BLA Clinical Review Memorandum

Application Type	Supplemental BLA
STN	125158.297
CBER Received Date	27 October 2023
PDUFA Goal Date	26 August 2024
Division / Office	DCTR/OVRR
Priority Review (Yes/No)	No
Reviewer Name(s)	Sixun Yang, MD, PhD
Review Completion Date / Stamped Date	26 April 2024/22 August 2024
Supervisory Concurrence	Sheral Patel, MD, Team Leader Andrea Hulse, MD, Branch Chief
Applicant	Emergent BioSolutions
Established Name	Smallpox and Mpox (Vaccinia) Vaccine, Live
Trade Name	ACAM2000
Pharmacologic Class	Vaccine
Formulation(s), including Adjuvants, etc.	Lyophilized preparation of purified live virus packaged with 0.6 mL of diluent in 3 mL clear glass vials
Dosage Form(s) and Route(s) of Administration	Approximately 0.0025 mL of ACAM2000 containing 2.5 – 12.5 x 10^5 PFU vaccinia virus administered percutaneously using 15 punctures with a bifurcated needle
Dosing Regimen	Single dose of ACAM2000 at 2.5 – 12.5 x 10^5 PFU vaccinia virus
Indication(s) and Intended Population(s)	For active immunization against smallpox or mpox disease for persons determined to be at high risk for smallpox or mpox infection
Orphan Designated (Yes/No)	No

TABLE OF CONTENTS

GLOSSARY

ACAM2000	Smallpox and Mpox (Vaccinia) Vaccine, Live
AE	adverse event
BLA	Biologics License Application
CBER	Center for Biologics Evaluation and Research
CI	confidence interval
CMC	chemistry, manufacturing, and controls
DRC	Democratic Republic of the Congo
GMT	geometric mean titers
LB	lower bound
MPXV	mpox virus
MSM	men who have sex with men
NHP	non-human primate
NYCBH	New York City Board of Health
OPXV	orthopoxvirus
PEP	post-exposure prophylaxis
PHEIC	Public Health Emergency of International Concern
PI	package insert
PREA	Pediatric Research Equity Act
PRNT50	plaque reduction neutralization test 50
USPI	U.S. package insert
WHO	World Health Organization

1. EXECUTIVE SUMMARY

To address an emerging mpox virus (MPXV) threat, Emergent (the Applicant) has requested to expand the indication of the live, vaccinia virus-based smallpox vaccine ACAM2000 to include active immunization for the prevention of mpox disease in persons determined to be at high risk for infection with MPXV. Since it is infeasible to directly assess the efficacy of ACAM2000 against mpox in humans, the Applicant submitted data from a controlled study evaluating the immunogenicity and protective activity of ACAM2000 against a lethal challenge dose of MPXV in cynomolgus macaques, as well as published reports of similar nonclinical evaluations of ACAM2000 against MPXV lethal challenge. The effectiveness of ACAM2000 against mpox is inferred from its protective capacity against lethal dose challenge with MPXV in the animals and supported by a published observational study in humans that estimated prior vaccination with the smallpox vaccine Dryvax was 85% effective in preventing infection with MPXV. CBER granted the Applicant's request to extrapolate effectiveness of ACAM2000 against mpox in adults to all pediatric populations because the pathogenesis of MPXV in adults and pediatric populations is sufficiently similar.

The safety profile of ACAM2000 in adults was documented in 2007 when it was approved for smallpox and is described in the package insert. The safety profile of ACAM2000 in pediatric populations has not been assessed in clinical trials and is considered to be comparable to that of Dryvax, from which ACAM2000 was cloned.

Available data support approval of ACAM2000 for use in individuals at high risk of exposure to MPXV. Mitigation of the observed risks and uncertainties will be accomplished through labeling (including the existing Boxed Warning and Warnings and Precautions) and shared decision making between healthcare providers and potential vaccinees.

2. CLINICAL AND REGULATORY BACKGROUND

ACAM2000 is a second-generation live, vaccinia virus-based smallpox vaccine. ACAM2000 was derived by plaque purification cloning from a first-generation smallpox vaccine Dryvax [Wyeth Laboratories, Marietta, PA, calf lymph vaccine, New York City Board of Health (NYCBH) Strain], which is no longer available.

ACAM2000 was initially approved in 2007 for an indication of active immunization against smallpox disease for persons determined to be at high risk for smallpox infection based on non-inferiority comparisons with Dryvax in vaccine take and vaccinia-specific neutralizing antibody titers.

To address an emerging MPXV threat, Emergent is pursuing an expansion of the ACAM2000 indication to active immunization against mpox disease for persons determined to be at high risk for mpox infection.

2.1 Disease or Health-Related Condition Studied

Mpox, also known as monkeypox before the World Health Organization (WHO) renamed it in 2022, is a rare but serious illness endemic to the tropical rain forests of central and western Africa. The disease has several similarities to smallpox. The pathogenic agents MPXV and variola virus (the causative agent for smallpox) are both members of the genus *Orthopoxvirus* in the family *Poxviridae*, and the infections have similar time courses and clinical features. In general, the severity of mpox is intermediate between that of variola major and variola minor,

with approximately 60% of cases requiring medical care (Fine, et al., 1988). and an overall case-fatality rate of 8.7% (Bunge, et al., 2022).

Mpox was first identified in 1959 after two pox-like disease outbreaks occurred in the Statens Serum Institut animal facilities in Denmark among captive cynomolgus monkeys imported from Singapore (Magnus, et al., 1959). Since then, several mpox outbreaks have been reported in institute animal facilities in other countries among captive monkeys imported from southeast Asia (Arita and Henderson, 1968).

The first human mpox infection was identified in 1970 in a nine-month-old child from the Democratic Republic of the Congo (DRC) (Ladnyi, et al., 1972). As of 2019, human mpox had appeared in 10 African countries and 4 other countries, with most of the mpox cases being reported in the DRC (Bunge, et al., 2022). The burden of disease in endemic countries was primarily in children with a median age of 4 to 5 years old at presentation during the 1970-1989 time frame; increasing to 10 years of age in the 2000-2009 time frame and to 21 years in 2010-2019 (Bunge, et al., 2022). The rate of death in mpox cases in children younger than 10 years of age was 100% (47/47) in the 1970-1989 time frame and 37.5% (6/16) in the 2010-2019 time frame (Bunge, et al., 2022). During the 2017 outbreak in Nigeria, persons vaccinated against smallpox prior to 1980 had a five-fold lower risk of mpox disease compared to those who had not been vaccinated (Simpson, et al., 2020).

The first cases of mpox to be reported outside of Africa occurred in the U.S. in 2003 when infected Gambian rats, dormice, and rope squirrels imported into the U.S. spread the virus to captive American prairie dogs and then to individuals who handled infected animals (CDC, 2023a).

In the first half of 2022, a significant and concerning mpox outbreak occurred in the U.S. and other non-endemic regions around the world. During January 1, 2022 to June 6, 2023, a total of 87,942 confirmed cases of mpox with 146 deaths were identified, including 86,157 cases and 127 deaths identified in 104 countries that had not historically reported mpox, and 1,785 cases with 19 deaths identified in 7 countries that had historically reported mpox (CDC, 2023b). In the U.S, 26,384 mpox cases were reported during May 17 to October 6, 2022 (Kava, et al, 2022). As cases of mpox continued to rise and spread across the globe, the WHO declared a Public Health Emergency of International Concern (PHEIC) on July 23, 2022 (WHO, 2022). Soon after, on August 4, 2022, the U.S. government declared a public health emergency (U.S. DHHS, 2022). Unlike smallpox, where the only known reservoir for the variola virus was humans, MPXV can be transmitted through rodent reservoirs (Isidro, et al., 2022). As the 2022 global mpox outbreak evolved, there was increasing concern over reverse zoonosis and the establishment of an animal reservoir that would allow mpox to become endemic in regions outside of Africa (Koening, et al., 2022). Even though establishment of the animal reservoir of mpox outside of endemic countries was not reported during the 2022 outbreak, this possibility still exists, as evidenced by a report of the transfer of mpox from infected owners to pets (Seang, et al., 2000).

MPXV is transmitted from infected animals to humans via indirect or direct contact, but human-to-human transmission can also occur through direct contact with infectious skin or mucocutaneous lesions (Thornhill, et al., 2022). Transmission can also occur from the environment to humans from contaminated clothing or linens that have infectious skin particles (CDC, 2024a). Vertical transmission of mpox to the fetus and fetal deaths have been described in the DRC (Mbala, et al, 2017). The risk of airborne transmission is considered to be extremely low.

The MPXV strains that have been transmitted to humans can be classified into the two clades (Antinori et al, 2023):

- Clade I (former Clade I, also known as the Central Africa [Congo Basin] clade)
- Clade IIa (former Clade II, also known as the West Africa clade)
- Clade IIb lineage B.1 I (mpox strain in the 2022 outbreak).The isolate was initially designated as lineage B.1 of Clade III (Isidro, et al., 2022) but was currently recognized by WHO as Clade IIb lineage B.1 (Antinori et al, 2023):

The clinical picture of mpox closely resembles that of smallpox but the major difference distinguishing mpox from smallpox is the lymph node enlargement that occurs early, often at the onset of fever. A rash usually appears 1-3 days after the onset of fever and lymphadenopathy, with lesions appearing simultaneously, and evolving at a similar rate. Their distribution is mainly peripheral but can cover the whole body during a severe illness. The infection can last up to 4 weeks until the lesion desquamates. Patients may experience a range of complications including respiratory distress, bronchopneumonia, gastrointestinal involvement, dehydration, sepsis, encephalitis, myocarditis/pericarditis, corneal infection with ensuing loss of vision, and secondary bacterial infections (Sklenovska and Van Ranst, 2018). The case fatality rate of mpox lies between the case fatality rate of variola major (30%) and variola minor (1%) and appears to be dependent on virus clades. As shown in a systemic review (Bunge, et al., 2022), the reported case-fatality rates for Central African clade, West African clade, and West African clade in African countries only are 10.6% (95%CI 8.4%, 13.3%), 3.6% (95%CI 1.7%, 6.8%) and 4.6% (95%CI 2.1%, 8.6%), respectively.

Signs and symptoms of mpox, which was caused by clade IIb lineage B.1 during 2022 outbreaks, were less severe compared with mpox caused by clades I and IIa (Borges et al, 2023). The death rate in the 2022 global mpox outbreak was less than 1% (CDC, 2023b). However, HIV infection was associated with a higher risk of mpox infection and higher mortality rate after mpox infection (Yinka-Ogunleye, et al., 2023). Additionally, children and adolescents who are immunocompromised are at increased risk of severe mpox (Beeson, et al., 2023).

2.2 Currently Available Preventions and Treatments for the Proposed Indication

Jynneos vaccine is the only FDA-approved 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 approval of Jynneos for mpox was inferred from non-inferior vaccinia-specific antibody titers induced by two doses of Jynneos administered 28 days apart compared to a single dose of ACAM2000, and the protective efficacy of Jynneos from wild-type MPXV challenge in non-human primates (NHPs).

The U.S. Centers for Disease Control and Prevention opened an Expanded Access protocol for post-exposure prophylaxis (PEP) of ACAM2000 against mpox due to the first travel-associated mpox case in the U.S. in July 2021 (CDC, 2024b). While no individuals received ACAM2000 vaccination during the 2022 outbreak, the protocol is maintained to allow ACAM2000 for PEP use in the event of future isolated incidents or outbreaks.

Reviewer Comment: *Even though the Expanded Access protocol is active, no individual received ACAM2000 during the 2022 mpox outbreaks due to safety concerns of ACAM2000 and availability of Jynneos.*

There are no approved therapies in the U.S. for the treatment of mpox disease. Antiviral treatments indicated for smallpox, Tpoxx (tecovirimat) and Tembexa (brincidofovir) as well as

the human immune globulin CNJ-016 (vaccinia immune globulin intravenous [human]; VIGIV) indicated for treatment of complications of replication competent vaccinia vaccine, have been used to treat mpox in the 2022 outbreak under expanded access IND protocol or single patient emergency use IND (CDC, 2024c, FDA 2023, FDA, 2024). Both Tpoxx and Tembexa were approved for smallpox under the Animal Rule. The benefit of Tpoxx and Tembexa for mpox is uncertain. Cidofovir has been shown to be effective against orthopoxviruses (OPXVs) in vitro and animal studies; however, it is unknown whether a person with severe mpox would benefit from treatment (CDC, 2023c).

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

No new clinical study was conducted to support the proposed indication. The data to support the proposed indication, including non-human primate challenge data, were submitted and reviewed in the original BLA. In the Clinical Overview, the Applicant summarized an observational study which showed that previous smallpox vaccines offered protection against mpox. This review will summarize the non-clinical data and clinical data in Section 6 and provide risk-benefit analysis of ACAM2000 for the prevention of mpox in Section 11.

5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review

- STN125158/297.0, Module 1.9 (Pediatric Assessment Plan)
- STN125158/297.0, Module 1.14 (Labeling)
- STN125158/297.0, Modules 2.2, 2.4, 2.5 and 2.7 (Introduction, Nonclinical Overview, Clinical Overview, and Clinical Summary)
- STN125158/297.0, Module 5.3.5.1 (Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication)
    - H-400-009
    - H-400-012
- STN125158/297.3 Module 1.11.3, Jan 17th IR regarding pediatric assessment plan
- STN125158/297.5 Module 1.11.3, Feb 12th IR regarding pediatric assessment plan
- STN125158/297.7 Module 1.11.3, May 23rd IR regarding photographs showing the progression of major cutaneous reaction after primary vaccination and revaccination
- STN125158/297.9 Module 1.11.3, Jul 26th IR regarding the time frame of scab separation in USPI

5.5 Literature Reviewed

Antinori S, Casalini G, Giacomelli A, Rodriguez-Morales AJ. Update on Mpox: a brief narrative review. Infez Med. **2023** Sep 1;31(3):269-276.

Arita I, Henderson DA. Smallpox and monkeypox in non-human primates. Bull World Health Organ. **1968**;39(2):277-83.
Borges, V., Duque, M.P., Martins, J.V. et al. Viral genetic clustering and transmission dynamics of the 2022 mpox outbreak in Portugal. Nat Med 29, 2509–2517 (**2023**). https://doi.org/10.1038/s41591-023-02542-x

Bunge EM, Hoet B, Chen L, Lienert F, Weidenthaler H, Baer LR, Steffen R. The changing epidemiology of human monkeypox-A potential threat? A systematic review. PLoS Negl Trop Dis. **2022** Feb 11;16(2):e0010141. doi: 10.1371/journal.pntd.0010141.

Beeson AM, Haston J, McCormick DW, Reynolds M, Chatham-Stephens K, McCollum AM, Godfred-Cato S. Mpox in Children and Adolescents: Epidemiology, Clinical Features, Diagnosis, and Management. Pediatrics. **2023** Feb 1;151(2):e2022060179. doi: 10.1542/peds.2022-060179.

Centers for Disease Control and Prevention (CDC). Update: Multistate Outbreak of Monkeypox - Illinois, Indiana, Kansas, Missouri, Ohio, and Wisconsin, 2003. MMWR: Morbidity and Mortality Weekly Report. July 11, **2003a** / 52(27);642-646

CDC. MMWR. Household Transmission of Vaccinia Virus from Contact with a Military Smallpox Vaccinee --- Illinois and Indiana, 2007. **2007** May 18. Household Transmission of Vaccinia Virus from Contact with a Military Smallpox Vaccinee -- Illinois and Indiana, 2007 (cdc.gov)

CDC. 2022 Monkeypox Outbreak Global Map. 2023 June 06, **2023b**. https://www.cdc.gov/poxvirus/monkeypox/response/2022/world-map.html. Accessed June 12, 2023.

CDC. Smallpox, Transmission. **2024a**. https://www.cdc.gov/smallpox/transmission/index.html. Accessed 28 June 2024.

CDC. Poxvirus, Mpox, Vaccination. **2024b**. https://www.cdc.gov/poxvirus/mpox/interim-considerations/overview.html. Accessed 06 May 2024.

CDC. Patient's Guide to Mpox Treatment with TPOXX (tecovirimat). **2024c**. July 26, 2024. https://www.cdc.gov/poxvirus/mpox/if-sick/treatment.html

CDC. Poxvirus, Mpox, Treatment Information for Healthcare Professionals. **2023c**. https://www.cdc.gov/poxvirus/mpox/clinicians/treatment.html#anchor_1666886385143. Accessed 06 May 2024.

CDC. Update: multistate outbreak of monkeypox--Illinois, Indiana, Kansas, Missouri, Ohio, and Wisconsin, 2003. MMWR Morb Mortal Wkly Rep. **2003** Jul 11;52(27):642-6. PMID: 12855947.

FDA. FDA Mpox response. August 15, **2024**. https://www.fda.gov/emergency-preparedness-and-response/mcm-issues/fda-mpox-response

FDA. Expanded Access IND Protocol: Use of Vaccinia Immune Globulin Intravenous (VIGIV, CNJ-016) for Treatment of Human Orthopoxvirus Infection in Adults and Children. May 1, **2023**. https://www.cdc.gov/poxvirus/mpox/data/vigiv-protocol.pdf

Fine PE, Jezek Z, Grab B, Dixon H. The transmission potential of monkeypox virus in human populations. Int J Epidemiol. **1988** Sep;17(3):643-50. doi: 10.1093/ije/17.3.643

Garde V, Harper D, Fairchok MP. Tertiary contact vaccinia in a breastfeeding infant. JAMA. **2004** Feb 11;291(6):725-7. doi: 10.1001/jama.291.6.725.

Gessain A, Nakoune E, Yazdanpanah Y. Monkeypox. N Engl J Med. **2022** Nov 10;387(19):1783-1793. doi: 10.1056/NEJMra2208860. Epub 2022 Oct 26. PMID: 36286263.

Hatch GJ, Graham VA, Bewley KR, Tree JA, Dennis M, Taylor I, Funnell SG, Bate SR, Steeds K, Tipton T, Bean T, Hudson L, Atkinson DJ, McLuckie G, Charlwood M, Roberts AD, Vipond J. Assessment of the protective effect of Imvamune and Acam2000 vaccines against aerosolized monkeypox virus in cynomolgus macaques. J Virol. **2013** Jul;87(14):7805-15. doi: 10.1128/JVI.03481-12. Epub 2013 May 8.

Hennessee I, Shelus V, McArdle CE, et al. Epidemiologic and Clinical Features of Children and Adolescents Aged <18 Years with Monkeypox — United States, May 17–September 24, **2022**. MMWR Morb Mortal Wkly Rep 2022;71:1407–1411. DOI: http://dx.doi.org/10.15585/mmwr.mm7144a4

Hoxha A, Kerr SM, Laurenson-Schafer H, Sklenovská N, Mirembe BB, Nezu IH, Ndumbi P, Fitzner J, Almiron M, Vila M, Pebody R, Vaughan AM, Haussig JM, de Sousa LA, Lukoya OC, Sanni OF, Nabeth P, Naiene JD, Kato M, Matsui T, Kuppalli K, Mala PO, Lewis RF, de Waroux OLP, Pavlin BI; WHO Mpox surveillance and Analytics Team. Mpox in Children and Adolescents during Multicountry Outbreak, 2022-2023. Emerg Infect Dis. **2023** Oct;29(10):2125-2129. doi: 10.3201/eid2910.230516. Epub 2023 Aug 30.

Isidro J, Borges V, Pinto M, Sobral D, Santos JD, Nunes A, Mixão V, Ferreira R, Santos D, Duarte S, Vieira L, Borrego MJ, Núncio S, de Carvalho IL, Pelerito A, Cordeiro R, Gomes JP. Phylogenomic characterization and signs of microevolution in the 2022 multi-country outbreak of monkeypox virus. Nat Med. **2022** Aug;28(8):1569-1572. doi: 10.1038/s41591-022-01907-y. Epub 2022 Jun 24. Erratum in: Nat Med. 2022 Oct;28(10):2220-2221.

Kava CM, Rohraff DM, Wallace B, et al. Epidemiologic Features of the Monkeypox Outbreak and the Public Health Response — United States, May 17–October 6, 2022. MMWR Morb Mortal Wkly Rep 2022;71:1449–1456. DOI: http://dx.doi.org/10.15585/mmwr.mm7145a4

Koenig KL, Beÿ CK, Marty AM. Monkeypox 2022: A Primer and Identify-Isolate-Inform (3I) Tool for Emergency Medical Services Professionals. Prehosp Disaster Med. **2022** Oct;37(5):687-692. doi: 10.1017/S1049023X22001121. Epub 2022 Aug 4. PMID: 35924712; PMCID: PMC9470524.

Ladnyj ID, Ziegler P, Kima E. A human infection caused by monkeypox virus in Basankusu Territory, Democratic Republic of the Congo. Bull World Health Organ. **1972**;46(5):593-7.

Laurenson-Schafer H, Sklenovská N, Hoxha A, Kerr SM, Ndumbi P, Fitzner J, Almiron M, de Sousa LA, Briand S, Cenciarelli O, Colombe S, Doherty M, Fall IS, García-Calavaro C, Haussig JM, Kato M, Mahamud AR, Morgan OW, Nabeth P, Naiene JD, Navegantes WA, Ogundiran O, Okot C, Pebody R, Matsui T, Ramírez HL, Smallwood C, Tasigchana RFP, Vaughan AM, Williams GS; laurenson Jul;11(7):e1012-e1023. doi: 10.1016/S2214-109X(23)00198-5.

Magnus Pv, Andersen EK, Petersen KB, Birch-Andersen A. A pox-like disease in cynomolgus monkeys. Acta Pathologica Microbiologica Scandinavica, **1959** 46: 156-176. https://doi.org/10.1111/j.1699-0463.1959.tb00328.x

Martin RM, Burke K, Verma D, Xie H, Langer J, Schlaberg R, Swaminathan S, Hanson KE. Contact Transmission of Vaccinia to an Infant Diagnosed by Viral Culture and Metagenomic Sequencing, Open Forum Infectious Diseases, Volume 7, Issue 4, April **2020**, ofaa111, https://doi.org/10.1093/ofid/ofaa111

Mbala PK, Huggins JW, Riu-Rovira T, Ahuka SM, Mulembakani P, Rimoin AW, Martin JW, Muyembe JT. Maternal and Fetal Outcomes Among Pregnant Women With Human Monkeypox Infection in the Democratic Republic of Congo. J Infect Dis. **2017** Oct 17;216(7):824-828. doi: 10.1093/infdis/jix260.

Otter AD, Jones S, Hicks B, Bailey B, Callaby H, Houlihan C, Rampling T, Gordon NC, Selman H, Satheshkumar PS, Townsend M, Mehta R, Pond M, Jones R, Wright D, Oeser C, Tonge S, Linley E, Hemingway G, Coleman T, Millward S, Lloyd A, Damon I, Brooks T, Vipond R, Rowe C, Hallis B. medRxiv **2022**.12.22.22283648; doi: https://doi.org/10.1101/2022.12.22.22283648

Russo AT, Berhanu A, Bigger CB, Prigge J, Silvera PM, Grosenbach DW, Hruby D. Co-administration of tecovirimat and ACAM2000™ in non-human primates: Effect of tecovirimat treatment on ACAM2000 immunogenicity and efficacy versus lethal monkeypox virus challenge. Vaccine. **2020** Jan 16;38(3):644-654. doi: 10.1016/j.vaccine.2019.10.049. Epub 2019 Oct 31.

Seang S, Burrel S, Todesco E, Leducq V, Monsel G, Le Pluart D, Cordevant C, Pourcher V, Palich R. Evidence of human-to-dog transmission of monkeypox virus. Lancet. **2022** Aug 27;400(10353):658-659. doi: 10.1016/S0140-6736(22)01487-8. Epub 2022 Aug 10.

Simpson K, Heymann D, Brown CS, Edmunds WJ, Elsgaard J, Fine P, Hochrein H, Hoff NA, Green A, Ihekweazu C, Jones TC, Lule S, Maclennan J, McCollum A, Mühlemann B, Nightingale E, Ogoina D, Ogunleye A, Petersen B, Powell J, Quantick O, Rimoin AW, Ulaeato D, Wapling A. Human monkeypox - After 40 years, an unintended consequence of smallpox eradication. Vaccine. **2020** Jul 14;38(33):5077-5081. doi: 10.1016/j.vaccine.2020.04.062. Epub 2020 May 13.

Sklenovská N, Van Ranst M. Emergence of Monkeypox as the Most Important Orthopoxvirus Infection in Humans. Front Public Health. **2018** Sep 4;6:241. doi: 10.3389/fpubh.2018.00241.

Tack DM, Karem KL, Montgomery JR, Collins L, Bryant-Genevier MG, Tiernan R … Reynolds, MG. Unintentional transfer of vaccinia virus associated with smallpox vaccines: ACAM2000 compared with Dryvax®. Human Vaccines & Immunotherapeutics. **2013** 9(7), 1489–1496. https://doi.org/10.4161/hv.24319

Thornhill JP, Barkati S, Walmsley S, Rockstroh J, Antinori A, Harrison LB, Palich R, Nori A, Reeves I, Habibi MS, Apea V, Boesecke C, Vandekerckhove L, Yakubovsky M, Sendagorta E, Blanco JL, Florence E, Moschese D, Maltez FM, Goorhuis A, Pourcher V, Migaud P, Noe S, Pintado C, Maggi F, Hansen AE, Hoffmann C, Lezama JI, Mussini C, Cattelan A, Makofane K, Tan D, Nozza S, Nemeth J, Klein MB, Orkin CM; SHARE-net Clinical Group. Monkeypox Virus Infection in Humans across 16 Countries - April-June 2022. N Engl J Med. **2022** Aug 25;387(8):679-691. doi: 10.1056/NEJMoa2207323. Epub 2022 Jul 21.

U.S. Department of Health & Human Services. Biden-Harris Administration Bolsters Monkeypox Response; HHS Secretary Becerra Declares Public Health Emergency. 04 August **2022**

Wertheimer ER, Olive DS, Brundage JF, Clark LL. Contact transmission of vaccinia virus from smallpox vaccinees in the United States, 2003-2011. Vaccine. **2012** Feb 1;30(6):985-8. doi: 10.1016/j.vaccine.2011.12.049. Epub 2011 Dec 20.

World Health Organization. WHO Director-General declares the ongoing monkeypox outbreak a Public Health Emergency of International Concern, WHO, Editor. **2022**, WHO

Yinka-Ogunleye A, Dalhat M, Akinpelu A, Aruna O, Garba F, Ahmad A, Adeleye A, Botson I, Oluwafemi B, Ogunbode O, Amao L, Ekripo U, Aliyu GG, Adetifa I, Ihekweazu C, Abubakar I. Mpox (monkeypox) risk and mortality associated with HIV infection: a national case-control study in Nigeria. BMJ Glob Health. **2023** Nov 30;8(11):e013126. doi: 10.1136/bmjgh-2023-013126.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

To support the proposed indication, the Applicant provided:

1. Primary nonclinical pharmacology data generated using ACAM2000 vaccine against MPXV lethal challenge in the nonhuman primate (NHP) model (T-400-001)
2. Published reports of nonclinical evaluations of ACAM2000 against MPXV lethal challenge in NHPs
3. Clinical experiences demonstrating:
    a. Equivalent immunogenicity between ACAM2000 and Dryvax for protection against smallpox. This information was reviewed in the original BLA and will be summarized briefly in this sBLA
    b. Protection against mpox offered by previous vaccination with Dryvax.

The Applicant also submitted nonclinical studies of the efficacy of ACAM2000 and/or Dryvax against challenge with multiple orthopoxviruses (OPXV) including MPXV, vaccinia, ectromelia and rabbitpox viruses. See the CMC review for discussion of these studies.

No additional clinical data supporting efficacy claims of ACAM2000 vaccine were included in the submission.

6.1 Non-Clinical Data

6.1.1 Immunogenicity and Protective Activity of ACAM2000 and Dryvax Smallpox Vaccines in Cynomolgus Macaques Challenged with Mpox Virus by Intravenous Route (Study T-400-001)

Overview of Study Design

Twenty-four (12 male and 12 female) cynomolgus macaques *(Macaca fascicularis*), aged a minimum of 22 months and weighing between 2.1 and 2.8 kg, were equally randomized to receive either placebo control (diluent), ACAM2000 (4.4×10^8 PFU/mL), or Dryvax (1.5×10^8 PFU/mL) administered using a minimum of 15 jabs percutaneously (scarification) with a sterile, bifurcated needle on Day 0. Blood was collected on Day 0, 30, and 60 for antibody titer determinations. Animals were challenged with 3.8×10^7 PFU MPXV intravenously (IV) on Day 61. Monkeys were monitored for a minimum of 30 days post-challenge for signs and symptoms of clinical disease.

Results

Mortality, Morbidity, Clinical Observations

During the first 60 days of the study period (i.e., prior to MPXV challenge), there was no mortality or morbidity observed in any animal from any study group. All animals in ACAM2000 (8/8) and Dryvax (8/8) survived the MPXV challenge. All animals in the placebo control group (8/8) succumbed to the MPXV challenge and either died (2 animals at 8 days and 1 at 6 days

post challenge) or were euthanized when moribund (4 animals at 8 days and 1 animal at 6 days post challenge). All animal deaths were attributed to the MPXV challenge.

No pox lesions developed in any monkey in either ACAM2000 or Dryvax groups following MPXV challenge. All 8 animals in the control group developed significant mpox-related clinical symptoms post-challenge which included cessation of voluntary eating, lethargy, diarrhea, non-responsiveness, and skin or mucosal lesions (i.e., pox, >100 pox lesions in every monkey), especially in the head, mouth, and leg regions.

Mean temperatures in the ACAM2000 and Dryvax groups remained relatively consistent throughout the 30 days post-challenge observation period, with an overall mean temperature of 102.2°F. Each monkey in the control group displayed at least one day of elevated temperature (104°F or greater).

Antibody Response

All monkeys were seronegative for vaccinia neutralizing antibodies prior to immunization.

All monkeys immunized with ACAM2000 or Dryvax vaccines seroconverted by Day 30 and remained unchanged at Day 60. There were no statistical differences in geometric mean neutralizing antibody titers (GMTs) between ACAM2000 (Day 30 GMT=160 and Day 60 GMT=174) and Dryvax (Day 30 GMT=174 and Day 60 GMT=190) treatment groups at either Day 30 ($p>0.8473$) or Day 60 ($p>0.6505$).

Post-challenge antibody results (Day 91) showed a marked boost in the antibody titers in all monkeys vaccinated with ACAM2000 or Dryvax. The GMTs on Day 91 for the ACAM2000 and Dryvax groups, respectively, were 43782 (range 12047 to 88037) and 46072 (range 33483 to 74688). There was no statistically significant difference in GMTs between these groups ($p>0.8456$).

Several monkeys in the control group developed a detectable antibody titer by the final day of serum collection (Day 67 or 69) with a GMT of 227 (range 70 to 946).

Conclusions

ACAM2000 was immunogenic and efficacious in protecting cynomolgus macaques from a fatal MPXV challenge. All ACAM2000 vaccinated animals were protected from a lethal MPXV challenge, demonstrating robust antibody titers following vaccination that were substantially boosted upon challenge with MPXV.

Reviewer Comment: *For a comprehensive review of the non-clinical studies, please refer to the CMC review memo. All ACAM2000-vaccinated animals had pre-challenge vaccinia-specific antibody titers of 1:80 to 1:640, which was similar to the range of titers observed in human recipients of ACAM2000. In the animal study, a PRNT50 of ≥1:80 was associated with 100% survival against MPXV challenge and the absence of illness, cutaneous lesions, viremia and virus shedding. Since the same PRNT50 assay was used to determine the PRNT50 titer in both NHPs and humans, it is reasonable to infer a protective effect of ACAM2000 in humans.*

6.1.2 Supportive Nonclinical Evidence in Literature

The Applicant also summarized two articles describing MPXV challenge studies in ACAM2000 vaccinated NHPs as supportive evidence for the proposed new indication for mpox.

The first article described a study that assessed the protective capacity of Jynneos and ACAM2000 against mpox in cynomolgus macaques following an aerosolized MPXV challenge (Hatch, et al., 2013). Cynomolgus macaques were randomized into 4 groups (n=6/group): placebo control; single dose of Jynneos; two doses of Jynneos administered at 28 days apart; and single dose of ACAM2000. Animals were challenged with a lethal dose of MPXV 28 days after vaccination. All six animals in the control group died in 7 to 11 days after MPXV challenge. Protection from MPXV challenge was achieved in 6 of 6 animals in the single-dose ACAM2000 group, 6 of 6 animals in the two-dose Jynneos group, and 4 of 6 animals in the single-dose Jynneos group. No significant difference (P>0.05) was observed in vaccinia-specific neutralizing antibody titers between animals vaccinated with a single dose of ACAM2000 (132 U/ml) and the two doses of Jynneos (69 U/ml) prior to challenge with MPXV. Post MPXV challenge, viral excretion was isolated from the throats of 2 of 6 animals in the two-dose Jynneos group, whereas there was no confirmation of excreted live virus in the ACAM2000 group.

The second article described three studies that assessed the potential interaction between ACAM2000 and Tecovirimat (Tpoxx) in a post-exposure prophylaxis NHP model (Russo, et al., 2020). Animals in all three studies were vaccinated with ACAM2000 vaccine and immune responses to the vaccine and protective efficacy versus a lethal MPXV challenge were evaluated. Vaccinated animals were treated with Tpoxx at 10 mg/kg or a vehicle for 14 consecutive days. Animals in Study 1 (n=3 in vehicle control, n=6 in ACAM2000+placebo, n=7 in ACAM2000+Tpoxx) and Study 2 (n=3 each for ACAM2000+placebo and ACAM2000+Tpoxx) were cynomolgus macaques and were challenged via IV injection with MPXV (1.65×10^7 to 5.4×10^7 PFU/mL) at 45 and 30 days, respectively, after vaccination. Animals in Study 3 (n=3 each for ACAM2000+placebo and ACAM2000+Tpoxx) were rhesus macaques and were challenged with MPXV at 32 days after the vaccination.

In Studies 1 and 2, primary and anamnestic humoral immune responses were similar regardless of Tpoxx treatment while Study 3 showed reduction in vaccine elicited humoral immunity with concomitant administration of Tpoxx. Following lethal MPXV challenge, 12 of 12 vaccinated/placebo-treated animals survived (100%), and 12 of 13 vaccinated/Tpoxx-treated animals survived (92.3%). No animal in the control group (0%, n=3) survived MPXV challenge. Clinical signs of disease were evident in Tpoxx treated animals compared to placebo treated animals. The authors concluded that the result suggests that Tpoxx may affect the immunogenicity of ACAM2000 if administered concomitantly.

Reviewer Comment:

The results of the concomitant studies of Tpoxx and ACAM2000 were from a limited number of animals. The clinical relevance and significance of the potential interaction between Tpoxx and ACAM2000 are unknown.

*The Applicant also summarized data from publications showing that ACAM2000 or Dryvax protected animals from lethal challenge with ectromelia (mousepox) and rabbitpox in mice and rabbits, respectively. Results from published non-clinical studies are consistent with those of the Applicant's non-clinical study (*T-400-001*) and provide supportive evidence for protective efficacy of ACAM2000 against mpox. Please refer to the Non-Clinical Studies review memo for details.*

6.2 Clinical Data

6.2.1 Safety in Humans

The safety profile of ACAM2000 in adults has been established and documented in the original Biologics License Application (BLA) and are described in the U.S. package insert (USPI). No new safety signal has been identified since the original approval of the vaccine on 31 August 2007.

Reviewer Comment: *In the USPI, the Applicant included Section 6.2 Postmarketing Experience. Events described in Section 6.2 are also described in Section 6.1 Overall Adverse Reaction Profile, or are known to be associated with live, replicating vaccinia-based vaccines as described Section 5. Please refer to the Pharmacovigilance review memo for details.*

The safety profile of ACAM2000 was not assessed in pediatric populations. However, Dryvax, the precursor of ACAM2000, was routinely administered to children prior to smallpox eradication era, and its estimates of the risks of occurrence of serious complications following primary vaccination and revaccination in pediatric populations are presented in Tables 1 and 2, respectively, in the current USPI. It was concluded that the safety profile of ACAM2000 would be comparable to the historical safety data associated with Dryvax.

Reviewer comment: *This section describes the safety profile of ACAM2000 in humans. The risk-benefit assessment of ACAM2000 in prevention of mpox is discussed in Section 11 Risk Benefit Analysis and Assessment.*

Note, the 2007 approval of ACAM2000 weighed the risks of the vaccine against the benefit of preventing smallpox (if used as a bioweapon). A key safety consideration for expanding the indication to include prevention of mpox is that individuals at high risk of infection with mpox via skin-to-skin contact would also be at high risk of contact transmission of live vaccina virus via skin-to-skin contact. Following the approval of ACAM2000, rates of contact transmission of vaccinia virus in vaccinated military personnel were estimated at approximately 5.4 events per 100,000 vaccinees (Tack, et al., 2013; Wertheimer, et al., 2012). However, this is from surveillance data and likely underestimates the actual rate of contact transmission. Cases of tertiary transmission of vaccinia from non-vaccinated individuals to their close contacts have been described (Martin, et al., 2020; Garde, et al., 2004). Contact transmission of live vaccinia virus typically manifests as a limited, local skin reaction, but it can be life-threatening in persons with eczema (CDC, 2007) and immunocompromising conditions. ACAM2000 for orthopoxviruses is contraindicated where household contacts have such conditions (ACIP 2022)

Applicant Proposed Labeling Changes and Rationale

The Applicant proposes changes to the USPI regarding scab separation, virus shedding, and postmarketing experience.

- Scab separation: The original USPI described that vaccination scab separation occurs within 14 to 21 days after primary vaccination. This description is incorrect based on the pre-licensure clinical studies. The Applicant revised the scab separation in the proposed USPI based on the post-licensure study VA-008 from “within 14 to 21 days” to “4 to 6 weeks” after vaccination. The objective of study VA-008 was to vaccinate healthy adults with ACAM2000 to product vaccinia immune globulin intravenous (VIGIV) for treatment of human orthopoxvirus infection in adults and children. The scab separation timelines in VA-008 were consistent with those observed in the pre-licensure studies. An information

request (IR) was sent to the Applicant on 26 July 2024 to verify the time frame of scab separation. The Applicant submitted its response to STIN125158/297.9 on 02 August 2024 confirming that the time frame of scab separations ranged from 3 to 6 weeks.

Reviewer Comment: *Based on the Applicant's input, the scab separation of 3 to 6 weeks was the final wording for the label.*

- Virus Shedding: The virus shedding window was changed from 14-21 days after vaccination to state that virus could shed until the lesion is re-epithelialized, typically 3-6 weeks after vaccination. The Applicant stated that re-analyzed data from the Dryvax, ACAM2000 and ACAM2000 precursor vaccine clinical studies, as well as data from the VA-008 study, suggest that the cessation of viral shedding does not coincide with the scab separation (can occur until the skin is fully healed) and that the scab separation generally occurs over a longer time frame than 14-21 days after vaccination.

- Postmarketing experience: The Applicant added a subsection listing adverse events (AEs) reported since licensure of ACAM2000 in August 2007.

Reviewer Comment: *The AEs listed in Postmarketing Experience were either reported in pre-licensure studies of ACAM2000, or reported to be associated with another vaccine, Dryvax, and are considered adverse reactions because there are reasonable possibilities that they are caused by the vaccines. Per 21 CFR 201.57(c)(7)(ii)(B). "the post-marketing experience section labeling must list the adverse reactions, as defined in paragraph (c)(7) of this section, that are identified from domestic and foreign spontaneous reports. This listing must be separate from the listing of adverse reactions identified in clinical trials."*

This reviewer recommends deleting the Postmarketing Experience subsection from the USPI to limit this section to adverse reactions that are unknown prior to licensure. This recommendation was communicated to the Pharmacovigilance reviewer, as well as OVRR leadership during internal labeling meetings. OVRR leadership decided to include the adverse events in the subsection of Postmarketing Experience to include serious adverse reactions reported in postmarketing to be consistent with other vaccine labels.

6.2.2 Vaccine Effectiveness in Humans

No clinical effectiveness study of ACAM2000 against mpox has been conducted. The effectiveness of ACAM2000 against mpox is inferred from the non-inferior vaccinia-specific neutralizing antibody titers generated by ACAM2000 compared with those generated by Dryvax in the pre-licensure studies. In the clinical trials to support the original BLA of ACAM2000 for the indication of smallpox, the data was reviewed and documented in the original BLA review and was also submitted to this supplement as a reference. The effectiveness data of ACAM2000 are summarized below.

In addition, the effectiveness of ACAM2000 against mpox is supported by the effect of Dryvax against mpox as reported in an observational study published by other investigators in the literature. The Applicant also submitted two additional published reports from which conclusions regarding effectiveness of ACAM2000 and mpox cannot be drawn.

Summary of Effectiveness Data from the Original BLA

Two phase 3 studies, H-400-009 and H-400-012, were performed to support the original BLA of ACAM2000 indicated for smallpox and are described in the current USPI. H-400-009 and H-400-012 were randomized double-blind studies in vaccine-naïve and previously vaccinated participants, respectively. In both studies, the co-primary efficacy endpoints were: 1) Proportion of participants with a take (a major cutaneous response considered to be an indicator of successful vaccination/revaccination) on Day 6-11; and 2) Vaccinia-specific neutralizing antibody GMT on Day 30. Both studies were terminated early due to myopericarditis observed in H-400-009. ACAM2000 was non-inferior to the comparator in the rate of major cutaneous reaction in those naïve to the vaccine, and the strength of the neutralizing antibody immune response in those previously exposed to vaccinia-based smallpox vaccines.

Summary of the Historical Observational Study of Dryvax Against Mpox

Shortly after routine smallpox vaccination stopped around the world, the WHO instituted an active surveillance program for mpox during 1981-1986 in Zaire (now the DRC). In the epidemiological surveillance study, Fine, et al. identified 209 mpox-infected individuals and their 1573 contacts in the five years of study and estimated that previous smallpox vaccination (3-19 years prior to the outbreak) provided 85% effectiveness against mpox infection based on MPXV infection rates in close household contacts who had a history of vaccination in comparison to those who were unvaccinated (Fine, et al., 1988). Because ACAM2000 was cloned from Dryvax, which was used during the vaccination program that led to smallpox eradication, the Applicant states that it is reasonable to conclude that efficacy against MPXV observed in this study would also be seen after ACAM2000 administration.

Reviewer Comment: *The surveillance study conducted by Fine, et al. was based primarily upon health institutions in endemic regions. The protective efficacy of smallpox vaccination against mpox was based on mpox attack rates among individuals who had received smallpox vaccination (i.e., skin scars) and individuals who had not been vaccinated with smallpox vaccines (i.e., no skin scars). The authors did not discuss the potential for bias and confounding in estimating vaccine effectiveness against mpox. In addition, details of the study and datasets are not available for our review. The results should be interpreted with caution.*

Summary of Two Additional Studies Submitted by the Applicant

The Applicant cited a report using Dryvax to prevent mpox in a 2003 mpox outbreak in the U.S. (CDC, 2003). In the report, 30 participants received Dryvax in either a pre-exposure prophylaxis or post-exposure prophylaxis setting and one of the 30 vaccinated participants developed mpox. Since there was no control, no meaningful conclusion regarding the effectiveness of ACAM2000 for prevention of mpox disease could be reached from the report.

Additionally, the Applicant cites a publication where the authors evaluated panels of serum samples for poxvirus-induced antibodies from individuals vaccinated with ACAM2000 or Jynneos, and those with prior mpox infection (Otter, et al., 2022). The authors concluded that antigen recognition between smallpox vaccinated individuals and mpox convalescent individuals is analogous; however, in the smallpox-vaccinated group, only 5 of the 45 samples were collected from individuals vaccinated with ACAM2000. Given the small sample size and lack of clinical correlation, these results do not inform the effectiveness of ACAM2000 for prevention of mpox disease.

Reviewer Comment: *Results from the two additional published studies submitted by the Applicant should be interpreted with caution with respect to effectiveness of ACAM2000 for prevention of mpox disease due to limited information about study participants, small sample size, and lack of a control group.*

6.2.3 Safety and Effectiveness Conclusion

The safety profile of ACAM2000 has been established in adults and is described in the current PI, including a Boxed Warning. The safety profile of ACAM2000 in the pediatric population was not assessed in clinical trials and is considered comparable to Dryvax, which is described in the current PI. The benefit-risk assessment of ACAM2000 may be favorable, depending on MPXV clades and associated disease severity during a certain outbreak.

Efficacy of ACAM2000 against mpox has not been assessed directly in humans. However, effectiveness of ACAM2000 against mpox can be reasonably inferred through the following evidence:

- Protection of ACAM2000-vaccinated NHPs against subsequent challenge with lethal dose of MPXV
- Non-inferiority of vaccinia-specific neutralizing antibody titers compared to Dryvax in both humans and NHPs
- Protection from mpox among Dryvax recipients reported in a published observational study (acknowledging potential for bias and confounding)

9. Additional Clinical Issues

9.1 Special Populations

9.1.3 Pediatric Use and PREA Considerations

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), this application is required to contain an assessment of the safety and effectiveness of the product for the claimed indication in all pediatric age groups. The Applicant requested to extrapolate the effectiveness of ACAM2000 for the prevention of mpox in adults to the pediatric population ages birth to 17 years, based on the FDA statute, Section 505B(a)(2)(B)(i) of the PREA.

In the pediatric assessment document, the Applicant demonstrated that transmission and clinical presentations of mpox in outbreaks before the most current mpox outbreak in 2022 are similar amongst children and adults (Gessain, et al., 2022; Laurenson-Schafer, et al., 2023). The average of the median age of mpox infection in Africa has evolved from 4 and 5 years old in the 1970s and 1980s to 10 and 21 years old in the 2000s and 2010s (Bunge, et al., 2022).

During the 2022 mpox outbreaks, the majority of cases were reported in men who have sex with men (MSM) and skin lesions were generally observed in genital areas. Epidemiologic and clinical characteristics were similar for the age groups 0 to 4 and 5 to 12 years, whereas mpox patients 13 to 17 years of age who were more likely to be sexually active and commonly reported MSM sexual behavior, had more genital lesions than observed in adults (Hoxha, et al., 2023). The differences of clinical presentation of mpox between individuals ≤12 years of age and those >13 years of age (i.e., potentially sexually active) were likely due to transmission between MSM during the 2022 mpox outbreaks. However, the transmission in general (i.e., close contacts) and the pathogenesis of mpox are considered to have been similar amongst children and adults during the 2022 mpox outbreaks.

Based on historical data, the safety profile and effectiveness of Dryvax in prevention of smallpox and mpox were similar in children and adults. Since ACAM2000 was cloned from Dryvax and demonstrated non-inferiority in terms of vaccinia-specific neutralizing antibody titers and vaccine take rates compared with Dryvax in adults during pre-licensure clinical trials, it is reasonable to expect that ACAM2000 is effective against mpox in children. Note, for the smallpox indication, clinical trials evaluating ACAM2000 vaccine were not conducted in children and the level of nAB induced after smallpox vaccination in this population is not known.

Therefore, CBER agreed to grant the Applicant's request to extrapolate effectiveness of ACAM2000 against mpox disease in adults to all pediatric populations.

10. CONCLUSIONS

Based on the protective capacity of ACAM2000 of NHPs from lethal challenge with MPXV, the non-inferior vaccinia-specific neutralizing antibody titers generated by ACAM2000 compared to Dryvax, and potential protective capacity of Dryvax recipients against mpox in a published study, it is reasonable to conclude that ACAM2000 may protect individuals from mpox disease.

The safety profile of ACAM2000 has been established and adequately described in the current USPI. No additional safety data was provided in this submission. The safety profile of ACAM2000 in prevention of mpox in general is acceptable; however, the final assessment of acceptability of the safety profile of ACAM2000 for this indication depends on the virulency of MPXV (i.e., MPXV clades and associated disease severity) during mpox outbreaks.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Table 1. Risk Benefit Considerations

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Mpox is a classical zoonosis, most human infections being attributable to contact with infected animals. • Mpox can be transmitted from humans to humans via close skin-to-skin contact, sexual activity or through handling infected clothing or bedding. • The global Mpox outbreak in 2022 predominantly impacted men who have sex with men. However, anyone in close contact with mpox patients may be at risk. • The most common symptom is rash that may be located on hands, feet, chest, face, mouth or near the genitals and will go through painful or itchy pimples, blisters and scabs before healing. • Case fatality rates vary greatly, from over 10% to <1%, depending on MPXV clades. • It is unknown whether MPXV can be spread via the respiratory route by contact droplets and by aerosol.	• MPVX infection is associated with significant mortality. • Skin lesions caused by MPVX infection have significant impact on physical and psychosocial well-being. Mpox is a serious medical condition.
Unmet Medical Need	• Jynneos is the only vaccine licensed for indication of mpox in individuals 18 years of age and older who are at high risk to exposure to MPXV based on non-inferior vaccinia-specific neutralizing antibody titers elicited by 2 doses of Jynneos compared with a single dose of ACAM2000 and protection against MPXV challenge in animal studies. • No licensed drug is available for treatment of mpox. • A single licensed vaccine may not meet the public health supply-demand needs during an mpox outbreak, as occurred with Jynneos during the 2022 global mpox outbreak. • Uncertainties: The only currently licensed vaccine against mpox, Jynneos, is a two-dose regimen administered at 28 days apart. The effectiveness of a two-dose Jynneos regimen vs a one-dose ACAM2000 regimen in reactive vaccination or post-exposure prophylaxis setting is unknown.	• An unmet medical need exists for effective mpox vaccine for individuals <18 years of age. • Potential vaccine shortage was a concern during the 2022 global outbreak and may be a public health concern in future outbreaks. Licensure of ACAM2000 would provide another vaccine option during future outbreaks. • A single dose regimen of ACAM2000 may have advantage over a two-dose regimen for Jynneos in reactive vaccination or post-exposure prophylactic settings.
Clinical Benefit	• A single dose of ACAM2000 in humans elicited vaccinia-specific neutralizing antibody responses that are believed to be effective to prevent mpox. • A single dose of ACAM2000 vaccination completely protects NHPs from challenge with lethal dose of MPXV. • An observational study in literature demonstrated that vaccination with ACAM2000's predecessor, Dryvax, offered 85% protection compared with people who were not vaccinated with Dryvax, although the results should be interpreted with caution. • Uncertainties: No randomized controlled clinical efficacy study is available to confirm the efficacy of ACAM2000 against mpox.	• Available evidence indicates that a single dose of ACAM2000 is likely effective in prevention of mpox.
Risk & Risk Management	• ACAM2000 may cause myocarditis, pericarditis, encephalitis, encephalomyelitis, encephalopathy, progressive vaccinia, generalized vaccinia, severe vaccinial skin infections, erythema multiforme major, eczema vaccinatum, accidental eye infection, fetal vaccinia and fetal death.	• The risks of ACAM2000 may result in severe disability, permanent neurological sequelae or death. • Risk mitigation strategies include communication of risks and benefits by including a Box Warning and Warnings and Precautions in Section 5 of the PI to describe the risks of ACAM2000, and direct counseling prior to vaccination according to individual risks and benefits.

11.2 Risk-Benefit Summary and Assessment

Mpox is a serious condition of global relevance. Severity and fatality rates of mpox vary greatly and appear to be dependent on MPXV clades. Recently, a systemic review showed that the overall fatality rate of mpox regardless of clade was 8.7%, with the fatality rate of 10.6% and 3.6% for the Central African clade and the West African clade, respectively (Bunge, et al., 2022). However, the overall mortality rate was <1% during the global 2022 mpox outbreak for all age groups (Laurenson-Schafer, et al., 2023; Kava, et al, 2022). Although symptoms of mpox observed during 2022 outbreaks appeared to be less severe, future mpox global outbreaks could occur with a more virulent mpox strain, impacting the overall case fatality rate for mpox disease.

Pre-licensure clinical trials demonstrated that a single dose of ACAM2000 elicited non-inferior vaccinia-specific neutralizing antibody titers compared with Dryvax. Historical data indicated that vaccination with Dryvax protected the vaccine recipients from mpox. In addition, vaccination with ACAM2000 prevented NHPs from subsequent challenge with a lethal intravenous or inhalational dose of MPXV. It is reasonable to expect that ACAM2000 can prevent mpox in humans.

The risks of ACAM2000 are well established and described in the current USPI. ACAM2000 vaccination may result in myocarditis, pericarditis, severe disability, permanent neurological sequelae or even death.

Uncertainties in the benefit-risk assessment include severity of mpox during actual outbreaks and the potential effectiveness of ACAM2000 for the prevention of mpox, in the context of the risks of ACAM2000. It is possible that the benefit-risk profile could become less favorable if the disease caused by some MPXV clades is only moderate as reported in the 2022 mpox outbreaks (Hennessee, et al., 2022).

In conclusion, the currently available data support a benefit-risk profile that is favorable for approving ACAM2000 for use in individuals at high risk of exposure to MPXV. Mitigation of the observed risks and uncertainties will be accomplished through labeling, including a Boxed Warning and Warnings and Precautions regarding the risks of ACAM2000 that are already in the current USPI, and shared decision making between healthcare providers and potential vaccinees.

11.3 Discussion of Regulatory Options

In the opinion of this reviewer, the available data support the approval of the proposed labeling changes to expand the indication to mpox.

11.4 Recommendations on Regulatory Actions

This reviewer recommends approval of the proposed labeling changes.

11.5 Labeling Review and Recommendations

The following major labeling changes are agreed upon by the Applicant and the Agency:

- In Section 2.7, scab separation was changed from “within 14 to 21 days” to “3 to 6 weeks” after vaccination.

- Section 13.2 was updated to include the efficacy of ACAM2000 to protect Cynomolgus macaques against mpox virus challenge.
- Section 14 of the PI was updated to include a sentence, “The effectiveness of ACAM2000 for the prevention of mpox is based on its effectiveness for the prevention of smallpox and efficacy in animal challenge studies”.

The Applicant proposed to replace the photos of cutaneous reactions following live replicating vaccinia virus-based vaccines in Section 2.7 of the current UPSI with the photos from CDC. The cutaneous reaction photos in the current USPI were derived from a publication with an unknown vaccine. The Agency asked the Applicant to provide the photos from ACAM2000 clinical trials, and the Applicant responded that such photos are not available. The Applicant explained that, based on history of Dryvax availability, and the date the photos were taken, the CDC images were likely cutaneous reactions following ACAM2000 vaccination, although they could not confirm it. The Agency agreed to use the photos from CDC in the revised USPI.

11.6 Recommendations on Postmarketing Actions

No additional postmarketing assessment is recommended.