# Participant Information Sheet and Consent Form for Participation in Research of the Vaccine "Stamaril" against Yellow Fever

Research Title: Clinical Research to Collect Safety Information Obtained Following Vaccination with "Stamaril"

This brochure consists of participant information sheet and consent form to request participation in clinical research using the vaccine "Stamaril" against yellow fever. With funds and the vaccine provided by Sanofi Pasteur SA in France, this research will be conducted at domestic institutions designated by the Ministry of Health, Labour and Welfare where certificates of vaccination against yellow fever can be issued. This research is approved by the administrator of each institution.

The contents of this research will be registered at jRCT (https://jrct.niph.go.jp/) based on the Clinical Research Act. However, information that may identify you as an individual will not be disclosed. You can search on this website at any time.

## 1. Introduction

This participant information sheet is provided to help you accurately understand the contents of this research and judge whether or not to participate in the research based on your own free will. Please decide if you would like to participate in the research after you read the participant information sheet, received an explanation from the doctor in charge, and sufficiently considered it. If your decision changed after you gave consent to participate, you have the right to withdraw your consent and quit participating in the research. In such cases that you decided not to give consent or chose to withdraw your consent for research participation, you will not be treated unfavourably. If there is anything you do not understand or if you have any concern about this research, feel free to ask whatever it is. If you would participate in the research, please sign and date the consent form and give the form to the doctor in charge. If you would like to withdraw your consent, please sign and date the consent withdrawal form and provide the form to the doctor in charge.

## 2. What is Specified Clinical Research?

The study which is conducted on people to elucidate the cause of disease or improvement of prevention, diagnosis, and treatment is called "Clinical Research".

This research is distinctively called "Specified Clinical Research" as it involves domestically unapproved vaccine with fund from a pharmaceutical company. It will be conducted following the Japanese regulation called the Clinical Research Act. This research is not a clinical study (clinical trial) intended to obtain approval for manufacture and market pharmaceuticals from the Ministry of Health, Labour and Welfare.

3. About Yellow Fever

Yellow fever is a systemic viral disease which is transmitted by mosquitos (particularly Aedes aegypti). When transmission of the disease occurs, symptoms such as fever, headache, muscle pain, and queasiness would appear after an incubation period of 3 to 6 days. It is said that most of these symptoms resolve and improve in 3 to 4 days, but when is becomes severe, symptoms such as bleedings from nose, gum and other various organs and jaundice will appear and 50% of the severe cases will lead to death. There is no special treatment for the disease, so symptomatic therapies to diminish symptoms will be performed. Human-to-human transmission will not occur with Yellow fever.

Yellow fever is prevalent in the tropical areas of Africa and Latin America. Since 2015, yellow fever has been prevalent in the Republic of Angola and the Federative Republic of Brazil. In Brazil, at the beginning of 2018, the number of patients definitively diagnosed with yellow fever increased three-fold in several weeks. Also, there have been reports that travelers who stayed in Angola or Brazil without prophylactic vaccination had developed yellow fever after returning home.

The most important prophylactic measure against yellow fever is prophylactic vaccination. Once if sufficient immunity against yellow fever is acquired by a single dose of vaccine, lifelong immunity may be maintained.

4. Purpose of and Background of This Research

"Yellow Fever Vaccine" distributed by Sanofi K.K. is the only vaccine against yellow fever which is approved by the Ministry of Health, Labour and Welfare and marketed in Japan. The "Yellow Fever Vaccine" is currently temporarily unavailable due to switching manufacturing equipment to a new facility in the United States where this vaccine is manufactured. This means that it could cause a big impact on travellers entering the epidemic area since they could not get vaccinated with the yellow fever vaccine in Japan. Such being the situation, we would like you to get vaccinated with the vaccine "Stamaril" against yellow fever which is manufactured by Sanofi Pasteur SA in France, as an alternative, and participate in this research to confirm its safety. Sanofi K.K. in Japan and Sanofi Pasteur SA in France are both the members of the Sanofi Group.

5. About the Vaccine "Stamaril"

"Stamaril" and "Yellow Fever Vaccine" are both made from the same viral strain and by using almost the same method. The intended population for vaccination, the method of vaccination, and the amount of vaccination are also similar to each other. The only difference is that "Stamaril" does not contain gelatine as an additive agent (stabilizer). For this reason, "Stamaril" can be injected safely to people who are allergic to gelatine. "Stamaril" is a vaccine approved in advance by the World Health Organization (WHO). It has been approved as a product in more than 70

countries and regions since 1986, and to date, more than 400 million doses of the vaccine have been shipped. Countries that approve “Stamaril” includes Asian countries such as Korea and Hong Kong.

6. Other Options

If you participate in this research, you will be vaccinated with “Stamaril” and will receive a certificate (yellow card). “Yellow Fever Vaccine” is approved in the United States and Canada, other than Japan. “Yellow Fever Vaccine” will also be temporarily unavailable in these two countries; therefore, there is no way to obtain a certificate (yellow card) by “Yellow Fever Vaccine” injection, both domestically and internationally.

If you do not wish to participate but need to obtain the certificate, you could receive it overseas. As “Stamaril” is approved in many developed countries such as European countries, you will be able to receive certificate abroad by injecting the same vaccine as being used in this research. Some developing countries approve other vaccines that are unique to their country.

For those who cannot receive injection due to the mismatch to participation criteria, can request a certificate of exemption to prove that you are not eligible for immunization. Other options are to postpone, cancel or abort your travel to the risk area.

7. The Scheduled Period of Research and Scheduled Number of Participants

We will start the research from around November 2018 and maximum 13,000 persons will be participating in this research. We expect the enrollment period to last till August 2019.

8. Research Methods

Eligibility Criteria for Participation

First, your doctor will check if you meet the criteria to participate in this research.

The criteria for participation are as follows:

1) Person who may be exposed to the risk of yellow fever.
2) Person aged 9 months or older on the day of vaccination with “Stamaril”.
3) Person who gave written consent to get vaccinated with “Stamaril” which is unapproved in Japan, as an alternative to “Yellow Fever Vaccine”.
   *Note: For persons aged 16 to less than 20 years, written consent from their legal representative is also needed in addition to written consent from the participant.
   *Note: For persons aged less than 16 years, written consent from their legal representative is needed.
4) For persons aged 6 months to less than 9 months, persons who are or are possibly pregnant, persons aged 60 years or older, and persons infected with asymptomatic human immunodeficiency virus not associated with immune dysfunction, their doctor should judge that the expected benefits of vaccination outweigh the risks.

*Note: The doctor will give the final decision for vaccination eligibility, considering the area, length, and purpose of the travel.

Persons meeting any of the following criteria cannot participate in the research:

1) Person with hypersensitivity to any of the additives contained in “Stamaril”, chicken eggs, or chicken meat proteins
   *Note: Additives contained in “Stamaril” are: lactose; sorbitol E420; L-histidine monohydrochloride; L-alanine; sodium chloride; potassium chloride; disodium phosphate, anhydrous; potassium dihydrogen phosphate; calcium chloride; and magnesium sulphate. These additives generally do not cause any allergic problems. However, if you have any concern, for example, if you have previous experience of adverse reaction, please consult the doctor beforehand.
2) Person with congenital or acquired immunodeficiency, such as those receiving immunosuppressive therapy with chemotherapy, systemic administration of corticosteroids, etc.
3) Person with a history of thymic dysfunction (including myasthenia gravis, thymoma, and thymectomy)
4) Person infected with symptomatic human immunodeficiency virus
5) Person infected with asymptomatic human immunodeficiency virus associated with immune dysfunction
6) Person with fever (≥37.5°C)
7) Person who is judged by the doctor to have severe acute disease
8) Breastfeeding women who cannot suspend breastfeeding for at least 14 days after vaccination with “Stamaril”
9) Other persons who are judged by their doctor to be not appropriate for getting vaccinated prophylactically

Research Procedures

If you gave written consent to participate in this research and met all of the conditions necessary for participation, you will receive 0.5 mL of “Stamaril” subcutaneously after a medical interview by a doctor.

After that, you will be asked to stay in the vaccination facility for about 30 minutes so that appropriate measures can be taken immediately if any acute adverse reaction has occured, and to check the safety of “Stamaril”.

You will need to pay attention to changes in your physical condition for about 30 days after vaccination.If you feel any problem, you should visit a medical institution as needed, and undergo a medical examination by a doctor after telling that you got vaccinated with “Stamaril”. Also, contact the facility where you got vaccinated with “Stamaril.” In this regard, you will be asked

about things such as the time of occurrence or detailed description of your condition and the treatment you received when you visited the medical institution.

Other Things You Need to Report

If you found to be pregnant within 30 days after "Stamaril" vaccination or if you breastfed within 14 days after "Stamaril" vaccination, please contact the facility where you got vaccinated.

If New Information is acquired

If new information, which may affect your will regarding this research participation, is acquired, we will provide it to you.

Discontinuation of Research

If you wish to withdraw consent to participate in this research, or if the doctor in charge judges that participation in the study is not appropriate due to a change in the condition, etc. after you signed this consent form, or if this research itself is aborted, your participation in research will be discontinued.

9. Expected Benefits and Disadvantages

Expected Benefits

There is no special treatment for yellow fever, so if you contract the disease, symptomatic therapies will be given. It is said that 20% of the patients infected and 50% of the severe cases will result in death. By participating in this research, you will get vaccinated against yellow fever, obtain a certificate of vaccination, and may acquire lifelong immunity against yellow fever. Also, you may be able to avoid the risk of mortality by protecting yourself from the disease.

Expected Disadvantages

When a person gets vaccinated with "Stamaril," it is known that he/she will acquire protective immunity against yellow fever for a long period, but alike "Yellow Fever Vaccine," it is not certain that "Stamaril" injection will 100% protect people from yellow fever.

Like other vaccines, adverse reactions may occur due to vaccination with "Stamaril." Frequently reported adverse reactions are headache, muscle pain, fatigue or weakness, and injection-site pain. Children who get vaccinated with it may react to a slight stimulus, may not stop crying even when someone is trying to soothe them or may develop anorexia or sleepiness. Other common adverse reactions are fever, queasiness, rash, and injection-site redness or swelling. Many of these adverse reactions occur within 3 days after vaccination (fever often occur in 4 to 14 days after vaccination), but these symptoms usually subside within 3 days.

In addition, like other vaccines, allergic reactions may occur due to vaccination with "Stamaril." Symptoms include itchy skin, urticaria, rash, swelling of the lips, face, or throat,

tachycardia, sweating, fear, respiratory discomfort, and dizziness or light-headed feeling due to blood pressure decrease. These allergic reactions are usually seen almost immediately after vaccination.

After vaccination with vaccines against yellow fever including "Stamaril," serious adverse reactions may occur. There have been reports of yellow fever vaccine-associated neurotropic disease (YEL-AND) which affects the cranial nerves, and yellow fever vaccine-associated viscerotropic disease (YEL-AVD) which causes symptoms similar to those of infection with yellow fever and rapidly affects multiple organs.

- Yellow fever vaccine-associated neurotropic disease (YEL-AND) is reported to occur usually within 30 days after vaccination. There may be symptoms such as high fever associated with a headache, confusion, convulsion, and immobility or numbness of a part of the body or the whole body. Almost all the persons who were affected by this disease recovered.
- Yellow fever vaccine-associated viscerotropic disease (YEL-AVD) is reported to occur usually within 10 days after vaccination. There may be symptoms such as fever, muscle pain, fatigue, headache, and hypotension, and subsequently, severe liver disorder with yellowing of the skin or eyes, muscle disorder, internal bleeding, haemorrhage, and abnormal function of the respiratory apparatus or kidneys. About a half of people who were affected by this disease had died, and the other half had recovered.

Although these adverse reactions occur very rarely, it may lead to death in some cases. Persons aged 60 years or older, infants aged less than 9 months exposed to the vaccine against yellow fever via breastfeeding, persons with congenital or acquired immunodeficiency, and persons with thymic dysfunction are known to be at high risk of these adverse reactions.

Regarding the incidences and types of adverse reactions, please see the list on page 8.

<u>About Pregnancy</u>

From the previous experience of the use of "Stamaril," it has been suggested that "Stamaril" has no harmful influence on the health of pregnant women or unborn or newborn babies. However, the data providing evidence for it are limited, and therefore, pregnant or possibly pregnant women should avoid vaccination in principle. This shall not apply when traveling cannot be avoided and when their doctors judged it as necessary to get vaccinated. If you are found to be pregnant within 30 days after vaccination with "Stamaril," please contact the facility where you got vaccinated. You will be contacted until the end of pregnancy to check the health status of you and your baby.

<u>About Breastfeeding</u>

The vaccine virus may move to the infant by breastfeeding, and therefore you should avoid breastfeeding for at least 14 days after vaccination with "Stamaril." If you breastfed within 14

days after vaccination with “Stamaril” by mistake, please contact the facility where you got vaccinated with the vaccine. You will be contacted for 30 days to check the health status of you and your baby.

List of Adverse Reactions

| Type | Incidence of Adverse Reactions | | | | | |
|---|---|---|---|---|---|---|
| | ≥10% | 1% to <10% | 0.1% to <1% | 0.01% to <0.1% | <0.01% | Incidence unknown*3 |
| Infections | | | | Rhinitis | yellow fever vaccine-associated viscerotropic disease (YEL-AVD) | |
| Lymphatic system disorders | | | | | | Lymphadenopathy |
| Immune system disorders | | | | | | Anaphylactoid reaction (including angioedema) |
| Metabolic and nutritional disorders | Loss of appetite*1 | | | | | |
| Nervous system disorders | Headache, drowsiness *1 | | Dizziness | | Yellow fever vaccine-associated neurotropic disease (YEL-AND) | Paresthesia |
| Gastrointestinal disorders | Vomiting*2 | Nausea | Abdominal pain | Diarrhea | | |
| Skin disorders | | Rash | Pruritus | | | Urticaria |
| Musculoskeletal disorders | Muscle pain | Joint pain | | | | |
| General and inoculation-site reactions | Irritability *1, crying*1, pyrexia*2, asthenia, injection-site pain/tenderness | Injection-site erythema/redness, injection-site hematoma, injection-site induration, injection-site edema/swelling | Injection-site papule | | | Influenza-like illness |

*1: Adverse reactions particularly frequently seen in children.
*2: Adverse reactions seen in 10% or more of children and 1% to <10% of the general population.
*3: It is not possible to estimate the incidence from the data obtained to date.

10. Rules We Want You to Follow

- Please stay in the vaccination facility for about 30 minutes after vaccination with “Stamaril.”
- Please pay attention to changes in your physical condition for about 30 days after vaccination. If you feel any problem, you should visit a medical institution as necessary and receive medical examination by a doctor. In this regard, please tell the doctor that you got vaccinated with “Stamaril.”
- If you notice any change to your physical condition within about 30 days after vaccination, please report the details via internet, facsimile or phone call. Please access the designated website and report details in the form or send a survey sheet via facsimile. If you would like to report by phone call, please contact the facility where you got vaccinated.
- If you are female and found to be pregnant within 30 days after vaccination or if you breastfed by mistake within 14 days after vaccination, please contact the facility where you got vaccinated.
- Please follow other instructions written in this participant information sheet.

11. Action and Compensation in case Health Injury Occurs

If you feel any abnormality in your body or have any concern due to participation in this research, you may visit medical institution as necessary and receive medical examination by a doctor. In this regard, please tell the doctor that you got vaccinated with “Stamaril.” Also, contact the institution where you got vaccinated. If your case meets compensation standards, medical expenses which were considered necessary for the treatment will be paid by the insurance company. However, if the doctor judged that the abnormality has no causal relationship to this research or if the abnormality occurred due to your non-compliance to this participant information sheet or doctor’s instruction, the insurance will not cover this. Generally, compensation will be applied to health injury requiring hospitalization or equivalent to hospitalization (See the attached compensation summary sheet for details).

12. Access to Records & Protection of Personal Information

If you wish to see materials pertaining to this research, please make a request, and we will enable you to access those materials to the possible extent.

During and at the end of this research, your age, gender, information on safety, etc. will be provided to the domestic and overseas regulatory authorities, the authorized institutional review board, and the company providing the vaccine “Stamaril,” but your name will be all replaced with a control number so that the personal information including your name and address will not be provided at all.

In addition, examination will take place to confirm if this research had been conducted accurately and your medical records may be accessed by parties concerned, such as the person designated by the research representative, the authorized institutional review board, and persons

in charge at the Ministry of Health, Labour and Welfare. These parties concerned are obliged to keep secrets by law, so that your personal information will not be disclosed. Your agreement to participate in the research means that you also permit these parties to access to your medical records.

13. About the Burden of Expenses

The vaccine "Stamaril" used in this research, will be provided free of charge by Sanofi Pasteur SA in France. Therefore, your expenses will be the medical interview fee, consultation fee, and the fee for issuance of the certificate, excluding vaccination expenses.

14. Research expenses and conflicts of interest

Conflict of interest (COI) in research is the state in which there is a risk of distorting the research results. For example, if the person in charge of a research was an employee of the pharmaceutical company manufacturing the drug being used for the research, research data could be falsified or the results will be falsely interpreted, so that research will not be disadvantageous to the pharmaceutical company.

This research is conducted based on research agreement (contract) between Sanofi Pasteur SA and Research Institute National Center for Global Health and Medicine, and the fund will be provided by Sanofi Pasteur SA. Sanofi Pasteur SA is a company manufacturing the vaccine "Stamaril®", and "Stamaril®" will be provided pro bono by the manufacturer. We will declare conflicts of interest in advance, along with the COI management plan to the review board noted in item #15. Then we will appropriately manage and publicize the COI according to the management plan approved by the board. In addition, Sanofi Pasteur SA will not analyze research data so that the research results are not distorted.

15. Authorized Institutional Review Board

The following institutional review board is authorized by the Ministry of Health, Labour and Welfare, and had reviewed that the contents of the research plan are scientifically and ethically reasonable in consideration of human rights and safety, and had approved the research plan. The research plan was also submitted to the Minister of Health, Labour and Welfare.

Name of the authorized institutional review board: Institutional Review Board, Research Institute National Center for Global Health and Medicine

Address of the authorized institutional review board: 1-21-1 Toyama, Shinjuku-ku, Tokyo

Authorization No. and authorization date: CRB3180021, March 30, 2018

Contact: 03-3202-7181, Secretariat, Institutional Review Board

16. Research Representative & Doctor in Charge of Research

This research will be conducted at hospitals and quarantine stations authorized by the Ministry of Health, Labour and Welfare where certificates of vaccination against yellow fever can be issued. The research representative, Dr. Norio Ohmagari is the director of the Disease Control and Prevention Center, Research Institute National Center for Global Health and Medicine. Regarding the research representative and doctor in charge of research at your vaccination facility, please see the attached list of research sites.

17. Contact for Consultation

If you want to know more information or have any concern about this research or your rights, etc., please contact the vaccination facility. Regarding your vaccination facility and contact information, please see the attached list of research sites.

If you could not reach your vaccination facility in case of an urgency, please contact National Center for Global Health and Medicine, which is listed on top.

For Doctor

# Consent Form for Research Participation

Research Title: Clinical Research to Collect Safety Information Obtained Following Vaccination with "Stamaril"

Contents Explained



Signature Field for the Consenter *The research participant shall fill in the below field if he/she is older than 16 years.

I have received the participant information sheet, read it in advance, received sufficient explanation about the research from the doctor in charge, and understood the contents well. I hereby agree to participate in the research.

Signature: _____ Date of Consent: _____ (mm-dd-yyyy)

Signature Field for the Legal Representative

* If the research participant is aged 16 to less than 20 years, the legal representative shall fill in the below field, in addition to the participant filling in the above field.
* If the research participant is aged less than 16 years, the legal representative shall fill in the below field and leave the above field blank.

I have received the participant information sheet, read it in advance, received sufficient explanation about the research from the doctor in charge, and understood the contents well. I hereby agree to the participation in the research.

Name of participant: _____ Date of Consent: _____ (mm-dd-yyyy)

Signature: _____ Relation: □ Father □ Mother □ Other (_____)

Signature Field for the Doctor in Charge

I have provided sufficient explanation using the participant information sheet.

Signature: _____ Date of Explanation: _____ (mm-dd-yyyy)

For Participant / Legal Representative

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