U.S. FOOD & DRUG ADMINISTRATION

Our STN: BL 125678/0

BLA APPROVAL

Bavarian Nordic A/S
Attention: Renee Boerner, PhD
3025 Carrington Mill Boulevard
Morrisville, NC 27560

September 24, 2019

Dear Dr. Boerner,

Please refer to your Biologics License Application (BLA) submitted October, 25, 2018, received October 25, 2018, under section 351(a) of the Public Health Service Act (PHS Act) for Smallpox and Monkeypox Vaccine, Live, Non-replicating.

LICENSING

We are issuing Department of Health and Human Services U.S. License No. 2096 to Bavarian Nordic A/S, Hejreskovvej 10A, 3490 Kvistgaard, Denmark, under the provisions of section 351(a) of the PHS Act controlling the manufacture and sale of biological products. The license authorizes you to introduce or deliver for introduction into interstate commerce those products for which your company has demonstrated compliance with establishment and product standards.

Under this license, you are authorized to manufacture the liquid-frozen suspension of Smallpox and Monkeypox Vaccine, Live, Non-replicating, which is indicated for the prevention of smallpox and monkeypox disease in adults 18 years of age and older determined to be at high risk for smallpox or monkeypox infection.

The review of this product was associated with the following National Clinical Trial (NCT) number(s): NCT01144637, NCT00189943, NCT00316524, NCT00686582, NCT00857493, NCT00316589, NCT00082446, NCT01913353, NCT00189917, NCT00316602, NCT02038881, NCT01668537, NCT00189956, NCT00189904, NCT00565929, NCT00437021, NCT00879762, NCT00914732, NCT01827371, NCT03472014, NCT00189930, NCT00390078.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture Smallpox and Monkeypox Vaccine, Live, Non-replicating drug substance at Bavarian Nordic A/S, Hejreskovvej 10A, 3490 Kvistgaard, Denmark. The final formulated product will be manufactured at IDT Biologika GmbH Am Pharmapark 06861 Dessau-Roßlau, Germany, labeled and packaged at IDT Biologika GmbH Am Pharmapark 06861 Dessau-Roßlau, Germany. You may label your product with the proprietary name JYNNEOS and market it in 0.5 mL single-dose vials.

We did not refer your application to the Vaccines and Related Biological Products Advisory Commitee because our review of information submitted in your BLA, including the clinical study design and trial results, did not raise concerns or controversial issues that would have benefited from an advisory committee discussion.

DATING PERIOD

The dating period for Smallpox and Monkeypox Vaccine, Live, Non-replicating shall be 36 months from the date of manufacture when stored at -25 °C to -15°C and 60 months from the date of manufacture when stored at -60°C to -40°C. The date of manufacture shall be defined as the date of formulation of the final bulk of the drug product. The dating period for your drug substance shall be 36 months when stored at -60°C to -40°C. We have approved the stability protocols in your license application for the purpose of extending the expiration dating period of your drug substance and drug product under 21 CFR 601.12.

FDA LOT RELEASE

Please submit final container samples of the product in final containers together with protocols showing results of all applicable tests. You may not distribute any lots of product until you receive a notification of release from the Director, Center for Biologics Evaluation and Research (CBER).

BIOLOGICAL PRODUCT DEVIATIONS

You must submit reports of biological product deviations under 21 CFR 600.14. You should identify and investigate all manufacturing deviations promptly, including those associated with processing, testing, packaging, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA 3486 to the Director, Office of Compliance and Biologics Quality, at the following address:

Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center
10903 New Hampshire Ave.
WO71-G112
Silver Spring, MD 20993-0002

MANUFACTURING CHANGES

You must submit information to your BLA for our review and written approval under 21 CFR 601.12 for any changes in, including but not limited to, the manufacturing, testing, packaging or labeling of Smallpox and Monkeypox vaccine, live, non-replicating, or in the manufacturing facilities.

LABELING

We hereby approve the draft package insert labeling submitted under amendment 60, dated Septmeber 20, 2019, and the draft carton labeling submitted under amendment 61, dated September 24, 2019, and container labeling submitted under amendment 59, dated September 20, 2019.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the final content of labeling (21 CFR 601.14) in Structured Product Labeling (SPL) format via the FDA automated drug registration and listing system, (eLIST) as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As* at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

PACKAGE AND CONTAINER LABELS

Please electronically submit final printed package and container labels that are identical to the package and container labels submitted on September 24, 2019 and September 20, 2019, respectively, according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/providing-regulatory-submissions-electronic-format-certain-human-pharmaceutical-product-applications.

All final labeling should be submitted as Product Correspondence to this BLA STN 125678 at the time of use (prior to marketing) and include implementation information on Form FDA 356h.

ADVERTISING AND PROMOTIONAL LABELING

You may submit two draft copies of the proposed introductory advertising and promotional labeling with Form FDA 2253 to the Advertising and Promotional Labeling Branch at the following address:

Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center
10903 New Hampshire Ave.
WO71-G112
Silver Spring, MD 20993-0002

You must submit copies of your final advertising and promotional labeling at the time of initial dissemination or publication, accompanied by Form FDA 2253 (21 CFR 601.12(f)(4)).

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have substantial evidence or substantial clinical experience to support such claims (21 CFR 202.1(e)(6)).

ADVERSE EVENT REPORTING

You must submit adverse experience reports in accordance with the adverse experience reporting requirements for licensed biological products (21 CFR 600.80), and you must submit distribution reports as described in 21 CFR 600.81. For information on adverse experience reporting, please refer to the guidance for industry *Providing Submissions in Electronic Format —Postmarketing Safety Reports for Vaccines* at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/providing-submissions-electronic-format-postmarketing-safety-reports-vaccines. For information on distribution reporting, please refer to the guidance for industry *Electronic Submission of Lot Distribution Reports* at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Post-MarketActivities/LotReleases/ucm061966.htm.

MATERIAL THREAT MEDICAL COUNTERMEASURE PRIORITY REVIEW VOUCHER

We also inform you that you have been granted a material threat medical countermeasure priority review voucher, as provided under section 565A of the FDCA. This priority review voucher (PRV) has been assigned a tracking number, PRV BLA 125678. All correspondences related to this voucher should refer to this tracking number.

This voucher entitles you to designate a single human drug application submitted under section 505(b)(1) of the FDCA or a single biologic application submitted under section 351 of the Public Health Service Act as qualifying for a priority review. Such an application would not have to meet any other requirements for a priority review. The list below describes the sponsor responsibilities and the parameters for using and transferring a material threat medical countermeasure priority review voucher.

- The sponsor who redeems the priority review voucher must notify FDA of its intent to submit an application with a priority review voucher at least 90 days before submission of the application and must include the date the sponsor intends to submit the application. This notification should be prominently marked, "**Notification of Intent to Submit an Application with a Material Threat Medical Countermeasure Priority Review Voucher.**"

- This priority review voucher may be transferred, including by sale, by you to another sponsor of a human drug or biologic application. If the PRV is transferred, the sponsor to whom the PRV has been transferred should include a copy of this letter (which will be posted on our website as are all approval letters) and proof that the PRV was transferred. When redeeming this PRV, you should refer to this letter as an official record of the voucher.

For additional information regarding the priority review voucher, see FDA's draft guidance, *Material Threat Medical Countermeasure Priority Review Voucher Program* at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/material-threat-medical-countermeasure-priority-review-vouchers-draft-guidance-industry. This guidance when finalized, will represent the current thinking of FDA on this topic.

PEDIATRIC REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for this application because the necessary studies are impossible or highly impracticable since smallpox has been eradicated and pediatric populations at risk of monkeypox are limited to small and dispersed communities living in areas lacking sufficient infrastructure and stability to support clinical trials.

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biological products qualify for inclusion for three years after approval.

Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST APPROVAL FEEDBACK MEETING

New biological products qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, please contact the Regulatory Project Manager for this application.

Sincerely,

Mary A. Malarkey -S
Digitally signed by Mary A. Malarkey -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300054353, cn=Mary A. Malarkey -S
Date: 2019.09.24 12:14:28 -04'00'

Mary Malarkey
Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research

Marion F. Gruber -S
Digitally signed by Marion F. Gruber -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300077111, cn=Marion F. Gruber -S
Date: 2019.09.24 12:25:35 -04'00'

Marion Gruber, PhD
Director
Office of Vaccines Research and Review
Center for Biologics Evaluation and Research

Danish Medicines Agency

CERTIFICATE NUMBER : ***DK H 10000249***

CERTIFICATE OF GMP COMPLIANCE OF A MANUFACTURER [1, 2]

Part 1

Issued following an inspection in accordance with :
Art. 111(5) of Directive 2001/83/EC as amended

The competent authority of Denmark confirms the following:
The manufacturer :***Bavarian Nordic A/S***
Site address :***Hejreskovvej 10 A, Kvistgård, 3490, Denmark***

Has been inspected under the national inspection programme in connection with manufacturing authorisation no. ***100692*** in accordance with Art. 40 of Directive 2001/83/EC .

From the knowledge gained during inspection of this manufacturer, the latest of which was conducted on ***2021-06-29*** , it is considered that it complies with :

- The principles and guidelines of Good Manufacturing Practice laid down in Directive 2003/94/EC [3]

This certificate reflects the status of the manufacturing site at the time of the inspection noted above and should not be relied upon to reflect the compliance status if more than three years have elapsed since the date of that inspection. However, this period of validity may be reduced or extended using regulatory risk management principles by an entry in the Restrictions or Clarifying remarks field. This certificate is valid only when presented with all pages and both Parts 1 and 2. The authenticity of this certificate may be verified in EudraGMDP. If it does not appear, please contact the issuing authority.

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[1] *The certificate referred to in paragraph 111(5) of Directive 2001/83/EC and 80(5) of Directive 2001/82/EC, shall also be required for imports coming from third countries into a Member State.*

[2] *Guidance on the interpretation of this template can be found in the Help menu of EudraGMDP database.*

[3] *These requirements fulfil the GMP recommendations of WHO.*

Part 2

Human Medicinal Products

1 MANUFACTURING OPERATIONS	
1.1	**Sterile products**
	1.1.1 Aseptically prepared (processing operations for the following dosage forms) 1.1.1.2 Lyophilisates 1.1.1.4 Small volume liquids
	1.1.3 Batch certification
1.3	**Biological medicinal products (list of product types)**
	1.3.1 Biological medicinal products (list of product types) 1.3.1.2 Immunological products
	1.3.2 Batch Certification (list of product types) 1.3.2.2 Immunological products
1.6	**Quality control testing**
	1.6.1 Microbiological: sterility *1.6.2 Microbiological: non-sterility* *1.6.3 Chemical/Physical* *1.6.4 Biological*

2021-08-16

Name and signature of the authorised person of the Competent Authority of

Mr. Poul Vibholm Petersen
Danish Medicines Agency
Tel:***+45 2095 0567***
Fax:

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use JYNNEOS safely and effectively. See full prescribing information for JYNNEOS.

JYNNEOS (Smallpox and Monkeypox Vaccine, Live, Non-replicating) suspension for subcutaneous injection
Initial U.S. Approval: 2019

----------INDICATIONS AND USAGE----------
JYNNEOS is a vaccine indicated for prevention of smallpox and monkeypox disease in adults 18 years of age and older determined to be at high risk for smallpox or monkeypox infection. (1)

----------DOSAGE AND ADMINISTRATION----------
For subcutaneous injection only.
Administer two doses (0.5 mL each) 4 weeks apart. (2.1, 2.2)

----------DOSAGE FORMS AND STRENGTHS----------
Suspension for injection. Each dose (0.5 mL) is supplied in a single-dose vial. (3)

----------ADVERSE REACTIONS----------
- In smallpox vaccine-naïve healthy adults, the most common (> 10%) solicited injection site reactions were pain (84.9%), redness (60.8%), swelling (51.6%), induration (45.4%), and itching (43.1%); the most common solicited systemic adverse reactions were muscle pain (42.8%), headache (34.8%), fatigue (30.4%), nausea (17.3%) and chills (10.4%). (6.1)
- In healthy adults previously vaccinated with a smallpox vaccine, the most common (> 10%) solicited injection site reactions were redness (80.9%), pain (79.5%), induration (70.4%), swelling (67.2%), and itching (32.0%); the most common solicited systemic adverse reactions were fatigue (33.5%), headache (27.6%), and muscle pain (21.5%). (6.1)
- The frequencies of solicited local and systemic adverse reactions among adults with HIV-infection and adults with atopic dermatitis were generally similar to those observed in healthy adults. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Bavarian Nordic at toll-free phone 1-800-675-9596 or VAERS at 1-800-822-7967 or www.vaers.hhs.gov.

See 17 for PATIENT COUNSELING INFORMATION

Revised: 09/2019

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

For subcutaneous injection only.

2.1 Dose and Schedule

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

2.2 Preparation and Administration

Allow the vaccine to thaw and reach room temperature before use. Once thawed, the vaccine may be kept at +2°C to +8°C (+36°F to +46°F) for 12 hours. Do not refreeze.

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

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

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

3 DOSAGE FORMS AND STRENGTHS

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

5 WARNINGS AND PRECAUTIONS

5.1 Severe Allergic Reactions

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

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

5.2 Altered Immunocompetence

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

5.3 Limitations of Vaccine Effectiveness

Vaccination with JYNNEOS may not protect all recipients.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

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

The overall clinical trial program included 22 studies and a total of 7,859 individuals 18 through 80 years of age who received at least 1 dose of JYNNEOS (7,093 smallpox vaccine-naïve and 766 smallpox vaccine-experienced individuals).

Solicited Adverse Reactions

Solicited Adverse Reactions in Smallpox Vaccine-Naïve Individuals:

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

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

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

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

Reaction	JYNNEOS N=2943 %	Placebo N=980 %
Local (Injection site)	--	--
Pain	84.9	19.1
Pain, Grade 3[a]	7.4	1.0
Redness	60.8	17.7
Redness ≥ 100 mm	1.5	0.0
Swelling	51.6	5.6
Swelling ≥ 100 mm	0.8	0.0
Induration	45.4	4.6
Induration ≥ 100 mm	0.3	0.0
Itching	43.1	11.7
Itching, Grade 3[b]	1.6	0.2
Systemic	**--**	**--**
Muscle Pain	42.8	17.6
Muscle Pain, Grade 3[b]	2.6	0.7
Headache	34.8	25.6
Headache, Grade 3[b]	2.4	2.1
Fatigue	30.4	20.5
Fatigue, Grade 3[b]	3.0	1.3
Nausea	17.3	13.1
Nausea, Grade 3[b]	1.5	1.2
Chills	10.4	5.8
Chills, Grade 3[b]	1.0	0.3
Fever[c]	1.7	0.9
Fever, Grade ≥ 3[c]	0.2	0.0

[x] NCT01144637

[a] Grade 3 pain defined as spontaneously painful

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

[c] Fever defined as oral temperature ≥ 100.4°F (≥ 38°C), Grade ≥ 3 fever defined as ≥ 102.2°F (≥ 39.0°C)

N=number of subjects

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

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

Three studies (Study 2, Study 3, and Study 4, [2-4]) conducted in the US and Germany evaluated the safety of JYNNEOS in 409 persons previously vaccinated with a smallpox vaccine who received one or two doses of JYNNEOS (mean age 39 years, range 20-80 years; 59% women; 98.8% white/Caucasian; 0.7% Asian; 0.5% black/African American). Subjects were monitored for local and systemic adverse reactions using diary cards for an 8-day period starting on the day of each

vaccination. Across all three studies, solicited local adverse reactions reported following any dose of JYNNEOS were redness (80.9%), pain (79.5%), induration (70.4%), swelling (67.2%), and itching (32.0%) at the injection site; solicited systemic adverse reactions reported following any dose of JYNNEOS were fatigue (33.5%), headache (27.6%), muscle pain (21.5%), nausea (9.8%), chills (0.7%), and fever (0.5%).

Solicited Adverse Reactions in HIV-infected Individuals:

The safety of JYNNEOS in HIV-infected individuals was evaluated in Study 5 [5], an open label trial conducted in the US that included 351 HIV-infected smallpox vaccine-naïve subjects, 131 HIV--infected subjects who previously received smallpox vaccine, 88 non-HIV-infected smallpox vaccine-naïve subjects and 9 non-HIV-infected subjects who had previously received a smallpox vaccine. The racial/ethnic and gender compositions of HIV-infected smallpox vaccine-naïve subjects and those who had previously received smallpox vaccine were similar and overall were 17.0% women; 45.8% white/Caucasian; 0.4% Asian; 33.2% black/African American; 19.0% Hispanic/Latino ethnicity; the HIV-infected smallpox vaccine-naïve group tended to be younger (mean age 37 years) compared to those who had previously received a smallpox vaccine (mean age 45 years). Subjects had CD4 counts ≥ 200 and ≤ 750 cells/μL at study entry.

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

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

Solicited Adverse Reactions in Individuals with Atopic Dermatitis:

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

Serious Adverse Events

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

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

Cardiac Adverse Events of Special Interest

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

The numbers of JYNNEOS and placebo recipients, respectively, with troponin-I data were: baseline level (6,376 and 1,203); level two weeks after first dose (6,279 and 1,166); level two weeks after second dose (1,683 and 193); unscheduled visit, including for clinical evaluation of suspected cardiac adverse events (500 and 60).

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

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

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically

recognized pregnancies is 2% to 4% and 15% to 20%, respectively. Available human data on JYNNEOS administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy.

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

Data

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

8.2 Lactation

Risk Summary

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

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

8.4 Pediatric Use

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

8.5 Geriatric Use

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

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

11 DESCRIPTION

When thawed, JYNNEOS (Smallpox and Monkeypox Vaccine, Live, Non-replicating) is a milky, light yellow to pale white colored suspension for subcutaneous injection.

JYNNEOS is a live vaccine produced from the strain Modified Vaccinia Ankara-Bavarian Nordic (MVA-BN), an attenuated, non-replicating orthopoxvirus. MVA-BN is grown in primary Chicken Embryo Fibroblast (CEF) cells suspended in a serum-free medium containing no material of direct animal origin, harvested from the CEF cells, purified and concentrated by several Tangential Flow Filtration (TFF) steps including benzonase digestion. Each 0.5 mL dose is formulated to contain 0.5×10^8 to 3.95×10^8 infectious units of MVA-BN live virus in 10 mM Tris (tromethamine), 140 mM sodium chloride at pH 7.7. Each 0.5 mL dose may contain residual amounts of host-cell DNA (≤ 20 mcg), protein (≤ 500 mcg), benzonase (≤ 0.0025 mcg), and gentamicin (≤ 0.1 mcg).

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

JYNNEOS has not been evaluated for carcinogenic or mutagenic potential, or for impairment of male fertility in animals. Developmental toxicity studies conducted in rats and rabbits vaccinated with JYNNEOS revealed no evidence of impaired female fertility *[see Use in Specific Populations (8.1)]*.

13.2 Animal Toxicology and/or Pharmacology

The efficacy of JYNNEOS to protect cynomolgus macaques (*Macaca fascicularis*) against a monkeypox virus (MPXV) challenge was evaluated in several studies. Animals were administered

Tris-Buffered Saline (placebo) or JYNNEOS (1 x 10^8 $TCID_{50}$) sub-cutaneously on day 0 and day 28. On day 63, animals were challenged with MPXV delivered by aerosol (3 x 10^5 pfu), intravenous (5 x 10^7 pfu) or intratracheal (5 x 10^6 pfu) route. Across all studies, 80-100% of JYNNEOS-vaccinated animals survived compared to 0-40% of control animals.

14 CLINICAL STUDIES

14.1 Vaccine Effectiveness

Vaccine effectiveness against smallpox was inferred by comparing the immunogenicity of JYNNEOS to a licensed smallpox vaccine (ACAM2000) based on a Plaque Reduction Neutralization Test (PRNT) using the Western Reserve strain of vaccinia virus and was supported by efficacy data from animal challenge studies. *[see Nonclinical Toxicology (13.2)]*

Vaccine effectiveness against monkeypox was inferred from the immunogenicity of JYNNEOS in a clinical study and from efficacy data from animal challenge studies. *[see Nonclinical Toxicology (13.2)]*

14.2 Immunogenicity

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

The primary immunogenicity endpoint was geometric mean titer (GMT) of vaccinia neutralizing antibodies assessed by PRNT at “peak visits” defined as two weeks after the second dose of JYNNEOS and four weeks after the single dose of ACAM2000. Analyses of antibody responses were performed in the per-protocol immunogenicity (PPI) population, consisting of individuals who received all vaccinations and completed all visits up until the peak visit without major protocol violations pertaining to immunogenicity assessments. Table 2 presents the pre-vaccination and “peak visit” PRNT GMTs from Study 7.

Table 2: Comparison of Vaccinia-Neutralizing Antibody Responses Following Vaccination with JYNNEOS or ACAM2000 in Healthy Smallpox Vaccine-Naïve Adults 18 through 42 Years of Age, Study 7[x], Per Protocol Set for Immunogenicity[y]

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

[x] NCT01913353

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

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

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

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

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

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

15 REFERENCES

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

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Package of 20 single-dose vials (Package NDC number: 50632-001-02; Vial NDC number: 50632-001-01)

16.2 Storage Conditions

Keep frozen at -25°C to -15°C (-13°F to +5°F).
Store in the original package to protect from light.
Do not re-freeze a vial once it has been thawed.
Once thawed, the vaccine may be kept at +2°C to +8°C (+36°F to +46°F) for 12 hours.
Do not use the vaccine after the expiration date shown on the vial label.

17 PATIENT COUNSELING INFORMATION

- Inform vaccine recipient of the potential benefits and risks of vaccination with JYNNEOS.
- Inform vaccine recipient of the importance of completing the two dose vaccination series.
- Advise vaccine recipient to report any adverse events to their healthcare provider or to the Vaccine Adverse Event Reporting System at 1-800-822-7967 and www.vaers.hhs.gov.

Manufactured by:
Bavarian Nordic A/S
Hejreskovvej 10a
DK-3490 Kvistgaard
Denmark

Summary Information to support Request for supply of IMVANEX for EU

24 May 2022

IMVANEX

Suspension for injection

Smallpox Vaccine

EU/1/13/855/001

1 Introduction

An informal meeting on European Monkeypox situation and IMVANEX was held with EMA Emergency Task Force (ETF) on Friday 20 May 2022. Participants were from EMA, ETF, HERA and Bavarian Nordic (BN).

BN was asked to outline the overall supply of IMVANEX to EMA /EFT.

The topic of expansion of indication of IMVANEX to include Monkeypox indication in addition to the existing smallpox indication will be handled in close dialogue with EMA/EFT.

BN informed the audience that a type II variation (grouping complex type II variation) to change the existing Drug Product (DP) manufacturing site from IDT to Bavarian Nordic in Denmark (BN-K) will be submitted to Imvanex marketing authorization in the near future. A GMP inspection already took place at the Bavarian Nordic manufacturing site in Denmark. Valid manufacturing authorization and GMP certificate is available. BN-K was already approved as a DP manufacturing site by Health Canada.

EMA clarified that it may be possible to expedite the review of this upcoming variation in order to ensure faster release of DP manufactured at BN-K. BN has discussed the planned variation submission timeline for the new DP manufacturing site with the quality assessors at the Rapporteurs (Paul Ehrlich Institute).

2 Differences of Product compared to current approved EU Dossier

To fulfill the request of product delivery on short notice from the different European Authorities BN is exploring the use of DP batches manufactured for US (JYNNEOS –smallpox and monkeypox vaccine). The relevant DP batches were manufactured at BN-K in connection with the DP manufacturing site transfer from current approved manufacturer (IDT) to BN-K in 2021.

The BN-K facility is approved by the local authority (DKMA). Valid manufacturing authorization and GMP certificate are available.

The JYNNEOS DP batches in question were part of the process performance qualification (PPQ) campaign used for final validation of the manufacturing site Bavarian Nordic (Kvistgaard, Denmark) or manufactured subsequently as routine commercial batches.

The DP batches are using Drug Substance (DS) batches manufactured in 2016/2017.

2.1 Drug Substance

BN has manufactured MVA-BN DS batches for stockpiling since 2016. Over the years, the DS process was optimized and revalidated in several revalidation campaigns. Additionally, there were changes in the test program, analytical procedures, test laboratories, and/or acceptance criteria applied for the different DS manufacturing campaigns. Comparability was demonstrated for each campaign.

The following table provides a high-level overview of the differences in process and controls from 2016 to current approved process.

Table 1 Process Variants from 2016 to 2020 (current approved process)

Parameter	**2016**	**2017**	**2019/2020 (current approved process in EU)**
DS process	3 stream CEF preparation Virus growth for 40-44 h Use of antibiotics (gentamicin)	3 stream CEF preparation Prolonged virus growth (58-66 h) Use of antibiotics (gentamicin)	2 stream CEF preparation Prolonged virus growth (58-66 h) Use of antibiotics (increased gentamicin concentration and ciprofloxacin)
Test program	Routine US test program does not include host cell protein and genomic quantification	Routine US test program does not include host cell protein and genomic quantification	Routine US test program does not include host cell protein and genomic quantification Additional testing of DS for identity and ciprofloxacin
Methods		Change in method for virus titer assay from TCID50 to flow cytometer	Change in method for gentamicin assay from cylinder plate to ELISA
Test Laboratory			Change in test lab for Q-PERT, Identity and host cell DNA from BN-K to BN-M
Acceptance Criteria DS		Change in acceptance criteria for host cell DNA from ≤ 100 to ≤ 40 µg/mL	Change in acceptance criteria for endotoxins from ≤ 15 to ≤ 5 EU/mL Change in acceptance criteria for gentamicin from ≤ 150 to ≤ 325 ng/mL
Acceptance Criteria intermediates		Change in acceptance criteria for host cell DNA and virus titer at intermediates	Change in acceptance criteria for cell count at intermediates
DS Shelf life	82 months in US 60 months in EU/CAN/UK	82 months in US 60 months in EU/CAN/UK	82 months in US 60 months in EU/CAN/UK

In summary, compared to the current approved manufacturing process and controls in EU, the following differences exist:

- Process: DS manufactured with a 3 stream CEF preparation process, with/or without prolonged incubation, use of gentamicin only
- Test program:
  - Routine US test program does not include host cell protein and genomic quantification
  - DS batches were not tested for identity yet
  - DS is not tested for ciprofloxacin (as process did not include ciprofloxacin yet)
- Different specifications for host cell DNA, bacterial endotoxins and gentamicin
- Different test labs for Q-PERT, identity and host cell DNA (BN-K / BN-M)
- Different test method for virus titer (comparability shown)
- Different DS shelf life in US (82 months) and EU/UK (60 months)
  - The DS batches used for filling of the PPQ DP batches were at the time of use not older than 60 months
  - The DS batches used for filling of subsequent commercial DP batches are at the time of filling up to 6 years.

An overview of the DS specifications in US from 2016 and current approved specifications in EU is shown in the following table.

Table 2 Drug Substance Release Test Methods and Specifications

Test Parameter	**2016 – US Specifications**		**2022 – Current approved Specifications in EU**	
	Method	**Specification**	**Method**	**Specification**
Appearance	Visual inspection Ph. Eur. 2.2.1 Ph. Eur. 2.2.2	Transparency/turbidity: Clear to milky Color: Light yellow State: Suspension	Visual inspection Ph. Eur. 2.2.1 Ph. Eur. 2.2.2	Transparency/turbidity: Clear to milky Color: Light yellow State: Suspension
pH	Potentiometric method USP<791>; Ph. Eur. 2.2.3	7.7 ± 0.2 (7.5-7.9)	Potentiometric method USP<791>; Ph. Eur. 2.2.3	7.7 ± 0.2 (7.5-7.9)
Bacterial endotoxins	Gel-clot test USP<85>; Ph. Eur. 2.6.14	≤ 15 EU/mL	Gel-clot test USP<85>; Ph. Eur. 2.6.14	≤ 5 EU/mL

Test Parameter	2016 – US Specifications		2022 – Current approved Specifications in EU	
	Method	**Specification**	**Method**	**Specification**
Sterility	Direct inoculation USP <71>; Ph. Eur. 2.6.1	No growth of bacteria and fungi detected	Direct inoculation USP <71>; Ph. Eur. 2.6.1	No growth of bacteria and fungi detected
Infectious virus titer	$TCID_{50}$	Release ≥ 8.7 log10 $TCID_{50}$/mL Shelf-life ≥ 8.4 log10 $TCID_{50}$/mL	Flow cytometry	Release ≥ 8.7 log10 Inf. U/mL Shelf-life ≥ 8.4 log10 Inf. U/mL
Genomic quantification	Not applicable for US batches	Not applicable for US batches	Quantitative PCR	Report results (molecules/mL)
Ratio (infectious virus titer/genomic quantification)	Not applicable for US batches	Not applicable for US batches	Calculation	Report results
Identity	PCR	Identity confirmed	PCR	Identity confirmed
Total protein	BCA assay USP <1057>; Ph. Eur. 2.5.33	≤ 1.30 mg/mL	BCA assay USP <1057>; Ph. Eur. 2.5.33	≤ 1.30 mg/mL
Host cell (CEF) protein	Not applicable for US batches	Not applicable for US batches	ELISA	≤ 200 µg/mL
Host cell DNA	Quantitative PCR	≤ 100 µg/mL	Quantitative PCR	≤ 40 µg/mL
Benzonase	ELISA	≤ 5 ng/mL	ELISA	≤ 5 ng/mL
Gentamicin	Cylinder plate method	≤ 150 ng/mL	ELISA	≤ 325 ng/mL
Ciprofloxacin	N/A	N/A	ELISA	≤ 10 ng/mL

An overview of approved DS shelf life is provided in the following table.

Table 3 Overview of approved DS Shelf life in different Markets

Storage Temperature	Market	Approved Shelf Life
-50°C ± 10°C	US	82 months
	EU/UK	60 months*
	CAN	60 months*

* Data available to support a shelf life extension to 82 months

2.2 Drug Product

The DP batches in question were part of the process performance qualification (PPQ) campaign used for final validation of the manufacturing site Bavarian Nordic (Kvistgaard, Denmark). The DP batches were manufactured for US under a BARDA contract.

The new DP manufacturing site (BN-K) is not yet approved in Europe nor in US, but it is already approved by Health Canada.

As part of the manufacturing site transfer from current approved manufacturing site (IDT) to BN-K, the following changes were introduced:

- BN-K as drug product manufacturer
- Minor process changes
  - Use of more DS bags without changing the target batch size
  - Thawing of DS at room temperature and 5°C
  - Minor adjustment of formulation process and hold times (all validated)
- New supplier of the formulation buffer (excipients). No change in composition
- Minor modifications to the container closure system
- Minor changes to the test program:
  - An additional test for osmolality was added for drug product release.
  - The test method for bacterial endotoxins was changed from kinetic-turbidimetric method to gel-clot method. Both methods are pharmacopoeia methods.

There are no differences in test methods between JYNNEOS in US and IMVANEX in EU. In relation to the approved specifications, the following differences exist:

- Different specification for total protein: ≤ 1.00 mg/mL in US and 0.50 mg/mL in EU/UK (it should be noted that the PPQ DP batches complied with the tighter EU specifications)
- Different shelf life at -20°C: 3 years in US and 2 years in EU/UK

An overview of the DP specifications in US and EU is shown in the following table.

Table 4 Specifications for Drug Product Release Testing

Test	Analytical Procedure	Acceptance Criteria US	Acceptance Criteria EU
Sterility	Membrane filtration USP <71>, Ph. Eur. 2.6.1	No growth of bacteria and fungi detected	No growth of bacteria and fungi detected
Appearance	Visual inspection Ph. Eur. 2.2.1, Ph. Eur. 2.2.2 and Ph. Eur. 2.9.20	Transparency/Turbidity: Milky Color: Light yellow to pale white State: Suspension Particles: Free from visible extraneous particles Closure: Completely closed vial with no external damage. Caps firmly and evenly attached	Transparency/Turbidity: Milky Color: Light yellow to pale white State: Suspension Particles: Free from visible extraneous particles Closure: Completely closed vial with no external damage. Caps firmly and evenly attached
Extractable volume	Ph. Eur. 2.9.17 USP <697>	≥ 0.50 mL	≥ 0.50 mL
pH	Potentiometric USP <791>, Ph. Eur. 2.2.3	7.5–7.9	7.5–7.9
Bacterial endotoxins	Gel clot test USP <85>, Ph. Eur. 2.6.14	≤ 5 EU/mL	≤ 5 EU/mL
Osmolality	Freezing point depression USP <785>, Ph. Eur. 2.2.35	260-300 mOsmol/kg	260-300 mOsmol/kg
Identity	PCR	Identity confirmed	Identity confirmed
Infectious virus titer	Flow cytometry	8.4–8.9 log10 Inf. U/mL*	8.4–8.9 log10 Inf. U/mL*
Total protein	BCA assay USP <1057>, Ph. Eur. 2.5.33	≤ 1.00 mg/mL	≤ 0.50 mg/mL

* For information, corresponds to $2.5x10^8$-$7.9x10^8$ Inf. U/mL

Full overview of approved DP shelf life is provided in the following table.

Table 5 Overview of approved DP Shelf Life in different Markets

Storage Temperature	Market	Approved Shelf Life
-20°C ± 5°C	US	3 years
	EU/UK	2 years*
	CAN	2 years*
-50°C ± 10°C	US	5 years
	EU/UK	5 years
	CAN	2 years
-80°C ± 10°C	US	N/A

Storage Temperature	Market	Approved Shelf Life
	EU/UK	5 years
	CAN	9 years

* Data available to support a shelf life extension to 3 years

In summary, for the DP batches in question, the following applies

DP Manufacturing Site

Manufacturer, Name and Address	Responsibility
Bavarian Nordic A/S Hejreskovvej 10A 3490 Kvistgaard Denmark	Drug product manufacture, labelling and packaging Drug product storage Batch release of drug product

DP Testing Sites

Testing Sites, Name and Address	Responsibility
Bavarian Nordic A/S Hejreskovvej 10A 3490 Kvistgaard Denmark	Drug product, process intermediate and stability testing: Appearance, pH, osmolality, extractable volume, total protein, bacterial endotoxins, bioburden
Bavarian Nordic GmbH Fraunhoferstraße 13 82152 Martinsried Germany	Drug product and stability testing: Identity Infectious virus titer
SGS Institut Fresenius GmbH Im Maisel 14 65232 Taunusstein Germany	Drug product and stability testing: Sterility

Shipment

Shipment of DP will be performed at ≤-15°C.

2.3 Indication

An overview of the current indication in US and EU is provided in the following table.

Table 6 Indication

JYNNEOS – US BRAND NAME	IMVANEX - EU BRAND NAME
Prevention of smallpox and **monkeypox** disease in adults 18 years of age and older determined to be at high risk for smallpox or monkeypox infection.	Active immunization against smallpox in adults.
Indication approved September 2019	Indication approved in July-2013

3 Exemptions

Exemptions to be addressed

- Exemption for manufacture of DP at BNK
- Exemption for minor DS specification differences
  - Batches not tested for HCP and genomic quantification and other minor specification differences (see above)
- Exemption for indication (monkeypox) off-label use
- Exemption for delivering with US JYNNEOS label
  - US label text in English language
  - -20°C storage temperature on label
  - 3 year shelf life at -20°C storage
- Exemption of OMCL release testing, release based on CoA