****Obtain informed consent prior to VIGIV initiation****

Expanded Access IND Protocol: Use of Vaccinia Immune Globulin Intravenous (VIGIV, CNJ-016) for Treatment of Human Orthopoxvirus Infection in Adults and Children

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ATTACHMENTS

1.0 INTRODUCTION AND BACKGROUND

Orthopoxviruses (OPXVs) in the *Poxviridae* family comprise the following species which can infect humans: *variola virus*, *vaccinia virus* (the virus in smallpox vaccine ACAM2000 and smallpox/mpox vaccine JYNNEOS), *monkeypox virus* (MPXV), *cowpox virus*, *Akhmeta virus*, and *Borealpox virus (formerly known as Alaskapox virus)*. V*ariola virus* causes smallpox in humans exclusively while the other viruses cause zoonotic infections that can also be transmitted person-to-person. Infections by *OPXVs*, such as mpox (formerly known as monkeypox) may be localized to the skin or disseminated along the mucosal surface or the respiratory tract. Infected persons may present with serious illnesses including, but not limited to encephalitis, severe inflammatory response syndrome, respiratory failure, painful lymphadenopathy of head or neck with/without associated dysphagia or compromised airway, extensive dermal disruption during rash phase, and other septic syndromes.

After the World Health Organization announced global eradication of smallpox in 1979, the routine use of vaccinia virus smallpox vaccine was nearly eliminated; certain U.S. military personnel and persons at risk for occupational exposure to OPXV are recommended to receive smallpox and/or mpox vaccine per the Advisory Committee on Immunization Practices (ACIP) recommendations. There are two vaccines approved by the Food and Drug Administration (FDA) for OPXV infections: ACAM2000 (replication-competent, live vaccinia vaccine approved for smallpox for adults and children) and JYNNEOS (replication-deficient, Modified Vaccinia Ankara-Bavarian Nordic [MVA-BN] approved for smallpox and mpox in adults 18 years and older). ACAM2000, given it is a replication-competent live *vaccinia virus* vaccine, carries a risk for serious adverse events (e.g., progressive vaccinia and eczema vaccinatum), for which treatment with vaccinia immune globulin intravenous (VIGIV) and antivirals may be used. For more information, see Vaccine Adverse Events | Smallpox | CDC and Medical Management of Adverse Reactions to Vaccinia Virus Vaccination | Smallpox | CDC.

Virulent OPXVs including v*ariola virus* and MPXV pose a public health concern given the potential for rapid transmission especially among unvaccinated populations. There are two genetic clades of MPXV: Clade I and Clade II. Since January 2023, the Democratic Republic of the Congo (DRC) is experiencing its largest surge of Clade I mpox cases in history with more than 19,000 suspect cases and more than 900 deaths as of April 2024 (2023 Outbreak in Democratic Republic of the Congo | Mpox | Poxvirus | CDC).

The ongoing 2022 global outbreak of Clade IIb mpox has led to over 94,000 mpox cases from 117 countries and over 32,000 cases in the U.S. as of April 2024 [1]. The ACIP recommends 2-dose JYNNEOS vaccination for persons aged 18 years and older at risk of mpox during an mpox outbreak. Currently, there are no available treatments for mpox approved by FDA. However, antivirals and other medical countermeasures (MCMs) developed by the U.S. government for smallpox preparedness may be beneficial against mpox. The stockpiled MCMs available as treatment options for mpox in the Strategic National Stockpile (SNS) include intravenous (IV) and oral (PO) tecovirimat (TPOXX), and VIGIV. Brincidofovir (Tembexa) is available from the FDA upon request. Despite the paucity of information on VIGIV efficacy against mpox, the presumed potential clinical benefit is that the antibodies against *vaccinia virus* present in VIGIV might provide passive immunity against mpox based on serologic cross-reactivity between OPXVs [2]. Comparison of mpox virus genome sequences in the 2022 outbreak to those of *vaccinia virus* suggests that *vaccinia virus*-based vaccines induced immunogenicity which was highly cross-reactive against mpox virus [4].

Use of VIGIV as treatment of OPXV infections, especially in severe manifestations of mpox observed in immunocompromised patients during the 2022 mpox outbreak, may be clinically necessary. Please refer to CDC's clinical guidance for treatment of poxvirus diseases. For up-to-date information, please refer to the CDC websites: Clinical Guidance | Mpox | Poxvirus | CDC, Treatment Information for Healthcare Professionals | Mpox | Poxvirus | CDC, Interim Clinical Treatment Considerations for Severe Manifestations of Mpox — United States, February 2023 | MMWR.

1.1 Unmet Medical Need and Rationale for Use of VIGIV under Expanded Access IND

Currently, there is no treatment approved by the FDA for non-variola OPXVs (NV-OPXVs), including mpox. Although vaccinia immune globulin intravenous (VIGIV, CNJ-016) is FDA-approved for use in adults and children, its approved indications are limited to the treatment and/or modification of the following complications due to replication-competent, live *vaccinia virus* vaccine:

- Eczema vaccinatum
- Progressive vaccinia
- Severe generalized vaccinia
- Vaccinia infections in individuals who have skin conditions such as burns, impetigo, varicella-zoster, or poison ivy; or in individuals who have eczematous skin lesions because of either the activity or extensiveness of such lesions

Aberrant infections induced by *vaccinia virus* that include its accidental implantation in eyes (except in cases of isolated keratitis), mouth, or other areas where vaccinia infection would constitute a special hazard

Therefore, this intermediate-size patient population expanded access Investigational New Drug (IND), sponsored by CDC and authorized by FDA, is to allow continued access to and use of stockpiled VIGIV for treatment or post-exposure prophylaxis (PEP) of OPXV infections in adults and children, including mpox and complications from vaccination with replication-competent vaccina virus vaccine not covered by its FDA-approved labeling [3].

2.0 PROGRAM OBJECTIVES

The purpose of this expanded access IND ("compassionate use") program is to provide access to and use of stockpiled VIGIV for treatment or PEP of OPXV infections not covered by its FDA-approved labeling in adults and children who meet eligibility criteria under this EA-IND protocol [3].

To monitor the clinical use of VIGIV under this EA-IND program, serious adverse events (SAE), patient treatment, clinical progress, and outcomes information are intended to be collected to the extent feasible (e.g., baseline clinical conditions, progression/improvement during or post-treatment, recovered or not recovered from OPXV infection). Please refer to **Section 7.0** Clinical Assessment and Monitoring of Patients.

2.1 VIGIV Eligibility

Patients, who meet eligibility criteria noted below, can receive VIGIV under this IND program (e.g., children and all adults including pregnant and nursing individuals, and prisoners). Clinical considerations of VIGIV during an outbreak may evolve depending on the duration and nature of the outbreak and event-based information that may become available during the outbreak. Treatment of OPXV infections under this protocol is intended to be in concert with CDC's clinical guidance for treatment of poxvirus diseases. For up-to-date information and clinical guidance for treatment of poxvirus diseases, please refer to CDC websites at: Poxvirus | CDC,

Treatment Information for Healthcare Professionals | Mpox | Poxvirus | CDC, and Interim Clinical Treatment Considerations for Severe Manifestations of Mpox — United States, February 2023 | MMWR.

2.1.1 Treatment

Mpox

Treatment should be considered for use in patients who have clinical manifestations of:

- Severe disease (e.g., hemorrhagic disease, large number of lesions, necrotic lesions, severe lymphadenopathy, involvement of multiple organ systems and associated comorbidities, other conditions requiring hospitalization)
- Involvement of anatomic areas which might result in serious sequelae that include scarring or strictures; anorectal lesions interfering with bowel movements; and severe infections, especially those that require surgical intervention such as debridement

Treatment should also be considered for use in patients who are at high risk for severe disease:

- Persons with severe immunocompromise due to conditions such as advanced or poorly controlled human immunodeficiency virus (HIV), leukemia, lymphoma, generalized malignancy, solid organ transplantation, therapy with alkylating agents, antimetabolites, radiation, tumor necrosis factor inhibitors, high-dose corticosteroids, being a recipient of a hematopoietic stem cell transplant <24 months post-transplant or ≥24 months but with graft-versus-host disease or disease relapse, or having autoimmune diseases with immunodeficiency as a clinical component
- Children, particularly younger than 8 years of age
- Pregnant or breastfeeding women
- Persons with a condition affecting skin integrity — conditions such as atopic dermatitis, eczema, burns, impetigo, varicella zoster virus infection, herpes simplex virus infection, severe acne, severe diaper dermatitis with extensive areas of denuded skin, psoriasis, or Darier disease (keratosis follicularis)

Other OPXV infections

VIGIV may be used if a patient is ineligible for antiviral treatments including tecovirimat, after antiviral treatment options have been exhausted, or in conjunction with antivirals and/or other therapies for severe manifestations of OPXV infections based on the treating provider's clinical judgment. This includes patients who have serious clinical illness manifestations that are not covered by the FDA-approved indications (e.g., vaccinia keratitis, post-vaccinial encephalitis) following vaccination or exposure to *vaccinia virus* that is suspected of being the result of continued virus proliferation and would, therefore, be expected to respond to VIGIV treatment for viral neutralization by the treating clinician. For detailed information about medical management of smallpox vaccine (vaccinia) complications, please refer to: Medical Management of Adverse Reactions to Vaccinia Virus Vaccination | Smallpox | CDC.

2.1.2 Post-Exposure Prophylaxis (PEP)

VIGIV may be considered for PEP on a **case-by-case basis** in consultation with CDC by contacting poxvirus@cdc.gov or after hours, CDC Emergency Operations Center (EOC) at (770) 488-7100, for the following:

- Individuals with known high-risk exposure to a confirmed or probable case of OPXV infection as defined on Poxvirus | CDC and clinical conditions that necessitate an alternative or complementary option to PEP vaccination based on clinical judgment (e.g.,

those who have a severe allergic reaction to vaccine or vaccine components, or are immunocompromised, are neonates, or are pregnant)
    - VIGIV may be considered given the lack of effectiveness data for using JYNNEOS and tecovirimat as PEP in neonates and the potential safety concern of using a live attenuated vaccine, JYNNEOS, or accurately dosing oral tecovirimat in a neonate
- Prevention of serious complications from replication-competent *vaccinia virus* vaccination in individuals, including close contacts of vaccinees, with conditions for increased risk of complications (e.g., immunocompromising conditions)

2.2 VIGIV Ineligibility

VIGIV should not be administered in the following individuals:

1. Persons with a history of anaphylactic or severe systemic reactions to human globulins or any ingredient contained in VIGIV*
2. Persons with selective immunoglobulin A (IgA) deficiency. These individuals have the potential for developing antibodies to IgA and could have anaphylactic reactions to subsequent administration of blood products that contain IgA*

*Note: The above precaution criteria are valid except in cases of patients with serious or life-threatening vaccinia or other OPXV infections unresponsive to all other treatments. The treating clinicians may make a risk-benefit assessment and administer VIGIV if they determine that the potential benefits outweigh the risks and closely monitor the patients and their vital signs before, during, and immediately after VIGIV infusion.

3.0 PROGRAM PROCEDURE

VIGIV is available upon CDC's receipt of a clinician's request for use in an individual patient, who requires VIGIV for PEP, treatment of OPXV infections, or complications from replication-competent *vaccinia virus* vaccination. The treating clinician can contact CDC's poxvirus team (poxvirus@cdc.gov) or after hours, CDC's EOC at (770) 488-7100, to request the product. The decision to release VIGIV from SNS for clinical use under this IND program will be made by CDC once VIGIV therapy is determined to be clinically appropriate upon CDC's consultation with the requesting clinician. The decision to administer VIGIV will be made solely by the requesting/treating clinician and upon patient/guardian consent.

For requests of VIGIV as PEP in individuals following exposure to an OPXV, including laboratory and other workers with known occupational exposure, each case will be evaluated in terms of the type of virus involved, route of exposure, and concentration of virus at the time of exposure. VIGIV as a preventive therapy for laboratory and other workers with known high-risk occupational exposures would be initiated in anticipation of the probable development of an OPXV-type infection, or recombinant vaccinia-vectored virus infection of the skin epithelium or of the eye that may be expected to clinically manifest similar to eczema vaccinatum, progressive vaccinia, ocular vaccinia, generalized vaccinia, or other serious OPXV infections (e.g., mpox).

4.0 PRODUCT DESCRIPTION

VIGIV is manufactured using plasma collected from healthy, screened donors with high titers of anti-vaccinia antibody (meeting minimum potency specifications) that is purified by an anion-exchange column chromatography method. The plasma donors were boosted with vaccinia vaccine prior to donating plasma. Each plasma donation used for manufacturing VIGIV is tested for the presence of hepatitis B virus (HBV) surface antigen (HBsAg), antibodies to human

immunodeficiency virus (HIV) types 1/2, and hepatitis C virus (HCV) using FDA-licensed serological tests. For more details, refer to the FDA-approved VIGIV package insert [3].

4.1 VIGIV Formulation and Storage

VIGIV contains human *vaccinia virus* immune globulin and inactive ingredients, maltose and polysorbate 80. VIGIV is a preservative-free injection product that is supplied in a 20 mL single-dose vial containing ≥ 50,000 Units (U) per vial of neutralizing vaccinia immune globulin antibodies. 20 mL refers to the vial size, **not the fill volume**, which varies by lot (~ 8-12 mL/vial). Each VIGIV vial is filled to contain ≥ 50,000 U regardless of the fill volume. The exact volume or concentration (U/mL) is NOT indicated on the vial label itself. VIGIV does not contain natural rubber latex.

VIGIV is kept frozen at/below 5°F (≤ -15°C) for long-term storage in the SNS. The product may be shipped from SNS refrigerated at 36°F to 46°F (2°C to 8°C). Once thawed, VIGIV should be used within 60 days of thawing when kept refrigerated at 36°F to 46°F (2°C to 8°C). Do NOT refreeze. Do not use after the expiration date. All vials must remain upright protected from light. If the product is received frozen at/below 5°F (≤ -15°C), VIGIV vials may be maintained frozen by placing into freezer ≤ 5°F (≤ -15°C) at the hospital/facility, which provides longer expiry. Otherwise, store refrigerated at 36°F to 46°F (2°C to 8°C) and use within 60 days of thawing.

Intravenous infusion should begin within 4 hours after puncturing the vial. Do not save punctured VIGIV vials for future use since it contains no preservatives. Discard partially used vials.

5.0 DOSAGE AND ADMINISTRATION OF VIGIV

5.1 VIGIV Dose

- VIGIV is for intravenous use only.
- VIGIV dose is based on actual body weight: 6,000 U/kg is administered as soon as symptoms appear and are judged to be due to OPXV infections or severe *vaccinia virus* vaccination complications. Higher, initial dose (e.g., 9,000 U/kg) may be considered for patients with severe disease based on clinical judgment.
- Higher doses (e.g., 9,000 U/kg, 24,000 U/kg) may be considered in the event that the patient does not respond to the initial 6,000 or 9,000 U/kg dose. In clinical trials, administration of higher doses of up to 24,000 U/kg was shown to be safe and well tolerated and to decrease the endogenous immune response to vaccinia vaccine along with a concomitant decrease in vaccination lesions.
- Consideration for additional VIGIV dosing, i.e., repeat course(s), will be based on the treating clinician's request and in consultation with CDC depending on the individual clinical characteristics (e.g., a large percent of a patient's body surface area affected by lesions at the time of diagnosis, emergence of new or worsening lesions several days after VIGIV dose, lesions affecting mobility or concerning for long-term sequelae, persistent severe immunocompromise, and inability to maximally use other MCMs due to adverse events or contraindications).
- To request clinical consultation regarding redosing or dosing adjustments, contact the CDC poxvirus clinical consultations team at poxvirus@cdc.gov or after hours, CDC Emergency Operations Center at (770) 488-7100.

Instructions on How to Calculate the Weight-Based VIGIV Dose by Units and Corresponding Volume for Dosing Preparation

The VIGIV vial does not have the fill volume printed on the vial label. The extractable volume of a VIGIV vial varies per lot and ranges from about 8–12 mL. The vial size is 20 mL but please **do not mistake the vial size as the volume of VIGIV liquid contained in the vial.** Regardless of fill volume, each vial contains ≥ 50,000 U/vial. It is not necessary to calculate the concentration (U/mL) to determine the volume corresponding to the dose. Follow the instructions below for calculating the number of VIGIV vials needed to prepare a VIGIV dose for infusion.

Calculate the Number of VIGIV vials Needed to Prepare a Dose*	**Example**
Obtain patient's weight (actual body weight)	45.5 kg
Select a dose (e.g., 6,000 U/kg, 9,000 U/kg)	6,000 U/kg
Multiple the weight and dose (U/kg) to get the total units (U) of VIGIV needed	45.5 kg x 6,000 U/kg = 273,000 U
Divide the total Units (U) of VIGIV needed for the dose by 50,000 (U/vial)	273,000 U ÷ 50,000 U/vial = 5.5 vials
For the number of whole vials: pool the entire volume of the vials. Then add the volume needed from the partial vial if needed (described below). **For a partial vial, if needed*:** If a partial vial is needed: extract the entire contents of the vial to measure the total volume (mL) contained in the vial. Use the measured volume (mL) of the vial to calculate the amount (mL) from the vial needed.	**Using the above example of VIGIV dose that requires 5.5 vials, see below:** **A.** Extract the entire volume of 5 vials. Add the volume needed from the 6th vial (steps below). **For volume needed from the 6th vial:** **B.** Extract the entire contents of the 6th vial and measure it (example: 10 mL). **C.** Multiply the portion of the vial needed by the measured volume: 0.5 vial x 10 mL/vial = 5 mL The total volume of the VIGIV dose 5.5 vials = Contents of 5 vials (**A**) + 5 mL (**C**).

* The volume of a vial only needs to be measured if the dose involves a partial vial.

The weight-range tables below are provided to help quickly determine the number of VIGIV vials that are needed to prepare a VIGIV dose of 6,000 U/kg or 9,000 U/kg based on patient's actual body weight. Follow the more detailed instructions above on calculating the number of vials to prepare a VIGIV dose for infusion.

VIGIV Dose of 6,000 U/kg	
Patient Weight (kg) (actual body weight)	Number of vials needed to prepare a VIGIV dose of 6,000 U/kg
≤ 8.3	1
8.4 – 16.6	2
16.7 – 25.0	3
25.1 – 33.3	4
33.4 – 41.6	5
41.7 – 50.0	6
50.1 – 58.3	7
58.4 – 66.6	8
66.7 – 75.0	9
75.1 – 83.3	10
83.4 – 91.6	11
91.7 – 100.0	12
100.1 – 108.3	13
108.4 – 116.6	14
116.7 – 125.0	15
125.1 – 133.3	16
133.4 – 141.6	17
141.7 – 150.0	18
150.1 – 158.3	19
158.4 – 166.6	20
166.7 – 175.0	21
175.1 – 183.3	22
183.4 – 191.6	23

VIGIV Dose of 9,000 U/kg	
Patient Weight (kg) (actual body weight)	Number of vials needed to prepare a VIGIV dose of 9,000 U/kg
≤ 5.5	1
5.6 – 11.1	2
11.2 – 16.6	3
16.7 – 22.2	4
22.3 – 27.7	5
27.8 – 33.3	6
33.4 – 38.8	7
38.9 – 44.4	8
44.5 – 50.0	9
50.1 – 55.5	10
55.6 – 61.1	11
61.2 – 66.6	12
66.7 – 72.2	13
72.3 – 77.7	14
77.8 – 83.3	15
83.4 – 88.8	16
88.9 – 94.4	17
94.5 – 100.0	18
100.1 – 105.5	19
105.6 – 111.1	20
111.2 – 116.6	21
116.7 – 122.2	22
122.3 – 127.7	23
127.8 – 133.3	24
133.4 – 138.8	25
138.9 – 144.4	26
144.5 – 150.0	27
150.1 – 155.5	28
155.6 – 161.1	29
161.2 – 166.6	30
166.7 – 172.2	31
172.3 – 177.7	32
177.8 – 183.3	33
183.4 – 188.8	34

5.2 Preparation of VIGIV for Infusion

- Bring VIGIV vials to room temperature prior to preparing the dose.
- If frozen, thaw vial by placing in a refrigerator at 36°F to 46°F (2°C to 8°C) until the contents are thawed completely (may take approximately 14 hours). Frozen VIGIV vials may be thawed rapidly by placing at room temperature for one hour followed by a water bath at 98.6°F (37°C) until thawed. Do not refreeze the vial.
- Inspect the VIGIV vial prior to use and do not use if solution is cloudy, discolored or contains particulates.
- DO NOT SHAKE VIAL. SHAKING VIAL MAY CAUSE FOAMING.
- VIGIV is compatible with 0.9% Sodium Chloride USP. No other drug interactions or compatibilities have been evaluated. VIGIV may be administered either undiluted or diluted no more than 1:2 (v/v).
- VIGIV vial is for single use only. Do not reuse or save VIGIV for future use.
- VIGIV contains no preservatives. Discard partially used vials.

5.3 Administration of VIGIV

- Administer VIGIV intravenously through a dedicated intravenous line at the rate of infusion of no greater than 2 mL/minute.
- For patients weighing less than 50 kg, infuse the product at a rate no greater than 0.04 mL/kg/minute (133.3 U/kg/minute).
- Adverse drug reactions may be related to the rate of infusion. Slower infusion rate may be needed for patients who develop a minor adverse reaction (e.g. flushing) or for patients with risk factors for thrombosis/thromboembolism. For instance,
    - VIGIV administration should be initiated at an infusion rate of 0.01-0.02 mL/kg/minute for the first 30 minutes then increased by 0.01-0.02 mL/kg/minute from the initial infusion rate for the next 30 minutes. The remaining infusion may be administered at an infusion rate of 2 mL/minute.
- Closely monitor and carefully observe patients and their vital signs before, during, and immediately after VIGIV infusion:
    - For instance, monitor vital signs before infusion, then every 30 minutes during infusion and 1 hour following completion of infusion.
- For patients with pre-existing renal insufficiency, or at increased risk of acute kidney injury, thrombosis, or volume overload, do not exceed the recommended infusion rate and follow the infusion schedule closely.
- For patients with risk factors for thrombosis, the maximum daily dose of VIGIV should not exceed 12,000 Units per kg.

Appropriate equipment, oxygen, medication (including epinephrine, diphenhydramine, and corticosteroids) and personnel trained in the management of infusion or hypersensitivity reaction must be available.

Discontinuation of VIGIV Infusion or Treatment:
At any time during VIGIV treatment, a patient may voluntarily discontinue or refuse VIGIV for any reason, or infusion may be paused or stopped due to serious adverse events (SAEs), clinically significant abnormalities in laboratory values, or per the clinical judgment of the treating clinician.

- If hypotension, anaphylaxis, or a severe allergic reaction (e.g., angioneurotic edema or respiratory distress) occurs, discontinue the VIGIV infusion immediately and administer epinephrine (1:1000) as needed. Administer corticosteroids and diphenhydramine, assist respiration, and provide other resuscitative measures as appropriate. If hypotension occurs, stop the infusion of VIGIV and stabilize blood pressure with pressors, if necessary.
- If mild or moderate non-anaphylactoid reactions (e.g., headache, chills, nausea) occur, closely observe patient. If the reaction is causing substantial discomfort but is not otherwise serious, the rate of infusion can be reduced by half. Closely monitor for any worsening or additional reactions during the remainder of the infusion and further discontinued if the patient experiences more severe reactions to VIGIV.

Non-anaphylactic reactions are the most common type of reactions to immune globulin injections. These reactions include back or abdominal pain, nausea, and vomiting within the first 10 minutes of injection. Usually, there is no dyspnea or other change in vital signs. Chills, fever, headache, myalgia, and fatigue may begin at the end of infusion and continue for several hours. More severe reactions of this type may require pretreatment with corticosteroids or acetaminophen. See **Section 5.0** for possible adverse reactions with VIGIV.

Drug-Drug Interactions:

- Since efficacy of live attenuated virus vaccines (e.g., measles, rubella, mumps, and varicella) may be impaired by immune globulin administration, revaccination may be necessary. Vaccination with live virus vaccines should be deferred until approximately three months after administration of VIGIV. Persons who receive VIGIV shortly after live virus vaccination should be revaccinated 3 months after the administration of the immune globulin.
- JYNNEOS is a live, replication-deficient *vaccinia virus* vaccine for prevention of mpox and smallpox. Since VIGIV contains antibodies to OPXVs, VIGIV could interfere with desired immunogenicity to JYNNEOS if it is administered in close temporal proximity to VIGIV. It is ideal to delay administration of JYNNEOS if VIGIV was recently administered. During outbreaks or depending on specific individual cases, however, administering a dose of JYNNEOS after VIGIV administration without delay may be appropriate. Case specific consultation with the CDC poxvirus clinical team is available.
- Admixtures or VIGIV with other drugs have not been evaluated. It is recommended that VIGIV be administered separately from other drugs that the patient may be receiving. If a pre-existing catheter must be used, the line should be flushed with 0.9% Sodium Chloride USP and not with other solutions such as dextrose in water.

Laboratory Test Interactions:

- VIGIV contains maltose, which can be misinterpreted as glucose by certain types of blood glucose testing systems (for example, those based on the GDH-PQQ or glucose-dye-oxidoreductase methods). Due to the potential for falsely elevated glucose readings that can lead to untreated hypoglycemia or inappropriate insulin administration, only testing systems that are glucose-specific should be used to test or monitor blood glucose levels in patients receiving VIGIV.
- Antibodies present in VIGIV may interfere with some serological tests. After administration of immune globulins like VIGIV, a transitory increase of passively

transferred antibodies in the patient's blood may result in positive results in serological testing (e.g., Coombs' test).

6.0 POSSIBLE RISKS OF VIGIV TREATMENT

Adverse Reactions

The adverse drug reactions to VIGIV treatment in clinical trials (>10%) include headache, nausea, rigors, and dizziness. Other adverse events associated with infusion of immunoglobulins include hypotension, pallor, diarrhea, joint pain, dizziness, hyperkinesis, drowsiness, pruritis, rash, renal dysfunction, perspiration, and vasodilation.

Although there were no serious adverse drug reactions reported following administration of VIGIV in clinical trials, there has been a post-marketing case of severe vaccinia infection that developed intravascular hemolysis, leucopenia, and thrombocytopenia during VIGIV treatment.

Contraindications

VIGIV should not be administered in individuals with a history of anaphylaxis or prior severe systemic reaction associated with the parenteral administration of this or other human immune globulins or any ingredient contained in VIGIV. VIGIV contains trace amounts of IgA. While VIGIV contains less than 40 µg/mL of IgA, persons with selective IgA deficiency can develop antibodies to IgA and therefore could have anaphylactic reactions to subsequent administration of blood products that contain IgA, including VIGIV. See **Section 2.2** VIGIV Ineligibility for exceptions.

Warnings and Precautions

Isolated vaccinia keratitis

Caution needs to be exercised when using VIGIV in the treatment of patients having complications due to vaccinia vaccination that include concomitant vaccinia keratitis, since a single study in rabbits demonstrated increased corneal scarring upon VIGIM administration in vaccinia keratitis [6]. Individuals with vaccinia keratitis should not be excluded from treatment with VIGIV because of this condition if other serious vaccine complications or sight threatening manifestations of ocular vaccinia are present and the treating clinician feels that the benefit of VIGIV treatment outweighs the potential risk of corneal scarring. While VIGIV should be considered in treatment of severe ocular complication due to *vaccinia virus*, it is contraindicated for use in the presence of isolated vaccinia keratitis per FDA labeling [3]. However, patients having other complications due to vaccinia vaccination that include vaccinia keratitis, may still be treated with VIGIV in addition to trifluridine, and ophthalmologic consultation.

Hypersensitivity to human immune globulin (acute anaphylaxis)

Anaphylactic reactions to injections of immune globulin products such as VIGIV are rare. The symptoms of classic anaphylactic reactions are: flushing, facial swelling, dyspnea, cyanosis, anxiety, nausea, vomiting, malaise, hypotension, loss of consciousness, and in some cases, death. They may appear within seconds to several hours after infusion.

Although acute systemic allergic reactions were not seen in clinical trials with VIGIV, administer the product only in a setting where appropriate equipment and personnel trained in the management of acute anaphylaxis are available. In case of hypotension, allergic or anaphylactic reactions, discontinue the administration of VIGIV immediately and give supportive care as needed. In case of shock, observe the current medical standards for shock treatment.

During administration of VIGIV, vital signs should be monitored closely, and careful observation made for any symptoms throughout the infusion. Epinephrine and other standard drugs (e.g., antihistamines, intravenous steroids) and devices should be available for the treatment of an acute anaphylactic reaction. Clinical anaphylaxis may occur even when the patient is not known to be sensitized to IG products. A reaction may be related to the rate of infusion; therefore, careful adherence to the infusion rates as outlined is important. If anaphylaxis or drop in blood pressure occurs, discontinue infusion and treat appropriately.

Infusion-related reactions

Non-anaphylactic reactions are the most common type of reactions to immune globulin injections. These reactions include back or abdominal pain, nausea, and vomiting within the first 10 minutes of injection. Usually, there is no dyspnea or other change in vital signs. Chills, fever, headache, myalgia, and fatigue may begin at the end of infusion and continue for several hours. More severe reactions of this type may require pretreatment with corticosteroids or acetaminophen.

Acute Renal Dysfunction/Failure

Renal dysfunction, acute renal failure, osmotic nephropathy, proximal tubular nephropathy, and death may occur upon use of immune globulin intravenous (Human) (IGIV) products. Use VIGIV with caution in patients with pre-existing renal insufficiency and in patients at risk of developing renal insufficiency (including, but not limited to those with diabetes mellitus, age greater than 65 years, volume depletion, paraproteinemia, sepsis, and patients receiving known nephrotoxic drugs), and administer VIGIV at the minimum rate of infusion appropriate.

Blood Glucose Monitoring

Per Black Box Warning, some types of blood glucose testing systems (for example, those based on the glucose dehydrogenase pyrroloquinoline quinone or glucose-dye-oxidoreductase methods) could falsely interpret the maltose contained in VIGIV as glucose. This could result in falsely elevated glucose readings and, consequently, in the inappropriate administration of insulin, resulting in life-threatening hypoglycemia. Also, cases of true hypoglycemia may go untreated if the hypoglycemic state is masked by falsely elevated glucose readings. Blood glucose measurement in patients receiving VIGIV must be done with a glucose-specific method (monitor and test strips) to avoid interference by maltose contained in VIGIV.

Thrombosis

Thrombotic events may occur in association with IGIV treatment. At-risk patients include those with a history of atherosclerosis, multiple cardiovascular risk factors, advanced age, impaired cardiac output, hypercoagulable disorders, prolonged periods of immobilization, and/or known or suspected hyperviscosity. Weigh the potential risks and benefits of VIGIV against those of alternative therapies for all patients for whom VIGIV administration is being considered.

Aseptic Meningitis Syndrome (AMS)

AMS has been reported to occur infrequently in association with IGIV treatment. AMS usually begins within several hours to 2 days following IGIV treatment and is characterized by a range of signs and symptoms including severe headache, nuchal rigidity, drowsiness, fever, photophobia, painful eye movements, nausea, and vomiting. In these patients, a thorough neurological examination, including cerebrospinal fluid (CSF) studies, should be done to rule out other causes of meningitis. CSF studies frequently show a pleocytosis of several thousand cells per cu mm, predominantly granulocytes, and elevated protein levels up to several hundred

mg/dL. AMS may occur more frequently in association with high dose (2 g/kg) IGIV treatment. Discontinuation of IGIV treatment has resulted in remission of AMS within several days without sequelae.

Hemolysis or Hemolytic Anemia
IGIV products can contain blood group antibodies which may act as hemolysins and induce *in vivo* coating of red blood cells with immune globulin, causing a positive direct antiglobulin reaction and hemolysis. Hemolytic anemia can develop subsequent to IGIV therapy due to enhanced red blood cell sequestration and acute hemolysis, consistent with intravascular hemolysis, has been reported.

Transfusion-related Acute Lung Injury (TRALI)/Noncardiogenic pulmonary edema
Noncardiogenic pulmonary edema may occur in patients administered IGIV. TRALI is characterized by severe respiratory distress, pulmonary edema, hypoxemia, normal left ventricular function, and fever and typically occurs within 1 to 6 hours after transfusion. Patients with TRALI may be managed using oxygen therapy with adequate ventilatory support.

Transmissible Infectious Agents from Human Plasma
VIGIV is prepared from human plasma and, like other plasma products, carries the possibility for transmission of blood-borne viral agents and, theoretically, the Creutzfeld-Jakob disease agent. The risk of transmission of recognized blood-borne viruses has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current viral infections, and by implementing process steps for the inactivation and/or removal of certain potential viruses during manufacturing. Despite these measures, some as yet unrecognized blood-borne viruses may not be removed by the manufacturing process; therefore, VIGIV should be given only if benefit is expected.

7.0 SPECIAL POPULATIONS

Pregnancy
Animal reproduction studies have not been conducted with VIGIV; therefore, it is not known whether VIGIV can cause fetal harm when administered during pregnancy or whether it can affect reproductive capabilities. However, immune globulins have been widely used during pregnancy for many years without any apparent negative reproductive effects. The risk/benefit of VIGIV administration should be assessed for each individual case.

A consideration for administering VIGIV in pregnant women may be whether replication-competent *vaccinia virus* vaccine was inadvertently administered, particularly within the last 10 days. This is because women who have a positive serum or urine pregnancy test within the 10-day period following smallpox vaccination (replication-competent *vaccinia virus* vaccine) are at the greatest possibility of viremia resulting in infection of the fetus before the expected appearance of vaccination-induced neutralizing antibodies. After 10 days, neutralizing antibodies would be expected to have appeared in response to vaccination in a pregnant primary or repeat vaccinee recipient with an otherwise normal immune system and additional VIGIV would not be expected to provide any additional theoretical benefit.

Lactation
It is not known whether VIGIV is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when VIGIV is administered to a woman who is nursing.

Pediatric and Geriatric Populations
Safety and effectiveness in the pediatric population (< 16 years of age) and geriatric population (> 65 years of age) have not been established for VIGIV.

Patients with Renal Insufficiency
Use VIGIV with caution in patients with pre-existing renal insufficiency and in patients at increased risk of developing renal insufficiency. Monitor renal function and urine output in patients at risk of renal failure. Check baseline blood viscosity in patients at risk of hyperviscosity and conduct confirmatory tests if hemolysis or TRALI is suspected.

8.0 CLINICAL ASSESSMENT AND MONITORING OF PATIENTS

Upon presentation, the patient should be thoroughly assessed per clinician's judgment to determine if VIGIV treatment is appropriate. This may include a medical history, review of concomitant medications, clinical laboratory testing (e.g., hematology, chemistry, liver function tests, urinalysis, pregnancy), determination of immune status (e.g., through evaluation of CD4 count and HIV viral load as well as awareness of other immunocompromising conditions), and a physical examination with vital signs (e.g., weight, blood pressure, pulse, respiratory rate, and temperature).

Patients should be monitored for clinical response and any occurrence of adverse events after VIGIV administration through discharge. For patients who receive VIGIV for PEP, monitor through 3 weeks after VIGIV administration. For patients pregnant at the time of VIGIV administration, follow up if feasible within 1 month of pregnancy outcome (defined as full-term or premature delivery of live or non-viable infant, or spontaneous abortion). Follow-up can be conducted by telemedicine or in-person visit(s) to assess and monitor for any occurrences of serious adverse events, medically attended adverse events, and adverse events of special interest (e.g., symptoms consistent with vaccinia vaccine complications or OPXV infections including mpox). The patient will be advised to report any suspected adverse reactions to his/her treating clinician for reporting to CDC.

Treating clinicians or their designees will be responsible for patient assessment, monitoring, and reporting information to CDC. The following case report forms are required to be completed, retained, and/or returned to CDC. Please return required forms to CDC via encrypted email (regaffairs@cdc.gov) upon completion. Personally identifiable information should not be emailed without encryption.

- Obtain **Informed Consent** (Attachment 2) – prior to VIGIV administration; provide a copy to the patient and retain a copy at the treating facility/institution. A copy does NOT need to be returned to CDC. Only if the signed informed consent forms cannot be maintained at the treating facility/institution, then they can be sent to CDC within 7 calendar days of VIGIV administration.
- Complete and return **Form FDA 1572** to CDC prior to VIGIV administration to the extent feasible but no later than 7 calendar days after VIGIV administration.
- Complete and return **Patient Intake Form** (Attachment 3 – Form A) to CDC no later than 7 calendar days after administering the initial single- or 2-dose regimen of VIGIV. The required fields on the form are noted with an asterisk (*). The relevant information at the time of VIGIV treatment include:
    - Medical history, baseline signs/symptoms, vital signs, concomitant medications

    - For clinical laboratory parameters tested, attach a copy of the results (e.g., hematology, chemistry, renal and liver function tests,
- Complete **Record of VIGIV Administration Form** (Attachment 3 – Form B) if **repeat** VIGIV dose or dose-regimen is administered after the initial VIGIV treatment. Return to CDC no later than 7 calendar days after administering each **repeat course(s)** VIGIV after the initial single- or 2-dose regimen. The relevant information includes:
    - The sequential number and administration date of each VIGIV dose, occurrence of any serious/suspected adverse events with each repeat dose, and observation of any changes in patient's overall clinical status since the last VIGIV dose
    - Results of any recent, pertinent clinical laboratory testing performed (e.g., CD4 cell count, IgA)
- Complete and return **Clinical Outcome Form** (Attachment 3 – Form C) to CDC no later than 7 calendar days after discharge. For patients who receive VIGIV for PEP, complete 3 weeks after VIGIV administration. The relevant information includes:
    - Progress of VIGIV therapy and clinical outcomes, clinical labs, and lesion/scab and serum specimens (if collected).
- **Adverse Event (AE) Reporting** – If any serious or life-threatening AEs and/or medication errors occur that have not yet been reported to CDC, complete a PDF MedWatch Form (Form FDA 3500) and return it to CDC via encrypted email (regaffairs@cdc.gov). SAEs must be reported within 72 hours of awareness or sooner if possible. All SAEs, whether or not the treating clinician considers the event to be drug-related, must be reported:
    - SAE defined as death, life-threatening AE, inpatient hospitalization, or prolongation of existing hospitalization, persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions; congenital anomaly/birth defect; an important medical event that based on appropriate medical judgement may jeopardize the patient and may require medical or surgical intervention to prevent one of the aforementioned outcomes.
- If a patient is pregnant at the time of VIGIV treatment, complete and return **Pregnancy Outcome Form** (Attachment 3 – Form D) to CDC within 1 month of the pregnancy outcome (defined as full-term, premature delivery of live or non-viable infant, or spontaneous abortion).

Considerations for Clinical Laboratory Monitoring:

- Monitor hematology, chemistry, urinalysis, renal and hepatic function before and after administration of VIGIV as appropriate based on clinical judgment of the treating clinician. Periodic monitoring of renal function and urine output is particularly important in patients judged to be at increased risk of developing acute renal failure. Assess renal function, including measurement of BUN and serum creatinine before the initial infusion of VIGIV and at appropriate intervals thereafter. For patients with HIV/AIDS, monitor CD4 counts and HIV viral load, if appropriate.
- Because of the potentially increased risk of thrombosis, consider baseline assessment of blood viscosity in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies.
- If signs and/or symptoms of hemolysis are present after an infusion of VIGIV, perform appropriate laboratory testing for confirmation.

- If TRALI is suspected, perform appropriate tests for the presence of anti-neutrophil antibodies in both the product and patient's serum.

Table 1. Summary of Clinical Assessment and Monitoring Parameters

Parameters*	**Pre-VIGIV Treatment**	**During VIGIV Treatment**	**Post Completion of VIGIV Treatment**
	Prior to/at the time of VIGIV Treatment	**For subsequent VIGIV doses following the initial VIGIV dose(s)**	**At last follow-up/upon discharge for treatment or 3 weeks after last dose of VIGIV for PEP**
	Patient Intake Form (Attachment 3-A)	Record of VIGIV administration form (Attachment 3-B)	Clinical Outcome Form (Attachment 3-C)
Signed Informed Consent	X	N/A	N/A
Inclusion/Exclusion Criteria	X	N/A	N/A
Baseline clinical assessment	X	N/A	N/A
CD4 count/HIV viral load if appropriate, Hematology, chemistry, urinalysis, renal and liver function tests	X	X	Monitor based on clinical judgment of treating clinician
Clinical progress	N/A	X	Report clinical outcomes following VIGIV therapy (Attachment 3-C)
Serious Adverse Events/Medication Errors*	Report to CDC within 72 hours or sooner using MedWatch Form	Report to CDC within 72 hours or sooner using MedWatch Form	Report to CDC within 72 hours or sooner using MedWatch Form
Suspected Adverse Events	Report to CDC within 7 calendar days of the last VIGIV administration or sooner	Report to CDC within 7 calendar days of the last VIGIV administration or sooner	Report to CDC within 7 calendar days of the last VIGIV administration or sooner
Pregnancy outcome, if applicable	N/A	N/A	Report pregnancy outcome within 1 month of pregnancy outcome (Attachment 3-D)#
Lesion specimens	Optional	Optional (for any new lesions during treatment)	Optional (for any new lesions post-treatment)

* Additional information regarding patient monitoring:
– SAEs must be reported by emailing a completed MedWatch form to CDC (regaffairs@cdc.gov) within 72 hours of awareness or sooner if possible.
– Serology testing at CDC may be available on a case-by-case basis as determined during consultation with CDC.
For patients pregnant at the time of VIGIV administration, the Pregnancy Outcome Form is to be completed within 1 month of pregnancy outcome (defined as full-term or premature delivery of live or non-viable infant, or spontaneous abortion).

Inadvertent Vaccination or Inoculation of Individuals with Major Contraindications to Replication-Competent *Vaccinia Virus* Vaccine.

In the cases of patients who receive VIGIV due to inadvertent vaccination or inoculation with replication-competent *vaccinia virus* vaccine, the treating clinician should be advised to

immediately report any of the following during their observation periods for vaccine-related adverse events:

- Development of rash before primary vaccine site has completely healed (scab has separated with healed skin underneath)
- Failure of primary vaccine site to heal or development of other similar lesions on other areas of body
- For pregnancy, development of any of the following complications during the pregnancy
    - Spontaneous abortion or intrauterine fetal death
    - Pre-term delivery
    - Low birth weight infant
    - Infant death occurring in the perinatal period
    - Congenital malformations
    - Delivery of an infant with evidence of intrauterine vaccinia infection manifested by the presence of vaccinial type skin lesions or scarring (Fetal Vaccinia)

9.0 ALTERNATIVES TO VIGIV

At this time, no FDA-approved therapy is available to treat NV-OPXV infections. Furthermore, there are no proven alternatives to VIGIV for PEP of serious complications in laboratory and other workers with high-risk accidental exposures to *vaccinia virus*, treating and preventing serious complications from the infection, or preventing serious complications in individuals with major contraindications to non-emergency vaccination who have been inadvertently vaccinated or inoculated with replication-competent vaccinia vaccine. Refer to CDC's website for additional information: Treatment Information for Healthcare Professionals | Mpox | Poxvirus | CDC and Prevention and Treatment | Smallpox | CDC.

Tecovirimat (TPOXX)

Tecovirimat is available under a separate CDC-sponsored EA-IND protocol (IND 116,039, CDC IRB #6402). Tecovirimat is an FDA-approved antiviral drug; however, this proposed use is investigational and has not been studied in humans. Therefore, the benefit of tecovirimat therapy in vaccinia-vaccine related complications is uncertain. The efficacy of tecovirimat for the treatment of other related OPXV infections is also unknown. VIGIV is considered the primary treatment for replication-competent vaccinia vaccine (e.g., ACAM2000) related complications. However, tecovirimat may be considered as a possible secondary treatment for complications from vaccinia vaccination in individuals who are non-responsive to VIGIV therapy and who are seriously ill from vaccinia vaccine-related adverse events (e.g., clinical progression with possibility of death or permanent impairment such as loss of sight). Tecovirimat should only be used for the treatment of vaccinia-related complications if VIGIV treatment is unavailable (i.e., supplies are exhausted) or in conjunction with VIGIV or other therapies based on the treating clinician's clinical judgment.

Cidofovir (VISTIDE)

Cidofovir is an FDA-approved antiviral drug; however, its use for OPXV infection is investigational and has not been studied in humans. Therefore, the benefit of cidofovir therapy in vaccinia-vaccine related complications is uncertain. The efficacy of cidofovir for the treatment of non-vaccinia OPXV infections is also unknown. VIGIV is considered the primary treatment for vaccinia-vaccine related complications. However, cidofovir may be considered as a possible secondary treatment for complications from vaccinia vaccination in individuals who are non-responsive to VIGIV therapy and who are seriously ill from vaccinia vaccine-related adverse

events (e.g., clinical progression with possibility of death or permanent impairment such as loss of sight). Cidofovir should only be used for the treatment of vaccinia-related complications if VIGIV treatment is unavailable (i.e., supplies are exhausted) or in conjunction with VIGIV or other therapies based on the treating clinician's clinical judgment.

Cidofovir is commercially available and can be used under practice of medicine for treatment of OPXV infections by treating clinicians. While IV cidofovir should not be used concurrently with brincidofovir, a drug holiday is not necessary when transitioning between IV cidofovir and brincidofovir (and vice versa) based on available information on the concentrations of plasma cidofovir and its relevance to the toxicity of concern (nephrotoxicity).

Brincidofovir (Tembexa)
Brincidofovir, a prodrug of cidofovir, is FDA-approved for the treatment of human smallpox disease in adult and pediatric patients, including neonates. Data are not available on the effectiveness of brincidofovir as a treatment for mpox. However, it has shown to be effective against OPXVs in *in vitro* and animal studies. While brincidofovir should not be used concurrently with IV cidofovir, a drug holiday is not necessary when transitioning between IV cidofovir and brincidofovir (and vice versa) based on available information on the concentrations of plasma cidofovir and its relevance to the toxicity of concern (nephrotoxicity). Brincidofovir is available under single-patient emergency use IND (EIND) by submitting an EIND request to FDA.

For additional alternative therapies, please see: Prevention and Treatment | Smallpox | CDC.

10.0 RECORDING AND REPORTING SERIOUS ADVERSE EVENTS

10.1 Definitions (21 CFR 312.32)

An **ADVERSE EVENT** (AE) is any untoward medical occurrence associated with the use of VIGIV in humans, whether or not considered related to VIGIV. It can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of VIGIV, without any judgment about causality.

A **SUSPECTED ADVERSE REACTION** is any AE for which there is a reasonable possibility that VIGIV caused the AE. It is a subset of all AEs for which there is a reasonable possibility that VIGIV caused the event. "Reasonable possibility" means there is evidence to suggest a causal relationship between VIGIV and the AE. "Suspected adverse reaction" implies a lesser degree of certainty about causality than "adverse reaction."

An **ADVERSE REACTION** is any AE caused by VIGIV. Adverse reactions are a subset of all suspected adverse reactions for which there is a reason to conclude that VIGIV caused the event.

UNEXPECTED: An AE is considered "unexpected" if it is not listed in this protocol or Package Insert [3], or is not listed at the specificity or severity observed.

SERIOUS: An AE or suspected adverse reaction is considered "serious" if, in the view of either the treating clinician or CDC, it results in any of the following outcomes:

- Death
- a life-threatening AE
- inpatient hospitalization or prolongation of existing hospitalization

- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions

a congenital anomaly/birth defect

NOTE: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes previously listed.

LIFE-THREATENING: An AE or suspected adverse reaction is considered "life-threatening" if, in the view of either the treating clinician or CDC, its occurrence places the patient at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused a death.

10.2 Treating Clinician Reporting Requirements to CDC

All SAEs must be reported. These include all SAEs that the patient reports spontaneously, those the clinician observes, and those the clinician elicits in response to open-ended questions. All SAEs, whether or not the treating clinician considers the event to be drug-related, must be reported by emailing a completed PDF MedWatch Form (Form FDA 3500) to CDC (regaffairs@cdc.gov) within 72 hours of awareness or sooner if possible (see **Section 7.0**).

CDC Reporting Requirements to FDA and CDC Institutional Review Board (IRB)

CDC will review all SAEs and report serious, unexpected suspected adverse reactions to FDA within 15 calendar days of initial receipt or after determining that the information qualifies for reporting under 21 CFR 312.32(c)(1).

In cases of unexpected, suspected adverse reactions that are fatal or life-threatening (serious), CDC will report to FDA as soon as possible, but no later than 7 calendar days after initial receipt of the information (21 CFR 312.32(c)(2)).

All three (3) of the definitions contained in the requirement must be met for expedited reporting to FDA:

1. Serious,
2. Unexpected, and
3. Suspected Adverse Reaction.

CDC will report all serious and unexpected suspected adverse reactions and incidents to CDC IRB according to CDC IRB's policy and procedures.

AEs that are voluntarily reported by providers to CDC that do not meet the requirements for expedited reporting to FDA will be submitted under the IND in Annual Reports.

11.0 REGULATORY AND ADMINISTRATIVE REQUIREMENTS

CDC, the sponsor of the IND, and all licensed healthcare providers who request and receive VIGIV under this IND protocol will abide by the Code of Federal Regulations (in particular, 21 CFR Parts 50, 56, and 312). The IND protocol is subject to FDA's review and authorization as well as review and approval by an Institutional Review Board (IRB). CDC IRB serves as the central IRB for review and approval of this VIGIV IND protocol, and has determined it non-

research (i.e., does not constitute human subjects research per 45 CFR 46.102(l)). Therefore, participating sites may use CDC IRB's approval of this protocol that meets FDA's requirements regarding IRB review per 21 CFR Parts 50 and 56.

Any change or modification to the IND protocol that affects purpose, procedures, or significant data or administrative aspects of the program will require a formal amendment. Such amendments will be submitted to FDA for review and approved by the CDC IRB prior to implementation. Revised IND protocol and/or procedural modifications will be communicated by CDC to the clinicians and medical facilities participating in the VIGIV treatment.

Data Management and Handling:
IND case report forms (**Attachment 3**), laboratory results, visit summaries, hospital discharge summaries, medical records, etc., may be used as source documents. The information obtained through the case report forms of this IND protocol and additional supplemental information provided by treating clinicians to CDC will be maintained by the CDC. Any analysis of data contents will be conducted without individual identifiers. The information gathered under this expanded access IND program and any analysis generated will be reported to the FDA as part of the annual report for this IND. Data from case report forms and other related information collected under this IND may also be provided to Emergent BioSolutions Canada, Inc., and the Department of Health and Human Services/Biomedical Advanced Research and Development Authority (HHS/BARDA). Information about specific treating clinicians (i.e., names, CVs, or Form FDA 1572) and/or hospitals/sites may be shared with FDA, and local public health jurisdictions, and the manufacturer. Any information pertaining to treating clinicians and/or participating sites that are provided to the manufacturer is limited to use in the manufacturer's discussions with health authorities concerning this CDC-sponsored IND program.

Informed Consent:
Informed consent in compliance with 21 CFR 50 must be obtained via the enclosed informed consent/permission form **(Attachment 2)** from the patient, including adolescents, deemed as mature or emancipated minors by state and/or local law who can consent for themselves, before VIGIV is administered. If the patient is unable to give consent, consent can be obtained from a legally authorized representative (LAR).

A single consent form **(Attachment 2)** will be used to obtain informed consent/parental permission. Waiver of assent for children (7–11 years of age) under 21 CFR 50.55(c)(1) and for children (12–17 years of age) under 21 CFR 50.55(c)(2) was approved by the CDC IRB for all patients under this IND program. Parental permission will be sought in accordance with 21 CFR 50.55 for children aged 12–17 years (permission of only one parent is required) with exceptions for adolescents, deemed as mature or emancipated minors by state and/or local law who can consent for themselves for medical care. The ultimate responsibility for decision-making regarding treatment with VIGIV in minors should lie with the parent or guardian, or by the adolescents, deemed as mature or emancipated minors by state and/or local law who can consent for themselves for medical care.

For patients with limited English proficiency, if a version of the informed consent form is not available in the patient's (LAR's) language, the form must be translated orally by a certified interpreter. If a certified interpreter is not available, another adult who is fluent in both English and the language needed may interpret, provided the patient (parent/LAR) is comfortable sharing medical information (i.e., the reason treatment is being offered) with that person. If a facility

wishes to create a written translation of the informed consent form, the CDC IRB-approved informed consent form must be translated by a certified translator and the translation must be submitted to and approved by the CDC IRB prior to use. A short form for obtaining informed consent from patients with limited English proficiency, along with a written summary of the information in the informed consent form for use with the short form will be available from CDC upon request. The same requirements for interpretation or translation additionally apply to the short form. Informed consent form and the short form are available in Spanish and may be obtained from CDC upon request.

In the situation that a patient is unable to respond and make wishes known about VIGIV treatment, no next-of-kin or legal representative is available, and the patient's illness is life-threatening, obtaining informed consent may be deemed not feasible per 21 CFR 50.23 "Exception from general requirements." In such situations that necessitate VIGIV treatment, the patient's treating clinician and a clinician who is not otherwise participating in this expanded access IND program will document the clinical determination on the last page of the informed consent form **(Attachment 2)**. The information in the consent form should be provided to the patient or LAR at the first available opportunity. Notify CDC via email (regaffairs@cdc.gov) within 3 working days of VIGIV initiation when the treatment determination was made based on the mentioned certification by the treating and an independent clinician.

12.0 SUMMARY OF AVAILABLE SAFETY AND EFFICACY DATA OF VIGIV

12.1 Human Safety and Pharmacokinetics and Pharmacodynamic Data of VIGIV

The safety of VIGIV has not been studied in patients with smallpox or non-vaccinia-OPXV disease. In the three clinical trials conducted that evaluated safety, pharmacokinetics and pharmacodynamic of VIGIV in healthy adult subjects, the most frequently reported adverse reactions were headache, nausea, rigors, and dizziness:

- safety/pharmacokinetics study: 60 healthy volunteers received a single intravenous dose of either 6000 U/kg or 9000 U/kg VIGIV;
- pharmacodynamic study: 32 healthy male and female volunteers were randomized to receive vaccinia vaccination (n=10), VIGIV (9000 U/kg) 4 days prior to vaccinia vaccination (n=10), or VIGIV (9000 U/kg) concurrent with vaccinia vaccination (n=12);
- pharmacodynamic study, 50 healthy volunteers received VIGIV at 9000 U/kg (n=20) or at 24,000 U/kg (n=20) or placebo (n=10) 4 days prior to vaccinia vaccination (n=30) or placebo (n=20)

Most adverse reactions were of mild intensity (defined in study protocols as awareness of a sign or symptom but subject can tolerate). One subject in the 9,000 Units per kg dosage group experienced syncope. There was a lower incidence of adverse reactions when VIGIV (9,000 Units per kg) was infused at 2 mL/min than 4 mL/min. There was a higher incidence of adverse reactions after administration of VIGIV in fasted subjects compared to subjects that were not fasted overnight. There were no serious adverse reactions or adverse reactions of severe intensity in the clinical studies. There were no instances of VIGIV discontinuation due to an adverse event, or reduction in dose or infusion rate. More detailed information about the three studies can be found in the VIGIV package insert [3].

Post-marketing experience
Severe vaccinia infection that developed possible intravascular hemolysis and transient renal injury has been reported. As VIGIV may contain blood group antigens that may have hemolysins, VIGIV doses may have contributed to the hemolysis. However, the hemolysis did not recur with continued VIGIV dosing. Mild and transient chest pain that occurred the same day of VIGIV infusion has been reported.

The following are adverse reactions listed by body system that have been identified and reported during the post-approval use of other IGIV products:

- Cardiovascular: Cardiac arrest, tachycardia
- Hematologic and Lymphatic: Neutropenia, leukopenia, anemia, lymphadenopathy
- Integumentary: Stevens-Johnson syndrome, epidermolysis, erythema multiforme, dermatitis (e.g., bullous dermatitis), urticaria or other skin reactions
- Gastrointestinal: Hepatic dysfunction, abdominal pain, diarrhea
- Muscular: Myalgia, arthralgia
- Neurological: Coma, loss of consciousness, seizures
- Renal: Acute kidney injury, osmotic nephropathy
- Respiratory: Apnea, Acute Respiratory Distress Syndrome (ARDS), cyanosis, hypoxemia, pulmonary edema, dyspnea, bronchospasm, wheezing
- General/Body as a Whole: Malaise, chest discomfort

Because post-marketing adverse reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to exposure to the product.

12.2 Human Effects Data

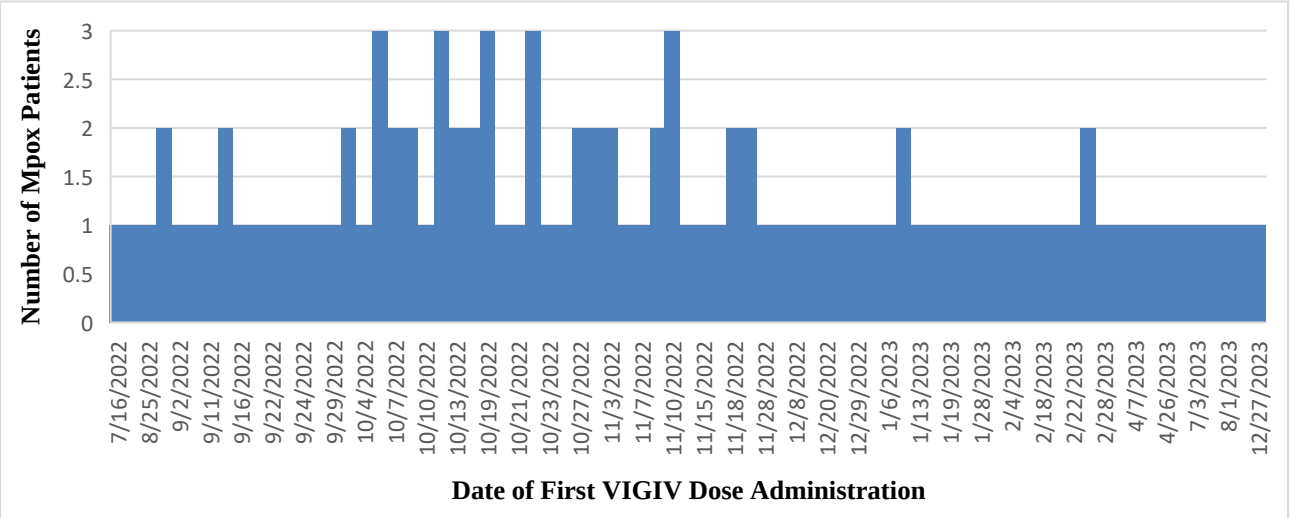
There are published VIGIV clinical use data for vaccinia-related infections [5-7]. The existence of shared serologic cross-reactivity between the OPXVs, and the ability of neutralizing antibodies to one OPXV to partially neutralize the infectivity of other members of the genus OPXV [8], speculates potential clinical benefit by the use of VIGIV for viral neutralization in instances where active replication of an OPXV other than variola and vaccinia is occurring. The fact that VIGIV may provide any amount of protection following variola exposure may presume that VIGIV could have clinically beneficial effect against an OPXV less virulent to humans, including mpox virus. Kempe, et al. reviewed this immune globulin generalized protection that described hyper-immune vaccinia immune globulin would neutralize the smallpox virus and suppress or diminish viremia, thereby suppressing or diminishing infection of skin epithelium [9]. The clinical expression of the disease would thus be modified or aborted, even though infection might still occur.

12.3 Clinical Use of VIGIV Under this Expanded Access IND

A total of 104 patients have been treated with VIGIV under this EA-IND as of January 31, 2024: 2 for treatment of ocular *vaccinia virus* infections, 1 for *vaccinia virus* PEP, 1 for treatment of *Alaskapox* virus infection, 1 for PEP of mpox, and 99 for treatment of mpox.

Cumulative Number of VIGIV-treated Patients during the 2022 U.S. Mpox Outbreak
As of January 31, 2024, 100 patients have received at least one dose of VIGIV under the EA-IND since the mpox outbreak emerged in the U.S. in mid-May 2022 (Figure 1).

Figure 1. Number of VIGIV-treated Mpox Patients by Date of First Dose (n=100)



Of the 100 VIGIV-treated patients, 34 patients received a single VIGIV dose while 66 patients received 2 or more doses (Table 2).

Table 2. Number of VIGIV Dose(s) Administered by Number of Patient(s) (n=100)

No. VIGIV Dose(s)	No. Patient(s)	(%)
1 dose	34	(34%)
2 doses	44	(44%)
3 doses	8	(8%)
4 doses	6	(6%)
5 doses	2	(2%)
6 doses	2	(2%)
7 doses	1	(1%)
8 doses	1	(1%)
9 doses	1	(1%)
10 doses	1	(1%)

As of January 31, 2024, the following adverse events were reported in 6 of the 104 VIGIV-treated patients (6%) based on returned IND forms (Patient Intake, Clinical Outcome, and Adverse Events or Form FDA 3500 MedWatch, and Record of Administration forms) to CDC: headache, rigors, elevated heart rate, fever, rash and eosinophilia, renal dysfunction, and hypotension. Thirty-two patients who were treated with VIGIV expired. While the possibility of VIGIV contributing to serious adverse events cannot be ruled out, none of the deaths were attributed to VIGIV but due to complications from severe mpox infection compounded by advanced HIV, co-infections, and/or other clinical conditions.

13.0 REFERENCES

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