Impact of Immunization Routes on the Immune Response to Influenza Vaccine

Randomized, open-label, single-center I/II Biomedical trial

Version 1 du 25/05/2012

translated from French to English July 31th, 2018

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Acronym of the clinical study: FLUWAY

Title: Impact of Immunization Routes on the Immune Response to Influenza Vaccine

The research will be conducted as outlined in the protocol and in compliance with Good Clinical Practices (GCPs) and with applicable regulatory requirements.

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This version of the protocol received a favorable opinion from the PPC IDF-3 date of ....../........../......... and ANSM authorization on the date of ....../...../.....
ABBREVIATIONS

AE: adverse event
AgHBs: hepatitis B virus surface antigen
ANSM: National Agency for Drug Safety (Agence nationale de sécurité du médicament et des produits de santé)
AP-HP: Assistance Publique des Hôpitaux de Paris (Paris Public Hospital System)
BMI: body Mass Index
CIC BT505: Clinical Research Center Vaccinology (Centre d’Investigation Clinique de Vaccinologie Cochin-Pasteur Biothérapie 505)
CNIL: Commission on Information Technology and Freedom (Commission Nationale de l'Informatique et des Libertés)
CRA: clinical research associate
CRF: case report form
CTL: cytotoxic T lymphocytes
DRCD: Department of Clinical Research and Development (Département de la Recherche Clinique et du Développement)
GCP: Good Clinical Practices
HA: hemagglutinin
HBV: hepatitis B virus B
HCV: hepatitis C virus
HIA : hemagglutination inhibition antibody
HIV: human immunodeficiency virus
ID: intradermal
IFN: interferon
Ig: immunoglobulin
IM: intramuscular
Inserm: National Institute for Health and Medical Research (Institut National de la Santé et de la Recherche Médicale)
NA: neuraminidase
NP: nucleoproteins
PBNC: peripheral blood mononuclear cells
PPC: Research Participant Protection Committee (Comité de Protection des Personnes)
SAE: serious adverse event
SPC: Summary of product characteristics
TC: transcutaneous
TNF: tumor necrosis
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1. SUMMARY OF THE PROJECT

Title: Impact of Immunization Routes on the Immune Response to Influenza Vaccine

Sponsor: Assistance Publique Hôpitaux de Paris (AP-HP) represented by DRCD (Département de la Recherche Clinique et du développement)

Principal Investigator: Pr Odile LAUNAY, CIC de Vaccinologie Cochin-Pasteur, Hôpital Cochin, Paris

Study center: CIC de Vaccinologie Cochin-Pasteur, Hôpital Cochin, Paris, France

Study objectives

Principal objective
To evaluate influenza-specific CD8 T-cell responses induced at D21 after seasonal influenza vaccination by the transcutaneous (TC, via vaccine targeted at hair follicles), intradermal (ID), and intramuscular (IM) routes in healthy adults.

Secondary objectives
To evaluate the local and systemic safety and tolerance of influenza vaccination by 3 routes of administration: TC, ID, and IM.

To measure neutralizing Ab titers at Day (D)0, D21 and Month (M)5 after vaccination by the TC, ID, and IM routes and hemagglutination inhibition antibody (HIA) titers against the 3 virus strains comprising the seasonal influenza vaccine.

To evaluate the CD4 effector T cell response specific to the influenza antigens induced by D21 after vaccination by the TC, ID, and IM routes: analysis of the production of cytokines by flow cytometry after ex vivo antigenic stimulation.

To measure influenza-specific CD4 and CD8 T-cell responses at 5 months after TC, ID, and IM vaccination by flow cytometric analysis of cytokine-producing T cells after ex vivo antigenic stimulation.

To study the innate immune response at D1 after TC, ID, and IM vaccination by analyzing the transcriptomic profile of whole blood cells by microarrays.

Inclusion criteria:
- Healthy volunteers, age between 18 and 45 years,
- BMI between 21-26,
- Phototype I to IV,
- Subjects able to receive vaccine administration by any of the three administration routes,
- Provided written informed consent,
- Affiliated with a national health insurance fund

Exclusion criteria
- Known pregnancy or positive urine pregnancy test for women of child-bearing age,
- Known infection with HIV or/and HCV or/and HBV (AgHBs+),
- Known or suspected immune dysfunction that is caused by a medical condition or any other cause,
- Use within the past 3 months of any topical or systemic treatment that might interfere with assessment and/or investigational treatment (anti-inflammatory drugs, immunosuppressant, or any immunomodulatory agent),
- Use of any topical treatment on the injection site within the preceding four weeks,
- Excessive terminal hair growth on the two investigational skin areas used for TC vaccination,
- Phototype V-VI,
- Any allergy or hypersensitivity to one of the components of the Investigational Product,
- Medical history of allergy or hypersensitization to any ingredient or colorant used in the TC route of administration,
- Administration of a live vaccine (≤28 days) or inactivated (≤14 days) or planned vaccination within 3 months of inclusion (D0),
- Medical history of skin cancer,
- Any acute skin condition that might interfere with the trial assessment of the injection site,
- Any acute or chronic infection that may interfere with the trial assessment four weeks before enrolment,
- Planned UV sessions or sun exposure 6 weeks before or during the study period,
- Febrile illness (at least ≥37.5°C), any acute infectious event within the week before enrolment,
- Flu confirmed by the presence of fever ≥38.5°C associated with respiratory symptoms
- History of Guillain-Barre syndrome or brachial neuritis after a previous vaccination.
- Participation in another biomedical research study, including its exclusion period, during this study period
- Subject in the exclusion period of a previous clinical trial

**Number of participants**

60 volunteers aged from 18 to 45 years:
The participants will be randomized 1:1:1 into 3 groups:

Group A: 20 volunteers receiving seasonal influenza vaccine on D0 by the TC route
Group B: 20 volunteers receiving seasonal influenza vaccine on D0 by the ID route
Group C: 20 volunteers receiving seasonal influenza vaccine on D0 by the IM route

<table>
<thead>
<tr>
<th>Randomization Arms</th>
<th>D0 vaccination</th>
<th>Number of participants</th>
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<tbody>
<tr>
<td>A</td>
<td>TC</td>
<td>20</td>
</tr>
<tr>
<td>B</td>
<td>ID</td>
<td>20</td>
</tr>
<tr>
<td>C</td>
<td>IM</td>
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**Study calendar**

*Estimated duration of the study: 7 months*

*Estimated study duration for participants: 5 months*

**Inclusion duration:** 2 months

*Study start: September 2012*
End of inclusion period: October 2012

Methodology
Randomized 1: 1, open-label, single-center Phase I/II study evaluating the immunogenicity and tolerance of seasonal influenza vaccine administered by the TC, ID, and IM routes to volunteers aged from 18 to 45 years old.

Treatment
Trivalent seasonal influenza vaccine containing A/H1N1, A/H3N2, and B available for the 2012-2013 seasonal vaccination campaign) at 15 µg of hemagglutinin (Vaxigrip® and Intanza® - Sanofi-Pasteur MSD)

Route of administration: TC, ID, and IM

Assessment criteria
Primary endpoint:
Influenza-specific CD8 T-cell responses will be evaluated at D21 post-vaccination by flow cytometric analysis of the production of cytokines (IFN-g, TNF-a, IL-2) and of the cytotoxic capacity (CD107a) of CD8 T cells after stimulation by the influenza A viral strains contained in the vaccine. The frequency of antigen-specific CD8 T cells at D21/D0 will be compared between the 3 groups of individuals vaccinated by the TC, ID, and IM routes.

Secondary endpoints:
- local and systemic tolerance of influenza vaccination by each route of administration (IM, ID, and TC) will be evaluated by the number and intensity of local and systemic clinical events as well as the events of degree ≥ 2 unrelated to vaccination
- humoral responses will be evaluated at D21 and M5 and compared to D0: seroprotection rate, seroconversion rate, and neutralizing antibody titers. Assessed by hemagglutination inhibition assays (HIA) and microneutralization assays specific to the 3 viral strains in the seasonal vaccine. Results will be compared between the 3 routes of administration (TC, ID, and IM).
- antigen-specific CD4 T-cell responses at D21, as well as of memory CD4 and CD8 T cells at M5, will be evaluated by flow cytometry by measuring cytokine production (IFN-g, TNF-a, IL-2) and cytotoxic capacity (CD107a) after in vitro stimulation by the viral antigens contained in the vaccine. The intensity and the quality of the effector (D0) and memory (M5) cell response will be evaluated in the 3 groups of vaccinated volunteers.
- innate immune response at D1 after TC, ID and IM vaccination by analyzing the transcriptomic profile of whole blood cells by microarrays will be evaluated at D1 after vaccination, compared with D0 and between the 3 routes of vaccination (TC, ID, and IM). The transcriptomic profiles will be correlated with humoral and cellular responses and the clinical observations of tolerance.

Summary outline:

<table>
<thead>
<tr>
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<th>Visit 1 at D0 (Inclusion &amp; Vaccination)</th>
<th>Visit 2 at D1</th>
<th>Visit 3 at D21</th>
<th>Visit 4 at M5</th>
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<tr>
<td>Acceptable delay</td>
<td></td>
<td>+/- 3 days</td>
<td>+/- 7 days</td>
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<tr>
<td>Informing the volunteer and his/her signing the informed consent form</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Clinical examination with</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
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| Collection of the Medical History | | | |
| Reports of the current medication and dosage | x | x | x | x |
| Verification of inclusion and exclusion criteria | x | | | |
| Inclusion and randomization with attribution of the identifying code | x | | | |
| PBMC samples for immune monitoring (35 ml) | x | x | x | x |
| Serum samples (5 ml) | X | X | X | X |
| PAXGENE samples (microarrays) (2.5 ml) | X | X | | |
| Urinary test for pregnancy ** | x** | | | |
| Vaccination (IM, ID, TC) | X | | | |
| Giving volunteers the self-monitoring notebook and patient card | x | | | |
| Collection of data from the self-monitoring notebook | x | x | | |
| Reports of adverse events and severe adverse events (AEs & SAEs)*** | x | x | x | | x |

** for women of child-bearing age.

*** The AEs and SAEs will not be entered in the e-CRF (electronic Case Report Form) until the end of the study. See the safety chapter for reporting SAEs to the sponsor.

2. STUDY RATIONALE

2.1. Challenges of influenza vaccination

Influenza (flu) A infection is a major cause of respiratory infections worldwide. Seasonal flu epidemics occur each year during autumn and winter, with prevalence of 5 to 10%. They are caused by A/H1N1, A/H3N2 and B type influenza viruses. Although most seasonal influenza infections are benign, in at-risk populations, they can induce severe forms of infection and cause hospitalization and even death. Each year, more than 300,000 people die from influenza throughout the world. The at-risk populations include elderly people, children, immunosuppressed individuals, and people with chronic diseases. Influenza viruses are extremely variable. This variability is mainly due to the nature of RNA and the segmentation of their genome. The accumulation of specific changes due to the misreadings of the polymerase, as well as exchanged of genomic segments between the influenza viruses present in the same infected cell results in the development of new virus variants.

These two phenomena are powerful drivers of evolution in epidemic strains; new genomic reassortments can cause pandemics such as those of 1918 (H1N1 Spanish influenza), 1957 (H2N2 Hong Kong influenza), 1968 (H3N2 Asian influenza), and 2009 (H1N1 California 2009). Mortality rate in pandemics can reach very high levels, in the absence of immune memory against these viruses. The severity of both influenza pandemics and seasonal influenza epidemics is linked to the immune status of the exposed populations, to their immune memory against related viruses, and to interstrain cross-reactivity, as well as to the intrinsic virulence of the viruses.¹
Currently, the trivalent vaccines against seasonal influenza used in France and elsewhere in Europe are inactivated, fragmented vaccines, administered without adjuvant and in a single dose comprising 15 µg of hemagglutinin (HA) protein for each of the 3 viral strains. These vaccines are composed of two type A (H1N1 and H3N2) viruses and one type B virus, injected by the conventional IM route. Nonetheless the immunogenicity of these seasonal vaccines is limited in its duration (approximately one year) and its nature (humoral response and little or no CD8 cell-mediated response) as well as in the range of the immune repertoire of cross-reactivity against viral variants. This requires that the vaccine be re-adapted annually to the current circulating seasonal strains.\(^2\) WHO proposes the composition of the vaccine each year, based on international surveillance data. Since 1972, 40 changes in vaccination composition have been recommended. The immunogenicity of these vaccines is modest; they induce a response judged protective in at least 60% of adults (18-65 years) and 17-53% of people older than 65 years, depending on the viruses circulating in a given year.\(^4\)

Protection against influenza viruses occurs simultaneously via a humoral immune response (neutralizing antibodies), a cellular response (CD4 and CD8 effector/memory cells), and a mucosal response, of an IgA type.\(^5\) The presence of antibodies directed against the two glycoproteins on the virus surface — HA and neuraminidase (NA), the principal targets of the humoral response and subject to substantial immune selection pressure — is considered the principal reference for protection against influenza viruses. Nonetheless, CD8 cytotoxic T cells also play a role in the mechanisms that protect against influenza.\(^6\) Responses of CD8 cells are generally directed against conserved internal proteins, especially nucleoproteins (NP) and proteins of the polymerase complex, which have a lower rate of variability associated with immune selection pressure. These responses also recognize HA, NA,\(^7, 8\) and non-structural proteins.\(^9, 10\) During the 1980s, Doherty's group demonstrated the protective role of CD8 T cells against influenza.\(^11, 12, 13, 14\) These influenza-specific T cells play a crucial role in the control of influenza; they are capable of producing cytokines and killing infected cells.\(^15, 16, 17, 18\) Various authors proposed that these CD8 T lymphocytes might provide protection against multiple subtypes (i.e., H1N1, H5N1, and H3N2).\(^19\) The persistence of cellular immunity against influenza virus variants may play an important role in reducing the severity of infections during epidemics and pandemics.\(^7\) This cellular immune memory against influenza viruses is conferred during benign infections. It may constitute an essential weapon against severe forms of influenza, especially among the elderly, whose humoral response declines with age.

The conventional IM route of immunization is not effective in inducing cytotoxic responses against influenza. The CD8 cell response remains low, even non-existent, in most subjects vaccinated against influenza by the IM route.\(^3\) We have reported the absence of CD8 T-cell responses specific for H1 and H3 proteins and for NP after vaccination in the Phase I study of IM vaccination. Moreover, CD8 cell-mediated immunity was measured in the FLU_HOP cohort in 138 subjects vaccinated against the H1N1 California 2009 vaccine and remained extremely low: fewer than 18% of vaccinated subjects had an increased CD8 T-cell response on D21 post-immunization by the IM route. For this reason, new vaccination strategies are being developed to induce cellular as well as humoral responses. Some strategies are also directed toward the use of conserved antigenic targets, such as the M1 and NP proteins common to influenza viruses, to induce the CD8 cell response essential for wider, more durable protection.\(^23\) Our strategy is based on the capacity of the skin's immune cells to guide immune response towards a more cellular and mucosal type of response.

### 2.2. Research justification

The inactivated vaccines, fragmented or sub-units, used for influenza vaccination are classically injected by intramuscular (IM) or subcutaneous routes. These vaccinations mostly induce a humoral IgG serum response that functions to inhibit hemagglutination (assessed by hemagglutination inhibition assays, HIA). Inactivated vaccines administered by the conventional IM route induce very weak cytotoxic CD8 T-cell response as well as mucosal IgA-type response.\(^25\) Although the presence of neutralizing antibodies remains the principal criterion for
assessing the efficacy of influenza vaccination, the CD8 T-cell response can provide a supplementary and durable line of defense. That is, when mutations begin to modify the HA protein, the humoral response is no longer effective enough to protect against the new viral variant. The induction and persistence of CD8 T-cell mediated immunity, directed against the virus’s most conserved proteins (M1, NP, PB1), can enable a broader line of defense against the diverse strains and thus limit infections during influenza epidemics.

The CD8 cell responses have a crucial role in viral infections, particularly in immunocompromised individuals (i.e., with HIV infection or cancers) and the elderly. Their role in protection against influenza has advanced since the studies by Doherty et al. and McMichael et al. More recently, their role as immune memory, able to persist and protect during influenza infections has moved substantially forward in the literature. For this reason, the new vaccination strategies proposed against influenza attempt to promote induction of CD8 T-cell responses, by several different methods: 1) targeting the viral proteins that promote a cell-mediated response (M1, NP); 2) using vaccines in the form of viral particles (virosomes, virus-like particles, DNA, live attenuated influenza vaccine) to promote humoral and cellular responses simultaneously; 3) modifying the route of vaccine administration to enable better uptake by antigen-presenting cells, especially via the cutaneous and intranasal routes.

It has been demonstrated that the first stage of antigen encounter is a crucial phase that enables the next phase—specific T-cell clonal expansion. That in turn is followed by a contraction phase, defined by the death of effector T cells and their programming for migration toward the peripheral tissues. This phase is crucial in the constitution of a compartment of memory T cells specific for influenza. Several theories currently feed the debate about the maintenance of immune memory and CD8 cells directed against viral infection, especially the roles of the initiation of the immune response and of antigen circulation in the persistence of immune memory. These theories have been revisited recently in the studies of immune response after the eradication of smallpox, both by our team and more generally in the literature.

Accordingly, the trends in vaccination strategies today promote administration of vaccine antigens by cutaneous routes and without adjuvant because the skin, composed of the epidermis and the dermis, is very rich in professional antigen-presenting cells (APCs). The epidermis contains a high density of Langerhans cells, recently reported to play a role in the induction of CD8 T-cell-mediated responses. The low immunogenicity of the conventional IM injection route has led to the development of alternative methods involving either routes of administration (microneedles, patches +/- adjuvant) (Figure 1) or adding an adjuvant. The recent progress in biotechnology adds modern resources that facilitate vaccination methods that do not use needles at all or that use microneedles to improve vaccination into the dermis. It has been demonstrated that a strong and effective immune response can be induced with lower doses of influenza vaccine administered by the ID route targeting the dendritic cells of the dermis and epidermis. The effectiveness of vaccination by the ID route has been demonstrated for different vaccines (smallpox, rabies, and HBV), most particularly for inducing humoral responses. Microneedles as well as a variety of methods of microinjection into the dermis facilitate ID vaccination. In a phase II clinical trial, Leroux-Roels et al. showed the safety of ID immunization by a trivalent inactivated influenza vaccine (9 µg HA), with a microinjection system. Compared with the IM route (Vaxigrip® vaccine, 15 µg HA), ID vaccination induces higher rates of seroconversion for the A strains (H1N1, H3N2) and identical rates for the B strain.
Figure 1: Diverse methods of vaccination through the skin and the relative distribution of vaccine components. These different methods make it possible to target different subpopulations of antigen-presenting cells.

Figure 2: Image of a hair follicle (cell nuclei = blue) where the Langerhans cells (red) are found around the hair follicles, with the cellular extensions (dendrites) accessible around the follicular duct. The infundibulum becomes a large, accessible area after it is opened by the cyanoacrylate to receive the vaccine components.

Although the skin is rich in diverse antigen-presenting cells, their role in inducing immune response — especially the nature and intensity of cellular and humoral responses — differs according to whether epidermal (Langerhans cells, LCs) or dermal (dermal dendritic cells) cells are targeted. At the same time as skin vaccination methods were developing, Behazine Combadiere’s group, in collaboration with dermatologists (Dr A Vogt, Dermatology, Charité Universitätsmedizin, Berlin) showed the importance of the Langerhans cells surrounding the follicles. The structure of the hair follicles make them an immunologically privileged site, even though surrounded by LCs. Concentrated around the follicles, LCs can receive antigenic vaccine material when the hair follicles are open (Figure 2). The size of the hair follicle, and in particular the volume of the upper part of the hair duct (the infundibulum) is an important determinant of vaccine penetration through the follicular reservoir, since this is the area surrounded by LCs (Figure 2). The terminal hair follicles have a greater volume of infundibulum than the small "velus" hair follicles.

Cyanoacrylate is used to open the hair follicles. Depositing the antigenic material in the hair follicles leads to the best uptake by LCs and its transport to the draining lymph node, a favored site of immune response. This preferential targeting of LCs for antigen vaccination promotes cell-mediated, especially CD8 response, which is absent from IM vaccination with inactivated vaccines, such as that for influenza.
A new method of antigen penetration into human hair follicles was therefore developed with human skin explants.\textsuperscript{49, 50} The safety of this method of standardized TC vaccine application and its effectiveness in inducing cell-mediated responses was validated by:

1) a pilot study during which we showed the safety of the TC compared with the IM route after influenza vaccination with the AGRIPPAL\textsuperscript{®} vaccine (Chiron);\textsuperscript{50}
2) a phase I study (multicenter, Berlin, Frankfurt, and Paris) that confirmed the safety of this immunization route in humans. We showed a CD8 cell response specific for the 3 strains comprising the trivalent influenza vaccine that was significantly greater than for the convention IM route.\textsuperscript{24} Nonetheless, the TC route was less effective in inducing a humoral IgG response. Unlike the IM route, TC vaccination into the skin induced more mucosal IgA responses.\textsuperscript{52–54} These results must still be confirmed in a clinical studies in humans.

2.3. Summary of the results of relevant and available nonclinical and clinical trials

Our group published two clinical studies of the safety and immunogenicity of the TC compared with the IM route in 2008 and 2010. A single study using the same technique of opening the hair follicles of melanoma patients by using cyanoacrylate-based glue for 5 vaccine applications was published in 2006. The 3 studies are described below:

Studies of patients with melanoma\textsuperscript{55}
Number of subjects: Six patients with stage IV and 2 with stage III
Vaccination with the immunodominant Melan-A peptide (ELAGIGILTV), MAGE-2 (EYLQLVFGI), MAGE-3 (IMPKAGLLL), and gp-100 (VWKTWGQYW). The patients received 7 TC applications of peptides at the rate of one application per month.

Study results
The authors observed a significant increase in CD8 T-cell responses specific for melanoma peptides and for IFN\textsubscript{γ}-producing HIV with cytotoxic activity. Tumor regression was observed in 4/6 subjects for 5 months.

Pilot study\textsuperscript{50}
Number of subjects: 11 healthy volunteers
7 subjects vaccinated by TC (application of 0.5 ml vaccine) and 4 subjects by the IM route (injection of 0.5 ml vaccine)
AGRIPPAL\textsuperscript{®} vaccine (Chiron): 2004-2005 influenza trivalent seasonal vaccine
Age: 25-52 years

Pilot study results
The safety of the TC route is similar to that of the IM route. Moreover, we did not detect any modification in the proinflammatory cytokines, including IL-12p70, TNF\textsubscript{α}, IL-10, IL-6, IL-1\textsubscript{β}, and IL-8 (measured with cytokine bead arrays) in the volunteers' serum on D14 and D28 after vaccination, regardless of the route of administration. This finding suggests there was no systemic inflammatory reaction that could lead to side effects and confirms the safety of the TC route of administration by the method used.

We showed that the TC vaccination induced detectable total IgG responses against influenza antigens but with substantial variability in the serum of subjects by the TC and IM routes at D28. The TC route induced a significant increase in CD4 T-cell responses against influenza, similar to that of the IM route. Nonetheless no CD8 cell responses against influenza were observed in subjects vaccinated by the IM route, while 4/6 subjects vaccinated by the TC route had CD8 T-cell responses again influenza more than 4 times higher than on D0.

Phase I study\textsuperscript{24}
Randomized multicenter study in Berlin, Frankfurt, and Paris in two groups of subjects: HIV-negative and HIV-positive

Number of subjects:
- 24 healthy HIV-negative subjects (12 subjects vaccinated by the TC route and 12 by the IM route)
- 14 HIV+ subjects (CD4 >500 cells/ml, controlled viral load <400) finished the trial: 6 TC-vaccinated and 8 IM-vaccinated

Age: 21-45 years
Vaccines: Non-adjuvanted tetanus+inactivated 2005-2006 seasonal influenza + antitetanus vaccine (TETAGRIP®, Sanofi-Pasteur)

Results of the Phase I study
This study confirmed the safety and efficacy of the TC immunization route on a 32-cm² area of skin in humans. We observed an absence of anti-tetanus and anti-influenza antibodies after vaccination by the TC route compared to the detection of neutralizing antibodies against the two components of the vaccine after IM vaccination.

The CD4 and CD8 cell responses were assessed by flow cytometry on D0 and D28 post-vaccination and detected cytokine-producing (IFN, TNF, and IL-2) T cells specific for the influenza virus. The most striking observation was the significant increase on D28 in healthy and HIV+ subjects vaccinated by the TC route of a CD8 cell response specific for the 3 strains composing the trivalent influenza vaccine. No such response was seen in subjects immunized by the conventional IM route, although the CD4 cell responses remained similar by both routes (Figure 3).

Figure 3: Intensity of the cell-mediated response specific for the trivalent vaccine influenza after TC and IM vaccination
2.4. Expected results, perspectives

Our project will enable the comparison in a single study of two new routes of immunization — the TC route via hair follicles, which induces a CD8 T cell response, and the ID route, which is currently under development, using microneedles, to conventional IM immunization conventional IM in volunteers aged 18 to 45 years. The project is thus a continuation of the phase I trial conducted in 2005 (in subjects aged 18-52 years). It will allow us to complete the study of immunity against influenza by comparing two routes of administration by the skin, the first aimed at epidermal antigen-presenting cells (TC) and the second, at dermal cells (ID), in volunteers aged 18-45 years, by measuring influenza-specific CD8 and CD4 T-cell responses. Our recently published results in mice suggest that the route of administration simultaneously dictates the intensity and the quality of the immune responses. We also showed that targeting the LCs (by the TC route) induced CD8 cell-mediated immunity, while targeting the dermal cells (ID route) induced a CD4-mediated response. IM injection continued to induce humoral but not CD8-cell-mediated responses. Our preceding studies showed that on D28 the healthy and HIV+ subjects vaccinated by the TC route showed a significantly increased CD8 cell response specific for the 3 strains composing the trivalent influenza vaccine, contrary to the conventional IM route; the CD4 cell responses nonetheless remained similar by both routes (Figure 2). Analysis of the maintenance at M5 after vaccination of the humoral (anti-HA and neutralizing antibodies) and the CD8 and CD4 T-cell immune memory will enable us to verify the persistence of both cellular and humoral protection against influenza according to the route of immunization: TC, ID, and IM.

An effective and protective response after vaccination implies the establishment of a polyfunctional response involving the interaction of numerous mediators and cell types of both innate and adaptive immunity. The development of techniques for the analysis of transcriptional profiles and of bioinformatics tools allows us to study these networks of cellular interaction and the complex mechanisms involved in the immune response to improve immunization strategies. Recent studies using microarray techniques show the importance of inflammation and of the innate immune response that intervenes in the first days after vaccination and determines the quality of the specific adaptive response. We propose to use microarrays to study the profiles of transcriptional expression of blood cells at D1 after the influenza vaccination (compared to the prevaccination profile) and thus to assess the inflammatory response according to the route of immunization. The important differences in the epidermal, dermal, and muscle immune environments imply an innate response and the uptake of influenza antigens by immune cells specific to each site. As assumed in the literature, this phenomenon plays an important role in the intensity of immune responses. The effect of the route of vaccine administration on the early innate response will thus be measured and compared between the 3 groups of subjects vaccinated by the TC, ID, and IM routes. Modifications of the expression of some factors at the transcriptional level may be measured at the protein level in serum at D1 post-vaccination by ELISA or cytometric bead arrays. The intensity and nature of the mechanisms of innate immunity will be correlated with the intensity and quality of the cellular and humoral responses. Moreover, the inflammatory phenomena will be correlated with clinical observations and possible side effects after vaccination by each of these routes.

2.5. Summary of known and predictable benefits, risks, and constraints

The safety of vaccination against influenza by the IM and ID routes is known and well documented. Vaccination by both routes is generally well tolerated and can lead to local reactions at the injection site (see vaccine SPCs) and systemic reactions (see SPCs). These reactions are harmless and disappear within 5 days. TC vaccination with a trivalent vaccine against influenza vaccines has already been assessed in independent clinical studies and presents no particular risk compared with IM administration. The events associated with TC vaccination are local allergic
reactions of the injection site, causing redness, itching, desquamation, or swelling. These reactions are benign and disappear within 5 days. Moreover, the study, using very sensitive microarray techniques, will enable us to show variations in the inflammatory response at the systemic level on D1 post-vaccination and to compare the systemic effect between the TC, ID, and IM immunization routes. We have already demonstrated the absence of any increase in serum proinflammatory cytokine concentrations (IL-12p70, TNFα, IL-10, IL-6, IL-1β, and IL-8 measured by the "cytokine bead array" method) on D14 and D28 after vaccination, together with the absence of side effects, observed in 7 subjects vaccinated by the TC route, compared with 4 subjects vaccinated by the IM route (unpublished results, Behazine Combadière).

The benefit lies in its induction of CD8 cell responses specific for the vaccine strains in the population vaccinated by the TC route, absent in groups vaccinated by the ID and IM routes. Moreover, we will evaluate the mucosal responses induced by the TC route, which has barely been examined in clinical studies of influenza vaccination. Cell responses might confer a cellular immune memory able to protect the individual against severe forms of influenza. Similarly, mucosal responses might enable early protection of the site of respiratory infections. Clinical examinations and blood samples done specifically for this study during follow-up will not increase the risk for participants.

2.6. Designation and description of the experimental drugs

The vaccine studied will be the vaccine against seasonal influenza by Sanofi-Pasteur MSD available for the winter 2012-2013 vaccination campaign.

This vaccine will comprise the influenza viruses (inactivated and fragmented) of the strains selected in compliance with the WHO recommendations (in the northern hemisphere) and the European Union decision for the 2012/2013 season.

The vaccine will be administered at a dose of 0.5 ml by the IM route and a dose of 0.1 ml by the TC and ID routes.

<table>
<thead>
<tr>
<th>Spécialité</th>
<th>Laboratoire pharmaceutique</th>
<th>Forme pharmaceutique et conditionnement</th>
<th>Administration par voie d’immunisation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccin grippal inactivé à virion fragmenté disponible pour la saison vaccinale de 2012-2013 &lt;br&gt; Vaxigrip®</td>
<td>SANOFI PASTEUR MSD, SNC 8, rue Jonas-Salk. 69007 Lyon Tél : 04 37 28 40 00. Fax : 04 37 28 44 00</td>
<td>Suspension injectable IM : Seringle pré-remplie de 0,5 ml, avec aiguille attachée, boîte unitaire. (Le vaccin, après avoir été agité doucement, est un liquide légèrement blanchâtre et opalescent.)</td>
<td>Injection en IM de 0,5ml (15 g HA)</td>
</tr>
<tr>
<td>Vaccin vaccin grippal inactivé à virion fragmenté disponible pour la saison vaccinale de 2012-2013 &lt;br&gt; INTANZA®</td>
<td>SANOFI PASTEUR MSD, SNC 8, rue Jonas-Salk. 69007 Lyon Tél : 04 37 28 40 00. Fax : 04 37 28 44 00</td>
<td>Suspension injectable ID et TC : système une seringue préremplie munie d’une micro-aiguille et d’un système de protection de l’aiguille</td>
<td>Application de 0.1 ml en TC et ID (15 g HA)</td>
</tr>
</tbody>
</table>

2.7. Potential recruitment

The clinical portion of the study and follow-up of the volunteers will take place at the Cochin Pasteur clinical research center in vaccinology (CIC BT505), coordinated by Dr. Odile Launay.
The volunteers will be recruited through the CIC’s computerized volunteer file and by posters (which must be approved by the research participant protection committee (PPC IDF 3 (see section 5.6.1)).

<table>
<thead>
<tr>
<th>Center</th>
<th>Potential inclusions /month</th>
<th>for 2 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIC BT505</td>
<td>30</td>
<td>60</td>
</tr>
<tr>
<td>TOTAL</td>
<td></td>
<td>60</td>
</tr>
</tbody>
</table>

**2.8. Declaration stating that the study will be conducted in compliance with the protocol, good clinical practices, and the applicable legislation and regulations**

I, the undersigned, Doctor Odile Launay certify that the biomedical research that I will coordinate will be conducted in compliance with the protocol, with Good Clinical Practices, and with the applicable legislation and regulations.

**3. STUDY OBJECTIVES AND OUTCOME MEASURES**

**3.1. Principal objective and principal endpoint**

The influenza antigen-specific CD8 T-cell response induced on D21 after vaccination against influenza by the 3 routes — TC, ID, and IM — will be assessed by flow cytometry. The A/H1N1 and A/H3N2 viral strains contained in the seasonal vaccine and inactivated will be used for *in vitro* stimulation of peripheral blood mononuclear cells (PBMCs) obtained at D21 and D0 post-vaccination for each subject. The capacity of the CD8 T cells to produce the cytokines IFN$\gamma$, TNF$\alpha$, and IL-2 and their cytotoxic capacity (CD107a marker expression) will be analyzed by intracellular labeling and flow cytometry. The percentages of specific CD8 T lymphocytes positive for 1, 2, 3, and/or 4 of the IFN$\gamma$, TNF$\alpha$, IL-2 and CD107a markers will be determined for each patient, in response to stimulation by vaccine antigens compared with unstimulated cells. The increase on D21 compared with D0 of the frequency of the viral antigen-specific CD8 T cells will be compared between the 3 groups.

**3.2. Secondary objectives and criteria**

- Local and general tolerance associated with influenza vaccination by the three routes of administration (IM, ID, and TC) will be evaluated by the number and intensity of local and systemic clinical events (some specifically asked about and others not after each vaccination) and by events of a degree ≥ 2 not associated with the vaccination. These events will be collected on D1 as well as during visits and with the aid of a self-monitoring notebook provided to subjects for the collection of all local and systemic events asked about and all events occurring during the 5-month period.

- The humoral response will be assessed by the increase at D21 and M5, compared with D0, of:
  - the seroprotection rate (defined by the percentage of patients with a serum titer of anti-hemagglutinin antibodies ≥ 1/40),
  - the seroconversion rate (defined by the percentage of patients with an antibody titer <1/10 before vaccination and ≥ 1/40 after vaccination or with a titer ≥ 1/10 before vaccination and at least 4 times higher after vaccination)
  - the seroconversion factor (defined by the post- and prevaccination ratio of the geometric means of the titers) measured by the HIA, performed by Sanofi-Pasteur (Lyon)
Levels of neutralizing antibodies against the 3 virus strains in the seasonal vaccine, measured by microneutralization assays

The antibody levels in each subject’s serum on D21 and M5, obtained by the 2 methods, HIA and microneutralization assays, will be defined in relation to the residual influenza-specific immune response measured in serum at D0. These results will be compared between the 3 groups according to route of administration.

- The CD4 effector T-cell response induced on D21, as well as the memory CD4 and CD8 T-cell responses induced at M5, will be evaluated by flow cytometry:
The A/H1N1 and A/H3N2 viral strains contained in the seasonal vaccine and inactivated will be used for in vitro stimulation of PBMCs obtained at D21 and M5 post-vaccination, and D0 (baseline) for each subject. The capacity of the T cells to produce the cytokines IFNγ, TNFα, and IL-2 and their cytotoxic capacity (CD107a marker expression) will be analyzed by intracellular labeling and flow cytometry. The percentages of each subpopulation of specific CD4 and CD8 T lymphocytes positive for 1, 2, 3 and/or 4 of the IFNγ, TNFα, IL-2 and CD107a markers will be determined for each patient, in response to stimulation by H1N1 and H3N2 (compared with unstimulated controls). The increase on D21 compared with D0 of the frequency of the viral antigen-specific CD4 T cells will be compared between the 3 groups, by route of vaccination. The quality of the memory CD4 and CD8 T-cell response at M5 post-vaccination will be studied and compared between the 3 groups.

- The innate immune response and inflammation will be assessed at D1 after vaccination, compared with the basal inflammatory status on D0, by studying the transcriptional profile of the blood cells by microarrays. 2.5 ml of blood will be sampled in PAXgene tubes on D0 and D1, after extraction and hybridization of total RNA (Agilent Platform, Gene Expression Profiling Department, Miltenyi); expression findings will analyzed with R and Ingenuity software (collaboration with Dr Nora Benhabiles, CEA Saclay). The variations in gene expression levels for some innate immunity factors may be measured at the protein level in the serum samples from D1 post-vaccination, either by ELISA or cytometric bead arrays. The inflammatory response and the mechanisms of innate immunity induced will be compared between the 3 vaccination routes. The transcriptional profile will be correlated with the specific humoral and cellular responses and with the clinical observations of tolerance.

4. SELECTION OF STUDY SUBJECTS

4.1. Inclusion criteria

Volunteers may be included in the study if they meet the following criteria:
- Healthy volunteers aged 18-45 years
- BMI ranging from 21 to 26
- Phototype I to IV
- Adults able to receive the vaccine by any of the three routes
- Provides free and informed written consent
- Covered by a national health insurance fund (excluding AME)

4.2. Exclusion criteria

The volunteers meeting the following criteria cannot be included in the study:
- Non-menopausal women with no effective means of contraception
- Known HIV and/or HBV (AgHBs +) and/or HCV infection
- Other cause of severe immunodeficiency
- Treatment by immunomodulatory, anti-inflammatory or immunosuppressant agents in the 3 months before inclusion
- Topical treatments by immunomodulatory or anti-inflammatory agents at the injection site the month before inclusion
- Excessive growth of terminal hairs at the skin sites planned for the TC vaccine administration
- Phototype V-VI
- Known allergy to a component of the study vaccine or history of hypersensitivity reaction to influenza vaccination
- Allergy or hypersensitivity to one of the substances used for the TC vaccination
- Administration of a live vaccine (≥ 28 days) or inactivated (≥ 14 days) or vaccination planned in the 3 months after inclusion (D0)
- History of skin cancer
- Acute skin infection that might interfere with the objectives of the study, linked to the injection site
- Acute or chronic infection that might interfere with the study objectives the month before inclusion
- Planned UV sessions or sun exposure 6 weeks before inclusion and throughout the study duration
- Febrile disease (at least 37.5°C measured orally) or acute infection in the week before the vaccination
- Influenza confirmed by the presence of a fever ≥ 38.5°C associated with a respiratory symptom
- Known history of progressive neuropathy or Guillain-Barré syndrome
- At inclusion in this study, participation in another biomedical research study, including during its exclusion period
- Volunteer who is under legal protection measures and unable to express consent

5. STUDY DESIGN

5.1. Type of study

Randomized three-arm (1:1:1), open-label, single-center, phase I/II vaccination trial, assessing the immunogenicity and tolerance of seasonal influenza vaccination administered by the TC, ID, and IM routes in volunteers aged from 18 to 45 years.

This vaccine trial is an interventional study classified as biomedical research concerning a drug, according to Public Health Code article L.1121-1.

Law n°2004-806 dated 9 August 2004 relative to public health policy is applicable to the volunteers who will be vaccinated against influenza during this biomedical research project.

5.2. Duration of research

Beginning of the study (set-up): September 2012
Duration of the inclusion period: 2 months
Inclusion period: October - November 2012
Duration of volunteers' participation: 5 months
Total study duration: 7 months
Study end date (last visit of last volunteer included): April 2013
5.3. **Description of measures taken to reduce and avoid bias**

5.3.1. **Randomization**

The randomization list will be prepared by the team of the study biostatistician. It will be balanced by blocs, with a ratio of 1 to 1.

The investigator will request randomization via Cleanweb (Telemédicine, S.A.).

5.3.2. **Blinding**

The study will be performed on an open basis.

5.3.3. **Simultaneous participation in another study, period of exclusion**

The volunteers may not participate simultaneously in another study assessing a drug, to avoid bias associated with the other products studied in the interpretation of the scientific results.

There will be no exclusion period at the end of the study, and volunteers can enter another clinical trial once their participation has been completed, that is, after visit 4 at M5.

5.3.4. **Study Outline**

The volunteers will be divided into 3 groups according to a 1:1:1 randomization to receive:

- **Group A**: 20 volunteers receiving on D0 a dose of seasonal influenza vaccine by the TC route
- **Group B**: 20 volunteers receiving on D0 a dose of seasonal influenza vaccine by the ID route
- **Group C**: 20 volunteers receiving on D0 a dose of seasonal influenza vaccine by the IM route

5.4. **Study design - practical organization**

5.4.1. **Study plan and procedures for the volunteer**

5.4.1.1. **Preselection and recruitment**

The participants will be identified

- from the computerized volunteer file of CIC BT505 according to administrative and age criteria, from the
beginning of 2012 (according to the R3-MOS-07 procedure established by CIC BT505). The volunteers will then be contacted by a physician-investigator from CIC BT505 responsible for this study.
- through a poster that will have been approved by the PPC. In this case, the volunteers will be able to contact a physician-investigator from CIC BT505.
The physician-investigator from CIC BT505 responsible for this study:
- will briefly present the study
- will question volunteers about their seasonal influenza vaccination and any influenza-like event
- will ask them to agree to participate
- will transmit the information leaflet to them; either by postal mail or email
- will offer to schedule an appointment for their inclusion/vaccination visit (V1)

5.4.1.2. Visit for inclusion and vaccination: V1 at D0

During this first visit, the physician investigator will:
- ensure that the volunteer has had the time to make his/her decision freely and was able to read and understand the information and the consent form
- answer the volunteer's questions, especially concerning the study's aim, course, constraints, risks, and benefits.
- obtain the patient's medical history:
  - previous history of influenza vaccination
  - other chronic disease or significant history
- obtain information about the medication (and dosage) of long-term medication still used at this visit
- perform a noninvasive clinical examination with measurements of vital constants (T°C, blood pressure, and pulse) and weight and height
- verify the inclusion and exclusion criteria
- verify all the criteria necessary for vaccination (especially allergies)
- collect the volunteer's signed informed consent.
- for non-menopausal women, a urinary pregnancy test will be performed.

Then the physician will:
- perform the patient's randomization via the study’s e-CRF (Cleanweb)
- prescribe a blood sample to perform the specific examinations for this study that must be performed before the vaccination: 35 ml collected into 7 tubes of 5 ml with ACD anticoagulant (for the cell and plasma banks, 1 dry tube of 5 ml (serum bank) and 1 PAXgene tube of 2.5 ml.
- perform the vaccination
- monitor the volunteer for 30 min after the injection
- perform a new clinical examination after the post-vaccination monitoring, again measuring the vital constants

At the end of the visit, the physician will give the volunteer
- a notebook for recording any events and reactions, which must be filled in from V1 to V3.
- a ruler to measure any cutaneous reactions and a thermometer
- the patient card
- will give to volunteers who had a TC vaccination the following instructions:
  - do not use any local treatment (oil or cream) on the TC vaccination zone between D0 and D21 and do not use any systemic immunomodulatory or immunosuppressant treatments at any time during the study
  - do not expose the TC application area to the sun or UV rays between D0 and D21.
  - do not wash the TC application area for the first 24 hours (keep the adhesive bandage on).
  - avoid all physical activity inducing intense sweating for the first 24 hours.
Concerning the local tolerance and general post-vaccination follow-up at visit V1:

**Immediate** local and general tolerance will be evaluated during a clinical examination performed at the end of the 30-min post-vaccination monitoring on D0, including:
- measurement of systolic and diastolic blood pressure and heart rate and questioning the volunteer about the general sensations perceived after the injection.

Tolerance will also be assessed for the **5 days after the vaccination** (from D0, the day of the vaccination to D+4) as a function of the data reported in the self-monitoring notebook, which includes a list of the most frequent local and general reactions (according to the SPC of the vaccine used).

Volunteers will systematically take their temperature orally from D0 to D+5, with the electronic thermometers furnished to them.

The volunteers will report in the notebook the maximum size (in cm) and intensity of cutaneous reactions.

All reactions will be assessed according to the National Research Agency severity scale (protocol appendix 19.2). All post-vaccination reactions reported in the notebook and ranked with an intensity equal to or greater than 4 will be especially followed up by the trial center.

5.4.1.3. Follow-up visit: V2 on D1

During visit V2, the investigator will:
- perform a noninvasive clinical examination with measurements of vital constants (T°C, blood pressure, and pulse) and weight and height
- obtain information about any new treatments taken and any changes in treatment or dosage since the preceding visit
- collect the self-monitoring notebook data (D0 to D1)
- collect any possible significant medical events, hospitalizations, and serious adverse events (SAE)
- prescribe the blood sample for the examinations specific for this study: 1 dry tube of 5 ml (serum bank) and 1 PAXgene tube of 2.5 ml.

5.4.1.4. Follow-up visit 3: V3 on D21

The investigator will:
- perform a noninvasive clinical examination with measurements of vital constants (T°C, blood pressure, and pulse) and weight and height
- obtain information about any new treatments taken and any changes in treatment or dosage since the preceding visit
- collect the self-monitoring notebook data (D1 to D5)
- obtain information about any possible significant medical events, hospitalizations, and serious adverse events (SAE)
- prescribe the blood sample for the examinations specific for this study: 35 ml in 7 5-ml tubes with ACD anticoagulant (cell bank and plasma bank) and 1 dry tube of 5 ml (serum bank).

5.4.1.5. Follow-up visit and study end: V4 on M5

The investigator will:
- perform a noninvasive clinical examination with measurements of vital constants (T°C, blood pressure, and pulse) and weight and height
- Obtain information about any new treatments taken and any changes in treatment or dosage since the preceding visit
- Obtain information about any possible significant medical events, hospitalizations, and serious adverse events (SAE)
- prescribe the blood sample for the examinations specific for this study: 35 ml in 7 5-ml tubes with ACD anticoagulant (cell bank and plasma bank) and 1 dry tube of 5 ml (serum bank).
### Summary Table of Visits

<table>
<thead>
<tr>
<th></th>
<th>Visit 1 at D0 (inclusion &amp; Vaccination)</th>
<th>Visit 2 at D1</th>
<th>Visit 3 at D21</th>
<th>Visit 4 at M5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acceptable delay</strong></td>
<td>+/- 3 days</td>
<td>+/- 7 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Information for the volunteer and signature of the written informal consent form</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical examination with collection of the medical history</td>
<td>x  x  x  x  x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reporting medication currently taken and dosage</td>
<td>x  x  x  x  x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verification of the criteria for inclusion and exclusion</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inclusion and randomization with attribution of the identifying code</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PBMC samples for immunomonitoring (35 ml)</td>
<td>x  x  x  x  x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum samples (5 ml)</td>
<td>X  X  X  X  X</td>
<td></td>
<td></td>
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<tr>
<td>PAXGENE samples (microarrays) (2.5 ml)</td>
<td>X  X  x  x  x</td>
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</tr>
<tr>
<td>Urinary test for pregnancy **</td>
<td>x**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Vaccination (IM, ID, TC)</strong></td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Handing-over of the self-monitoring notebook and patient card</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Collection of the data from the self-monitoring notebook</td>
<td>x  x  x  x  x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reporting of adverse events and severe adverse events (AE &amp; SAE)***</td>
<td>x  x  x  x  x</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

** for the women of child-bearing age.

*** AEs and SAEs will not be entered in the e-CRF until the end of the study. See safety chapter for the reporting of the SAE to and by the sponsor.

In the case of the onset of influenza during the study period, treatment for the volunteer will be done as for standard follow-up and will be handled, as the volunteer chooses, by a CIC physician or his/her general practitioner.

### 5.4.2. Management of examinations and samples

*Examinations specific for this study:*
• A urinary sample will be requested during V1 (D0) from all women of child-bearing age for a pregnancy test before any vaccination.

• Blood samples:
  
  **Quantity of blood necessary:**
  Around 42.5 ml at visit 1 on D0: 5 ACD tubes (7 ml par tube) + 1 dry tube of 5 ml + 1 PAXgene tube of 2.5 ml
  Around 8 ml at visit 2 on D1: 1 dry tube of 5 ml (serum bank) and 1 PAXgene tube of 2.5 ml
  Around 40 ml at D21 and M5: 5 ACD tubes (7 ml per tube) + 1 dry tube of 5 ml + 1 PAXgene tube of 2.5 ml

The sample tubes will be anonymized and labeled in listing the volunteer’s ID code, the visit number, and the date of the sample. The samples will be stored at ambient temperature at CIC BT505 until the arrival of the shipper the same time, and will be sent as soon as possible that day after the sampling to the following address:

**Laboratoire d’immunité et d’infection**
**Equipe de Behazine Combadière**
Hélène Perrin
INSERM U945 porte 605
Tel : +33 01 40 77 98 87
+33 06 87 14 54 19

What happens to the tubes after they arrive at the laboratory of immunity and infection (Team B Combadière)
Samples will be included in the cell bank, serum bank, and plasma bank at the laboratory in less than 24 h after the samples were taken, to be used by Behazine Combadière’s team for studies of immunity to vaccine antigens. These anonymized samples (as described above) will be able to be used to improve the laboratory’s tests as part of its research into influenza and vaccines, but only after the volunteer has received adequate information and provided informed consent. The samples will be stored in the laboratory responsible for the analyses for 5 years from the last visit of the last patient in this study. No genetic tests will be performed.

**a/ Constitution of a cell bank and a plasma bank:**

☞ For the cell bank, PBMCs are isolated from the peripheral blood in the 5 tubes with ACD anticoagulants at D0, D21, and M5. After centrifugation (2200 rpm for 20 minutes) on a Ficoll gradient and washing in RPMI 1640 medium (Gibco BRL®). The cells are counted in blue Trypan and then frozen in aliquots of 5 to 15 million cells in 20% dimethylsulfoxide (DMSO) and 80% fetal calf serum (FCS), stored for 24 to 72 hours in a cryopreservation box at -80°C, and then transferred into liquid nitrogen at -180°C.

☞ For the plasma bank, 2 ml of blood is sampled from 1 ACD tube at D0, D21, and M5 and centrifuged at 2500 rpm for 10 minutes. The supernatant is recovered and several aliquots of 1.5 ml are immediately placed at -80°C and frozen.

**b/ constitution of a serum bank**

☞ For the serum bank, 5 ml of blood is taken from 1 dry tube for all volunteers at each visit (D0, D1, D21, and M5) and centrifuged. The serum is then separated into aliquots stored at -20°C (2 aliquots of 1 ml).

The serum bank makes it possible to assess the responses to neutralizing antibodies in HIA. The plasma bank will allow us to assess the titers of anti-HA IgA and IgG antibodies.
2.5 ml of blood is taken at visits on D0 and D1, in PAXgene Blood RNA Tube (PreAnalytix, BD/Qiagen), which contain additives for the optimal storage of RNA. After 2 hours at ambient temperature, it is frozen at -20°C (for a minimum of 24 h) and then stored at -80°C before shipping to Affymetrix for extraction and hybridization of the RNA.

The samples stored that are not used during these analyses may be saved for a period of 5 years and used later to develop more sensitive tests and conduct, if it appears desirable, particular immunological research related to this study.

A research engineer (6 months FTE) and a postdoctoral fellow (1 year FTE) will be employed for immunomonitoring of responses in all three groups after this influenza vaccination: The research engineer will be responsible for receiving and treating the samples (freezing and storage of peripheral blood cells), immunological tests by multiparametric analyses of T-cell functions, Elispot B IgG and IgA specific for influenza HA proteins.

A clinical trial technician (4 months) will be employed at inclusion and for the follow-up of the volunteers during the study. This person will take the blood samples, ensure their shipping, complete the eCRF, plan the volunteers' visits, and ensure the smooth running of these monitoring visits.

5.4.3. **Compensation of volunteers**

During their first visit (V1) to CIC BT505, the healthy volunteers will provide bank account details (RIB) so that they can be compensated for their participation in the study. These details will be stored at CIC BT505 in each volunteer’s source folder. They will be attached to the compensation form completed by the physician-investigator so that the volunteers are paid at the conclusion of their participation in the study. This form, with the bank details, will then be transferred by the clinical study coordinator to the project direction office of the Broca-Cochin-Hôtel–Dieu Hospital group for it to make the wire transfer.

Volunteers participating in this study will receive compensation for the constraints they undergo in the amount of €50/visit.

6. **TREATMENTS ADMINISTERED**

6.1. **Description and justification of the route of administration, dosage, regimen, and duration of the treatment**

**Trial treatment:**

The vaccines used in this study will be the seasonal influenza vaccines by Sanofi-Pasteur MSD that will be commercially available for the winter 2012-2013 vaccination campaign.

**Vaxigrip**: injectable suspension (IM). Prefilled syringe 0.5 ml (15 µg HA) with needle attached. Single box.

**Intanza MC**: injectable suspension (ID and TC). Prefilled syringe 0.1 ml (15 µg HA) with microneedles and a needle protection system

**Composition:**

These vaccines will be composed of the influenza viruses (inactivated and fragmented) of the strains selected...
according to the WHO recommendations (in the northern hemisphere) and the European Union decision for the 2012/2013 season. The influenza virus is cultivated on embryonated eggs from hens from a healthy setting, fragmented, inactivated, containing antigens similar to the following strains:

- A/California/7/2009 (H1N1),
- A/Victoria/361/2011 (H3N2),
- B/Wisconsin/1/2010)

Excipients: buffer solution (sodium chloride, phosphate disodium dihydrate, monopotassium phosphate, potassium chloride, water for injectable preparations).

Origin and presentation:
The vaccines will be furnished by Sanofi-Pasteur MSD in their commercially available form to the Department of Clinical Trials of the general agency for equipment and health products (DEC-AGEPS), which will provide the labeling for the regulatory notices for biomedical research.

Route of administration/dosage:

For the IM route, the vaccine will be administered at a dose of 0.5 ml (15 mg) in accordance with the marketing authorization (appendix 19.4).

For the TC and ID routes, Intanza MC vaccine will be administered at the same dose of 0.1 ml (15 mg). For group A (TC), the vaccine will be applied to the skin after opening the hair follicles by cyanoacrylate skin surface stripping (CSSS) (Patent: French priority patent application filed on June 23, 2005, delivered on October 5, 2007, n°FR2887457- Pending in USA, Canada, Europe, Japan, India, and Australia. Owners: Université Pierre and Marie Curie, Charité Universitätsmedizin, Fondation Bettencourt Schueller - Representative: UPMC - Inventor: Behazine Combadière et al.)

Doctor Angèle Soria will be responsible for the vaccination. Before the study starts (June 2012), she will undergo training in administration by the TC route, at the dermatology clinical center of Charité Universitätsmedizin in the department of Pr Ulrike Blume (Charité Universitätsmedizin, Berlin, Germany). This vaccination by the hair follicles (TC application route) will be performed under the supervision of Dr Annika Vogt, who has standardized this method of application in several clinical studies in France, Germany, and England in collaboration with Behazine Combadière. This protocol was used in Phase I clinical studies (Manon 05) and will be used shortly in France and England for application of a vaccine against HIV (European CUTHIVAC EU_FP7 project).

The stages of vaccination by the TC route are described below

- The arm on which the vaccination is performed must be held in abduction at 90° and positioned horizontally with the outside part of the forearm upwards for the entire period of vaccine application and of drying after application the cyanoacrylate glue
- The zone for the transcutaneous vaccination is identified: 1 area of (3 × 5.3 cm) at the level of the deltoid
- The TC vaccine application area of 3 × 5.3 cm is delimited with a skin marker
- An area 8 cm long and 6 cm wide is dry-shaved gently
Cyanoacrylate glue (9 drops) (UHU-superglue, GmbH & co. KG Buehl/baden, Germany)* is applied and spread with a microscope slide. Then adhesive tape 6 x 5 cm (Nr. 57176-00000, 66 mm x 50 mm, Tesa®, Beiersdorf, Germany)* is applied. After the glue has been spread well and all the air bubbles eliminated (by passing a roller over it 10 times), the tape is left for 20 min and then detached manually. This opens the hair follicles. A mirror image of the skin is presented below, with a microscope view of an open follicular duct ready to receive the vaccine after application of the cyanoacrylate glue. CD1a+ LCs line the epidermis surrounding the follicular duct.

The zone for application of the vaccine fluid is limited by a medical silicone adhesive bandage (CEREDERM, Cereplas, France)*. 0.1 ml of vaccine INTANZA® influenza vaccine is applied and then lightly massaged in a circular pattern in the vaccine application area with a gloved finger presoaked for one min with the INTANZA® vaccine solution to allow favorable distribution of the vaccine over the application area and promote its penetration through the skin.

It is air dried for 15 min; the silicone bandage is then removed and a hydrocolloid adhesive bandage applied (Comfeel® Plus Transparent 9x14 cm, Coloplast, Denmark)*, to be left for 24 hours over the vaccine application area to protect it and to promote the transcutaneous penetration of the vaccine.

The patient should have already been informed (but should be reminded) not to take a bath or shower and not to perform any intense physical activity that could induce substantial sweating or mechanical stress around the vaccine application area for 24 hours post-vaccination.

The next day, 24 hours after the vaccine application, the physician removes the bandage.

* these products will be furnished by Charité Universitätsmedizin (Clinical research center for hair and skin physiology), Berlin, Germany.

Outline and duration of treatment:
The volunteers will receive only one injection.

<table>
<thead>
<tr>
<th>Randomization arm</th>
<th>D0 vaccination</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>TC</td>
</tr>
<tr>
<td>B</td>
<td>ID</td>
</tr>
<tr>
<td>C</td>
<td>IM</td>
</tr>
</tbody>
</table>

6.2. Drug circuit

This paragraph defines the key points of the circuit by which the sponsor makes evaluated medications available.

6.3. Initial supply to the center

The vaccines:
The AGEPS Department of Clinical Trials is responsible for the regulatory labeling and for supplying the medications to the CIC for the trial.

The labeling must indicate at least:
- the sponsor’s name and address
- the study codes
- the statement: "For biomedical research only"

A detachable sticker, intended to be placed on the vaccination form, will improve the traceability of the batches. The vaccines will be addressed to the in-house pharmacy at Cochin Hospital on receipt of the request for initial supplies issued by the CRA at the study set-up visit. (shipper's cold chain).

Contacts:

For any additional information about this circuit or in the case of problems, please contact the Pharmaceutical Management Unit of Institutional Clinical Trials, AGEPS, AP-HP (UGPECI). You can contact either the secretary, who will refer you according to your needs, or you may directly contact the persons concerned.

Secretariat
Tel. 01 46 69 14 02
Fax. 01 46 69 14 09

Pharmacists responsible for the study:
Kamyl BAGHLI /Annick TIBI
01 46 69 14 02

AGEPS Project head: F. CAPELLE
01 46 69 90 73

The products necessary for the TC administration of INTANZA will be sent directly by the Charité Universitätsmedizin, Berlin, to the CIC.

6.4. Storage conditions for experimental drugs

The experimental drugs will be stored between + 2 and + 8°C. Any temperature incident must be reported without delay to the AGEPS Department of Clinical Trials, which will manage the situation with Sanofi-Pasteur MSD and will, when necessary, arrange to exchange the supplies.

6.5. Dispensing treatment units

The vaccines will be stored by the in-house pharmacy and dispensed on presentation of a prescription made out to a name specific to this study.

6.6. Methods for monitoring adherence to treatment and returning treatments for destruction

Administration
The traceability of the vaccine administrations will be ensured with a vaccination form for each volunteer (nominative form included in the source file) on which the detachable sticker from the vaccine box has been attached.

The syringes used will be destroyed by the department that administered the vaccine.

Accounting
The pharmacy will manage the stock inventory on a provisional basis of two shipments. The in-house pharmacy of Cochin Hospital will send a request to DEC-AGEPS once the local inventory reaches 5 units of INTANZA or 10 units of VAXIGRIP.

Unused units will be returned to the pharmacy and stored until the visit of the CRA handling the product accounting.
Once all the treatments have been accounted for, and the sponsor's authorization obtained, the in-house pharmacy will destroy all remaining products, according to its local circuit. A written report of destruction will attest to this onsite destruction.

6.7. **Patient card**

In application of the obligations of Good Manufacturing Practices, dated May 26, 2006, a patient card will be systematically provided to each volunteer. It will state "Please keep this card with you at all times" and it will specify the name, address, and telephone number of the investigator, or of the principal contact (if different) for information about the experimental product or study, the study codes, the volunteer's identifier in the study, the nature of the study product, and the lot number of the commercial package.

Recto:

Verso:
6.8. **Authorized and forbidden medications and treatments**

- Seasonal influenza vaccine other than that administered in this study is contraindicated as is any other vaccination in the month before inclusion in the trial (2 weeks for inactivated vaccine) and in the 90 days after inclusion.

  If another vaccine is administered during the trial, the investigator must note its commercial name, lot number, and date of administration in the e-CFR in the appropriate place as well as in the source file.

- All systemic immunomodulatory or immunosuppressant treatments are forbidden throughout the entire study.

- Any medication taken by the volunteer at inclusion and during the trial must be mentioned in the CFR. Its commercial name, generic name, daily dose, route of administration, start and finish dates, as well as the indication for which it was prescribed must be reported in the CRF and in the source file.

7. **DESCRIPTION OF THE RULES FOR PERMANENTLY OR TEMPORARILY STOPPING TREATMENT OR WITHDRAWING FROM THE STUDY**

7.1. **RULES FOR PERMANENT PERMANENTLY OR TEMPORARILY WITHDRAWING FROM THE ALL OR PART OF THE STUDY**

The trial can be interrupted for administrative reasons or in cases where new data may be available about the trial product and/or on the advice of the sponsor, scientific council, and/or the PPC.

If the trial is stopped prematurely or suspended, the sponsor must inform the center investigators, the regulatory authorities, and the PPC of the reason for stopping or suspension.

7.2. **Criteria and methods of the early withdrawal or exclusion of a study participant**

The investigator can decide to stop the vaccination process of a volunteer during V1 if an event occurs that is a definitive contraindication:
- onset of a pregnancy
- onset of a serious or severe adverse event that may be linked to the product
- onset of influenza
- an allergic reaction to one of the vaccine components after administration

  In these cases, the volunteer can, if he/she wishes, continue the study and the follow-up visits (V2, V3, and V4) and thus be included in the analysis of the tolerance, effectiveness, and immunogenicity of the vaccine.

The investigator can decide to stop a volunteer’s participation in the study at any moment should any exclusion criterion appear other than those mentioned above.

7.3. **Volunteer dropping out of the trial**

Volunteers can leave the study at any moment if they decide they want to, regardless of the reason. Withdrawal from the trial may also be justified by the investigator. In this case the investigator must ensure that the reason for dropping out is not associated with the occurrence of an adverse event. The cause for dropping out during the trial will be specified in the case report form (CRF) and reported in the source file.

When a volunteer withdraws from the trial, it is imperative to ask if:
- they are withdrawing their consent, in which case the data collected about them must not be included in the statistical analysis or in the study results.
- or if they are withdrawing from the trial without withdrawing their consent, in which case these data can be included in the statistical analysis and in the results.

7.4. Procedure for volunteers lost to follow-up

Any prolonged interruption in the clinical or laboratory follow-up of a volunteer is considered a "loss to follow-up". For these volunteers, the CRF must be completed through the date of their last actual visit. In this case, the investigator must conduct an investigation to determine the cause and report it in the source file and the CRF.

7.5. Modalities and calendar of data collection

Volunteers with an allergy or a pregnancy or an allergic reaction to one of the vaccine components after administration (see paragraph 7.2) can, if they desire, continue the study through M5 in following the study outline.
Volunteers who have withdrawn from the study before vaccination will not be followed up as part of the protocol.

8. DATA MANAGEMENT

8.1. DATA COLLECTION AND ANALYSIS

- An electronic CRF (e-CRF) (Cleanweb, Telemedicine, S.A.) will be developed by a data manager of the URC-East, in collaboration with the investigator’s team and the study biostatistician.

- A self-monitoring notebook will be given to each volunteer at V1, the vaccination visit. It will allow them to note the possible onset of local reactions (monitoring the injection site) and systemic events (taking temperature to check for fever, headaches, muscle pain…) that might occur between 2 visits. These data will be collected at V2 and V3, reviewed, discussed with the volunteer and finally transcribed in the CRF at the end of the study.

- All consultations or hospitalizations, as well as the treatments received, will also be noted in the CRF.

- Volunteers' identification will be managed by a number including:
the center number, study entry number, initial of the last name and initial of first name.
Example: 001-0001-NP
- The immunological data from the analyses performed from the blood samples (indirectly anonymized) will be transmitted directly to the biostatistician by Dr Combadière’s immunology laboratory, Inserm Unit U945, Paris.

8.2. Identification of all data to collected directly in the CRFs, which will be considered to be source data

The information reported in the self-monitoring notebook given to each volunteer at V1 (vaccination visit) will be considered source data.

9. STATISTICS

9.1. DESCRIPTION OF THE STATISTICAL METHODS

No interim analysis is planned.

The analysis will be performed on an intention-to-treat basis.

The initial characteristics of the volunteers will be compared between the three groups (A, B, and C), to ensure their comparability and the successful execution of the randomization process. The qualitative variables will be compared by a Chi square test or Fisher’s exact test, as appropriate. The quantitative variables will be compared by a t test or a non-parametric test, when appropriate.

The frequency and type of protocol deviations and the frequency of early withdrawals from the vaccination process and from the study and their causes will be compared between groups A, B, and C by Fisher’s exact test.

Analysis of the principal criterion:

The mean difference (D21-D0) of the CD8 cell responses induced will be compared between the three groups by a non-parametric test.

Analysis of secondary criteria.

- Tolerance
  The serious and non-serious AEs will be described in detail by group (mean number per volunteer, frequency, type of AE).
  The frequency of serious and non-serious AEs and their type will be compared between the groups by an appropriate test (see comparison of initial characteristics).

- Memory B cell responses at D21
  The mean differences in the percentage of memory B cells (D21-D0) and (M5-D0) will be compared between groups A, B, and C by Student’s t test or a non-parametric test, as appropriate.

9.2. Number of persons whom it was planned to include in the study

The sample size for this study does not depend on a statistical hypothesis but on the feasibility of the performance of this pilot study.

9.3. Degree of statistical significance planned

The tests will performed at a threshold of significance of 5%

9.4. Method for taking missing, unused, or invalid data into account

The missing values will not be replaced except for the principal criterion: If the value at D21 is missing, the value at D0 will replace it.
9.5. **Management of modifications to the analysis plan of the initial strategy**

If any modification is made to the initial plan of analysis, it will be documented in the final study report.

9.6. **Selection of subjects to be included in the analyses**

All volunteers randomized into the study will be analyzed.

10. **SAFETY ASSESSMENT**

10.1. **DESCRIPTION OF THE INDICATORS FOR ASSESSING SAFETY**

10.1.1. **Adverse events**

**Adverse event**: Any noxious event occurring in a subject participating in biomedical research, whether or not the event is linked to the research or the study product.

10.1.2. **Adverse effect of the experimental treatment**

- **Adverse drug reaction (AE)**: *any noxious and undesired reaction to an experimental drug regardless of the dose administered.*

The following will be considered to be adverse effects linked to the study treatment: (see. SPC for the influenza vaccine, in the study appendix 19.4):

- **Local reactions at the injection site**: erythema, edema, pain, ecchymoses, induration. They last for 1 to 2 days and are of low intensity.
- **General reactions**: headaches, sweating, myalgia, arthralgia, fever, feeling of faintness, shivering, fatigue. They last for 1 to 2 days and are of low intensity.
- **Reactions called systemic**: fever, feeling of faintness, myalgia, and headaches. These reactions occur in 1 to 10% of cases, generally 6 to 12 hours after vaccination, and persist for 1 to 2 days.

10.1.3. **Serious adverse event or effect (SAE)**

- **Serious adverse events or effects (SAEs)**: any adverse event or effect that:
  - causes death,
  - threatens the life of a person who is participating in biomedical research,
  - requires hospitalization or the prolongation of hospitalization,
  - induces an important or lasting disability,
  - is expressed by an anomaly or congenital malformation,

And if related to a drug, regardless of the dose administered.

Other adverse events not meeting the definition of seriousness above must also be **reported immediately**:

- events requiring medical intervention to prevent their deterioration to one of the conditions described above
- potentially serious events in the investigator’s judgment.

10.1.4. **Unexpected adverse effect of the experimental treatment**

**Unexpected adverse effect** designates any adverse effect of the product, the nature, severity, or course of which do not accord with the SPC for authorized drugs or the investigators’ brochure for non-authorized drugs.
All the events presenting one of the criteria of seriousness\* noted below must be reported, with the exception of those previously identified:

\*Criteria of seriousness:
1. Death
2. Life-threatening situation
3. Requires or prolongs hospitalization
4. Long-term sequelae
5. Congenital malformation or anomaly
6. Event judged serious by the Investigator (specify the reason)
7. Grade 4 unexpected adverse event possibly linked to the study vaccine

ATTENTION: any discovery of a PREGNANCY during a biomedical study must be immediately reported to the sponsor and must be followed up until delivery.

10.1.5. New fact
Any new item of safety information that may lead to a reassessment of the benefit/risk ratio of the study or the study drug, or that may be sufficient to envision modifications in the administration of the study drug or in the conduct of the study.

10.2. Planned methods and calendar for the measurement, collection, and analysis of the safety variables
The Scientific Committee will meet before study start-up and then every 6 months. The meeting of the scientific committee will be the occasion to assess the advancement of the trial, and to provide feedback to all participants at the inclusion center.

10.3. Procedures set up for the recording and reporting of adverse events
Adverse events:
Any adverse event that is not serious according to the definition above but is observed during the study or in its aftermath shall be reported in the CRF in the section planned for this purpose.

One event must be reported per item. The event can correspond to a symptom, diagnosis or examination result considered significant. All the clinical or other elements helping to describe the event thoroughly shall be reported.

Serious adverse events (SAEs):
The investigators must immediately notify the sponsor, AP-HP, of any serious adverse events, such as those defined in appendix 19.3.
The investigator shall complete the serious adverse event form (from the study CRF) and send it to the DRCD by fax at 01 44 84 17 99 (if possible, after an immediate telephone call to 01 44 84 17 23 in the case of unexpected death or life-threatening situation).
The investigator must also inform the URC-East (Tel.: 01 49 28 22 02/Fax: 01 49 28 28 13).
For each serious adverse event, the investigator must express an opinion about the causal link of the event with the experimental drug and the other possible treatments.

It may not be possible to obtain information relative to the description and assessment of an adverse event within the time limit for an initial report.

Thus the clinical course as well as the results of clinical work-ups and diagnostic and/or laboratory examinations or any other information enabling an adequate analysis of the causal relation shall be reported:
- either on the initial SAE report, if this information is immediately available,
- or later and as rapidly as possible, by faxing a new complete SAE report (and stating that it is a follow-up to a previously reported SAE and the tracking number).

All reports made by the investigators must identify each subject participating in the study by the unique code number attributed to each subject.

In a report of the death of a study volunteer, the Investigator shall communicate to the sponsor all the additional information requested (hospital notes, autopsy results, etc.).

Any new fact occurring in the study or in the study context, coming from data in the literature or ongoing research, must be reported to the sponsor.

10.4. Report of serious adverse events to the health authorities

This will be provided by the DRCD adverse drug reaction reporting department after evaluation of the seriousness of the adverse event, the causal link with the experimental drug and the other possible treatments, as well as the unexpected character of the adverse effects.

All suspected unexpected SAEs shall be reported by the sponsor to the competent authorities within the legal deadlines.

The PPC and the study investigators must be informed of all unexpected serious adverse effects.

All safety data or any new fact that might significantly modify the evaluation of the risk/benefit ratio of an experimental drug or study, or that might lead to envisioning modifications concerning the administration of the drug or the conduct of the study shall be transmitted by the sponsor to the competent authorities, the PPC, and the study investigators. For example:
- Any clinically significant increase in the frequency of an expected serious adverse effect
- Suspicion of unexpected serious adverse effect in volunteers who have completed the trial and reported by the investigator to the sponsor, as well as reports of potential follow-up;
- Any new fact concerning the execution of the clinical study or the development of the drug when this new fact might negatively affect the volunteers' safety. For example:
  - A serious adverse event likely to be related to the trial's diagnostic investigations and procedures and that might modify the operation of this trial;
  - A significant risk to the trial population, such as, for example, the ineffectiveness of the drug used in the treatment of a life-threatening disease
  - Significant safety results from a recently completed animal study (such as a study of carcinogenicity),
  - A anticipated stop or temporary interruption for safety reasons of a trial conducted with the same drug in another country,
  - An unexpected serious adverse effect linked to a non-experimental drug and necessary for the operation of the trial.
- The recommendations of the independent monitoring committee, if any, and if relevant to human safety,
- Any unexpected serious adverse effect transmitted to the sponsor of a clinical trial conducted in another country of the same drug.

10.5. **Modalities and duration of follow-up of individuals after the onset of an adverse event**

Follow-up is required of any volunteer with an adverse event until it is resolved or stabilized.

- If the event is not serious, its course will be noted on the relevant section of the CRF.
- If the event is serious, follow-up of the SAE must be sent to the DRCD.

10.6. **Management in the case of pregnancy**

Once the investigator in charge of monitoring the volunteer knows about the pregnancy, he/she must send an SAE report to the URC-East and the DRCD by fax.

Any pregnancy detected at visit V1 before vaccination is an exclusion criterion. For any pregnancy detected during the trial after V1 (particular conditions; see paragraph 7.2), the volunteer may, if she wants, continue the study to M5 in accordance with the study calendar.

10.7. **Specific committees for the study**

**Steering committee**

A steering committee will be composed of the physicians initiating the project, the biostatistician responsible for the project, and the representatives of the sponsor and of the Clinical Research Unit named for this study.

It will define the general organization and conduct of the study and coordinate all information.

It will initially determine the methodology and will decide during the study how to manage unexpected circumstances, will monitor the course of the study, in particular in terms of tolerance and adverse events.

**Scientific Committee**

The **Scientific Committee** of Fluway will include at least one representative of each participating laboratory/department: Pr Odile Launay (principal investigator), Dr. Fabrice Carrat (biostatistician), Dr. Béhazine Combadière (scientific director), Lilia Ben Slama (clinical study coordinator), Cécile Kédzia (DRCD project leader); Alexandra Rousseau (study biostatistician) and Laura Wakselman (clinical research project coordinator (URC), Angèle Soria (Head of the clinical dermatology and allergy department, Hospital Tenon, Annika Vogt, Charité Universitätsmedizin, Berlin.

Its task is to make all important decisions requested by the principal investigator concerning the good conduct of the trial and compliance with the protocol. It verifies the ongoing stability of the benefit-risk ratio. It obtains information from the trial's Centre of Methodology and Management of trial progress, problems, and results. It decides on all relevant modifications of the protocol necessary for the continuation of the trial, especially:

- steps to facilitate recruitment for the trial,
- protocol amendments before their presentation to the PPC,
- decisions to open or close participating sites,
- steps to provide optimal safety to trial participants,
- discussion of the results and the publication strategy.

The Scientific Committee can propose prolonging or interrupting the trial if the rate of inclusion is too slow, or if there are too many volunteers lost to follow-up or major protocol violations or for medical and/or administrative
reasons. If people working on the study suggest new examinations of the study material that are not planned in the protocol, the scientific council will study them and define the conditions of data access and the rules of publication of the results.

In relation to monitoring tolerance of trial products and to treatment strategy, the Scientific Committee takes cognizance of the annual report on tolerance intended for the public health authorities and the PPC, discusses it, and validates it.

**Independent monitoring committee**

This study will not have an independent monitoring committee because the effects and events linked to the experimental treatments of the study (vaccines) and to the research procedures (blood samples) are well-known and well-tolerated. On the other hand, the procedure for TC vaccination does not appear likely to be a source of SAEs or of any notable risk (see publications 24, 50). This study has been classified as a B risk.

11. **RIGHT OF ACCESS TO DATA AND SOURCE DOCUMENTS**

Persons with direct access to the data in accordance with the legislative and regulatory provisions in force, specifically, articles 1121-3 and R.5121-13 of the Public Health Code (for example, the investigators, those responsible for quality control, the study monitors, clinical research assistants (CRAs), auditors, and all individuals whose work involves collaboration with clinical trials) shall take all necessary precautions to ensure the confidentiality of information related to any experimental drugs, trials, and participants, especially concerning their identity and the results. The data collected by these persons during quality controls or audits shall be anonymized.

12. **QUALITY CONTROL AND ASSURANCE**

The study shall be overseen according to the sponsor's standard operating procedures.

Its implementation at the CIC and the management of the volunteers will comply with the current Good Clinical Practices and with the Declaration of Helsinki.

12.1. **Monitoring procedures**

As the study is classified as risk B, monitoring will be performed at the B level.

Representatives of the sponsor will conduct inspections of the investigative centers at a rhythm corresponding to the patient follow-up schema in the protocol, to inclusions, and to the risk level attributed to the study.

- Study set-up visit to the CIC: before inclusion, to set up the protocol and become acquainted with the different participants in this study.

Before the study starts, each investigator participating in the study shall provide the sponsor with a recent copy of his/her curriculum vitae, dated and signed and including his/her membership number in the Ordre des Médecins. Moreover, the principal investigator shall, when appropriate, designate by name one or several co-investigators in his/her center who might include volunteers and complete a "delegation of task" form. Each co-investigator will provide the sponsor with a recent copy of his/her CV, dated and signed. The principal investigator shall sign a scientific undertaking to comply with the terms of the Declaration of Helsinki and to conduct this study in accordance with Good Clinical Practices and according to the protocol. A dated, signed copy of this undertaking shall be provided to the sponsor.

All of the study documents (protocol, eCRF, trial drug supply channel, randomization procedure, sample transport chain, trial contacts, SPCs, etc.) will be provided to the investigator during the study set-up visit by the CRA.

The CRA responsible for the study will conduct a study set-up visit to the in-house pharmacy of the participating center.
- During the following visits, the CRA will review the CRFs as the study advances. The principal investigator of each center and the other investigators who include or provide follow-up to volunteers agree to meet with the CRA at regular intervals. During these onsite inspections and in accordance with Good Clinical Practices, the following items will be reviewed:
  - Compliance with the protocol and the procedures defined for the study,
  - Verification of the volunteers' informed consent,
  - Examination of the source documents and comparison with the data in the CRFs for accuracy, missing data, and data consistency according to the rules of the DRCD procedures.
- Closing visits: recovery of the CRFs, pharmacy accounting, study documents, archiving.

12.2. Transcription of CRF data

The study data will be collected with a CleanWEB electronic CRF as part of the public contract between AP-HP and TELEMEDICINE TECHNOLOGIES S.A., declared on 17/11/2003 (as N° 033845) and renewed 21/11/2006 (as N° 063844). These data will be centralized on a server hosted at the Department of Operational Services (DSO) of the AP-HP, 67 boulevard Bessières, 75017 PARIS.

All the information required by the protocol must be furnished in the e-CRFs and investigators must explain each item of missing data.

Data must be entered in the e-CRFs as obtained, regardless of whether these are clinical or other data. Data observed to be erroneous on the e-CRF will be corrected by an investigator, who can be connected to the software with his/her access codes (identifier and password).

These codes are strictly personal and confidential and may not in any case be provided to a third person; they help to maintain the confidentiality of the data and to authenticate interventions. The access codes are associated with an electronic signature system that validates the data entered by the Investigator. Each signature is time-stamped and recorded in the study's audit trail. These signed data cannot be modified, but the Investigator can cancel his/her signature to correct a data item. The cancellation of the signature is also recorded by a time-stamp.

The anonymity of the subjects will be ensured by using their research number (including their initial) to the maximum extent possible on all the documents it requires, or by deletion by appropriate means (white-out) of names in the copies of source documents, intended to document the study.

The file of computerized data will be reported to the CNIL in accordance with the procedure appropriate to the case.

13. LEGAL AND ETHICAL CONSIDERATIONS

The Sponsor's role is defined by L. 2004-806 dated 9, August 2004. In this study, the AP-HP is the sponsor and the DRCD is responsible for fulfilling these regulatory tasks.

Before the research begins, all investigators will provide the Sponsor's representative with a copy of their personal curriculum vitae, dated and signed and including their membership number in the Order of Physicians and their RPPS (Répertoire Partagé des Professionnels de Santé, database of health-care professionals in France) number.

To be allowed to start the study, the AP-HP must, as sponsor, submit an application for authorization from the competent authority, ANSM. The competent authority specified in Article L. 1123-12 shall rule on the safety of the biomedical research participants with particular regard to the safety and quality of the products used in the study, based, where appropriate, on current standards, the conditions of the product use, and the safety of the participants in view of the procedures performed and methods used, as well as the arrangements made for the participants' follow-up.

13.2. **Request for an opinion from the Patient Protection Committee**

In accordance with article L. 1123-6 of the Public Health Code, the research protocol must be submitted by the Sponsor to a Patient Protection Committee. The Sponsor must report the opinion of this committee to the competent authority before the study starts.

13.3. **Modifications**

The DRCD must be informed of all plans to modify the protocol by the investigator-coordinator. The modifications shall be qualified as substantial or not substantial.

A substantial modification is one that is likely, in one way or another, to modify the guarantees provided to the people who agreed to participate in this biomedical research (modification of an inclusion criterion, prolongation of the duration of inclusion, participation of new centers...).

After the study has started, any substantial modification at the sponsor's initiative must obtain, before implementation, authorization from the PPC and from the competent authority. If necessary, the committee will ensure that participants are asked to consent to the new conditions and guarantees.

Any extension of the research (any profound modification of the treatment scheme or populations included, prolongation of treatments or addition of treatment procedures not initially planned in the protocol) must be considered to be a new study.

The Sponsor must request authorization of any substantial modifications by the ANSM and the PPC.

13.4. **CNIL Declaration**

The law requires that the declaration of computerized personal data files collected for the study must be made before the research actually begins.

In January 2006, the CNIL (Commission on Information Technology and Freedom) established reference methods for the treatment of personal data in the framework of biomedical research, as defined by L. 2004-806 dated 9 August, 2004, because these data are covered by articles L. 1121-1 et seq of the Public Health Code.

These methods allow a simplified reporting procedure when the nature of the data collected in the study is compatible with the list provided by the CNIL in its reference document.

When the protocol includes verification of data quality by a CRA representing the Sponsor and falls within the scope of the simplified CNIL procedure, the DRCD in its role as Sponsor shall ask the data manager to undertake in writing to comply with the simplified reference method MR001.

13.5. **Provision of information and collection of consent**

Written informed consent from all persons participating in research must be obtained by the study physicians-investigators, who must be members of the Order of Physicians and declared as physicians-investigators to the
Sponsor, before any action is taken as part of this study protocol and regardless of what action, in compliance with relevant regulations.

Information will be given orally and in writing in the first part of the information and consent form. The information shall be drafted in clear language and be perfectly understandable to the person whose consent is sought. It must contain all the elements about which the person is required to be informed according to the Public Health Code, article L 1122-1.

The person's consent to participate in the study must be collected in writing in the second part of the information and consent form. This second part must be drafted in clear language and be perfectly understandable to the person participating in the study. It must include all of the elements to which the person is consenting. The participant provides consent by placing his/her signature on the form and writing his/her first and last name and the date, all by hand.

A maximum reflection period of 15 days is allowed.

The information and consent form is a document that must be approved by the PPC, when it examines the protocol, before the study starts.

13.6. Final trial report

The final study report will be written jointly by the principal investigator and the biostatistician of this study. This report will be submitted to the investigators for an opinion. Once a consensus is obtained, the final version must be endorsed by the signature of each investigator and addressed to the sponsor as soon as practicable after the end of the study. A report drafted according to the reference outline of the competent authority must be forwarded to this authority and the PPC within a year after the end of the study, defined as the last follow-up visit of the last subject included. This deadline is shortened to 90 days if the study is stopped early.

14. DATA TREATMENT AND ARCHIVING

The documents of a study covered by the law concerning biomedical research must be archived by all parties for a duration of 15 years after the completion of the study.

(See BPC, section 8: essential documents)

This indexed archive shall include:

- Copies of the letter of authorization from ANSM and of the PPC's mandatory opinion
- The successive versions of the protocol (identified by version n° and date),
- Copies of all correspondence with the sponsor,
- The written consent of the subjects, under seal (for minors, signed by those with parental authority) with the corresponding list or register of inclusions,
- All completed, validated CRFs for all subjects,
- All appendices specific to the study,
- The final study report from the study's statistical analysis and quality control (copy transmitted to the sponsor),
- Certificates of any audits performed during the study
The database on which the statistical analysis was performed must also be archived by the person responsible for the analysis (on paper or computerized).

15. INSURANCE AND FUNDING

15.1. INSURANCE

Assistance Publique-Hôpitaux de Paris is the sponsor of this study. In accordance with the law on biomedical research, AP-HP has purchased an insurance policy from the HDI GERLING company for the entire duration of the research, guaranteeing its own civil liability as well as that of all participants (physicians or others involved in the research) (Act No°2004-806, CSP Art L.1121-10).

AP-HP reserves the right to interrupt this study at any moment for medical or administrative reasons; in this case, the Investigator will be notified.

15.2. Funding

This study is funded by the 2012 INSERM DGOS translational research project

16. SCIENTIFIC UNDERTAKING

Each investigator undertakes to comply with all legal obligations under the law and to conduct this study according to Good Clinical Practices, adhering to the terms of the Declaration of Helsinki then in effect. To do so, a copy of this scientific undertaking (DRCD form document) dated and signed by each investigator of each clinical department of all participating centers shall be provided to representatives of the sponsor.

17. RULES CONCERNING PUBLICATION

AP-HP is the owner of the data from this project and no use by or transmission to a third party may occur without its prior approval.

The results will be reported in a publication and submitted to a peer-reviewed journal. The order in which the authors are listed will be defined on the basis of each investigator's effective contribution to recruitment and each steering committee member's contribution to the conception and performance of the study and to the writing of the article, in accordance with the rules that will be defined at the first investigators' meetings.

The authors will be listed in the following order: (first author), study biostatistician (2nd or 3rd author), (last author).

The first authors of any publications shall be the people who actually participate in developing the protocol, implementing it, and drafting its results.

Assistance Public- Hospitals de Paris must be mentioned as the sponsor of this biomedical research and source of financial support where appropriate. The terms "Assistance Public- Hospitals de Paris" must appear in the authors' address.
Any publication, regardless of its nature, that received assistance from CIC BT505 as part of its responsibilities for design, protocol preparation, implementation, analysis, and interpretation, must recognize that assistance by an explicit mention in the publication.

URC-East will be thanked for its logistic support under the heading "Acknowledgment".
AGEPS will be thanked under the heading "Acknowledgment".

18. REFERENCES


43. Duggan ST, Plosker GL. Intanza 15 microg intradermal seasonal influenza vaccine: in older adults (aged >or=60 years). Drugs Aging;27:597-605.
19. Appendix

19.1. Declaration of Helsinki

Declaratio of Helsinki

World Medical Association Declaration of Helsinki

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 19th WMA General Assembly, Helsinki, Finland, June 1949; amended by the 29th WMA General Assembly, Tokyo, Japan, October 1975; 35th WMA General Assembly, Venice, Italy, October 1983; 41st WMA General Assembly, Hong Kong, September 1988; 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996; and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000

A. Introduction

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.

2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

5. In medical research on human subjects, considerations relating to the well-being of the human subject should take precedence over the interests of science and society.

6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of diseases. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.

7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.

8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. Basic principles for all medical research

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.

12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws, regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the
Declaration of Helsinki

subject of the research, even though the subject has given
consent.

16. Every medical research project involving human
subjects should be preceded by careful assessment of
predictable risks and burdens in comparison with foresee-
able benefits to the subject or to others. This does not
preclude the participation of healthy volunteers in medical
research. The design of all studies should be publicly
available.

17. Physicians should abstain from engaging in research
projects involving human subjects unless they are confident
that the risks involved have been adequately assessed and can
be satisfactorily managed. Physicians should cease any
investigation if the risks are found to outweigh the potential
benefits or if there is conclusive proof of positive and
beneficial results.

18. Medical research involving human subjects should only
be conducted if the importance of the objective outweighs
the inherent risks and burdens to the subject. This is
especially important when the human subjects are healthy
volunteers.

19. Medical research is only justified if there is a reasonable
likelihood that the populations in which the research is
carried out stand to benefit from the results of the research.

20. The subjects must be volunteers and informed
participants in the research project.

21. The right of research subjects to safeguard their
integrity must always be respected. Every precaution should
take to respect the privacy of the subject, the
confidentiality of the patient’s information and to minimize
the impact of the study on the subject’s physical and mental
integrity and on the personality of the subject.

22. In any research on human beings, each potential subject
must be adequately informed of the aims, methods, sources
of funding, any possible conflicts of interest, institutional
affiliations of the researcher, the anticipated benefits and
potential risks of the study and the discomfort it may entail.
The subject should be informed of the right to abstain from
participation in the study or to withdraw consent to
participate at any time without penalty. After ensuring that
the subject has understood the information, the physician
should then obtain the subject’s freely given informed
consent, preferably in writing. If the consent cannot be
obtained in writing, the non-written consent must be
formally documented and witnessed.

23. When obtaining informed consent for the research
project the physician should be particularly cautious if the
subject is in a dependent relationship with the physician or
may consent under duress. In that case the informed consent
should be obtained by a well-informed physician who is not
engaged in the investigation and who is completely
independent of this relationship.

24. For a research subject who is legally incompetent,
physically or mentally incapable of giving consent or is a
legally incompetent minor, the investigator must obtain
informed consent from the legally authorized representative
in accordance with applicable law. These groups should not
be included in research unless the research is necessary to
promote the health of the population represented and this
research cannot instead be performed on legally competent
persons.

25. When a subject deemed legally incompetent, such as a
minor child, is able to give consent to decisions about
participation in research, the investigator must obtain that
consent in addition to the consent of the legally authorized
representative.

26. Research on individuals from whom it is not possible to
obtain consent, including proxy or advance consent, should
be done only if the physical/mental condition that prevents
obtaining informed consent is a necessary characteristic of
the research population. The specific reasons for involving
research subjects with a condition that renders them unable
to give informed consent should be stated in the experi-
mental protocol for consideration and approval of the review
committee. The protocol should state that consent to remain
in the research should be obtained as soon as possible from
the individual or a legally authorized surrogate.

27. Both authors and publishers have ethical obligations. In
publication of the results of research, the investigators are
obliged to preserve the accuracy of the results. Negative as
well as positive results should be published or otherwise
publicly available. Sources of funding, institutional affilia-
tions and any possible conflicts of interest should be declared
in the publication. Reports of experimentation not in
accordance with the principles laid down in this Declaration
should not be accepted for publication.

C. Additional principles for medical
research combined with medical care

28. The physician may combine medical research with
medical care, only to the extent that the research is justified
by the potential prophylactic, diagnostic or therapeutic value.
When medical research is combined with medical care,
additional standards apply to protect the patients who are
research subjects.

29. The benefits, risks, burdens and effectiveness of a new
method should be tested against those of the best current
prophylactic, diagnostic, and therapeutic methods. This does
not exclude the use of placebo, or no treatment, in studies
where no proven prophylactic, diagnostic or therapeutic
method exists.

30. At the conclusion of the study, every patient entered
into the study should be assured of access to the best proven
prophylactic, diagnostic and therapeutic methods identified
by the study.

31. The physician should fully inform the patient which
aspects of the care are related to the research. The refusal of a
patient to participate in a study must never interfere with the
patient-physician relationship.

32. In the treatment of a patient, where proven prophylac-
tics, diagnostic and therapeutic methods do not exist or
have been ineffective, the physician, with informed consent
from the patient, must be free to use unproven or new
prophylactic, diagnostic and therapeutic measures, if in the
physician’s judgement it offers hope of saving life, re-
establishing health, or alleviating suffering. Where possible,
these measures should be the object of research, designed to
evaluate their safety and efficacy. In all cases, the conclusion
should be recorded and, where appropriate, published. The
other relevant guidelines of this Declaration should be followed.
19.2. Adverse event scoring for completing the CRF

ANRS Scale to Grade the Severity of Adverse Events in Adults

Version n° 1.0  4 November 2008

This severity scale is a working guide intended to harmonise evaluation and grading practices for symptomatology in ANRS biomedical research protocols.

In practice, the items evaluated are grouped according to the system taking the form of a non-exhaustive symptomatic table (and not a classification of pathologies). Our choices focus on the most frequently observed clinical and biological signs or those whose monitoring is essential to ensure the protection of the subjects participating in the research.

For abnormalities NOT found elsewhere on the Table, refer to the scale below to estimate grade of severity:

<table>
<thead>
<tr>
<th>GRADE 1</th>
<th>Mild</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mild or transient discomfort, without limitation of normal daily activities; no medical intervention or corrective treatment required.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GRADE 2</th>
<th>Moderate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mild to moderate limitation of normal daily activities; minimal medical intervention or corrective treatment required.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GRADE 3</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Marked limitation of normal daily activities; medical intervention and corrective treatment required, possible hospitalisation.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GRADE 4</th>
<th>Life-threatening</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Severe limitation of normal daily activities; medical intervention and corrective treatment required, almost always in a hospital setting.</td>
</tr>
</tbody>
</table>

Abbreviations used in the table:

ULN : Upper Limit of Normal
RBC : Red Blood Cells
FEV1 : Forced Expiratory Volume in one second
EMG : Electromyogram
Prothrombin Time (%) : Corresponds to Quick time (sec)
aPTT : activated Partial Thromboplastin Time

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Please note that this scale was devised for use in HIV, HCV or HBV related pathologies.
### ANRS scale to grade the severity of adverse events in adults (version no 1.0 4 November 2008)

#### GRADES

<table>
<thead>
<tr>
<th>Grades</th>
<th>Grade 1 (Mild)</th>
<th>Grade 2 (Moderate)</th>
<th>Grade 3 (Severe)</th>
<th>Grade 4 (Life-threatening)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HAEMATOLOGY</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Haemoglobin (g/dl)</td>
<td>8.0 – 9.4</td>
<td>7.0 – 7.99</td>
<td>6.5 – 6.99</td>
<td>&lt; 6.5</td>
</tr>
<tr>
<td>2 Leucocytes (/mm³)</td>
<td>3 000 – 3 900</td>
<td>2 000 – 2 999</td>
<td>1 000 – 1 999</td>
<td>&lt; 1 000</td>
</tr>
<tr>
<td>3 Neutrophils (/mm³)</td>
<td>1 000 – 1 500</td>
<td>750 – 999</td>
<td>500 – 749</td>
<td>&lt; 500</td>
</tr>
<tr>
<td>4 Platelets (/mm³)</td>
<td>75 000 – 99 000</td>
<td>50 000 – 74 999</td>
<td>20 000 – 49 999</td>
<td>&lt; 20 000 or generalized petechiae</td>
</tr>
<tr>
<td>5 Prothrombin Time (%)</td>
<td>/</td>
<td>45 – ≤ 70</td>
<td>20 – &lt; 45</td>
<td>&lt; 20</td>
</tr>
<tr>
<td>6 aPTT</td>
<td>1.0 – 1.66 x ULN</td>
<td>&gt; 1.66 – 2.33 x ULN</td>
<td>&gt; 2.33 – 3.0 x ULN</td>
<td>&gt; 3.0 x ULN</td>
</tr>
<tr>
<td><strong>BIOCHEMISTRY</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatic and pancreatic biochemistry</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7 AST (SGOT) (UI/l)</td>
<td>1.25 – 2.50 x ULN</td>
<td>&gt; 2.50 – 5.0 x ULN</td>
<td>&gt; 5.00 – 10.0 x ULN</td>
<td>&gt; 10.0 x ULN</td>
</tr>
<tr>
<td>8 ALT (SGPT) (UI/l)</td>
<td>1.25 – 2.50 x ULN</td>
<td>&gt; 2.50 – 5.0 x ULN</td>
<td>&gt; 5.00 – 10.0 x ULN</td>
<td>&gt; 10.0 x ULN</td>
</tr>
<tr>
<td>9 GAMMA GT (UI/l)</td>
<td>1.25 – 2.50 x ULN</td>
<td>&gt; 2.50 – 5.0 x ULN</td>
<td>&gt; 5.00 – 10.0 x ULN</td>
<td>&gt; 10.0 x ULN</td>
</tr>
<tr>
<td>10 Alkaline phosphatase (UI/l)</td>
<td>1.25 – 2.50 x ULN</td>
<td>&gt; 2.50 – 5.0 x ULN</td>
<td>&gt; 5.00 – 10.0 x ULN</td>
<td>&gt; 10.0 x ULN</td>
</tr>
<tr>
<td>11 Hyperbilirubinaemia (µmol/l)</td>
<td>1.25 – 2.50 x ULN</td>
<td>&gt; 2.50 – 5.0 x ULN</td>
<td>&gt; 5.00 – 10.0 x ULN</td>
<td>&gt; 10.0x ULN</td>
</tr>
<tr>
<td>12 Amylaseaemia / Lipasaemia / Pancreatitis (UI/l)</td>
<td>≥1.25 – 2.50 x ULN</td>
<td>&gt; 2.50 – 5.0 x ULN</td>
<td>&gt; 3.0 x ULN with acute abdominal pain and/or imaging indicating acute pancreatitis.</td>
<td>&gt; 3.0 x ULN with abdominal pain and signs of shock.</td>
</tr>
<tr>
<td>13 CPK (UI/l)</td>
<td>1.25 – 2.50 x ULN</td>
<td>&gt; 2.50 – 5.0 x ULN</td>
<td>&gt; 5.00 – 10.0 x ULN</td>
<td>&gt; 10.0 x ULN</td>
</tr>
<tr>
<td>Lipid status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14 Hypertriglyceridaemia (mmol/l)</td>
<td>/</td>
<td>4.50 – 8.59</td>
<td>8.60 – 13.70</td>
<td>&gt; 13.70</td>
</tr>
<tr>
<td>15 Hypercholesterolaemia (mmol/l)</td>
<td>&gt;ULN – 7.75</td>
<td>&gt;7.75 – 10.34</td>
<td>&gt;10.34 – 12.92</td>
<td>&gt;12.92</td>
</tr>
</tbody>
</table>
### Electrolytes / Evaluation of renal function / Metabolism

<table>
<thead>
<tr>
<th>GRADES</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>Hyponatraemia (mEq/l)</td>
<td>130 – 135</td>
<td>123 – 129</td>
<td>116 – 122</td>
</tr>
<tr>
<td>17</td>
<td>Hypernatraemia (mEq/l)</td>
<td>146 – 150</td>
<td>151 – 157</td>
<td>158 – 165</td>
</tr>
<tr>
<td>18</td>
<td>Hypokalaemia (mEq/l)</td>
<td>3.2 – 3.4</td>
<td>2.8 – 3.1</td>
<td>2.5 – 2.7</td>
</tr>
<tr>
<td>19</td>
<td>Hyperkalaemia (mEq/l)</td>
<td>5.6 – 6.0</td>
<td>6.1 – 6.5</td>
<td>6.6 – 7.0</td>
</tr>
<tr>
<td>20</td>
<td>Bicarbonate (mEq/l or mmol/l)</td>
<td>20.0 – 24.0</td>
<td>15.0 – 19.99</td>
<td>10.0 – 14.99</td>
</tr>
<tr>
<td>21</td>
<td>Creatininaemia (µmol/l)</td>
<td>1.0 – 1.50 x ULN</td>
<td>&gt; 1.50 – 3.0 x ULN</td>
<td>&gt; 3.0 – 6.0 x ULN</td>
</tr>
<tr>
<td>22</td>
<td>Blood Urea Nitrogen (UI/l)</td>
<td>1.25 – 2.5 x ULN</td>
<td>2.6 – 5.0 x ULN</td>
<td>5.1 – 10 x ULN</td>
</tr>
<tr>
<td>23</td>
<td>Hypocalcaemia (mmol/l)</td>
<td>1.95 – 2.10</td>
<td>1.75 – 1.94</td>
<td>1.50 – 1.74</td>
</tr>
<tr>
<td>24</td>
<td>Hypercalcaemia (mmol/l)</td>
<td>2.65 – 2.87</td>
<td>2.88 – 3.13</td>
<td>3.14 – 3.38</td>
</tr>
<tr>
<td>25</td>
<td>Hypophosphataemia (mg/dl)</td>
<td>2.0 – 2.4</td>
<td>1.5 – 1.9</td>
<td>1.0 – 1.4</td>
</tr>
<tr>
<td>26</td>
<td>Hyperuricaemia (µmol/l)</td>
<td>1.25 – 2.0 x ULN</td>
<td>&gt; 2.0 – 5.0 x ULN</td>
<td>&gt; 5.0 – 10.0 x ULN</td>
</tr>
<tr>
<td>27</td>
<td>Hypoglycaemia (mmol/l)</td>
<td>3.1 – 3.6</td>
<td>2.2 – 3.0</td>
<td>1.7 – 2.1</td>
</tr>
<tr>
<td>28</td>
<td>Hyperglycaemia (mmol/l)</td>
<td>6.1 – 7.0</td>
<td>&gt; 7.0 – 16.5</td>
<td>&gt; 16.5 without ketosis.</td>
</tr>
<tr>
<td>29</td>
<td>Hyperlactataemia (mmol/l) (venous blood sample)</td>
<td>2.0 – 2.99*</td>
<td>3.0 – 3.99**</td>
<td>4.0 – 4.99**</td>
</tr>
</tbody>
</table>

### Urinalysis

<table>
<thead>
<tr>
<th>GRADES</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>Proteinuria (dipstick)</td>
<td>+</td>
<td>++</td>
<td>≥ +++</td>
</tr>
<tr>
<td>31</td>
<td>Haematuria.</td>
<td>≥ 80 RBC/µl (dipstick).</td>
<td>≥ 200 RBC/µl (dipstick).</td>
<td>Macroscopic with or without clots.</td>
</tr>
</tbody>
</table>

* Lactataemia – GRADE 1: a confirmatory test is necessary within 8 to 10 days
** Lactataemia – GRADE 2, 3: a confirmatory test is necessary within 24 hours.

*** Lactataemia – GRADE 4: a confirmation test is necessary immediately.
### ANRS scale to grade the severity of adverse events in adults (version no 1.0 4 November 2008)

<table>
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<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
<td>Life-threatening</td>
</tr>
<tr>
<td><strong>Gastro-intestinal/hepatic/pancreatic abnormalities</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>32 Nausea.</td>
<td>Transient, normal diet.</td>
<td>Restricted diet for less than 3 days.</td>
<td>Restricted diet for more than 3 days.</td>
<td>Liquid only diet. Hospitalization required.</td>
</tr>
<tr>
<td>33 Vomiting.</td>
<td>Transient: 2 – 3 episodes / day or duration ≤ 1 week.</td>
<td>Repeated: 4 – 5 episodes / day or duration &gt; 1 week.</td>
<td>Solid/liquid vomiting for 24 h. Orthostatic hypotension. Perfusion required.</td>
<td>Hospitalization for hypovolemic shock.</td>
</tr>
<tr>
<td>34 Diarrhoea.</td>
<td>Transient, 3 – 4 stools / day, diarrhoea ≤ 1 week.</td>
<td>Persistent, 5-7 stools / day, diarrhoea &gt; 1 week.</td>
<td>&gt; 7 stools/day or requiring perfusion. Bloody stools.</td>
<td>Hospitalization, Hypovolemic shock, perfusion.</td>
</tr>
<tr>
<td>35 Constipation.</td>
<td>/</td>
<td>Moderate abdominal pain, 78 h without stools. Treatment required.</td>
<td>Meteorism. Requiring disimpaction or hospital treatment.</td>
<td>Meteorism with vomiting or occlusion.</td>
</tr>
<tr>
<td>36 Dysphagia.</td>
<td>Mild discomfort when swallowing.</td>
<td>Difficulty in swallowing but food intake possible.</td>
<td>Inability to swallow solids.</td>
<td>Inability to swallow liquids, perfusion required.</td>
</tr>
<tr>
<td>37 Oesophagitis.</td>
<td>Pyrosis occurring less than once a week</td>
<td>Pyrosis occurring at least once a week but relieved by PPIs*</td>
<td>Pyrosis occurring at least once a week but not relieved by PPIs*</td>
<td>Food intolerance and vomiting</td>
</tr>
</tbody>
</table>

*PPIs: proton pump inhibitors*
## ANRS scale to grade the severity of adverse events in adults (version no 1.0 4 November 2008)

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### Respiratory abnormalities

<p>| | | | | |</p>
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>38</td>
<td>Bronchospasm.</td>
<td>Transient, no treatment, FEV1 70% - &lt; 80%.</td>
<td>Permanent, Improvement under bronchodilation FEV1 50% - &lt; 70%.</td>
<td>Persistent under bronchodilation. FEV1 25% - &lt; 50%.</td>
</tr>
<tr>
<td>39</td>
<td>Dyspnoea</td>
<td>Dyspnoea upon exertion.</td>
<td>Dyspnoea during normal daily activities.</td>
<td>Dyspnoea at rest.</td>
</tr>
</tbody>
</table>

### Muscular abnormalities

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<tr>
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</thead>
<tbody>
<tr>
<td>40</td>
<td>Myalgia (excluding injection site).</td>
<td>Mild myalgia for less than 4 weeks. Not requiring analgesic treatment.</td>
<td>Presence of one of the following symptoms: 1 – Mild to moderate myalgia for more than 4 weeks and/or which may require treatment with level 1* analgesics. 2 – Predominance of difficulties upon exertion (difficulty in climbing stairs or rising from a sitting position). Can walk without assistance. Optional confirmation through the identification of biological (CPK), electromyographical (EMG) or histological (muscular biopsy) abnormalities.</td>
<td>Presence of one of the following symptoms: 1 – Moderate to severe myalgia for more than 4 weeks requiring treatment with level I/II* analgesics. 2 – Assistance required for walking and normal daily activities. Paraclinical confirmation recommended (CPK, EMG and/or muscular biopsy).</td>
</tr>
</tbody>
</table>
electrolytic disturbances and renal insufficiency. Paraclinical confirmation required (biology, EMG and/or muscular biopsy).

* Level I analgesics : Peripheral analgesics (paracetamol and/or salicylics or non-steroid anti-inflammatory drugs);
* Level II analgesics : Weak opiates (codeine, dextropropoxyphene), morphinic agonists-antagonists (buprenorphine, nalbuphine);
* Level III analgesics : Morphine.
**ANRS scale to grade the severity of adverse events in adults (version no 1.0  4 November 2008)**

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<tr>
<td><strong>Cardiovascular abnormalities</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>41 Arterial hypertension.</td>
<td>Transient or permanent. Increased blood pressure ≤ 20 mmHg and systolic BP 140-159 or diastolic BP 90-99.</td>
<td>Permanent. Increased blood pressure &gt; 20 mmHg and systolic BP 160-179 or diastolic BP 100-109.</td>
<td>Permanent. Systolic BP ≥ 180 or diastolic BP &gt; 110</td>
<td>Malignant or accelerated arterial hypertension.</td>
</tr>
<tr>
<td>42 Orthostatic hypotension.</td>
<td>Decreased systolic blood pressure ≤ 20 mmHg in orthostatic position. No treatment.</td>
<td>Decreased systolic blood pressure &gt; 20 mmHg, durable but corrected with liquid intake per os.</td>
<td>Perfusion required.</td>
<td>Hypovolemic shock requiring hospitalization.</td>
</tr>
<tr>
<td>43 Ventricular cardiac rhythm disorders.</td>
<td>/</td>
<td>Isolated ventricular extrasystoles, no treatment, symptomatic or asymptomatic.</td>
<td>Recurrent, persistent or symptomatic cardiac rhythm disorders. Treatment required.</td>
<td>Dysrhythmia requiring hospitalization.</td>
</tr>
<tr>
<td>44 Prolongation of the QT interval.</td>
<td>/</td>
<td>Man: &gt;450 and &lt; 500 ms Woman: &gt;470 and &lt;500 ms</td>
<td>&gt;500ms</td>
<td>&gt;500 ms with clinical symptoms (ventricular rhythm disorders, syncope, torsade de pointes)</td>
</tr>
<tr>
<td>45 Cardiac ischaemia.</td>
<td>/</td>
<td>Atypical pain under exploration.</td>
<td>Appearance of angina upon exertion, controlled with treatment.</td>
<td>Myocardial infarction, unstable angina, preinfarction syndrome.</td>
</tr>
<tr>
<td>46 Pericarditis.</td>
<td>Chance discovery of a small effusion during ultrasound scan</td>
<td>Moderate effusion with few symptoms. No treatment or intervention deemed necessary for the time being.</td>
<td>Moderate or significant symptomatic effusion but without tamponade. Treatment required and hospitalization to be considered.</td>
<td>Tamponade. Hospitalization and intervention required.</td>
</tr>
<tr>
<td></td>
<td>Stroke.</td>
<td>/</td>
<td>/</td>
<td>Transient Ischemic Attack (regressive focal neurological syndrome within 24 h).</td>
</tr>
<tr>
<td>---</td>
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<td>--------------------------------------------------------------------------------</td>
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<tr>
<td><strong>Endocrine abnormalities</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>52</td>
<td>Diabetes/hyperglycaemia.</td>
<td>Moderate fasting hyperglycaemia between 6.1 and 7 mmol/l. No immediate treatment required.</td>
<td>Fasting glycaemia: &gt; 7 mmol/l. Special diet required, possibly supplemented with oral antidiabetics.</td>
<td>Fasting glycaemia:&gt;16.5 mmol/l on an empty stomach, with or without clinical symptoms. Insulin therapy required.</td>
</tr>
<tr>
<td><strong>Cutaneous abnormalities</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>53</td>
<td>Cutaneous and/or mucosal eruptions.</td>
<td>Erythaema, Moderate pruritis.</td>
<td>Extended maculopapular eruption, with or without pruritis.</td>
<td>Extended papulovesicular or oozing eruption. Palpable purpura (suggestive of vasculitis). Polymorphous erythaema. Small-size cutaneous or mucous ulcerations.</td>
</tr>
<tr>
<td>54</td>
<td>Symptoms of immediate</td>
<td>Acute localised urticaria.</td>
<td>Giant urticaria,</td>
<td>Anaphylactic shock.</td>
</tr>
<tr>
<td>Hypersensitivity, with or without cutaneous symptoms.</td>
<td></td>
<td>Quincke's oedema.</td>
<td></td>
<td></td>
</tr>
</tbody>
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### ANRS scale to grade the severity of adverse events in adults (version no 1.0  4 November 2008)

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#### Neurological abnormalities

<table>
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<tr>
<th>GRADE</th>
<th>Condition</th>
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<th>GRADE 3</th>
<th>GRADE 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>55</td>
<td>Wakefulness / sleep disorders</td>
<td>Minor attention and concentration impairment.</td>
<td>Diurnal somnolence and/or difficulty falling asleep and/or night time awakening, mental activity decreased, obnubilation.</td>
<td>Sleep-wake cycle modification or insomnia requiring treatment or change in dream content. Obvious confusional syndrome with temporal disorientation.</td>
<td>Sleep-wake cycle disorganisation not responding to treatment. Dreamlike confusional syndrome, coma and/or convulsion.</td>
</tr>
<tr>
<td>56</td>
<td>Psychiatric disorders</td>
<td>Minor anxiety.</td>
<td>Anxiety requiring treatment or moderate depression.</td>
<td>Major anxiety or confirmed depressive episode requiring treatment.</td>
<td>Acute psychosis requiring hospitalization, including suicidal ideation, manic state, hallucinatory delusion.</td>
</tr>
<tr>
<td>59</td>
<td>Motor deficiency</td>
<td>Subjective feeling of weakness without objective impairment, no reflex changes.</td>
<td>Distal motor deficiency, moderate functional impairment or reflex changes.</td>
<td>Marked motor deficiency interfering with normal daily activities.</td>
<td>Confined to bed or a wheelchair because of motor deficiency.</td>
</tr>
<tr>
<td>60</td>
<td>Difficulty controlling</td>
<td>Occasional clumsiness, mild coordination difficulties.</td>
<td>Tremor or dyskinesia or dysmetria, or dysarthria, moderate limitation of upper or lower limbs ataxia or abnormal movements, limitation</td>
<td>Inability to stand up. Total dependence.</td>
<td></td>
</tr>
<tr>
<td>Movement</td>
<td>Normal daily activities</td>
<td>Of normal daily activities</td>
<td>Extensive sensory loss involving the trunk and four limbs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------</td>
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<td>--------------------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensory loss</td>
<td>Mild sensory loss, regardless of mode and distribution (focal or symmetric).</td>
<td>Moderate sensory loss.</td>
<td>Severe sensory loss.</td>
<td></td>
<td></td>
</tr>
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* Level I analgesics: Peripheral analgesics (paracetamol and/or salicylics or non-steroid anti-inflammatory drugs);
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miscellaneous</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>62</td>
<td>Fever (oral temperature, °C) for more than 12 h.</td>
<td>37.7 – 38.9</td>
<td>39 – 39.5</td>
<td>39.6 – 40.5</td>
</tr>
<tr>
<td>64</td>
<td>Fatigue.</td>
<td>Normal daily activities reduced by less than 25% for less than 48 h.</td>
<td>Normal daily activities reduced by 25 – 50 % for more than 48 h.</td>
<td>Normal daily activities reduced by more than 50%, cannot work for more than 48 h.</td>
</tr>
<tr>
<td>65</td>
<td>Arthritis / Arthralgia.</td>
<td>Arthralgia.</td>
<td>Arthralgia, with or without articular effusion or with moderate functional impairment.</td>
<td>Marked arthritis with or without effusion or with severe functional impairment.</td>
</tr>
</tbody>
</table>
## ANRS vaccine trials.

ANRS scale to grade the severity of adverse events in adults (version no 1.0 4 November 2008)

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<tbody>
<tr>
<td>1</td>
<td>Erythaema, oedema, nodule (induration).</td>
<td>&lt; 15 x 15 cm.</td>
<td>≥ 15 x 15 cm.</td>
<td>Ulceration or superinfection or superficial phlebitis.</td>
</tr>
</tbody>
</table>
FORMES et PRÉSENTATIONS (début page)
Suspension injectable IM ou SC (liquide légèrement blanchâtre et opalescent après avoir été agité doucement) :
Seringue préremplie de 0,5 ml, avec aiguille attachée, boîte unitaire.

COMPOSITION (début page)
Virus de la grippe (inactivé, fragmenté) des souches suivantes(1) :

<table>
<thead>
<tr>
<th>Souche</th>
<th>Hémagglutinine</th>
</tr>
</thead>
<tbody>
<tr>
<td>A/California/7/2009</td>
<td>15 μg HA(2)</td>
</tr>
<tr>
<td>A/Perth/16/2009</td>
<td>15 μg HA(2)</td>
</tr>
<tr>
<td>A/Victoria/210/2009</td>
<td></td>
</tr>
<tr>
<td>B/Brisbane/60/2008</td>
<td>15 μg HA(2)</td>
</tr>
</tbody>
</table>

Excipients : solution tampon (chlorure de sodium, phosphate disodique dihydraté, phosphate monopotassique, chlorure de potassium, eau ppi).
Le vaccin est conforme aux recommandations de l'OMS (dans l'hémisphère Nord) et à la décision de l'Union européenne pour la saison 2010/2011.
(1) cultivées sur œufs embryonnés de poules provenant d'élevages sains(2) hémagglutinine

INDICATIONS (début page)
Prévention de la grippe, en particulier chez les sujets qui présentent un risque élevé de complications associées.L'utilisation de Vaxigrip doit être fondée sur des recommandations officielles.

POSOLOGIE ET MODE D'ADMINISTRATION (début page)
Posologie :
Adulte et enfant de plus de 36 mois :
0,5 ml.
Enfant de 6 à 35 mois :
Les données cliniques sont limitées. Une dose de 0,25 ml ou de 0,5 ml a été utilisée.
Pour l'enfant n'ayant pas été vacciné auparavant, une seconde dose devra être injectée après un intervalle d'au moins 4 semaines.
Mode d'administration :
Administer par voie intramusculaire ou sous-cutanée profonde.
Concernant le mode de préparation, cf Modalités de manipulation et d'élimination.
**FLUWAY**

**CONTRE-INDICATIONS**

- Hypersensibilité aux substances actives, à l'un des excipients et aux traces par exemple d'oeufs, dont l'ovalbumine, de protéines de poulet.
- La vaccination doit être différée en cas de maladie fébrile ou d'infection aiguë.

**MISES EN GARDE et PRÉCAUTIONS D'EMPLOI**

Comme pour tous les vaccins injectables, il est recommandé de disposer d'un traitement médical approprié et de surveiller le sujet dans l'éventualité, rare, d'une réaction anaphylactique suite à l'administration du vaccin. Vaxigrip ne doit en aucun cas être administré par voie intravasculaire. La réponse en anticorps chez les patients présentant une immunodépression congénitale ou acquise peut être insuffisante.

**INTERACTIONS**

Vaxigrip peut être administré en même temps que d'autres vaccins. Cependant, les injections doivent être pratiquées sur deux membres différents. Il faut noter que les effets indésirables peuvent être intensifiés. La réponse immunitaire peut être diminuée si le patient est sous traitement immunosuppresseur. Après vaccination anti-grippale, il a été observé des réponses faussement positives aux tests sérologiques utilisant la méthode ELISA pour détecter les anticorps contre HIV1, hépatite C, et surtout HTLV1. Infirmées par le Western Blot, ces réactions transitoires faussement positives seraient dues à la réponse IgM induite par la vaccination.

**FERTILITÉ/GROSSESSE/ALLAITEMENT**

Les données limitées relatives à la vaccination de la femme enceinte n'indiquent pas que des effets indésirables sur le foetus ou la mère sont attribuables au vaccin. L'utilisation de ce vaccin peut être envisagée à partir du deuxième trimestre de la grossesse. Pour les femmes enceintes présentant un risque élevé de complications associées à la grippe, l'administration du vaccin est recommandée quel que soit le stade de la grossesse. Le vaccin peut être administré en cas d'allaitement.

**CONDUITE et UTILISATION DE MACHINES**

Il est improbable que la vaccination produise un effet sur l'aptitude à conduire des véhicules ou à utiliser des machines.

**EFFETS INDÉSIRABLES**

*Événements indésirables observés au cours des essais cliniques :

La tolérance des vaccins grippaux trivalents inactivés est évaluée au cours d'essais cliniques en ouvert, non contrôlés, réalisés annuellement en conformité avec les exigences réglementaires, et incluant au moins 50 adultes âgés de 18 à 60 ans et au moins 50 personnes âgées de 61 ans et plus.

L'évaluation de la tolérance est réalisée durant les 3 premiers jours suivant la vaccination. Les effets indésirables suivants ont été observés au cours des essais cliniques selon les fréquences suivantes : très fréquent (>= 1/10) ; fréquent (>= 1/100, < 1/10) ; peu fréquent (>= 1/1000, < 1/100) ; rare (>= 1/10 000, < 1/1000) ; très rare (< 1/10 000), y compris les cas isolés.

**Affections du système nerveux :**
- Fréquent : céphalées.

**Affections de la peau et du tissu sous-cutané :**
- Fréquent : sueurs*.

**Affections musculosquelettiques et systémiques :**
FLUWAY

- Fréquent : myalgies, arthralgies*

Troubles généraux et anomalies au site d'administration :
- Fréquent : fièvre, malaise, frissons, fatigue. Réactions locales : rougeur, gonflement, douleur, ecchymose, induration*.

* Ces réactions disparaissent généralement après 1 ou 2 jours sans traitement.

Événements indésirables rapportés au cours de la surveillance après commercialisation :
Les événements indésirables rapportés au cours de la surveillance après commercialisation, en plus de ceux déjà observés au cours des essais cliniques, sont les suivants :
- Affections hématologiques et du système lymphatique : thrombocytopénie transitoire, lymphadénopathie transitoire.
- Affections du système immunitaire : réactions allergiques, conduisant à un choc dans de rares cas, angioédème.
- Affections du système nerveux : névralgie, paresthésie, convulsions fébriles, troubles neurologiques, tels que encéphalomyélite, névrite et syndrome de Guillain-Barré.
- Affections vasculaires : vascularites avec atteinte rénale transitoire dans de très rares cas.
- Affections de la peau et du tissu sous-cutané : réactions cutanées généralisées incluant prurit, urticaire, rash non spécifique.

** SURDOSAGE (début page) **
Il est improbable qu’un surdosage provoque un effet nocif.

** PHARMACODYNAMIE (début page) **
Classe pharmacothérapeutique : Vaccin contre la grippe (code ATC : J07BB02).
La séroprotection est généralement obtenue dans les 2 à 3 semaines. La durée de l’immunité postvaccinale vis-à-vis des souches homologues ou très proches des souches du vaccin est variable, mais elle est en général de 6 à 12 mois.

** INCOMPATIBILITÉS (début page) **
En l’absence d’études de compatibilité, ce vaccin ne doit pas être mélangé avec d’autres médicaments.

** CONDITIONS DE CONSERVATION (début page) **

** MODALITÉS MANIPULATION/ÉLIMINATION (début page) **
Le vaccin doit être amené à température ambiante avant utilisation.
Agiter avant emploi.
Le vaccin ne doit pas être utilisé si des particules étrangères sont présentes dans la suspension.
Pour les enfants, lorsqu’une dose de 0,25 ml est indiquée, le bouchon-piston doit être poussé précisément jusqu’à la bordure de la marque de la seringue afin d’éliminer la moitié du volume. Le volume restant doit être injecté. Cf aussi Posologie et Mode d’administration.
Tout produit non utilisé ou déchet doit être éliminé conformément à la réglementation en vigueur.
Prix : 6.25 euros (1 seringue de 0,5 ml).
Remb Séc soc à 65 % pour les catégories de patients suivantes :

- Personnes âgées de 65 ans ou plus.
- Personnes atteintes des affections de longue durée suivantes : diabète insulino-dépendant ou non insulino-dépendant ne pouvant être équilibré par le seul régime ; accident vasculaire cérébral invalidant ; néphropathie chronique grave et syndrome néphrotique pur primitif ; forme grave d’une affection neuromusculaire (dont myopathie) ; mucoviscidose ; cardiopathie congénitale mal tolérée, insuffisance cardiaque grave et valvulopathie grave ; insuffisance respiratoire chronique grave ; déficit immunitaire primitif grave nécessitant un traitement prolongé, infection par le virus de l’immunodéficience humaine (s’agissant de personnes contaminées par le VIH, les dernières études ont révélé que la vaccination pouvait entraîner un accroissement transitoire de la charge virale et qu’il n’y avait pas lieu de la recommander systématiquement à ces personnes) ; drépanocytose homozygote (anémie hémolytique congénitale par hémoglobinopathie).
- Personnes atteintes d’asthme.
- Personnes atteintes de bronchopneumopathie chronique obstructive.
- Personnes séjournant dans un établissement de santé de moyen et long séjour, quel que soit leur âge.
- Enfants et adolescents (de 6 mois à 18 ans) dont l’état de santé nécessite un traitement prolongé par l’acide acétylsalicylique (essentiellement pour syndrome de Kawasaki compliqué et arthrite chronique juvénile).

Collect.

SANOFI PASTEUR MSD, SNC 8, rue Jonas-Salk. 69007 Lyon
Tél : 04 37 28 40 00. Fax : 04 37 28 44 00
Info médic et pharmacovigilance :Tél : 08 25 82 22 46 (08 25 VACCIN).
Site web : http://www.spmsd.fr
1. **DENOMINATION DU MEDICAMENT**

INTANZA 9 microgrammes/souche suspension injectable
Vaccin grippe (inactivé, à virion fragmenté)

2. **COMPOSITION QUALITATIVE ET QUANTITATIVE**

Virus grippe (inactivé, fragmenté) des souches suivantes*:

A/California/7/2009 (H1N1) – souche dérivée utilisée NYMC X-179A ......... 9 microgrammes HA**

A/Perth/16/2009 (H3N2) – souche analogue utilisée NYMC X-187 dérivée de A/Victoria/210/2009

................................................................. 9 microgrammes HA**

B/Brisbane/60/2008 ................................................................. 9 microgrammes HA**

Par dose de 0,1 ml

+ cultivé sur œufs embryonnés de poules provenant d’elevages sains
++ hémagglutinine

Ce vaccin est conforme aux recommandations de l’OMS (Hémisphère Nord) et à la décision de
l’Union Européenne pour la saison 2011/2012.

Pour la liste complète des excipients, voir rubrique 6.1.

INTANZA contient des traces d’œuf comme l’ovalbumine.

3. **FORME PHARMACEUTIQUE**

Suspension injectable.
Suspension incolore et opalescente.

4. **DONNEES CLINIQUES**

4.1 **Indications thérapeutiques**

Prévention de la grippe chez les adultes jusqu’à l’âge de 59 ans, en particulier chez ceux qui présentent
un risque élevé de complications associées.

L'utilisation d'INTANZA doit être fondée sur les recommandations officielles.

4.2 **Posologie et mode d'administration**

**Posologie**
Adultes jusqu’à l’âge de 59 ans : 0,1 ml.

**Population pédiatrique**
L'utilisation d'INTANZA n'est pas recommandée chez les enfants et adolescents de moins de 18 ans,
compte tenu de l'insuffisance des données de tolérance et d'efficacité.

**Mode d'administration**
La vaccination doit se faire par voie intradermique.
Le site d'administration recommandé est la région du deltoïde.
4.3 Contre-indications

Hypersensibilité aux substances actives, à l'un des excipients, aux traces d'œuf, comme l'ovalbumine, et aux protéines de poulet.


La vaccination doit être différée en cas de maladie fébrile ou d'infection aiguë.

4.4 Mises en garde spéciales et précautions d'emploi

Comme pour tous les vaccins injectables, il est recommandé de disposer d'un traitement médical approprié et de surveiller le sujet dans l'éventualité d'une réaction anaphylactique suite à l'administration du vaccin.

INTANZA ne doit en aucun cas être administré par voie intravasculaire.

La réponse en anticorps chez les patients présentant une immunodépression congénitale ou acquise peut être insuffisante.

En cas de présence de liquide au site d'injection après l'administration du vaccin, une re-vaccination n'est pas requise.

Interférence avec des tests sérologiques : voir rubrique 4.5

4.5 interactions avec d'autres médicaments et autres formes d'interactions

INTANZA peut être administré en même temps que d'autres vaccins. Les vaccinations doivent être pratiquées sur des membres différents. Il faut noter que les effets indésirables peuvent être intensifiés.

La réponse immunitaire peut être diminuée si le patient est sous traitement immunosuppresseur.

Après vaccination antigrippale, il a été observé des réponses fausses positives aux tests sérologiques utilisant la méthode ELISA pour détecter les anticorps contre HIV1, hépatite C, et surtout HTLV1. Infirmitées par la méthode Western Blot, ces réactions transitoires fausses positives pourraient être dues à la réponse IgM induite par la vaccination.

4.6 fécondité, grossesse et allaitement

Grossesse
Aucune donnée n'est disponible sur l'utilisation d'INTANZA chez la femme enceinte. En général, les données sur les vaccins grippaux administrés par voie intramusculaire chez la femme enceinte n'ont pas révélé d'effets délétères sur le fœtus et sur la mère attribuables au vaccin.
Une étude sur l'animal réalisée avec INTANZA n'a pas montré d'effets délétères directs ou indirects sur la gestation, le développement embryonnaire/fetal, l'accouchement ou le développement postnatal.

L'utilisation d'INTANZA peut être envisagée à partir du second trimestre de la grossesse. Pour les femmes enceintes présentant des conditions médicales qui augmentent leur risque de complications associées à la grippe, l'administration de ce vaccin est recommandée, quel que soit le stade de la grossesse.
Allaitement
Le vaccin INTANZA peut être administré durant l'allaitement.

Fécondité
Aucune donnée sur la fécondité n'est disponible chez l'Homme.
Une étude réalisée chez l'animal avec INTANZA n'a pas montré d'effet nocif sur la fécondité des femelles.

4.7 Effets sur l'aptitude à conduire des véhicules et à utiliser des machines
INTANZA n'a aucun effet ou un effet négligeable sur l'aptitude à conduire et à utiliser des machines.

4.8 Effets indésirables

a. Résumé du profil de tolérance
Au cours de 2 essais cliniques randomisés, en ouvert, la tolérance a été évaluée chez 2 384 sujets ayant reçu une injection d'INTANZA.

L'évaluation de la tolérance a été réalisée chez tous les sujets pendant les 3 premières semaines suivant la vaccination et les réactions indésirables graves ont été recueillies durant une période de suivi de six mois.

Les réactions les plus fréquentes survenant après l'administration du vaccin étaient des réactions locales au site d'injection.
Les réactions locales apparentes après administration intradermique étaient plus fréquentes qu'avec le vaccin comparateur administré par voie intramusculaire.
La plupart des réactions disparaissaient spontanément dans les 1 à 3 jours suivant leur apparition.

Le profil de tolérance systémique d'INTANZA est similaire à celui du vaccin comparateur administré par voie intramusculaire.

Suite à des injections anciennes répétées, le profil de tolérance d'INTANZA est similaire à celui des injections précédentes.

b. Résumé tabulé des effets indésirables
Les données ci-dessous résument les fréquences des effets indésirables qui ont été rapportées suite à la vaccination lors d'essais cliniques, en utilisant la convention suivante: très fréquent (≥1/10); fréquent (≥1/100 à <1/10); peu fréquent (≥1/1 000 à <1/100); rare (≥1/10 000 à <1/1 000); très rare (<1/10 000), fréquence indéterminée (ne peut être estimée sur la base des données disponibles).
<table>
<thead>
<tr>
<th>Classee d'organes</th>
<th>Très fréquent</th>
<th>Fréquent</th>
<th>Peu fréquent</th>
<th>Rare</th>
<th>Très rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Affections hématologiques et du système lymphatique</td>
<td></td>
<td></td>
<td>Lymphadénopathie</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Affections du système nerveux</td>
<td>Céphalées</td>
<td></td>
<td>Paresthésie</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Affections de la peau et du tissu sous-cutané</td>
<td></td>
<td></td>
<td>Prurit, rash</td>
<td>Sueurs</td>
<td></td>
</tr>
<tr>
<td>Affections musculosquelettiques et systémiques</td>
<td>Myalgies</td>
<td></td>
<td>Arthralgies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Troubles généraux et anomalies au site d'administration</td>
<td>Malaise, Réactions locales: rougeur*, gonflement, induration, douleur, prurit</td>
<td>Frissons, fièvre, Réactions locales: ecchymose</td>
<td>Fatigue</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*a Dans certains cas, les rougeurs locales ont persisté jusqu'à 7 jours.

c. **Evénements indésirables potentiels**

En se basant sur l'expérience obtenue avec des vaccins grippaux trivalents inactivés administrés par voie intramusculaire ou sous-cutanée profonde, les événements suivants peuvent être rapportés:

**Affections hématologiques et du système lymphatique**

Thrombocytopénie transitoire

**Affections du système immunitaire**

Réactions allergiques, conduisant à un choc dans de rares cas, angioœdème

**Affections du système nerveux**

Névralgie, convulsions fœcales, troubles neurologiques, tels que encéphalomyélite, névrite et syndrome de Guillaum-Barré

**Affections vasculaires**

Vascularites avec atteinte rénale transitoire dans de très rares cas

**Affections de la peau et du tissu sous-cutané**

Réactions cutanées généralisées incluant l'urticaire

4.9 **Surdosage**

Il est improbable qu'un surdosage provoque un effet nocif.
FLUWAY
5. PROPRIÉTÉS PHARMACOLOGIQUES

5.1 Propriétés pharmacodynamiques

Classe pharmacothérapeutique : vaccin grippal, code ATC : J07BB02

Immunogénicité
La séroprotection est généralement obtenue dans les 2 à 3 semaines. La durée de l'immunité post-vaccinale vis-à-vis des souches homologues ou très proches des souches du vaccin est variable mais elle est en général de 6 à 12 mois.

Au cours d'une étude comparative, randomisée, de phase III, 1 796 sujets âgés de 18 à 59 ans ont reçu 0,1 ml d'INTANZA par voie intradermique et 453 sujets âgés de 18 à 59 ans ont reçu 0,5 ml de vaccin grippal trivalent inactif administré par voie intramusculaire.

Dans cette étude comparative, le taux de séroprotection*, le taux de séroconversion ou d'augmentation significative** et le rapport de la moyenne géométrique des titres (RMGT) en anticorps anti-HA [mesurés par inhibition de l'hémagglutination (IH)] ont été évalués selon des critères prédéfinis.

Les données ont été les suivantes (les valeurs entre parenthèses indiquent les intervalles de confiance à 95%):

<table>
<thead>
<tr>
<th>Anticorps anti-HA spécifiques de la souche</th>
<th>A/H1N1 A/New Caledonia/20/99 N=1 296</th>
<th>A/H3N2 A/Wisconsin/67/2005 N=1 297</th>
<th>B B/Malaysia/2506/2004 N=1 294</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taux de séroprotection</td>
<td>87,2% (85,2; 89,0)</td>
<td>93,5% (92,0; 94,8)</td>
<td>72.9% (70,4; 75,3)</td>
</tr>
<tr>
<td>Taux de séroconversion ou d'augmentation significative</td>
<td>57.5% (54,7; 60,2)</td>
<td>66,5% (63,8; 69,0)</td>
<td>56,7% (54,0; 59,4)</td>
</tr>
<tr>
<td>RMGT</td>
<td>9,17 (8,33; 10,1)</td>
<td>11,5 (10,4; 12,7)</td>
<td>6,39 (5,96; 6,84)</td>
</tr>
</tbody>
</table>

*Séroprotection = titres mesurés par IH ≥ 40
**Séroconversion = titre mesuré par IH, négatif avant la vaccination et ≥ 40 après la vaccination, augmentation significative = titre mesuré par IH, positif avant la vaccination et multiplié par un facteur d'au moins 4 après la vaccination
RMGT: rapport de la moyenne géométrique des titres individuels (titres avant/après vaccination)

INTANZA est aussi immunogène que le vaccin grippal comparateur trivalent inactif administré par voie intramusculaire pour chacune des 3 souches grippales chez des sujets de 18 à 59 ans.

Parmi les trois souches grippales, les taux de séroprotection du vaccin comparateur administré par voie intramusculaire étaient compris entre 74,8% et 95,4%, les taux de séroconversion ou d'augmentation significative étaient compris entre 56,4% et 69,3% et les RMGT étaient compris entre 6,63 et 11,2 fois le titre mesuré par IH à l'inclusion dans l'étude.

5.2 Propriétés pharmacocinétiques

Sans objet

5.3 Données de sécurité préclinique
Les données non cliniques issues d'études chez l'animal n'ont pas révélé de risque particulier pour l'homme. Le vaccin était immunogène chez la souris et le lapin. Les études de toxicologie chez le lapin, en administration répétée, n'ont pas montré, de façon significative, de toxicité systémique. Cependant, les administrations uniques et répétées ont conduit à des érythèmes locaux transitoires et à des œdèmes. La génotoxicité et le potentiel carcinogène n'ont pas été évalués car ces études ne sont pas appropriées aux vaccins. Les études de fertilité et de toxicologie sur les fonctions de reproduction chez les femelles n'ont pas mis en évidence de risque potentiel spécifique pour l'homme.

6. DONNEES PHARMACEUTIQUES

6.1 Liste des excipients
Chlorure de sodium
Chlorure de potassium
Phosphate disodique dihydrique
Phosphate monopotassique
Eau pour préparations injectables

6.2 Incompatibilités
En l'absence d'études de compatibilité, ce médicament ne doit pas être mélangé avec d'autres médicaments.

6.3 Durée de conservation
1 an.

6.4 Précautions particulières de conservation
A conserver au réfrigérateur (entre 2°C et 8°C). Ne pas congeler.
Conservé la seringue dans l'emballage extérieur à l'abri de la lumière.

6.5 Nature et contenu de l'emballage extérieur
0,1 ml de suspension en seringue préremplie (verre) avec un système de micro-injection et une micro-aiguille attachée munie d'un bouchon piston en élastomère (chlorobutyle), d'un capuchon d'embout (élastomère thermoplastique et polypropylène) et d'un système de protection de l'aiguille. Boîtes de 1 ou 10 ou 20.

Toutes les présentations peuvent ne pas être commercialisées.

6.6 Précautions particulières d'élimination et manipulation
Tout vaccin non utilisé ou déchet doit être éliminé conformément à la réglementation en vigueur.

Le vaccin doit être amené à température ambiante avant utilisation.

Le vaccin ne devra pas être utilisé si des particules étrangères sont présentes dans la suspension.

Il n'est pas nécessaire d'agiter le vaccin avant utilisation.

Le Système de Micro-Injection pour injection intradermique est composé d'une seringue préremplie munie d'une micro-aiguille (1,5 mm) et d'un système de protection de l'aiguille.

Le système de protection de l'aiguille est conçu pour couvrir la micro-aiguille après utilisation.
Système de Micro-Injection

- Micro-aiguille
- Fenêtre
- Emplacements pour les doigts
- Piston
- Système de protection
- Capuchon de l’aiguille
- Vaccin
- Collet
INSTRUCTIONS D’UTILISATION

Veuillez lire les instructions avant emploi

1/ RETIRER LE CAPUCHON DE L’AIGUILLE

Retirer le capuchon de l’aiguille du système de micro-injection
Ne pas purger l’air par l’aiguille

2/ TENIR LE SYSTEME DE MICRO-INJECTION ENTRE LE POUCE ET LE MAJEUR

Tenir le système en plaçant le pouce et le majeur uniquement sur les emplacements prévus pour les doigts; l’index doit rester libre.
Ne pas placer les doigts sur la fenêtre.

3/ INTRODUIRE RAPIDEMENT L’AIGUILLE PERPENDICULAIREMENT À LA PEAU

Introduire l’aiguille perpendiculairement à la peau, dans la région du deltoïde, d’un geste bref et rapide.

4/ INJECTER EN UTILISANT L’INDEX

Une fois la micro-aiguille introduite, maintenir une légère pression sur la surface de la peau et injecter en utilisant l’index afin de pousser sur le piston.
Il n’est pas nécessaire de faire un retour veineux.

5/ ACTIVER LE SYSTEME DE PROTECTION DE L’AIGUILLE EN POUSSANT FERMEMENT SUR LE PISTON

Retirer l’aiguille de la peau.
Orienter l’aiguille loin de votre direction ou de celle d’autres personnes.
Avec la même main, pousser très fermement avec le pouce sur le piston pour activer le système de protection de l’aiguille.
Vous entendrez un clic et le système de protection viendra couvrir l’aiguille.
Jeter immédiatement le système dans la boîte à déchets médicaux la plus proche.
L’injection est considérée comme réussie que la présence d’une papule soit observée ou non.
En cas de présence de liquide au site d’injection après l’administration du vaccin, la re-vaccination n’est pas requise.
7. **TITULAIRE DE L'AUTORISATION DE MISE SUR LE MARCHE**

Sanofi Pasteur MSD SNC, 8 rue Jonas Salk, F-69007 LYON, France.

8. **NUMERO(S) D'AUTORISATION DE MISE SUR LE MARCHE**

EU/1/08/505/001
EU/1/08/505/002
EU/1/08/505/003

9. **DATE DE PREMIERE AUTORISATION/DE RENOUVELLEMENT DE L'AUTORISATION**

21 février 2009

10. **DATE DE MISE À JOUR DU TEXTE**

MM/AAAA

**FORMULAIRE DE DECLARATION D’UN EVENEMENT INDESIRABLE GRAVE (EIG) SURVENANT AU COURS D’UNE RECHERCHE BIOMEDICALE PORTANT SUR UN MEDICAMENT OU PRODUIT ASSIMILE**

**ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS**

**PARTIE RESERVEE AU PROMOTEUR : NE PAS REMPLIR**

|__|__|__|__|__|__|__|

Cette fiche doit être retournée dûment complétée (2 pages) au DRCD par fax : +33 (0)1 44 84 17 99

A l’attention de Cécile Kedzia et Fadela Amerali...

Date de notification : |__|__|__|__|

**Code de la Recherche** : P_120201

N° EudraCT : __2012-001967-55

Suivi d’EIG déclaré |__| N° du suivi |__|

**Titre de la Recherche Biomédicale** : Etude de l’influence de la voie d’immunisation sur la réponse immunitaire après vaccination antigrippale – Etude FLUWAY

1) Nom et adresse du centre :

Centre n° : |__|__|__|__|__|

Investigateur (Qualité - Nom - Prénom) :

2) Identification du patient :

Nom : |__|

Prénom : |__|

Patient n° : |__|__|__|__|__|__|__|__|

Sexe : Masculin |__| Féminin |__|

Date de naissance : |__|__|__|__|__|__|__|

Age : |__|__|__| ans

Poids : |__|__|__|__| kg

Taille : |__|__|__|__| cm

Date de randomisation : |__|__|__|__|__|__|__|

Bras de randomisation

Groupe A – TC |__|

Groupe B – ID |__|

Groupe C – IM |__|

3) Événement indésirable grave :

Décès |__|

Mise en jeu du pronostic vital |__|

Nécessite ou prolonge l’hospitalisation :

Du __/__/__ __/__/__ __/__/__ au __/__/__ __/__/__

|__|__|__|__|

en cours |__|

|__|__|__|__|

Incapacité ou invalidité |__|

Anomalie congénitale |__|

Autre(s) critère(s) médicalement significatif(s) (préciser) :

__________________________________________

|__|__|__|__|

|__|__|__|__|

|__|__|__|__|

|__|__|__|__|
FLUWAY

Antécédents (allergie, insuffisance rénale ...): ____________________________________________________________

4) Description complète de l'événement indésirable (diagnostic retenu, localisation anatomique, critères permettant de considérer l'événement comme grave):

Intensité : Légère □ Modérée □ Sévère □

Date de survenue : ____________________

Délai de survenue après la dernière prise : ______________________________________________________________

5) Médicament(s) expérimental(aux) administré(s) avant la survenue de l'événement indésirable :

<table>
<thead>
<tr>
<th>Nom commercial (de préférence) ou Dénomination Commune Internationale</th>
<th>Voie</th>
<th>Dos e/24 h</th>
<th>Date de début</th>
<th>En cours</th>
<th>Date de fin</th>
<th>Indication</th>
<th>Causalité* (1,2,3 ou 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>jj mm aaaa hh min</td>
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</tbody>
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<thead>
<tr>
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<td>jj mm aaaa hh min</td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

* 1 = Probable 2 = Possible 3 = Non liée 4 = Inconnue

6) Médicament(s) concomitant(s) à l’exclusion de ceux utilisés pour traiter l’événement indésirable :

<table>
<thead>
<tr>
<th>Nom commercial (de préférence) ou Dénomination Commune Internationale</th>
<th>Voie</th>
<th>Dos e/24 h</th>
<th>Date de début</th>
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<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* 1 = Probable 2 = Possible 3 = Non liée 4 = Inconnue

7) Evolution (indiquez si des mesures symptomatiques ont été prises : non □ oui □ Si oui, préciser) :

| | | | jj mm aaaa hh min | |

| | | | jj mm aaaa hh min | |

| | | | jj mm aaaa hh min | |
8) Date de disparition : jj mm aaaa et heure de disparition : hh min

9) Autre(s) étiologie(s) envisagée(s) :
   non ☐ oui ☐ Si oui, préciser :

10) Examen(s) complémentaire(s) réalisé(s) :
    non ☐ oui ☐ Si oui, préciser date, nature et résultats :

11) Traitements de la Recherche Biomédicale :
    Levée d’insu :
      non ☐ oui ☐ non applicable ☐ date :
                      jj mm aaaa
    Résultat de la levée d’insu :
      __________________________________________
    Ré-administration du (des) médicament(s) :
      non ☐ oui ☐ non applicable ☐ date :
                      jj mm aaaa
    Si oui, le(s)quel(s) :
      __________________________________________
    Récidive après ré-administration :
      non ☐ oui ☐ non applicable ☐ date :
                      jj mm aaaa

12) Selon l’investigateur, l’événement indésirable grave semble plutôt lié :
    ☐ au(x) médicament(s) de la recherche : le(s)quel(s) :
    ☐ au(x) médicament(s) concomitant(s) : le(s)quel(s) :
    ☐ aux procédures de la recherche biomédicale
    ☐ autre :
    Date : jj mm aaaa
    Tampon du service :
    Signature :
    Nom de l’Investigateur :
    ________________________________

Nom et fonction du Notificateur :
_______________________________ Téléphone ______________________
Signature :

PARTIE RESERVEE AU PROMOTEUR : NE PAS REMPLIR
Numéro d’identification de l’événement : EV I__I__I__I
Date de réception par le promoteur :
Date de ce rapport :
Selon le promoteur, l’événement indésirable semble plutôt lié :
FLUWAY

☐ au(x) médicament(s) de la recherche : le(s)quel(s) : ______________________ ☐ à une maladie intercurrente

☐ au(x) médicament(s) concomitant(s) : le(s)quel(s) : ______________________ ☐ à la progression de la maladie

☐ aux procédures de la recherche biomédicale  ☐ autre :__________________

Si selon le promoteur, l'événement semble plutôt lié au médicament :

☐ L'événement indésirable grave est attendu  ☐ L'événement indésirable grave est inattendu

Commentaires du promoteur : __________________________________________

Nom et qualité du représentant du promoteur :  Signature :

I received an injection of the seasonal influenza