A single-arm study to evaluate the immunogenicity and safety of smallpox vaccine as vaccination to monkeypox in Japanese healthy adults (MKP-3 study)

Investigator: Mugen Ujiie M.D, M.T.M, Ph.D.

Disease Control and Prevention Center
National Center for Global Health and Medicine (NCGM), Japan

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A Freeze-dried cell culture Smallpox Vaccine LC16 (LC16m8) manufactured by KM Biologics

- LC16 is a 3rd generation, live attenuated vaccine containing live vaccinia virus (LC16m8 strain) used to prevent smallpox (**market authorized for all ages in 1975 in Japan** / licensed under the emergency investigational new drug program in the U.S.).
- Since 1976, the Japanese government has discontinued the national vaccination program for smallpox.
- Ministry of Health, Labour and Welfare, Japan (MHLW) authorized LC16 for additional prevention from monkeypox (MPX) on 2nd August 2022.
- According to the U.S. CDC, vaccination with the smallpox vaccine within four days after exposure to the monkeypox virus (MPXV) has a protective effect against infection, whereas vaccination within 5-14 days after exposure has a protective impact on the severity.
- It is essential to estimate the protective effect against the MPXV.

Past reports of LC16' efficacy against MPX

- *J Infect Dis.* 2011; 204: 1395-402
- https://research-er.jp/projects/view/1044205 (in Japanese)
- *J Infect Dis.* 2011; 203: 1043-53
- *J Virol.* 2006; 80: 5179-88
- *Jpn J Infect Dis.* 2017; 70: 408-15

Our Study outline

- **Study aim**: to investigate the immunogenicity and safety of LC16 vaccination for healthy adults against MPXV.
- **Study type**: Interventional study
- **Design** : An open single-arm study
- **Study site**: Single center (NCGM)
- **Participants**: Fifty healthy adults (over 20 year old)
- **Study Drug**: Smallpox Vaccine LC16m8
- **Primary outcome**: The proportion of participants with neutralizing antibody seroconversion against MPXV 28 days after vaccination
- **Observation period:** Up to168 days

Participants selection

<Inclusion criteria>

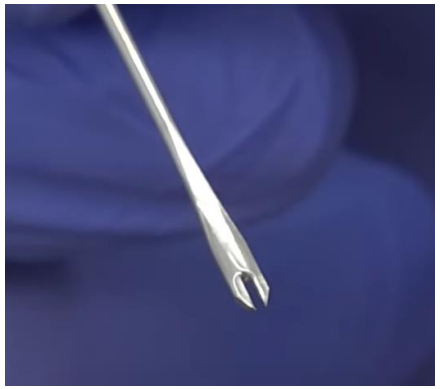
1) Persons who have given written consent to participate in the research in person
2) Men and women who are at least 20 years of age at the time consent is obtained
3) Persons who are expected to work for patients with monkeypox in NCGM
4) Persons who have developed neither monkeypox nor smallpox
5) Persons who have given written consent to participate in the research in person

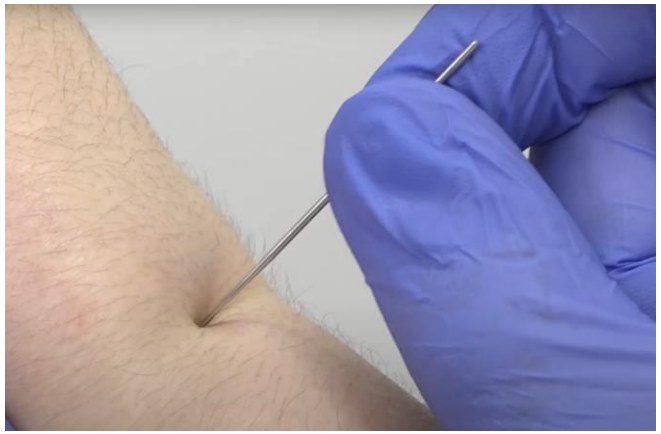
<Exclusion criteria>

1) Persons with diseases that are abnormal in immune function
2) Persons using corticosteroids or immunosuppressive drugs (cyclosporine, tacrolimus, azathioprine, biological drugs) that affect the immune system
3) Persons with an apparent history of anaphylaxis caused by components of the smallpox vaccine (gelatin and streptomycin etc.)
4) Patients with apparent fever
5) Persons who are suffering from a severe acute disease
6) Those who are pregnant
7) Persons suffering from chronic skin disease which may be exacerbated by immunization.
8) Persons who are in an unacceptable condition to be immunized.
9) Persons whom the principal investigator judges inappropriate for inclusion in the study.

Study drug administration

- Dissolve the test drug (smallpox vaccine) in 0.5 mL of the attached solvent (20 vol% glycerylated water for injection) and inoculate 0.01 mL into the skin of upper arm with a bifurcated needle (One vial is available for more than 50 persons' administration).
- The number of compressions at the site of vaccination is 5 for the first vaccination and 10 for the other vaccinations (the number of compressions with bifurcated needle was changed to 15, regardless of vaccination history on 2nd August, 2022).
- MHLW provided the study drug.





Video Guidance for vaccination: https://youtu.be/DTqUUTvRc7Q

Study outcome

Primary outcome： The proportion of participants with neutralizing antibody seroconversion against MPXV 28 days after vaccination

Secondary outcome：

1) The proportion of participants with neutralizing antibody seroconversion against MPXV at 14 and 168 days after vaccination
2) The proportion of participants with neutralizing antibody seroconversion against vaccinia virus (VACV) at 14, 28, and 168 days after vaccination
3) The proportion of participants who developed significant skin reactions after 14 days of vaccination
4) The proportion of participants who developed monkeypox within 168 days after vaccination
5) Safety issues

Study timeline

		IC	Inoculation	Observation period after vaccination						Out of appointment	Time of discontinuation
Day			0	1～13	14	15～27	28	29～167	168		
Visit			1		2		3		4		
Pre-inoculation checks	Qualification	X									
	Obtaining consent	X									
	Subject enrollment	X									
	Confirmation of Subject Background	X									
	To review concomitant medications	X									
	Vaccination		X								
Blood collection	Evaluation of their immunogenicity		X		X		X		X		
Subject Evaluation (subject diary)	Body temperature		X	X	X					Xa)	Xa)
	Chills		X	X	X					Xa)	Xa)
	Headache		X	X	X					Xa)	Xa)
	Fatigue and malaise		X	X	X					Xa)	Xa)
	Arthralgia		X	X	X					Xa)	Xa)
	Myalgia		X	X	X					Xa)	Xa)
	Skin rash		X	X	X					Xa)	Xa)
	Vomiting		X	X	X					Xa)	Xa)
	Diarrhoea		X	X	X					Xa)	Xa)
	Lymphadenopathy		X	X	X					Xa)	Xa)
	Injection site pain		X	X	X					Xa)	Xa)
	Injection site redness		X	X	X					Xa)	Xa)
	Injection site swelling		X	X	X					Xa)	Xa)
	Injection site induration		X	X	X					Xa)	Xa)
Physician evaluation	Examination		X		X		X		X	Xa)	Xa)
	Any local reaction on injection site (Zenkan).				X					Xb)	Xb)
Adverse events c)				←	—	—	—	—	→		
Diseases affecting immunity and concomitant medications				←	—	—	—	—	→		
History of contact with monkeypox and smallpox patients and onset of monkeypox				←	—	—	—	—	→		

a) Up to Visit3. b)10 days to 15 days post-vaccination c) All adverse events until Visit3 and thereafter only serious adverse events

Limitation of concomitant drugs and therapies

- Study participants should avoid any administration of other vaccinations for 28 days after vaccination with the study drug.
- If an adverse reaction occurs with administering a test drug, it is acceptable to use the necessary drugs for symptomatic treatment.

Disclosure of research information

- The outline of this study and results have been published in the Clinical Research Implementation Plan and Research Outline Disclosure System (jRCT) (https://jrct.niph.go.jp/).
- We will publish further research data in medical journals and conferences, excluding participants' personal information.

Institutional review board

This study has been reviewed by the following Clinical Research Review Board, certified by MHLW. NCGM has received the following certification.

Name	National Center for Global Health and Medicine (NCGM). Institutional review board
Address	1-21-1 Toyama, Shinjuku-ku, Tokyo
Certification information	Accreditation Number: CRB3200011 Accreditation Dates: 29 January 2021
Query	Clinical Research Review Board Secretariat 03-3202-7181