receive vaccination, potentially including immunocompromised individuals for whom an optimal alternative does not exist.

In contrast to the paucity of data for a single dose strategy, data are available from a clinical trial performed in accordance with Good Clinical Practice under the sponsorship of NIAID comparing the two dose SC regimen of JYNNEOS to a two dose ID regimen using a fifth of the SC dose.<sup>8</sup> These data have been published and have been submitted by NIAID in support of the current EUA.<sup>9,10</sup> In brief, the SC and ID routes of administration were found to have similar immunogenicity, which indicates that the ID route of administration may be effective. The local side effects of redness and induration were increased with the ID route of administration, whereas the SC route of administration was associated with more local pain at the site of administration. Supportive safety data for the ID route of administration come from a variety of studies of MVA conducted in Europe several decades ago.<sup>11</sup>

### Requirements for EUA

The EUA process allows the Secretary of HHS, in appropriate circumstances, to declare that EUAs are justified for products to respond to certain types of threats. On August 9, 2022, pursuant to section 564 of the Federal Food, Drug, and Cosmetic Act (the FD&C Act), the Secretary of HHS determined that there is a public health emergency, or the significant potential for a public health emergency, that has a significant potential to affect national security or the health and security of United States citizens living abroad, and that involves the virus that causes monkeypox. On the basis of such determination, on August 9, 2022, the Secretary then declared that circumstances exist justifying the authorization of emergency use of vaccines during the monkeypox outbreak, pursuant to section 564(b)(1) of the FD&C Act.<sup>12</sup>

Following the Secretary's EUA declaration, under section 564(c) of the FD&C Act, FDA may issue an EUA related to monkeypox after FDA concludes that the following statutory requirements are met:

---

<sup>7</sup> Pittman PR, Hahn M, Lee HS .et al. Phase 3 efficacy trial of Modified Vaccinia Ankara as a vaccine against smallpox. *N Engl J Med* 2019; 381:1897-1908, <https://www.nejm.org/doi/full/10.1056/NEJMoa1817307>.

<sup>8</sup> Prior to U.S. licensure in 2019, JYNNEOS was known by the name of IMVAMUNE, the name that is still used outside the U.S.

<sup>9</sup> Frey SE, Wald A, Edupuganti S et al. Comparison of lyophilized versus liquid modified vaccinia Ankara (MVA) formulations and subcutaneous versus intradermal routes of administration in healthy vaccinia-naïve subjects. *Vaccine* 2015; 33:5225-34, <https://www.sciencedirect.com/science/article/pii/S0264410X15008762?via%3Dihub>.

<sup>10</sup> Although the EUA request from NIAID was specifically requesting the FDA to consider an EUA for the ID route of administration of JYNNEOS and did not refer to authorization of the pediatric indication, FDA consulted with NIAID and NIAID raised no objections to authorizing the use of JYNNEOS to individuals under 18 years of age.

<sup>11</sup> Mayr A, Stickl H, Müller HK, et al. Der Pockenimpfstamm MVA: Marker, genetische Struktur, Erfahrungen mit der parenteralen Schutzimpfung und Verhalten im abwehrgeschwächten Organismus [The smallpox vaccination strain MVA: marker, genetic structure, experience gained with the parenteral vaccination and behavior in organisms with a debilitated defence mechanism (author's transl)]. *Zentralbl Bakteriol B.* 1978 Dec;167(5-6):375-90. German. PMID: 219640.

<sup>12</sup> U.S. Department of Health and Human Services, Determination of Public Health Emergency or Significant Potential for a Public Health Emergency and Declaration that Circumstances Exist Justifying an Authorization Pursuant to Section 564 of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3.



- The agent referred to in the August 9, 2022 EUA declaration by the Secretary of HHS (monkeypox virus) can cause a serious or life-threatening disease or condition.
- Based on the totality of scientific evidence available, including data from adequate and well-controlled trials, if available, it is reasonable to believe that the product may be effective to prevent, diagnose, or treat such serious or life-threatening disease or condition that can be caused by monkeypox virus, or to mitigate a serious or life-threatening disease or condition caused by an FDA-regulated product used to diagnose, treat, or prevent a disease or condition caused by monkeypox virus.
- The known and potential benefits of the product, when used to diagnose, prevent, or treat the identified serious or life-threatening disease or condition, outweigh the known and potential risks of the product.
- There is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating the disease or condition.<sup>13</sup>

If these criteria are met, under an EUA, FDA can authorize unapproved uses of approved medical products (or unapproved medical products) to be used in an emergency to diagnose, treat, or prevent serious or life-threatening diseases or conditions caused by threat agents.

#### Review of the NIAID Request for ID Vaccine Administration

The Division of Microbiology and Infectious Diseases (DMID) at NIAID submitted a EUA request to allow the administration of JYNNEOS vaccine by the ID route for the prevention of monkeypox infection in individuals 18 years and older. The core of the submission is DMID Protocol 09-0002 entitled: Comparison of the safety and immunogenicity of lyophilized IMVAMUNE<sup>®</sup> ( $1 \times 10^8$  TCID<sub>50</sub>) versus liquid formulation IMVAMUNE<sup>®</sup> ( $1 \times 10^8$  TCID<sub>50</sub>) administered by the subcutaneous route and a lower dose liquid formulation IMVAMUNE<sup>®</sup> ( $2 \times 10^7$  TCID<sub>50</sub>) administered by the intradermal route in healthy vaccinia-naïve individuals.<sup>14</sup>

In this Phase 2 study subjects were randomized 1:1:1 to receive two doses of vaccine 28 days apart. One group (n=167 subjects), “Liquid-SC” group, received JYNNEOS administered sub-cutaneously (each 0.5mL dose containing  $1 \times 10^8$  TCID<sub>50</sub> MVA-BN), a second group (n=191 subjects), “Liquid-ID” group, received JYNNEOS administered intradermally (each 0.1mL dose containing  $2 \times 10^7$  TCID<sub>50</sub> MVA-BN). A third group (n=165 subjects) received a different formulation of the vaccine administered subcutaneously “Lyophilized-SC” group. Per protocol, subjects were added to replace those who did not complete the study, in order to have adequate number of subjects who had received two doses of the vaccine for analysis. An approximately equal number of males and females were enrolled. The age range of enrolled subjects

---

<sup>13</sup> At this time the pace of the current outbreak indicates that the current supply of JYNNEOS vaccine will be exhausted prior to vaccinating the population of individuals at risk. ACAM2000 is not currently licensed for the prevention of monkeypox and is also associated with both significant local and systemic side effects that mitigate against its widespread use. FDA therefore concludes that there is currently not an available and adequate approved alternative product.

<sup>14</sup> For the purposes of this EUA only the liquid SC and liquid ID arms of this clinical trial will be discussed further. As noted above, prior to U.S. licensure in 2019, JYNNEOS was known by the name of IMVAMUNE, the name that is still used outside the U.S.



was 18-38 years. Most subjects were non-Hispanic and white, approximately 10% characterized their race as black and 4% as Asian. The study was performed at eight sites in the U.S. in accordance with good clinical practices. This review will focus on the data for the first two groups (Liquid-SC and Liquid-ID). The dosing interval between the first and second vaccinations was 4 weeks. When notable erythema was still present on the arm in which the first dose of JYNNEOS was administered dose, the second dose was administered into the opposite arm.

**Safety**

Safety data for the liquid SC and ID arms includes information on serious adverse events, systemic reactions and local reactions. Serious adverse events were uncommon overall (4 events) and were balanced on the different trial arms; all were considered not associated with vaccine. Feeling tired (fatigue) was the most prevalent systemic reaction reported and was similar between the two groups (49.7% for SC versus 51.3% for ID following either vaccine dose). Overall systemic reactions including elevated oral temperature, muscle aches, chills, headache, nausea, feeling tired, change in appetite, and joint pain were similar following either dose of the vaccine and were also similar between the two groups. Table 1 presents the frequency of adverse reactions reported in >10% of individuals within 15 days following any dose.

**Table 1. Adverse reactions reported in >10% of individuals within 15 days following any dose**

<b>Reactogenicity event</b>	<b>SC (%) N=166</b>	<b>ID (%) N=190</b>
Feeling Tired	49.7	51.3
Muscle Aches	41.3	30.4
Headache	43.1	41.4
Nausea	21.6	23.0
Change in Appetite	15.0	20.4
Chills	12.6	14.7
Joint Pain	9.0	17.8
Pain at injection site	91.0	65.4
Erythema at injection site	81.4	99.5
Induration at injection site	69.5	99.5
Itchiness	48.5	89.0
Underarm pain	18.0	20.9
Underarm swelling	6.0	10.5

Data were not available for one individual in each of the two groups

In terms of local reactogenicity, pain at the injection site was more prevalent in the Liquid-SC group (91.0% for SC versus 65.4% for ID) and itching (pruritis) was more prevalent in the Liquid-ID group (48.5% for SC versus 89% for ID). Redness (erythema) at the injection site was very common in both the SC-Liquid (81.4%) and ID-Liquid (99.5%) groups. In the SC arm this resolved within 14 days following the second vaccine dose in all individuals, whereas in the ID arm 44% still had erythema at the end of this period. In the publication reporting on the results of the study, it is noted that at Day 180, greater than a



third of subjects in the ID group continued to have minimal induration or erythema present on exam.<sup>15</sup> Additionally, a few patients receiving ID JYNNEOS developed small nodules or discoloration at the injection site.

As part of the EUA submission, NIAID provided a reanalysis of the local reactogenicity measurement for erythema and induration comparing the DMID criteria used and comparing it to the current FDA Toxicity Scale criteria for reactogenicity measurement.<sup>16</sup> A major difference between these two scales is that the definition of severe erythema and induration is a measurement of >30 mm with the DMID scale and >100 mm for the FDA scale. The DMID criteria (used for the publication of the results in Frey et al., 2015) indicated that the number of individuals experiencing a maximum grading of severe reactogenicity for any vaccination was 46.7% for the SC route and 74.9% for the ID route. Using the FDA criteria the number of individuals experiencing a maximum grading of severe reactogenicity for any vaccination was 7.8% for the SC route and 5.8% for the ID route.

***Immunogenicity***

Following vaccination with JYNNEOS SC and ID immunogenicity was evaluated using 4 different assays . These were plaque reduction neutralizing antibody titers (PRNT) obtained using assays performed at St. Louis University (SLU) and Bavarian-Nordic (BN) and enzyme linked immunosorbent assays (ELISA) values obtained at SLU and BN. The development of the immune response over time following SC and ID administration was nearly identical, and the log<sub>2</sub> transformed peak titers obtained following ID administration were non-inferior to the SC route using all four assays (Table 2).

**Table 2. Comparison of log<sub>2</sub> transformed peak titers following SC and ID vaccine administration**

<b>Assay</b>	<b>SC peak titer</b>	<b>ID peak titer</b>	<b>Difference</b>	<b>97.5% CI</b>
SLU PRNT	8.37	8.36	0.005	0.43, 0.44
BN PRNT	5.63	5.90	-0.27	-0.77, 0.23
SLU ELISA	9.66	9.52	0.14	-0.21, 0.49
BN ELISA	9.59	9.57	0.02	-0.31, 0.35

CI, confidence interval

In summary, the immunogenicity of JYNNEOS administered by the SC and ID routes appears to be nearly identical, which indicates that the ID route of administration may be effective. The systemic side effect profile with the two routes of administration is also very similar. In terms of local side effects, SC administration is more commonly associated with pain, and ID administration is more commonly associated with redness and itching, and the redness may persist for several weeks after administration of the doses.

Review of JYNNEOS for Administration to Individuals Under 18 Years of Age

<sup>15</sup> Frey SE, Wald A, Edupuganti S et al. Comparison of lyophilized versus liquid modified vaccinia Ankara (MVA) formulations and subcutaneous versus intradermal routes of administration in healthy vaccinia-naïve subjects. *Vaccine* 2015; 33:5225-34, <https://www.sciencedirect.com/science/article/pii/S0264410X15008762?via%3Dihub>.

<sup>16</sup> FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, <https://www.fda.gov/media/73679/download>, last accessed August 7, 2022.



FDA is now approaching 100 emergency individual patient Investigational New Drug Application requests for post exposure prophylaxis in children ranging from a few months of age through the teenage years. To date, there have been no safety signals of concern reported to the agency following the first doses of JYNNEOS administered to these individual under 18 years of age.

In support of SC administration of two doses (0.5 mL each) of JYNNEOS to individuals younger than 18 years of age, FDA has considered the available JYNNEOS safety and immunogenicity data in adults as well as the historical data with use of live vaccinia virus smallpox vaccine in pediatric populations. The benefit-risk profile of administering JYNNEOS intradermally to pediatric populations is less established than for adults because the study of intradermal administration involved adults only. Additionally, there may be practical challenges in the intradermal route of administration particularly in the youngest pediatric patients. As noted below, FDA will closely monitor the safety profile of JYNNEOS in the pediatric population.

### **Recommendation**

As summarized in the “Disease Background” section of this memorandum, the chemical, biological, radiological, or nuclear (CBRN) agent referred to in the August 9, 2022 declaration by the Secretary of HHS (monkeypox virus) can cause a serious or life-threatening disease or condition.

The available information provide evidence indicating that the immunogenicity of JYNNEOS administered by the SC and ID routes appears to be nearly identical, which suggests that the ID route of administration may be effective. The systemic side effect profile with the two routes of administration is also very similar. The local side effect profile using the route of ID administration is associated with less local pain, but more local redness and itching. It is expected that the local symptoms of local redness and itching will be readily manageable with provider and patient education. Considering the data supporting the licensure of JYNNEOS together with the data described in this review memorandum, the benefits and risks for the ID route of administration are favorable in individuals 18 years of age and older who are determined to be at high risk of monkeypox infection. In addition, in the current setting of an outbreak that is continuing to spread in the context of a limited number of vaccine doses, the additional doses of vaccine that will be made available may help to benefit public health measurably by assisting in containment efforts.

In addition to the ID use for adults, JYNNEOS administered by the SC route to individuals under 18 years of age determined to be at high risk for monkeypox infection is reasonable based on the available data in adults vaccinated with JYNNEOS, the historical data with use of live vaccinia virus smallpox vaccine in pediatric populations, and the recent experience with the pediatric individual patient Investigational New Drug Application requests.

Plans are in progress in the U.S. for the conduct of studies using real world data in order to assess both the safety and effectiveness of the JYNNEOS vaccine in the setting of this monkeypox disease outbreak, and these efforts will be coordinated with global efforts aimed as assessing the safety and effectiveness of the JYNNEOS vaccine in preventing monkeypox.

Based on the totality of evidence available, including NIAID DMID Protocol 09-0002, the review team concludes that the known and potential benefits of administering two doses (0.1 mL containing  $2 \times 10^7$



TCID<sub>50</sub> each) of JYNNEOS 4 weeks apart via the ID route of administration to individuals 18 years of age and older determined to be at high risk for monkeypox infection for prevention of monkeypox disease, outweigh the known and potential risks in those individuals. Additionally, based on available data in adults and the historical data with use of live vaccinia virus smallpox vaccine in pediatric populations, the review team concludes that the known and potential benefits of administering of two doses (0.5 mL containing 1 x 10<sup>8</sup> TCID<sub>50</sub> each) of JYNNEOS 4 weeks apart via the SC route of administration to individuals younger than 18 years of age determined to be at high risk for monkeypox infection for prevention of monkeypox disease, outweigh the known and potential risks.

The review team recommends authorizing the use of: (i) two doses (0.1 mL each) of JYNNEOS 4 weeks apart via the ID route of administration to individuals 18 years and older determined to be at high risk for monkeypox infection; and (ii) two doses (0.5 mL) of JYNNEOS 4 weeks apart via a SC route of administration to individuals younger than 18 years of age determined to be at high risk for monkeypox infection.