Protocol

Protocol for: Launay O, Cachanado M, Luong Nguyen LB, et al. Immunogenicity and safety of beta-adjuvanted recombinant booster vaccine. N Engl J Med. DOI: 10.1056/NEJMc2206711

This trial protocol has been provided by the authors to give readers additional information about the work.

Immunogenicity and Safety of Beta Adjuvanted Recombinant Booster Vaccine -Supplementary material.

This supplement contains the following items:

Immunogenicity and reactogenicity following a booster dose of a COVID-19 mRNA vaccine (Pfizer-BioNtech) and two adjuvanted sub-unit vaccines (SP/GSK) administered in adults who received 2 doses of Pfizer-BioNTech mRNA vaccine as a primary vaccination : A Randomized, single-blinded multicenter clinical trial

COVIBOOST

INTERVENTIONAL RESEARCH PROTOCOL INVOLVING HUMAN PARTICIPANTS CONCERNING A MEDICINAL PRODUCT FOR HUMAN USE

Version N°1.2 dated 20/10/2021
Project Code: APHP211184/ EUDRACT no: 2021-004550-33

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Network	I-REIVAC/COVIRIEIVAC Platform Launched in October 2020, the COVIREIVAC platform coordinated by Inserm & F-CRIN, in partnership with 32 university hospitals and a network of 11 immunology labs, is dedicated to clinical vaccine research in France.

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SIGNATURE page for a research PROTOCOL

Research code number: APHP211184

Title: **Immunogenicity and reactogenicity following a booster dose of COVID-19 mRNA vaccine (Pfizer-BioNtech) and two adjuvanted sub-unit vaccines (SP/GSK) administered in adults who received 2 doses of Pfizer-BioNTech mRNA vaccine as a primary vaccination: A Randomized, single-blinded multicenter, clinical trial - CoviBoost**

Version no. 1.2 dated: 20/10/2021

The study will be carried out in accordance with the protocol, with current good practices and with statutory and regulatory requirements.

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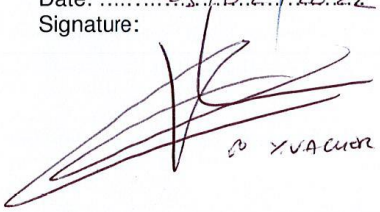

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1 SUMMARY

Full title	Immunogenicity and reactogenicity following a booster dose of COVID-19 mRNA vaccine (Pfizer-BioNtech) and two adjuvanted sub-unit vaccines (SP/GSK) administered in adults who received 2 doses of Pfizer-BioNTech mRNA vaccine as a primary vaccination: A randomized, single-blinded multicenter clinical trial
Acronym/reference	CoviBoost
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Sponsor	Assistance Publique – Hôpitaux de Paris
Scientific justification	The efficacy of COVID 19 vaccines for reducing the risk of severe COVID-19 infection has now been demonstrated in real life. In France, the vaccination campaign started on December 27th, 2020 and was launched rapidly for healthcare professionals and for individuals at risk of severe COVID on January 2021. On August 5th 30th, 2021, approximately 60% of the population (> 12 years) had already received complete vaccination. Out of approximately 74,3 million doses of vaccine administered, 58 million doses are Pfizer BioNTech vaccine (78%). Data currently available on the persistence of immunity on the one hand and the appearance of viral variants with reduced sensitivity to vaccine immunity on the other, raise the need to administer further additional dose at an interval from the primary vaccination that remains to be defined, possibly different according to age and co-existing diseases. Currently, the only data published are related to the administration of a third dose as booster of the same vaccine as the one used for primary vaccination. However, some vaccines developed more recently could be an interesting alternative for booster dose in terms of

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	reactogenicity, availability, cost and acceptance. Moreover heterologous vaccination could be more immunogenic than homologous scheme. The vaccine developed by Sanofi Pasteur is based on a conventional adjuvanted recombinant protein approach. Two candidate vaccines are under development, one based on the Spike protein of the SARS CoV-2 D614 strain, the other on the B.1.351 strain. Their interest as booster vaccines needs to be investigated. The objective of this trial is to assess the response induced by a booster dose of either recombinant protein-based subunit vaccine (targeting D614 strain or B.1.351 strain) or by a booster dose of Pfizer-BioNTech mRNA vaccine (targeting Wuhan strain) in individuals previously vaccinated with 2 doses of Pfizer-BioNTech mRNA vaccine. These results will provide important information for booster vaccination recommendations.
Main objective and primary endpoint	Main objective: To assess the immunogenicity of a booster dose of an adjuvanted subunit vaccine (SP vaccine) as between D614 or B.1.351 and a mRNA vaccine (Pfizer BioNTech) in adults who were primarily vaccinated with 2 doses of mRNA vaccine (Pfizer BioNTech) with the 2nd dose of vaccine received at least 6 months prior to the booster dose. Primary endpoint: Increased rate of at least 10 fold between D0 and D28 after the booster dose in neutralizing antibody titers against SARS-CoV-2 D614 and B.1.351 viral strains, measured by a microneutralisation technique in each group.
Secondary objectives and endpoints	Secondary objectives: 1. To compare the increase in neutralization antibody titers with regard to age groups (18-64 years old and >65 years or older) 2. To evaluate the local and general safety and tolerability of a booster dose of mRNA vaccine or adjuvanted subunit vaccine up to 28 days after administration; 3. To assess the humoral immune response by ELISA of a booster dose of mRNA vaccine or adjuvanted subunit vaccine at 15 and 28 days;

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	4. To assess the persistence of the immune response at 3 and 12 months after the booster dose of mRNA vaccine or adjuvanted subunit vaccine; 5. To evaluate the immunogenicity of the 3 vaccines on the D614, Alpha, Gamma and Delta viral variants; 6. To describe the associated factors and determinants of boost response in individuals previously vaccinated with 2 doses of mRNA vaccine 7. To assess the mucosal immunity following a booster dose of mRNA vaccine or adjuvanted subunit vaccine 8. To assess the early humoral response by ELISA of a booster dose of mRNA vaccine or subunit adjuvanted vaccine at 3 days (*ancillary analysis*) 9. To explore CD4 and CD8 cellular response induced by a booster dose of mRNA vaccine or adjuvanted subunit vaccine *(ancillary analysis)* <u>Secondary endpoints</u>: 1. Rate of increase in neutralizing antibody titers against SARS-CoV-2 D614 and B.1.351 viral strains, measured by a microneutralisation technique between 0 and 28 days after the booster dose in each group. 2. Quantity and intensity of local and systemic events of any grade occurring up to 7 days after boost injection (assessed from the list of solicited adverse events); Quantity and intensity of unsolicited local and systemic events up to 28 days; 3. Anti-Spike (D614) and anti-RBD (D614 and B.1.351) IgG levels, expressed in BAU/ml, according to WHO recommendations D15 and D28 after the booster dose mRNA or adjuvanted subunit vaccine; 4. Difference in Anti-Spike (D614) and anti-RBD (D614 and B.1.351) IgG levels between M3 and D0 and between M12 and D0; 5. Neutralizing antibody titers against D614, alpha, gamma, and delta variants at 28 days, 3 months and 12 months; 6. Factors of interest are age, gender, time interval between 2nd dose and boost dose, and vaccine boost type;

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	7. Mucosal SARS-CoV-2 specific antibodies via the measure of IgA in saliva by ELISA and PRNT assays at D0, D28 and D90 ; 8. Anti-Spike (D614) and anti-RBD (D614 and B.1.351) IgG levels, expressed in BAU/ml, according to WHO recommendations D3 after the booster dose mRNA or adjuvanted subunit vaccine 9. ELISpot IFN CD4 and CD8 response at 28 days, 3 months and 12 months (*ancillary analysis*);
Design of the study	Randomized, single-blinded, multicenter, trial with three parallel arms stratified on age groups: **ARM 1 receiving Pfizer-BioNTech vaccine** - Group 1.A: 18-64 years old - Group 1.B: 65 years and older **ARM 2 receiving SP/GSK subunit D614 vaccine** - Group 2.A: 18-64 years old - Group 2.B: 65 years and older **ARM 3 receiving SP/GSK subunit B.1.351 vaccine** - Group 3.A: 18-64 years old - Group 3.B: 65 years and older
Population of study participants	Adult who previously received two doses of mRNA vaccine (Pfizer-BioNTech), with the second dose received at least 6 months prior to the administration of the booster dose.
Inclusion criteria	1. Age ≥ 18 years 2. Adult in a healthy condition or with a stable health status if pre-existing medical history. Stable health status is defined as an existing disease that has not required a significant change in treatment or hospitalization for worsening in the 3 months before enrollment, and for which neither a significant change in treatment or hospitalization for worsening is expected in the near future 3. For women of childbearing age: a negative highly sensitive pregnancy urinary test during the inclusion visit AND use of an effective contraceptive method at least 4 weeks prior to vaccination and until at least 12 weeks after the vaccination 4. Who has received 2 doses of mRNA vaccine (Pfizer-BioNTech) with an interval of 3 to 6 weeks 5. Second dose of mRNA vaccine (Pfizer-BioNTech) administered at least 6 months before the booster dose

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	6. Understands and agrees to comply with the study procedures 7. Written informed consent signed by both the participant and the investigator 8. Subject affiliated to the French Social Security System.
Exclusion criteria	1. Acute febrile infection (body temperature ≥ 38.0°C) within the previous 72 hours and/or presenting symptoms suggestive of COVID-19 within the previous 28 days or having been in contact with an infected individual for the last 14 days before the inclusion visit; 2. Virologically documented history of COVID-19 (PCR or serology); 3. Immunosuppressive therapy such as corticosteroids > 10 mg prednisone equivalent/day (excluding topical preparations and inhalers) within 3 months prior to inclusion or within 6 months for chemotherapies; 4. Treatment with immunoglobulins or other blood derivatives within 3 months prior to inclusion or scheduled administration of immunoglobulins or blood derivatives before the end of the study; 5. Known HIV, HCV or HBV infection; 6. Any medical condition, such as cancer, that might impair the immune response; 7. Use of experimental immunoglobulins, experimental monoclonal antibodies or convalescent plasma is not permitted during the study; 8. Pregnancy or breastfeeding currently ongoing, or positive pregnancy test at enrolment visit; 9. History of severe adverse events following vaccine administration including anaphylactic reaction and associated symptoms such as rash, breathing problems, angioedema, and abdominal pain, or a history of allergic reaction that could be triggered by a component of the SARS-COV-2 vaccine at the time of the first vaccine injection; 10. Participant who has received BCG (tuberculosis) vaccine within the previous year; 11. Has received a vaccine within 2 weeks prior to the boost injection or is scheduled to receive a registered vaccine 2 weeks after the boost injection 12. Any bleeding disorder considered as a contraindication to an intramuscular injection, previous phlebotomy, or receipt of anticoagulants

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	13. Participation in other research involving humans (French classification Jardé 1 or Jardé 2) within 4 weeks prior to the inclusion visit, or participation in any other vaccine trial 14. Subject under legal protection (e.g. guardianship, tutorship)
Investigational medicinal product(s)	**Pfizer/bioNTech BNT132b2 (Comirnaty®)** mRNA vaccine, intramuscular administration. **Sanofi-Pasteur / GSK** recombinant protein vaccines, intramuscular administration : - Recombinant protein vaccine targeting SARS-CoV-2 D614 Spike protein - Recombinant protein vaccine targeting SARS-CoV-2 B.1.351 Spike protein
Interventions added for the study	Diary for local and general adverse events to be completed by the participant.
Expected benefits for the participants and for society	<u>Individual and collective benefit</u>: This study will allow participants to be informed about their antibody titers (ELISA and neutralization) in accordance with the vaccine received. The study will provide the opportunity to evaluate the reactogenicity and immunogenicity of a booster dose of mRNA or subunit vaccine.
Risks and burdens added by the study	The risk level of the study is **D** (AP-HP classification) <u>Risks added by the study</u>: - Risks related to blood sampling, similar to those of a routine blood test - Risks related to the vaccine injection, including additional risks related to the recombinant protein vaccines that have not yet been licensed and are still experimental
Practical process	Inclusion and randomization (D0) will be performed at each study site by the investigator, though CleanWeb e-CRF (Telemedecine Technologies, S.A.S) The booster dose will be administered at D0, then 4 follow-up visits will be performed at D15, D28, M3 and M12. At each visit, a blood sample of 5ml will be taken for humoral analysis and biobanking. Ancillary analysis: For 26 participants in each arm there will be additional samples for cell analysis (3 x 6 ml) and blood count (3ml) at V1, V2, V3, V4 and V5. Subjects involved in the ancillary analysis will also attend an additional visit at D3 during which a 5ml blood sampling for serological analysis will be performed.

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	In total there will be minimum 5 visits and maximum 6 visits per participant.
Number of participants included	300 participants (100 per vaccine group)
Number of centres	12 study centers in France.
Duration of the study	- inclusion period: 1 month - participation period (treatment + follow-up): 12 months - immunological analysis: 6 months - total duration: 19 months
Number of enrolments expected per site and per month	25 participants per study site in one month
Statistical analysis	The analysis will be performed in three stages: at D28 (primary and D15-D28 secondary endpoints), at M3 and M12 (secondary endpoints).
Funding sources	TBD
Study will have a Data Safety Monitoring Board	A DSMB is required for this study.

2 SCIENTIFIC JUSTIFICATION FOR THE STUDY

2.1 Hypothesis for the study

The efficacy of COVID 19 vaccines for reducing the risk of severe COVID-19 infection has now been demonstrated in real life. In France, the vaccination campaign started on December 27th, 2020 and was launched rapidly for healthcare professionals and for individuals at risk of severe COVID on January 2021. On August 5th, 2021, approximately 60% of the population (> 12 years) had already received complete vaccination. Out of approximately 74.3 million doses of vaccine administered, 58 million doses are Pfizer BioNTech vaccine (78%).

Data currently available on the persistence of immunity on the one hand and the appearance of viral variants with reduced sensitivity to vaccine immunity on the other, raise the need to administer additional doses at an interval from the primary vaccination that remains to be defined, possibly different according to age and co-existing diseases.

Since June 18th, new evidence supports the need for a third dose of COVID 19 vaccine, especially for people with immunodeficiency. The need of a booster dose in general population, particularly healthcare workers, is probable, given the increasingly active circulation of new variants since the beginning of summer 2021, and evidence of reduced protection against them. Recommendations for a booster dose are pending but some countries have already began the boost campaign for elderly and frail patients (for example people more than 60 years in Israel since the beginning of August 2021); in France, on August 23, 2021, the french Haute Autorité de Santé (HAS) has recommended an additional administration of the vaccine for persons aged 65 years and over, and fragile populations(1). On October 5, 2021, the HAS has extended this recommendation to health professionals, social care workers in contact with

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patients, health transport professionals, and people over 18 years old in contact with immunocompromised people (cocooning strategy)(2).

The French authorities do not currently support a mandatory administration of a booster dose outside the vulnerable/elderly individuals. However they highlight the need for studies in order to have data on the assessment of the impact or necessity of such a booster shot. It is thus essential to evaluate as soon as possible the efficacy of booster dose on viral variants, and their potential benefits in the general population.

This booster dose is meant to provide strengthened immune protection to individuals who have already received two doses. Currently, the only published data are related to the administration of a third dose as booster by the same vaccine used in primary vaccination. Official press releases from Pfizer and BioNTech regarding their ongoing study, estimate that a booster dose administered 6 months after the second dose has a consistent tolerability profile while generating high neutralization titers against the wild type and Beta variant, which are 5 to 10 times higher than after two primary doses(3). Furthermore, data from a recent publication in Nature shows that sera obtained two to four weeks after the second dose of the two-dose primary series of BNT162b2 present high neutralization titers (1:40 and higher) against the Delta B.1.617.2 variant. Thus, a booster dose should increase antibody titers even further, in the same way that the booster dose acts on the Beta B.1.351 variant(4).

However some vaccines which were developed more recently might offer an interesting alternative in terms of reactogenicity, accessibility, cost and acceptability. Furthermore boosting with another vaccine than the vaccine used for the primo vaccination could be more immunogenic as it is showed with heterologous vaccination. Some studies have already investigated an heterologous scheme with AstraZeneca/Oxford (Vaxzevira®) and Pfizer-BioNTech (Comirnaty®): the results showed increased anti-spike (S) IgG and IgA in both groups, but heterologous vaccination led to a significant 11.5-fold increase for anti-S IgG compared to a 2.9-fold increase after AstraZeneca/Oxford homologous vaccination, as well as a higher CD8+ and equivalent CD4 T cell production. One of the studies also found that homologous vaccination (AstraZeneca/Oxford) provided an increase neutralization of the B.1.1.7 variant in some individuals, but showed no effect against the P1 and B.1.351 variant; in contrast, heterologous vaccination provided neutralizing antibodies against the B.1.1.7, P1 and B.1.351 in almost all participants, as well as a higher neutralization capacity against the Wuhan strain (5,6). Adverse reactions were reported in heterologous and homologous schedules, with similar hematology and biochemistry profiles. Heterologous regimens induced slightly higher systemic reactogenicity: 34% of participants reported feverishness (versus 10% for homologous vaccination), and similar data was observed for chills, fatigue, headache, joint pain, and muscle ache, for participants aged < 50 years. All observed symptoms were short lived(7).

The vaccines developed by Sanofi Pasteur are based on a traditional recombinant protein approach adjuvant with the AS03 adjuvant from GSK. Two vaccine candidates are currently under development, the first one based on the SARS CoV-2 D614 Spike protein, the second one based on the B.1.351 strain(8). Their interest as boosters need to be evaluated.

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The objective of this trial is to assess the immune response induced by a booster dose of either recombinant protein-based subunit vaccine (D614 strain or B.1.351 strain) or by a booster dose of Pfizer-BioNTech mRNA vaccine in individuals previously vaccinated with 2 doses of Pfizer-BioNTech mRNA vaccine in two categories 18-64 years old and more than 64 years old. These results will provide important information for authorities, scientific communities, and the general population regarding the recommendations on booster vaccination.

Also, SARS-CoV2 is most commonly transmitted by the nasal or oral route and infects mucosal cells of the respiratory tract. Although serum antibodies may provide a correlate of protection against COVID-19, mucosal antibodies, especially IgA, may directly prevent or limit acquisition of the virus via the nasal, oral and conjunctival routes. To date, no data are available on the protective potential of the post-vaccination IgA response. We propose in this study to also measure the salivary anti-spike IgA response in order to evaluate its ability to predict vaccine efficacy.

2.2 Description of current knowledge related to COVID-19 and vaccines

Since the beginning of the pandemic, the SARS-CoV-2 virus has infected more than 200 million people worldwide (https://covid19.who.int/, data from August 5th, 2021) and more than 4 million of them have died. The most recent data from the World Health Organization (WHO) reports 6,168,252 confirmed cases of SARS-CoV-2 infection and 110,969 deaths in France (https://covid19.who.int/, data from August 5th, 2021).

The SARS-CoV-2 surface protein Spike (S), which contains the receptor-binding domain (RBD), is the predominant target of antibodies generated by natural infection. As a result, and according to WHO recommendations, most of the vaccine candidates against SARS-CoV-2 express the Spike protein or its RBD domain.

Therefore, it is possible that mutations affecting the Spike protein domain may interfere with the efficacy of either vaccine or natural immunity against SARS-CoV-2. Higher antibody titles have been demonstrated to increase neutralization of these variants, and potentially the protection against them.
Besides, several vaccine candidates targeting more specifically these variants are currently under development; hence, it is necessary to evaluate in parallel these new vaccines in the context of a “boost” regimen (homologous booster with a vaccine against the wild strain, or heterologous booster with a variant-targeted vaccine), to determine which would be more effective.

According to WHO, more than 100 vaccine candidates are currently under clinical development and more than 180 are being tested in preclinical phases. Several vaccines have been licensed worldwide, using many different vaccine platforms. However, mRNA vaccines such as Pfizer or Moderna’s remain the most widely used, especially in Europe and United States. In France, Pfizer’s COMIRNATY® vaccine is by far the most widely used, regardless of the age group.(9)

Since May 2021, the vaccine developed by Sanofi-Pasteur is undergoing clinical trials to evaluate its efficacy, immunogenicity and potential side effects.

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2.3 Summary of relevant pre-clinical experiments and clinical trials

2.3.1 BNT162b2 vaccine (COMIRNATY®) – Pfizer/BioNTech

This vaccine is composed of a single-stranded mRNA encoding the entire SARS-CoV-2 Spike (S) protein in a pre-fusion configuration, encapsulated in a lipid nanoparticle to protect it and facilitate its incorporation into the cell. The efficacy, immunogenicity and safety of two 30µg doses of BNT162b2 vaccine administered 21 days apart for the prevention of COVID-19 in individuals aged 16 years or older were evaluated in a 1:1 randomized, placebo-controlled, phase II/III study involving approximately 43,500 participants. The primary endpoint of the study was the incidence of a symptomatic COVID-19 infection from 7 days after the first vaccine injection in participants with no evidence of SARS-CoV-2 infection, until 7 days after the second dose.
An initial interim analysis of the study results, conducted in November 2020 (cut-off 14-Nov-2020) and published in December 2020 reported the following results(10,11):

1. **Vaccine efficacy**: among 43500 participants with no history of SARS-CoV-2 infection, 8 cases of COVID-19 were reported within 7 days after the second dose among the vaccine cohort (n = 18,198) while 162 cases were observed among placebo recipients (n = 18,235), corresponding to a vaccine efficacy of 95.0%. Among participants with and without evidence of prior SARS-CoV-2 infection, 9 cases of COVID-19 were observed 7 days after the 2nd dose in vaccine recipients, versus 169 cases in placebo recipients, corresponding to an efficacy of 94,6%.
2. **Local reactogenicity**: results from the sub-cohort of approximately 8000 subjects with a 7-day post-injection follow-up reported a significantly higher rate of local reactions among vaccine recipients – including mild to moderate pain at the injection site – with 71% of participants 55 years and older reporting local pain after the first dose and 66% after the second dose, versus 83% and 78% reported respectively in participants under 55 years old. Severe local reactions were reported in the BNT162b2 group with a frequency of less than 0.6%.
3. **Systemic reactogenicity**: systemic reactions in vaccine recipients were reported more frequently by younger subjects (16 – 55 years old) and more often after the second dose than after the first. The most commonly reported reactions were fatigue (62%), headache (55%), muscle pain (38%), chills (32%), joint pain (23%) and pyrexia (14%); most of these reactions were mild to moderate and resolved within a few days, regardless of the age group.

Real life data from the Israeli vaccination campaign, published in The New England Journal of Medicine, show an efficacy of 92% after the second dose, a result that is very close to the data observed in the phase III trial(12).

More recent data, published in the New England Journal of Medicine in July 2021 suggests however that the effectiveness of two doses of BNT162b2 vaccine was slightly reduced to 93.7% among patients with the Alpha variant and 88.0% among those with the delta variant (13). These data supports in parallel Pfizer's announcements, stating that a third dose as booster might be needed within 6 to 12 months after full vaccination, to maintain the highest level of protection, either against the wild strain or the variants(14).

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2.3.2 Sanofi-Pasteur / GSK CoV2 preS dTM-AS03 adjuvanted vaccine (product code No. 549 and 561)

The vaccines developed by Sanofi-Pasteur and GSK are recombinant protein-based adjuvanted vaccines, based on the same technology as the one used by Sanofi for one of its seasonal flu vaccines. It uses the truncated form of SARS-CoV-2 protein, deleted of its trans-membranary domain and stabilized on its pre-fusion configuration, as an antigen to support the immune system's ability to identify and fight the virus upon infection. The adjuvant used to enhance the immunological response produced by this vaccine is "AS03", a squalene-based immunologic adjuvant manufactured by GSK, and already used in several other vaccine products (such as Pandemrix® H1N1 flu vaccine).

On May 2021, results from **Sanofi and GSK phase II trial**, presented in their press release,(15,16) have shown that the recombinant COVID-19 vaccine candidate with GSK adjuvant induced high levels of neutralizing antibodies in non-naïve subjects who were previously affected by COVID-19 in all adult age groups. The study was conducted in 722 participants in the United States and Honduras, and assessed the safety, reactogenicity, and immunogenicity of 3 different doses of the adjuvanted vaccine, administered as 2 injections, 21 days apart.

Preliminary results (21 days post 2nd dose) reported 95% to 100% seroconversion following a second injection in all age groups (18 to 95 years) and for all doses; there were no death, no AEs leading to study discontinuation, and no AESIs reported during this period.

- **Solicited local reactions** within 7 days after each injection were mostly grade 1 and 2 intensity, with a higher frequency after the 2nd dose. The most frequently reported reactions were pain at the injection site, erythema and swelling. Grade 3 reactions were reported by 2.2% of the participants after the first dose, and 7.2% after the 2nd dose.
- **Solicited systemic reactions** within 7 days after each injection were also mostly grade 1 and 2: headache, myalgia and malaise were the most frequent. Grade 3 reactions were reported by 2.8% of the participants after the 1st dose and 16.9% after the 2nd.
- **Unsolicited adverse events** within 21 days after any injection occurred mainly 3 days after, were mostly Grade 1 and 2, and resolved within 7 days or less; the most commonly reported SOC AEs (≥ 5.0%) were "General disorders and administration site conditions", "gastrointestinal disorders", and "nervous system disorders"; PTs AEs (≥ 2.0%) reported reactogenicity-like events (i.e. fatigue, injection site pruritus, nausea, diarrhea).

Preliminary immunogenicity data based on the primary objective, determining the neutralizing antibody profile against the D614 variant, showed that, at 14 days post second injection (D36), the proportion of responders against the D614 variant with ≥ 4-fold rise GMT were 90% in both younger and older adult age groups (18-59 years and ≥ 60 years) in all dose groups. This proportion was similar between the subgroups of participants with and without a high-risk medical condition.

Interim primary analysis from this study showed that, in naïve participants, the proportion of participants having 2-fold and 4-fold or greater rise in neutralizing antibodies against D614 variant, at D36, was > 95% in the 18-59 years age group, and > 90% in the 60 years age group. In non-naïve participants, an increase in GMTs was observed 21 days after the first injection (D22); GMTs were higher in the 18-59 age group compared to the > 60 years age group.

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Overall, the encouraging results have allowed the two companies to start the phase III trial in May 2021(15).

The international, randomized, double-blind, placebo-controlled, multi-stage approach Phase III (CT registration No. PACTR202011523101903) study will enroll more than 35,000 participants. The primary endpoint is the prevention of symptomatic forms of Covid-19 in naïve adults. Prevention of severe forms and prevention of asymptomatic disease will also be evaluated. The study will investigate the potential of two different formulations, one targeting the original strain (D614 virus) and a second stage will include the B.1.351 variant (Bivalent vaccine with the B.1.351 variant) (17).

2.4 Description of the population to be studied and justification for the choice of participants

This trial will include men and women aged 18-64 years and over 65 years.
To be enrolled, participants must have previously received two doses of the BNT162b2 mRNA vaccine (COMIRNATY®, Pfizer/BioNTech). They will receive a booster dose of either a recombinant protein vaccine (Sanofi/GSK) or a BNT162b2 mRNA vaccine boost, at least six months after the second dose.

In order to optimize the interpretation of the immune response induced by the vaccine regimen studied, individuals with diseases/conditions that may compromise the immune response (such as autoimmune disease, cancer, HIV/HBV/HCV infection, or immunosuppressive therapy) will not be allowed to participate in this study.

2.5 Identification and description of the investigational medication or medications

The vaccines that will be evaluated in this study are:

1. A licensed vaccine: the Pfizer/BioNTech BNT162b2 mRNA vaccine (COMIRNATY®)
2. Two experimental vaccines: CoV2 preS dTM-AS03 adjuvanted vaccine: D614 recombinant protein vaccine, and B.1.351 recombinant protein vaccine, both developed by Sanofi-Pasteur/GSK

See section 7 for more details.

2.5.1 BNT162b2 mRNA vaccine (COMIRNATY®) from Pfizer/BioNTech

Comirnaty® is an mRNA (modified nucleoside) vaccine, indicated for active immunization for the prevention of Covid-19 caused by SARS-CoV-2, in individuals aged 12 years and older(18). The MA was obtained in Europe on December 21, 2020.

2.5.2 CoV2 preS dTM-AS03 adjuvanted vaccine from Sanofi-Pasteur/GSK

The two Sanofi-GSK vaccines are recombinant protein-based adjuvanted vaccines. Studies are currently being conducted to evaluate them. Depending on positive results and regulatory approvals, the vaccine candidate could receive marketing authorization by Q4 2021.

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2.6 Description and justification of the dosage, route of administration, administration schedule and treatment duration

Investigational products will be administered intra-muscularly into the deltoid muscle. Injection of a booster dose of recombinant protein-based subunit vaccine or mRNA vaccine in individuals previously vaccinated with two doses of BNT162b2 mRNA vaccine at least 6 months after the 2nd dose and before the booster dose.

See section 7 for more details.

2.7 Summary of the known and foreseeable benefits and risks for the research participants

Individual benefit: This study will allow participants to be informed about their antibody titers (ELISA and neutralization) in accordance with the vaccine received.

Collective benefit: The study will provide the opportunity to evaluate the reactogenicity and immunogenicity of a booster dose of mRNA or subunit vaccine.

There are limited risks associated with the blood collections: like any routine blood draw, it may causes pain, bruising, bleeding, and less frequently, a weakness or fainting.

General risks related to vaccination

In general, IM injection may cause local itching, pain, tenderness, erythema/redness, swelling, bruising, as well as systemic symptoms such as fever, chills, rash, myalgia, nausea, fatigue and dizziness. These reactions are usually short-term and will be monitored throughout the study.

As with any vaccine injection, allergic reactions may occur, causing a rash, urticarial, and less frequently, anaphylaxis. Therefore, participants with a known history of anaphylaxis or serious adverse reaction following a vaccine administration, or a known allergy to any of the excipients, will be not be allowed to participate in the study.

After the injection of the booster dose, participants will be under surveillance during 30 minutes at the study site, in order to detect any acute reactions. In addition, periodic phone calls from the medical staff will be conducted, from 48 hours to 28 days after the booster dose injection to check if adverse reactions occurred.

Risks related to Comirnaty® mRNA vaccine (Pfizer-BioNTech):

The following adverse reactions have been reported after the injection of Pfizer-BioNTech's Comirnaty® vaccine during post-approval surveillance in persons 12 years of age and older(19):

- Very common: pain at the injection site, fatigue, headache, diarrhea, muscle pain, chills, joint pain, fever and swelling at the injection site
- Common: Nausea, vomiting, redness at the injection site
- Uncommon: Lymphadenopathy, hypersensitivity reactions (rash, urticaria...), insomnia, pain in the extremities, discomfort, itching at the injection site
- Rare and undetermined frequency: acute peripheral facial paralysis, anaphylaxis, myocarditis, pericarditis, extensive swelling of vaccinated limb, facial swelling.

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Since the marketing authorization, 36,512 cases of adverse reactions have been reported, 73% of which were non-serious(20). The effects reported are as follows: general disorders and abnormalities at the injection site, nervous system, gastrointestinal, musculoskeletal, skin and cutaneous tissue disorders, vascular, hematological and lymphatic, respiratory and thoracic disorders, cardiac disorders, ear and labyrinth disorders.

Risks related to CoV2 preS dTM adjuvanted vaccine (Sanofi-Pasteur/GSK):
Available data from the previous studies reported the following adverse reactions (the majority were grade 1 and 2) after one or two injections of the vaccine in adults:

- Injection site reactions: injection site pain, erythema, swelling, pruritus, upper limb edema
- Systemic reactions: fatigue, nausea, diarrhea, fever, headache, malaise, myalgia, arthralgia and chills were the most common. Isolated cases of blood pressure elevation were reported and self-resolved.

As other COVID-91 vaccines, some AESIs need to be considered even if they were not observed during previous clinical trials: generalized convulsion, thrombocytopenia, Guillain-Barré Syndrome, acute disseminated encephalomyelitis, thrombo-embolic events.

Narcolepsy being part of Potential immune-mediated diseases (pIMDs) is included in the list of Adverse Event of Special Interests (AESIs). Potential immune-mediated diseases are a subset of adverse events that include autoimmune diseases and other inflammatory and/or neurologic disorders of interest which may or may not have an autoimmune etiology.

Potential risks associated with AS03 adjuvant:
Increased risk of narcolepsy (2- to 7- fold in adults) was observed in some cases after the Pandemrix® H1N1 flu vaccination campaign(21) .

3 OBJECTIVES

3.1 Primary objective

To assess the immunogenicity of a booster dose of an adjuvanted subunit vaccine (SP vaccine) as between D614 or B.1.351 and a mRNA vaccine (Pfizer BioNTech) in adults who were primarily vaccinated with 2 doses of mRNA vaccine (Pfizer BioNTech) and received the 2nd dose of vaccine at least 6 months before the booster dose.

3.2 Secondary objectives

1. To compare the increase in neutralization antibody titers with regard to age groups (18-64 years old and >65 years or older)
2. To evaluate the local and general safety and tolerability of a booster dose of mRNA vaccine or adjuvanted subunit vaccine up to 28 days after administration;
3. To assess the humoral immune response by ELISA of a booster dose of mRNA vaccine or adjuvanted subunit vaccine at 15 and 28 days;
4. To assess the persistence of the immune response at 3 and 12 months after the booster dose of mRNA vaccine or adjuvanted subunit vaccine;

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5. To evaluate the immunogenicity of the 3 vaccines on the D614, Alpha, Gamma and Delta viral variants;
6. To describe the associated factors and determinants of boost response in individuals previously vaccinated with 2 doses of mRNA vaccine
7. To assess the mucosal immunity following a booster dose of mRNA vaccine or adjuvanted subunit vaccine
8. To assess the early humoral response by ELISA of a booster dose of mRNA vaccine or subunit adjuvanted vaccine at 3 days (*ancillary analysis*)
9. To explore CD4 and CD8 cellular response induced by a booster dose of mRNA vaccine or adjuvanted subunit vaccine *(ancillary analysis)*

4 STUDY DESIGN

4.1 *Study endpoints*

4.1.1 Primary endpoint

Increased rate of at least 10 fold between D0 and D28 after the booster dose in neutralizing antibody titers against SARS-CoV-2 D614 and B.1.351 viral strains, measured by a microneutralisation technique in each group.

4.1.2 Secondary endpoints

1. Rate of increase in neutralizing antibody titers against SARS-CoV-2 D614 and B.1.351 viral strains, measured by a microneutralisation technique between 0 and 28 days after the booster dose in each group.
2. Quantity and intensity of local and systemic events of any grade occurring up to 7 days after boost injection (assessed from the list of solicited adverse events); Quantity and intensity of unsolicited local and systemic events up to 28 days;
3. Anti-Spike (D614) and anti-RBD (D614 and B.1.351) IgG levels, expressed in BAU/ml, according to WHO recommendations D15 and D28 after the booster dose mRNA or adjuvanted subunit vaccine;
4. Difference in Anti-Spike (D614) and anti-RBD (D614 and B.1.351) IgG levels between M3 and D0 and between M12 and D0;
5. Neutralizing antibody titers against D614, alpha, gamma, and delta variants at 28 days, 3 months and 12 months;
6. Factors of interest are age, gender, time interval between 2nd dose and boost dose, and vaccine boost type;
7. Mucosal SARS-CoV-2 specific antibodies via the measure of IgA in saliva by ELISA and PRNT assays at D0, D28 and D90 ;
8. Anti-Spike (D614) and anti-RBD (D614 and B.1.351) IgG levels, expressed in BAU/ml, according to WHO recommendations D3 after the booster dose mRNA or adjuvanted subunit vaccine
9. ELISpot IFN CD4 and CD8 response at 28 days, 3 months and 12 months (*ancillary analysis*);

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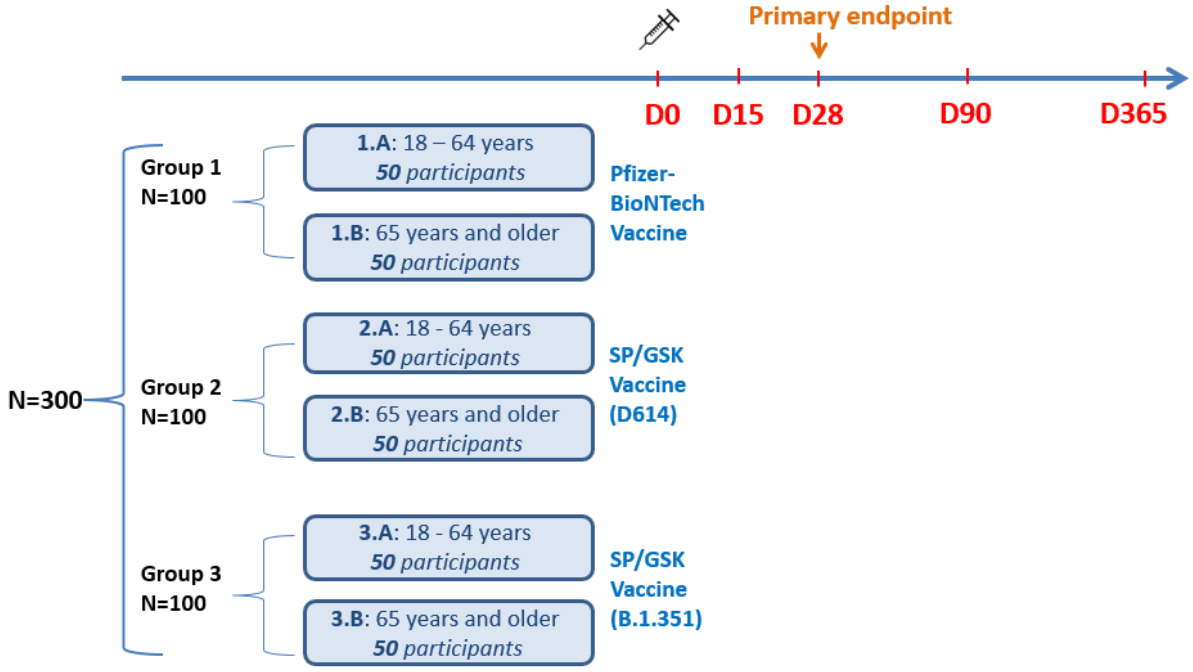
4.2 *Description of research methodology*

4.2.1 Design of the study

Randomized, single-blinded, multicenter trial in France to evaluate the immunogenicity and reactogenicity of a booster dose of a COVID-19 mRNA vaccine (Pfizer/BioNTech) or an adjuvanted subunit vaccine (SP/GSK strain D614 or strain B.1.351).

Randomization with a 1:1:1 ratio between the three different parallel arms will be applied with age stratification ([18-64] years or ≥ 65 years).



4.2.2 Number of participating sites

The study will be conducted in Clinical Investigation Centers (CIC), Clinical Research Centers (CRC) and hospital departments of the COVIREIVAC Network (French vaccine clinical research network COVID-19, INSERM) and in hospital vaccination centers.

- **Recruitment centres**

There will be 12 recruitment centers in France.

4.2.3 Identification of participants

The participants in this research will be identified as follows:

- Site number (3 digits)
- Sequential enrolment number for the site (4 digits)
- Surname initial – first name initial

This reference number is unique and will be used for the entire duration of the study.

A randomization number will also be assigned when the participant is randomized. This number will have the following format: RXXXX.

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4.2.4 Randomization

Participants who fulfill all eligibility criteria for the study and have signed informed consent will be enrolled and randomized in a 1:1:1 ratio between the 3 different parallel arms.

Randomization will be stratified on center and age group ([18-64] years or ≥ 65 years). In order to ensure the inclusion of all needed participants aged 65 years and older, inclusion of participants under 65 years will be stopped when 150 participants in this age range will be enrolled.

A statistician from the Clinical Research Unit (URC-EST), independent of the research, will edit the randomization list.

Randomization will be performed by the site staff using the centralized tool in the e-CRF just prior to the vaccine injection on D0 visit.

4.2.5 Blinding methods and measures put in place to protect blinding

The study will be performed in a single-blinded manner.

The healthcare professional administrating the vaccine will be aware of the treatment arm due to the differences between the vaccines, regarding their preparation: not only does the Sanofi-GSK vaccine require the mixing of two different vials (antigen and adjuvant), but also the amount to be withdrawn per syringe is different. Therefore, the injection will be carried out by a person external to the study.

Only the investigating physician will not be aware of which treatment the volunteer has received.

The central laboratories performing antibodies analyses will also be blinded, in order to limit measurement bias.

Sponsor blinding:
The sponsor staff (clinical research associates) who will perform the monitoring at the study site will be blinded. The staff who will perform the monitoring at the pharmacy will not be blinded.

4.2.6 Unblinding procedures

Unblinding will be requested for any reason considered essential by the investigating physician by calling upon:

- **In emergency cases** at the poison control centre at Fernand Widal Hospital, Telephone: **+33 (0)1 40 05 48 48.**

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- **Apart from an emergency situation** at the DRCI (Clinical Research and Innovation Department) to the DRCI project advisor whose contact informations are listed on the protocol cover page

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5 IMPLEMENTATION OF THE STUDY

Before any examination or intervention related to the study may be carried out, the investigator must obtain the *freely given, informed and written consent of the participant, or of his/her legal representative* where applicable.
Individuals liable to participate in studies stipulated in line 1° of article L. 1121-1 of the *Code de la Santé Publique* (French Public Health Code) benefit from a preliminary medical examination adapted to the study.

A single administration of COVID-19 vaccine will be performed at D0: Pfizer/BioNTech mRNA vaccine (Comirnaty®), or adjuvanted subunit vaccine (Sanofi-Pasteur/GSK strain D 614 or strain B.1.351), depending on randomization.
Four follow-up visits will be conducted at D15, D28, M3 and M12. An additional follow-up visit will be conducted at D3 for subjects participating in the ancillary study.

Study days should be calculated based on the date of the first vaccination (Day 0).
Visit at D3 and D15 should be performed ± 1 day compared to reference visit (D0), D28 should be performed ± 3 days from D0, visit at M3 ± 5 days from D0, and visit M12 ± 10 days from D0.

During the inclusion visit, participants will receive a self-report diary, which will be the baseline document for follow-up.
The diary will be reviewed and collected by the investigator at M1. The participants will report their temperature everyday for 7 days after vaccine administration, and collect safety information for 28 days after vaccine administration, including local (pain/swelling at the injection site) and systemic (temperature rise, headache, muscle pain, etc.) reactions, as well as concomitant treatments.

The diary will be collected at V3 and kept at the site until the last visit. The information collected in the diary will be used as a basis for the safety assessment performed by the investigator to determine if an adverse event (AE) has occurred between the three visits.

At the end of the third visit (D28), participants will be provided a memo to help them collect reactions that might occur between two visits. The memo will be reviewed at V4 and V5 and will be collected at the end of the last visit.

At the end of the first visit, participants will be provided with a ruler for daily measurement of the size of local reactions at vaccination site, and with a thermometer for daily measurement of temperature.

5.1 *Screening visit*

Participants will be recruited mainly from the COVIREIVAC volunteer platform, but they can also be recruited in collaboration with hospital vaccination centers, and traditional means of communication (poster, announcement on social networks, mailing lists).

A phone contact will be made by the investigator or a clinical research associate to explain the study (objectives, benefits and risks, and answer participants' questions), to inform the

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participant that his participation is voluntary and that he will be free to withdraw his consent at any time, without justification.

If the participant agrees on-principle to participate, a copy of the information notice will be sent to them for reading and having further information about the study, so that they can take the time to read it, and have enough time to make their decision.

After the patient has consented to participate to the study, the baseline visit will be planned.

Whose consent must be obtained	**Who informs the individuals and collects their consent**	**At what point the individuals are informed**	**At what point the consent is obtained**
The individual willing to participate in the study	The principal investigator or collaborating physician declared and trained in the study	Screening visit (by phone) and at the beginning of the inclusion visit	*Inclusion visit*

5.2 Baseline visit and randomization visit – V1 = D0

During this visit, investigator or authorized study staff will:

- Ensure that the participant has had enough time to take freely their decision, to read and understand the informed consent form
- Review all inclusion and non-inclusion criteria for eligibility of the participant. In the event that the participant is deemed ineligible for participation in the study, they will be considered as a “screen failure”. The reason for screen failure has to be documented on the screening log and into the eCRF.
- Obtain ICF signed by both the participant and the investigator
- Collect demographic data (including age and sex) and information about the medical history of the participant:
    - Any condition or medical history that may interfere with the participant’s eligibility or participation in the study, such as previous vaccinations, concomitant treatments initiated within the last month, previous or ongoing diseases
    - Any significant medical condition or history that may impair the assessment of the study or be relevant to the analyses of the immunological data
- Perform a clinical examination with measurement of vital signs (temperature, blood pressure, heart rate)
- Randomized the participant after verification of the eligibility criteria by entering the data collected into the eCRF
- Perform, before the injection of the vaccine:
    - Urinary pregnancy test for women of childbearing potential
    - Naso pharyngeal SARS-CoV-2 PCR
    - Saliva sampling (3 ml) for assessment of mucosal immunity
    - Blood sampling for :

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        - Humoral analysis and biobank (5 ml) for all participants
        - For 26 participants per group
            - Blood count (3 ml)
            - Cellular analyses (3 x 6 ml)

- Perform injection of mRNA or recombinant subunit vaccine (without waiting for the SARS-CoV-2 PCR result)
- Perform a 30-min follow-up after the administration, including a measurement of the vital signs (temperature, blood pressure, heart rate) and a recording of any significant medical event
- Report all the data into eCRF.

<u>At the end of the visit, the investigator or authorized staff will</u>:

- Deliver to the participant:
    - A self-monitoring diary that should be filled until the next visit
    - A ruler to measure any skin reactions
    - A digital thermometer
    - A participant card that must constantly be kept with the participant
- Explain to the participant how and how often the diary should be completed
- Schedule the appointment for the V2 visit

5.3 Telephone contact between V1 and V3

During the first month of participation, participants will be followed-up via periodic telephone calls from the investigation team, in order to monitor post-vaccination adverse events:

- 48 to 72 hours after boost vaccine administration, except for subjects involved in the ancillary study.
- Then D7 and D21

5.4 Follow-up visits: V2 = D15 (± 1 day), V3 = D28 (± 3 days) / V4 = M3 (D90 (± 5 days)) / V5 = M12 (D365 (± 10 days))

During this visit, investigator or authorized study staff will:

- Ask the participant about medical history since last visit, intercurrent events and current treatments,
- V2 and V3: review and collect (collection at V3 only) the self-monitoring diary
- Perform a clinical examination, including vital signs (temperature, blood pressure and heart rate)
- Perform a saliva sampling (3 ml) for assessment of mucosal immunity
- Perform a blood sampling for :
    - Humoral analysis and biobank (5 ml) for all participants
    - For 26 participants per group:
        - Blood count (3 ml)
        - Cellular analyses (3 x 6 ml)
- Provides memo to the participant

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- Report all the data into eCRF

After each visit, an appointment is scheduled for the next visit.

5.5 Ancillary analysis additional visit : VX = D3 (± 1 day)

This visit only apply to the participants involved in the ancillary analysis. During this visit, investigator or authorized study staff will:

- Ask the participant about post-vaccination adverse events
- Perform a blood sampling for humoral analysis and biobank (5ml)
- Report all the data into eCRF

5.6 Expected length of participation and description of the chronology and duration of the study.

The inclusion period will be 1 month, the duration of participation for each participant will be 12 months, and the total duration of the research will be 19 months including the analysis.

Inclusion period	1 month
Participation period, including : – Treatment duration – Follow-up duration	 1 day 12 months
Immunological analyses :	6 months
Total duration of the research :	19 months

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5.7 Table summarizing the chronology of the study

	Inclusion + boost vaccination **V1**	Safety phone call	Early follow-up (*ancillary analysis*)[a] VX	Follow-up V2	Follow-up **V3**	Follow-up **V4**	Follow-up **V5**
	D0	**48 to 72h[b] post D0 then D7 and D21**	**D3**	**D15**	**D28 (M1)**	**D90 (M3)**	**D365 (M12)**
Authorized visit interval (days)		*+/- 1 d*	*+/- 1 d*	*+/- 1 d*	*+ / -3 d*	*+/-5 d*	*+/-10 d*
Informed consent	x						
Verification of inclusion and non-inclusion criteria	x						
Clinical examination	x		x	x	x	x	x
Medical history	x						
Concomitant therapy	x		x	x	x	x	x
Naso pharyngeal SARS-CoV-2 PCR	x						
Saliva (3 ml)	x				x	x	
Blood sampling for humoral analysis and biobanking (5mL)	x		x	x	x	x	x
CBC (3 mL) [a]	x			x	x	x	x
Blood sampling for cellular analysis (3x6mL) [a]	x			x	x	x	x
Urinary pregnancy test (U)	x (U)						
Adminisatration of the vaccine Pfizer-BioNTech / SP-GSK							
Post-vaccination follow-up (30 minutes)	x						
Delivery of the self-monitoring diary (C) / Memo (A)	x (C)				x (A)		
Review of the self-monitoring diary (C) / Memo (A)			x (C)	x (C)	x (C)	x (A)	x (A)
Adverse events	x	x	x	x	x	x	x
Blood volume (mL)	**5**		**5**	**5**	**5**	**5**	**5**
Blood volume (mL) for sub-analysis (CBC and cellular analyses) [a]	***21***			***21***	***21***	***21***	***21***
Cumulative blood volume (mL)	**5**			**10**	**15**	**20**	**25**
Cumulative blood volume (mL) with sub-analysis [a]	***26***		***31***	***57***	***83***	***109***	***135***

[a]: on a sub-population of 26 participants per group.
[b] the telephone call at 48-72h will not be performed for participants in the ancillary study, who will be seen at the study site (VX).

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5.8 Pregnancy test

A urine pregnancy test will be performed on women of childbearing potential before vaccination. They will be asked to keep using their contraception during the study.
The contraception used must be considered "highly effective", i.e. one of the following methods of contraception: Oral/intra-vaginal/transdermal hormonal contraception; Intrauterine device or intrauterine hormone delivery system; Bilateral occlusion/ligation of the fallopian tubes; Partner vasectomy; Abstinence (when consistent with subject's preferred lifestyle).
Periodic abstinence (e.g., calendar, thermal...), and withdrawal are not acceptable methods of contraception.

Note: The subject undertakes to use an effective contraceptive method (or the investigating physician ensures that effective contraception has been put in place at least 4 weeks prior to the vaccination and until at least 12 weeks after the last vaccination according to the recommendations "Recommendations for Contraception and Pregnancy Tests in Clinical Trials - Clinical Trials Facilitation and Coordination Group CTFG version 1.1 (21-Sept-2020)".

5.9 Biological samples circuit

At each visit, blood samples collected from the participant will be technically processed (decantation, centrifugation, aliquoting) at each study site (laboratory, CRB, CIC, CRC...) and stored temporary as described in the laboratory manual.

The samples will be periodically sent from the study sites to the CRB APHP.SU (central biological resources center). After verification, the CRB APHP.SU will ship the samples for analysis to the following laboratories:

- For humoral analyses: Unité des Virus Emergents, UMR190, IHU Méditerranée Infection, under the supervision of Pr De Lamballerie
- For cellular analyses: Laboratoire d'Immunologie Biologique, Hôpital Européen Georges Pompidou, under the supervision of Pr Tartour.
- For mucosal analyses: Laboratoire d'immunologie, CHU Saint Etienne, under the supervision of Pr Paul.

During the study, the samples will be sent from the investigation sites to the CRB APHP.SU and then to the corresponding laboratories at 4 separate timepoints:

- a shipment of all V1, VX, V2 and V3 samples after the last V3 visit
- a shipment of all V4 samples after the last V4 visit
- a shipment of all V5 samples after the last V5 visit

5.10 Biological samples collection

At each visit, an aliquot will be stored as biological sample collection. During the study the sample collection(s) will be stored at the laboratory CRB SAT APHP.SU (site Hôpital St Antoine) under the supervision of Pr Tabassome Simon.

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At the end of the study, the samples may be used throughout a period of 3 years for further analysis not described in the initial protocol but which may be useful for investigation about COVID-19 infection related to SARS-CoV-2 virus, in light of advances in scientific knowledge, provided the participant is informed and does not oppose this, as stated in the information note/consent form. If the samples are kept at the end of the study, the sample collection will be declared to the ministry of research and to the director of the competent regional healthcare authority (Article L. 1243-3 of the *Code de la Santé Publique* [French Public Health Code]).

5.11 Distinction between standard care and study

TABLE: "Standard care" vs. "additional interventions" required specifically for the study

Interventions, procedures and treatments carried out for research purposes	**Interventions, procedures and treatments associated with <u>standard care</u>**	**Interventions, procedures and treatments added for <u>research purposes</u>**
Treatments	None	Vaccination at D0
Visits	None	4 follow-up visits at D15, M1, M3 and M12
Blood samples	None	Blood samples taken at each visit
Saliva sample	None	3ml saliva sample taken at D0, D28 and D90
Urinary sample	None	Urinary pregnancy test at D0 (females of childbearing potential only)

6 <u>ELIGIBILITY CRITERIA</u>

6.1 Inclusion criteria

1. Age ≥ 18 years
2. Adult in a healthy condition or with a stable health status if pre-existing medical history. Stable health status is defined as an existing disease that has not required a significant change in treatment or hospitalization for worsening in the 3 months before enrollment, and for which neither a significant change in treatment or hospitalization for worsening is expected in the near future
3. For women of childbearing age: a negative highly sensitive pregnancy urinary test during the inclusion visit AND use of an effective contraceptive method at least 4 weeks prior to vaccination and until at least 12 weeks after the vaccination
4. Who has received 2 doses of mRNA vaccine (Pfizer-BioNTech) with an interval of 3 to 6 weeks
5. Second dose of mRNA vaccine (Pfizer-BioNTech) administered at least 6 months before the booster dose
6. Understands and agrees to comply with the study procedures
7. Written informed consent signed by both the participant and the investigator
8. Subject affiliated to the French Social Security System

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6.2 Exclusion criteria

1. Acute febrile infection (body temperature ≥ 38.0°C) within the previous 72 hours and/or presenting symptoms suggestive of COVID-19 within the previous 28 days or having been in contact with an infected individual for the last 14 days before the inclusion visit;
2. Virologically documented history of COVID-19 (PCR or serology);
3. Immunosuppressive therapy such as corticosteroids > 10 mg prednisone equivalent/day (excluding topical preparations and inhalers) within 3 months prior to inclusion or within 6 months for chemotherapies;
4. Treatment with immunoglobulins or other blood derivatives within 3 months prior to inclusion or scheduled administration of immunoglobulins or blood derivatives before the end of the study;
5. Known HIV, HCV or HBV infection;
6. Any medical condition, such as cancer, that might impair the immune response;
7. Use of experimental immunoglobulins, experimental monoclonal antibodies or convalescent plasma is not permitted during the study;
8. Pregnancy or breastfeeding currently ongoing, or positive pregnancy test at enrolment visit;
9. History of severe adverse events following vaccine administration including anaphylactic reaction and associated symptoms such as rash, breathing problems, angioedema, and abdominal pain, or a history of allergic reaction that could be triggered by a component of the SARS-COV-2 vaccine at the time of the first vaccine injection;
10. Participant who has received BCG (tuberculosis) vaccine within the previous year
11. Has received a vaccine within 2 weeks prior to the boost injection or is scheduled to receive a registered vaccine 2 weeks after the boost injection
12. Any bleeding disorder considered as a contraindication to an intramuscular injection, previous phlebotomy or receipt of anticoagulants
13. Participation in other research involving humans (French classification Jardé 1 or Jardé 2) within 4 weeks prior to the inclusion visit, or participation in any other vaccine trial
14. Subject under legal protection (e.g. guardianship, tutorship)

6.3 Recruitment procedure

The study will be conducted in Clinical Investigation Centers (CIC), Clinical Research Centers (CRC) and hospital departments of the national vaccine clinical research network COVID-19 COVIREIVAC (Inserm).

The recruitment of participants will be carried out mainly by phone using the COVIREIVAC platform, but also in relation with the vaccination campaign coordinators of the Hospital Groups (GH) involved. An informative e-mail will be sent to all hospital staff. Posters will be displayed in the hospitals. A diffusion via social networks (Twitter, Facebook...) can be carried out.

	Number of participants
Total number of participants to be included	*300*
Number of centres	*12*

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Enrollment period (months)	*1*
Number of participants/centre	*25*
Number of participants/centre/month	***25***

In order to ensure a sufficient number of participants aged 65 and over, the inclusion of participants under 65 will be stopped when 150 participants in this age group are included.

6.4 Termination rules

6.4.1 Criteria and procedures for premature withdrawal of a participant from the study

- Participants may exit the study at any time and for any reason.
- The investigator can temporarily or permanently withdraw a participant from the study for any safety reason or if it is in the participant's best interests.
- Participant lost to follow-up: the participant cannot be located. The investigator must make every effort to reconnect with the participant (and document his attempts in the source file), at least to determine whether the participant is alive or dead

If a participant exits the study prematurely or withdraws consent, any data collected prior to the date of premature exit may still be used.
- In case of serious adverse events, see the corresponding section on vigilance.

The case report form must list the various reasons why the participant has discontinued the study:
- Lack of efficacy
- Adverse reaction
- Another medical issue
- Personal reasons of the participant
- Explicit withdrawal of consent
- Lost to follow-up

6.4.2 Procedures for replacing participants

Participants who signed the informed consent form but were not randomized may be replaced. Participants who discontinued participation or withdrew their consent after V1 will not be replaced.

6.4.3 Full or partial discontinuation of the study

AP-HP as sponsor or the Competent Authority (ANSM) can prematurely discontinue all or part of the study, temporarily or permanently, if suspected unexpected serious adverse reactions (SUSARs) are observed in one of the treatment arms or if there is a discrepancy in the serious adverse reactions between the treatment arms, requiring a reassessment of the benefit-risk ratio for the study.

Similarly, AP-HP, as the sponsor, or the Competent Authority (ANSM) may decide to prematurely discontinue the study due to unforeseen issues or new information about the product, in light of which the objectives of the study or clinical program are unlikely to be achieved.

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AP-HP as sponsor reserves the right to permanently suspend enrolment at any time if it appears that the inclusion objectives are not met.

If the study is prematurely discontinued for safety reasons, the decision and justification will be provided by the sponsor (AP-HP) to the Competent Authority (ANSM) and to the CPP (Research Ethics Committee) within a period of 15 days.

7 TREATMENT ADMINISTERED TO STUDY PARTICIPANTS

7.1 *Description of the investigational medicinal products*

7.1.1 Pfizer-BioNTech COVID-19 mRNA vaccine (COMIRNATY®)

Pfizer-BioNTech COVID-19 (COMIRNATY®) vaccine is a lipid nanoparticle dispersion (LNP) of a 5'-capped single-stranded mRNA produced by cell-free in vitro transcription from the corresponding DNA templates and encoding the SARS-CoV-2 viral Spike (S) protein.

Indications:
The vaccine is indicated for active immunization for the prevention of COVID-19 caused by SARS-CoV-2 virus, in individuals aged 12 years and older. Pfizer-BioNTech COVID-19 vaccine received conditional marketing authorization (MA) in Europe on December 21st, 2020 for “active immunization against COVID-19 caused by SARS-CoV-2 virus in persons aged 16 years and older," with an extension of the indication to teenagers from 12 to 15 years old on May 28th, 2021.
The vaccine is administered by intra-muscular (IM) injection, using a 2-dose schedule with a minimum interval of 3 weeks after the first dose.

Product description:
The product is supplied in a multi-dose vial and must be diluted before use. The vial can be stored at a temperature between +2°C and +8°C during one month, otherwise it must be stored at a temperature of -80°C. The shipment of the vial can be done at -20°C.
One vial (0.45 mL) contains 6 doses of 0.3 mL after dilution.
One dose (0.3 mL) contains 30 micrograms of COVID-19 mRNA vaccine (encapsulated in lipid nanoparticles).

Product composition:

Active substance: The vaccine contains a nucleoside-modified messenger RNA encoding the SARS-CoV-2 spike virus glycoprotein (S).

Excipients:
- ALC-0315 = ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate)
- ALC-0159 = 2-[(polyethylene glycol)-2000]-N,N-ditradecylacetamide
- 1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC)
- Cholesterol
- Potassium chloride
- Monopotassium phosphate
- Sodium chloride
- Disodium phosphate dihydrate
- Sucrose

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- Water for injection

7.1.2 Sanofi Pasteur / GSK COVID-19 recombinant protein vaccines (SARS-CoV-2 D614 or B.1.351 Spike protein)

CoV2 preS dTM-AS03 adjuvanted vaccines (product code No. 549 and 567) are candidate vaccines consisting both of a stabilized pre-fusion trimer of the SARS-CoV-2 Spike (S) protein, and including the AS03 α-tocopherol and squalene oil/water emulsion adjuvant manufactured by GSK, to optimize the immune response.
Administration:
One of these vaccines is administered by intra-muscular (IM) injection.

Product description:
The product is a liquid formulation made of recombinant protein, placed in a formulation buffer and stored in glass vials at +2°C to +8°C. The product should be stored in a place protected from light.
The CoV2 preS dTM vaccine has to be mixed with equal volumes of adjuvant AS03 at the study site before administration.
One vial contains 10 doses of 0.5ml and can be used up to 12 hours after reconstitution.

Product composition:
- CoV2 preS dTM vaccine contains phosphate-buffered saline (PBS) buffer, residual amount of baculovirus and *Spodoptera frugiperda* cell proteins, baculovirus and cellular DNA. It **does not** contain egg protein, antibiotics, or preservatives.
- AS03 adjuvant contains α-tocopherol, squalene and polysorbate.

7.2 *Description of traceability elements accompanying the investigational medicinal product(s)*

The pharmaceutical circuit and the storage/dispensing methods will be described in a specific procedure (see SOP Pharmacy Manual).

The reference documents for each vaccines used in this study are:
- COMIRNATY® Summary of Product Characteristics (SmPC), the most up-to-date version. The EMA site will be regularly consulted and the most up-to-date COMIRNATY® SmPC will be taken into account throughout the duration of the trial: https://www.ema.europa.eu/en/documents/product-information/comirnaty-epar-product-information_en.pdf
- Sanofi Pasteur / GSK CoV2 preS dTM-AS03 adjuvanted vaccine (D614) Investigator's Brochure version 10.0 dated 03/08/2021
- Sanofi Pasteur / GSK CoV2 preS dTM-AS03 adjuvanted vaccine (B.1.351) Investigator's Brochure version 10.0 dated 03/08/2021

A vaccination certificate will be provided to the participant after vaccination.

7.3 *Authorized and prohibited treatments (medicinal, additional medicinal, surgical), including rescue medications*

7.3.1 Authorized treatments

All treatments are authorized, they will be reported in the eCRF.

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7.3.2 Prohibited treatments

- Any other COVID-19 vaccine, including non-specific vaccines used in a clinical trial to evaluate their effectiveness against COVID-19 infection (e.g. BCG vaccine)
- Licensed vaccine within 2 weeks before and after the boost injection
- Immunosuppressive therapies, such as corticosteroids at a dose > 10mg prednisone equivalent per day (excluding topical preparations and inhaled products), within 3 months prior to inclusion, or within 6 months for chemotherapies
- Treatment with immunoglobulins or any other derived blood product within 3 months prior to inclusion, or planned administration before the study completion.
- Experimental immunoglobulins, experimental monoclonal antibodies, convalescent plasma.

7.4 *Methods for monitoring compliance with the study procedures*

A self-monitoring diary will be provided to the participant after the boost injection. This diary will be completed by the participant in order to record all the adverse events that occurred between D0 and D28.

8 EFFICACY ASSESSMENT

8.1 *Description of efficacy endpoints assessment parameters*

- **Anti SARS-CoV-2 antibodies anti-Spike, anti-RBD and anti-NP (Pr X. De Lamballerie, IHU Méditerrannée, Marseille, France)**

The ELISA kit from Euroimmun® (Luebeck, Germany) targets anti-SARS-CoV-2 IgG antibodies directed against the S1 domain of the virus' Spike protein. It is used according to the recommendations given by the manufacturer.

- **Neutralizing antibodies against European strain of SARS-CoV-2 and variants D614, alpha, gamma and delta (Pr X. De Lamballerie, IHU Méditerrannée, Marseille, France)**

The microneutralization test is performed according to the published protocol (Gallian P. et al, 2002). The test uses a clinical strain of SARS-CoV-2 (100 TCID50/well), VeroE6 cells and a readout by the reading of the cytopahic effect (CPE) at 5 days post-infection.
It is a VNT100 (100% of wells lysed in quadruplicate format).
Its performance is very close to a PRNT90 test. The test is automated in the NSB3 laboratory for all dilution and distribution steps and for the reading of the CPE.
The dilutions tested are 20, 40, 80, 160, 320, 640, 1280. The range is extended if a titre of 1280 is observed at first intension.

- **ELISpot IFN CD4 and CD8 (Pr E. Tartour, laboratoire d'immunologie biologique, Hôpital Européen Georges Pompidou, APHP, Paris, France)**

This test will be performed for 26 participants in each group. ELISpot uses a commercially available kit from Mabtech or C.T.L. The peptides are purchased for JPT technologies. This technique has been accredited by the French accreditation agency Cofrac.

- **Anti SARS-CoV-2 IgA anti-spike (Pr S. Paul, CHU Saint-Etienne, France)**

The measurement of anti-spike secretory IgA will be performed by ELISA technique and the measurement of the neutralizing activity of salivary IgA will be performed by PRNT technique.

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8.2 *Anticipated methods and timetable for measuring, collecting and analyzing the efficacy data*

Blood samples for humoral and cellular analyses will be taken before the boost dose, 28 days after, at M3 and at M12.The follow-up of the adverse events post-vaccination will be carried out immediately during 30 minutes after the administration of the boost dose, then at D28, M3 and M12.

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9 SPECIFIC STUDY COMMITTEES

9.1 *Steering Committee*

The steering committee is composed of the coordinating investigator and coordinating team.

- Committee members: Odile Launay, Laureen Curci, Amel Touati, Alexandra Rousseau, Laurence Bérard, Tabassome Simon, Florence Capelle, Fatiha Djennaoui, and principal investigators from the study sites.

- Roles: Define the overall structure of the study, coordinate information, determine the initial methodology and oversee the study

- Operating procedures: the steering committee will meet:
  - Before the first inclusion
  - When 50% of participants are enrolled
  - When 100% of participants are enrolled
  - When 100% of the visits have been completed
  - An additional meeting could be scheduled in case of unexpected problem

10 SAFETY ASSESSMENT - RISKS AND BURDEN ADDED BY THE STUDY

10.1 *Description of Safety endpoints assessment parameters*

Vaccines will be monitored for reactogenicity and safety.
The term "reactogenicity" refers to selected signs and symptoms occurring immediately after vaccination or in the days following vaccination, which are recorded by the participant for seven consecutive days in their self-monitoring diary.

10.2 *Anticipated methods and timetable for measuring, collecting and analyzing the safety endpoints*

Vaccine safety will be monitored by collecting the following data:

- Vaccine-related adverse events (AEs) of any grade:
  - Any adverse event occurring within 30 minutes following the boost injection
  - Solicited local (pain, erythema/redness, itching, swelling, bruising) and systemic (pyrexia, chills, headache, fatigue, arthralgia, myalgia, nausea/vomiting, faintness, insomnia, pain in the extremities, lymph nodes) adverse events, routinely collected within the 7 days post-vaccination, and reported in the diary.
  - Unsolicited events, or events occurring after the 7 self-monitoring days, up to 28 days after the boost injection
  - AEs of grade ≥ 4, reported by the participant at the next visit

- Serious adverse events occurring throughout the entire study period.

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10.3 *Recording and reporting adverse events*

10.3.1 Definitions

According to Article R.1123-46 of the *Code de la Santé Publique* (French Public Health Code):

- **Adverse event**

Any untoward medical occurrence in a study participant, which does not necessarily have a causal relationship with the study or with the product subject to the study.

- **Adverse reaction**

An adverse event occurring in a study involving human participants when this event is related to the study or to the product being studied.

- **Adverse reaction to an investigational medicinal product**

Any untoward and unwanted reaction to an investigational medication regardless of the dose administered.

- **Serious adverse event or reaction**

Any adverse event or reaction that results in death, threatens the life of the participant enrolled in the study, requires hospitalization or prolongs existing hospitalization, causes a severe or long-term disability or handicap, or results in a congenital abnormality or deformity, and in the case of a medication, regardless of the dose administered.

- **Unexpected adverse reaction to an investigational medicinal product**

Any adverse reaction to the product whose nature, severity, frequency or outcome is inconsistent with the standard safety information described in the summary of the product characteristics, or in the investigator's brochure if the product is not authorized.

According to Article R.1123-46 of the Code de la Santé Publique and the guidelines for sponsors of clinical trials (ANSM):

- **Emerging safety issue**

Any new information that may lead to a reassessment of the risk/benefit ratio of the trial or of the product under investigation, modifications in the investigational medicinal product use, the conduct of the clinical trial or the clinical trial documents, or a suspension, interruption or modification of the clinical trial or of similar trials.
For studies involving the first administration of a health product in healthy volunteers: any serious adverse reaction.

Examples:

- any clinically significant increase in the frequency of an expected serious adverse reaction;

  any new fact relating to the conduct of the clinical trial or the development of the investigational medicinal product, if the new fact is likely to affect participant safety.
  For example:
  - a serious adverse event that may be related to the trial's interventions and diagnostic procedures and which may impact the conduct of the clinical trial, if this event could affect the safety of the participants,
  - a significant risk for the trial participants such as a lack of efficacy of the investigational medicinal product used in the treatment of a life-threatening disease,
  - significant safety results from a recently completed research on animals (such as a carcinogenicity research),

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- the premature termination, or temporary suspension for safety reasons, of a trial conducted in another country by the same sponsor using the same investigational medicinal product
- a serious adverse event related to a auxilliary medicinal product required to conduct the trial and without interaction with the investigational medicinal product, if this event could affect the safety of the participants (e.g.: challenge agents, emergency treatment)

- recommendations from the Data Safety Monitoring Board (SMB), wherever applicable, if they are relevant to the safety of the participants

- for clinical trial conducted on an advanced therapy medicinal product for human use, any relevant information about safety (e.g.: about the supply and cell donation).

- any unexpected serious adverse reaction with the IMP reported to the sponsor by spontaneous notifications, by publications or health authorities, if this adverse reaction could affect the safety of the participants of the clinical trial conducted by the sponsor.
For example:
- adverse reactions occurring in a clinical trial, partially or entirely, conducted in European Union (EU), by another sponsor,
- adverse reactions occurring in a third-party country not involved in a clinical trial, caused by a medicinal product commercialized in this third-party country but exclusively used in EU as an IMP.

Solicited *versus* unsolicited adverse events:
Solicited and unsolicited adverse events must be recorded in the electronic case report form (eCRF).

- **Solicited adverse events following vaccination**

Solicited adverse events are a list of events/symptoms that participants are specifically asked to record for the week after vaccination.

Local solicited adverse events are:
- Injection site pain
- Injection site erythema (redness)
- Injection site swelling/induration (hardness)
- Injection site itching

Systemic solicited adverse events are:
- Axillary (underarm) swelling or tenderness ipsilateral to the side of injection
- Lymphadenopathy
- Headache
- Fatigue
- Malaise
- Nausea/vomiting
- Diarrhea
- Insomnia
- Chills
- Fever
- Myalgia (muscle aches all over body)
- Arthralgia (joint aches in several joints)
- Pain in the extremities

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- **Unsolicited adverse events**

The solicited symptoms can also occur after the diary-keeping period – as well as unexpected adverse events that aren't on the solicited list, or any safety issues that people are asked to watch out for and notify. Those are grouped into unsolicited adverse events time-limited to the month after vaccination.

10.3.2 The role of the investigator

The investigator must **assess the seriousness of each adverse event** and record all serious and non-serious adverse events in the electronic case report form (eCRF).

The investigator must **document** serious adverse events **as thoroughly as possible** and provide a definitive medical diagnosis, if possible.

The investigator must **assess the intensity** of the adverse events:

- Either by using the toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (Modified FDA scale / September 2007) here below:

Reaction	**Grade 0**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4* Potentially Life Threatening**
Injection site pain	None	Does not interfere with activity	Repeated use of over-the-counter pain reliever > 24 hours or interferes with activity	Any use of prescription pain reliever or prevents daily activity	Requires emergency room visit or hospitalization
Injection site erythema (redness)	< 25 mm/ < 2.5 cm	25 - 50 mm/ 2.5 - 5 cm	51 - 100 mm/ 5.1 - 10 cm	> 100 mm/ > 10 cm	Necrosis or exfoliative dermatitis
Injection site swelling/induration (hardness)	< 25 mm/ < 2.5 cm	25 - 50 mm/ 2.5 - 5 cm	51 - 100 mm/ 5.1 - 10 cm	> 100 mm/ > 10 cm	Necrosis
Axillary (underarm) swelling or tenderness ipsilateral to the side of injection*	None	No interference with activity	Repeated use of over-the-counter (non-narcotic) pain reliever > 24 hours or some interference with activity	Any use of prescription (narcotic) pain reliever or prevents daily activity	Emergency room visit or hospitalization
Headache	None	No interference with activity	Repeated use of over-the-counter pain reliever > 24 hours or some	Significant; any use of prescription pain reliever or	Requires emergency room visit or hospitalization

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			interference with activity	prevents daily activity	
Fatigue	None	No interference with activity	Some interference with activity	Significant; prevents daily activity	Requires emergency room visit or hospitalization
Myalgia (muscle aches all over body)	None	No interference with activity	Some interference with activity	Significant; prevents daily activity	Requires emergency room visit or hospitalization
Arthralgia (joint aches in several joints)	None	No interference with activity	Some interference with activity	Significant; prevents daily activity	Requires emergency room visit or hospitalization
Nausea/vomiting	None	No interference with activity or 12 episodes/ 24 hours	Some interference with activity or > 2 episodes/24 hours	Prevents daily activity, requires outpatient intravenous hydration	Requires emergency room visit or hospitalization for hypotensive shock
Chills	None	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	Requires emergency room visit or hospitalization
Fever (oral)	< 38.0°C < 100.4°F	38.0 – 38.4°C 100.4 – 101.1°F	38.5 – 38.9°C 101.2 – 102.0°F	39.0 – 40.0°C 102.1 – 104.0°F	> 40.0°C > 104.0°F

Table : Modified from final US FDA guidance: Toxicity Grading Scale for Healthy Adult and Adolescent Subjects Enrolled in Preventive Vaccine Clinical Trials (September 2007)

- Or by using
- Common Terminology Criteria for Adverse Events [National Cancer Institute]
- general terms if the above-mentioned scale cannot be used for a specific case:
    - *Mild: tolerated by the patient, does not interfere with daily activities*
    - *Moderate: sufficiently uncomfortable to affect daily activities*
    - *Serious: prevents daily activities*

The investigator must **assess the causal relationship** between serious adverse events and the investigational medicinal products.

The method used by the investigator uses the following 2 causality terms:

1. Reasonable possibility
2. No reasonable possibility

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10.3.2.1 Serious adverse events that require the investigator to notify the sponsor without delay

As per article R.1123-49 of the *Code de la Santé Publique* (French Public Health Code), the investigator notifies the sponsor without delay on the day the investigator becomes aware of any serious adverse event which occurs during a study that meets the description in line 1° of Article L.1121-1 of the Code de la Santé Publique, with the exception of any event which is listed in the protocol and, if applicable, in the investigator's brochure as not requiring notification.

A serious adverse event is any untoward medical occurrence that:

- results in death
- is life-threatening to the participant enrolled in the study
- requires hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect

10.3.2.2 Specific features of the protocol

10.3.2.2.1 Other events that require the investigator to notify without delay the sponsor

The investigator must notify the sponsor without delay on the day the investigator becomes aware of these adverse events described here-below, in the same manner and within the same deadline as for serious adverse events (see above).

- **Adverse events deemed "medically significant"**

  - Solicited adverse events **grade ≥4 according to FDA modified scale** following vaccination up to D7:
    Local solicited adverse events are:
    - Injection site pain
    - Injection site erythema (redness)
    - Injection site swelling/induration (hardness)

    Systemic solicited adverse events are:
    - Axillary (underarm) swelling or tenderness ipsilateral to the side of injection
    - Headache
    - Fatigue
    - Nausea/vomiting
    - Chills
    - Fever
    - Myalgia (muscle aches all over body)
    - Arthralgia (joint aches in several joints)

  - Zona

  - Uncontrolled diabetes in contexts of reactogenicity.

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- Acute pancreatitis.

- Rheumatoid arthritis.

- Neuroinflammatory disorders:
  - Cranial nerve neuropathy, including paralysis and paresis (eg, Bell's palsy).
  - Optic neuritis.
  - Multiple sclerosis.
  - Transverse myelitis.
  - Myasthenia gravis, including Lambert-Eaton myasthenic syndrome.
  - Demyelinating peripheral neuropathies including:
    - Chronic inflammatory demyelinating polyneuropathy.
    - Multifocal motor neuropathy.
    - Polyneuropathies associated with monoclonal gammopathy.
  - Narcolepsy.

- **Adverse events of special interest (AESIs)**

Adverse Event of Special Interest (AESI) is further defined in Council for International Organizations of Medical Sciences (CIOMS)VII as:
"An adverse event of special interest (serious or non-serious) is one of scientific and medical concern specific to the sponsor's product or program, for whichongoing monitoring and rapid communication by the investigator to the sponsor could be appropriate. Such an event might require further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial sponsor to other parties (e.g., regulators) might also be warranted."

As other COVID-91 vaccines, some AESIs need to be considered, they are listed in the table n°1 here below:

Table n°1: Adverse Events of Special Interest

Body system	AESIs type
Neurologic	Generalized convulsion
	Guillain-Barré Syndrome (GBS)
	Acute disseminated encephalomyelitis (ADEM)
	Aseptic meningitis
	Anosmia, ageusia
Hematologic	Thrombocytopenia
	Thrombo-embolic events
Immunologic	Anaphylaxis
	Vasculitides
	Arthritis
	Enhanced disease following immunization
Repiratory	Acute respiratory distress syndrome (ARDS)
Cardiac	Acute cardiac injury including: • Microangiopathy • Heart failure and cardiogenic shock • Stress cardiomyopathy • Coronary artery disease • Arrhythmia • Myocarditis, pericarditis
Renal	Acute kidney injury
Dermatologic	Chiblain-like lesions

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	Single organ cutaneous vasculitis
	Erythema multiforme
Other	Serious local/systemic adverse event following immunization Potential Immune-mediated Diseases with the adjuvant use (AS03)

- ✓ **Collection, documentation and monitoring of Potential Immune-mediated Diseases (pIMDs) with adjuvanted vaccines**

- **Potential Immune-mediated Diseases (pIMDs)**

To date there are no guidelines for collection, documentation and monitoring of pIMDs reported in the course of clinical trials with adjuvanted vaccines (20).

Potential immune-mediated diseases are a subset of AEs that include autoimmune diseases and other inflammatory and/or neurologic disorders of interest which may or may not have an autoimmune etiology. AEs that need to be recorded and reported as pIMDs include those listed in table n°2.

However, the investigator will exercise their medical and scientific judgement in deciding whether other diseases have an autoimmune origin (that is pathophysiology involving systemic or organ-specific pathogenic autoantibodies) and should also be recorded as a pIMD.

When there is enough evidence to make any of the diagnoses mentioned in table n°2, the AE must be reported as a pIMD. Symptoms, signs or conditions which might (or might not) represent the above diagnoses, should be recorded and reported as AEs but not as pIMDs until the final or definitive diagnosis has been determined, and alternative diagnoses have been eliminated or shown to be less likely.

Once a pIMD is diagnosed (serious or non-serious) in a study subject, the investigator must notify the sponsor without delay on the day the investigator becomes aware of these adverse events, in the same manner and within the same deadline as for serious adverse events (see above).

Table N°2: List of Potential Immune-mediated Diseases *(adapted from suggested list of pIMDs of interest for possible evaluation in clinical vaccine studies (20))*

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Neuroinflammatory disorders	Musculoskeletal disorders	Skin disorders
• Cranial nerve neuropathy, including paralysis and paresis (eg, Bell's palsy). • Optic neuritis. • Multiple sclerosis. • Transverse myelitis. • Guillain-Barré syndrome, including Miller Fisher syndrome and other variants. • Acute disseminated encephalomyelitis, including site specific variants, eg, noninfectious encephalitis, encephalomyelitis, myelitis, myeloradiculoneuritis. • Myasthenia gravis, including Lambert-Eaton myasthenic syndrome. • Demyelinating peripheral neuropathies including: - Chronic inflammatory demyelinating polyneuropathy. - Multifocal motor neuropathy. - Polyneuropathies associated with monoclonal gammopathy. • Narcolepsy.	• Systemic lupus erythematosus and associated conditions. • Systemic scleroderma (systemic sclerosis), including: - Diffuse scleroderma. - CREST syndrome. • Idiopathic inflammatory myopathies, including: - Dermatomyositis. - Polymyositis. • Anti-synthetase syndrome. • Rheumatoid arthritis and associated conditions including: - Juvenile idiopathic arthritis. - Still's disease. • Polymyalgia rheumatica. • Spondyloarthropathies, including: - Ankylosing spondylitis. - Reactive arthritis (Reiter's syndrome). - Undifferentiated spondyloarthritis. - Psoriatic arthritis. - Enteropathic arthritis. • Relapsing polychondritis. • Mixed connective tissue disorder. • Gout.	• Psoriasis. • Vitiligo. • Erythema nodosum. • Autoimmune bullous skin diseases (including pemphigus, pemphigoid, and dermatitis herpetiformis). • Lichen planus. • Sweet's syndrome. • Localized scleroderma (morphea).
Vasculitis	**Blood disorders**	**Others**
• Large vessels vasculitis including: - Giant cell arteritis (temporal arteritis). - Takayasu's arteritis. • Medium sized and/or small vessels vasculitis including:	• Autoimmune hemolytic anemia. • Autoimmune thrombocytopenia. • Antiphospholipid syndrome. • Pernicious anemia.	• Autoimmune glomerulonephritis including: - IgA nephropathy. - Glomerulonephritis rapidly progressive. - Membranous glomerulonephritis.

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- Polyarteritis nodosa. - Kawasaki's disease. - Microscopic polyangiitis. - Wegener's granulomatosis (granulomatosis with polyangiitis). - Churg–Strauss syndrome (allergic granulomatous angiitis or eosinophilic granulomatosis with polyangiitis). - Buerger's disease (thromboangiitis obliterans). - Necrotizing vasculitis (cutaneous or systemic). - Antineutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified). - Henoch-Schonlein purpura (IgA vasculitis). - Behcet's syndrome. - Leukocytoclastic vasculitis.	• Autoimmune aplastic anemia. • Autoimmune neutropenia. • Autoimmune pancytopenia.	- Membranoproliferative glomerulonephritis. - Mesangioproliferative glomerulonephritis. - Tubulointerstitial nephritis and uveitis syndrome. • Ocular autoimmune diseases including: - Autoimmune uveitis. - Autoimmune retinitis. • Autoimmune myocarditis. • Sarcoidosis. • Stevens-Johnson syndrome. • Sjögren's syndrome. • Alopecia areata. • Idiopathic pulmonary fibrosis. • Goodpasture syndrome. • Raynaud's phenomenon.
Liver disorders	**Gastrointestinal disorders**	**Endocrine disorders**
• Autoimmune hepatitis. • Primary biliary cirrhosis. • Primary sclerosing cholangitis. • Autoimmune cholangitis.	• Inflammatory bowel disease, including: - Crohn's disease. - Ulcerative colitis. - Microscopic colitis. - Ulcerative proctitis. • Celiac disease. • Autoimmune pancreatitis.	• Autoimmune thyroiditis (Hashimoto thyroiditis). • Grave's or Basedow's disease. • Diabetes mellitus type 1. • Addison's disease. • Polyglandular autoimmune syndrome. • Autoimmune hypophysitis.

- ***In utero* exposure**

  The investigator must notify the sponsor without delay on the day the investigator becomes aware of any pregnancy that occurs during the study, even if it is not associated with an adverse event.

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If the investigational medicinal product is genotoxic, every case of maternal or paternal exposure must be notified.

10.3.2.2.2 Serious adverse events that do not require the investigator to notify the sponsor without delay

These serious adverse events are only recorded in the electronic case report form (eCRF).

- *Special circumstances*

- Hospitalization for a pre-existing illness or condition
- Hospitalization for a medical or surgical treatment scheduled prior to the study
- Admission for social or administrative reasons
- Emergency care (< 12 hours)

- *Adverse events potentially related to treatments prescribed as part of the care provided during the study follow-up*

The investigator must report these adverse events to the relevant regional pharmacovigilance centre, Centre Régional de Pharmacovigilance (CRPV):

- *Confirmed COVID-19 infections <u>that do not meet</u> at least one of the seriousness criteria.*
- *Solicited adverse events grade <4 according to FDA modified scale following vaccination up to D7.*

10.3.2.3 Period during which SAEs must be notified without delay by the investigator to the sponsor

The investigator must notify the sponsor without delay of any serious adverse events as defined in the corresponding section:

- from the date on which the participant signs the consent form / begins treatment with the investigational medicinal product,
- throughout the whole follow-up period required for the trial
- indefinitely, if the SAE is likely to be due to the investigational medicinal product or to the study interventions (e.g. serious reactions that could appear long after exposure to the medication, such as cancers or congenital abnormalities)

10.3.2.4 Procedures and deadlines for notifying the sponsor

The initial notification of an SAE must be provided in a written report signed by the investigator using a SAE notification form specific to the study and intended for this purpose (in the case report form).

Each item in this form must be completed by the investigator so that the sponsor can carry out the appropriate analysis.

The initial notification to the sponsor of a serious adverse event must be quickly followed by an additional detailed written report (or reports) so that the case outcome may be monitored by the Safety Department or to provide further information.

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Whenever possible, the investigator will provide the sponsor with any documents that may be useful (medical reports, laboratory test results, results from additional examinations, etc.). These documents must be non-identifying. In addition, the documents must include the following: study acronym, number and participant's initials.

Any adverse event will be monitored until fully resolved (stabilization at a level considered acceptable by the investigator, or return to the previous state) even if the participant has left the study.

The initial notification, the SAE follow-up reports and all other documents must be sent to the sponsor's Safety Department by email (eig-vigilance.drc@aphp.fr). It should be noted that it is possible to send SAE reports to the Safety Department by fax to +33 (0)1 44 84 17 99 only in the event of a failed attempt to send the SAE report by email (in order to avoid duplication).

As the study uses an e-CRF:

- the investigator completes the SAE notification form in the e-CRF, then validates, prints, and signs the form before sending it by email;
- if it is not possible to connect to the e-CRF, the investigator should complete, sign, and send the SAE notification form to the Safety Department. As soon as the connection is restored, the SAE notification form in the e-CRF must be duly completed.

The investigator must respond to all requests from the sponsor for additional information.
For all questions relating to the notification of an adverse event, the Safety Department can be contacted via email: vigilance.drc@aphp.fr.

For cases of *in utero* exposure, the investigator will complete the Notification and Follow-up form for a pregnancy occurring during participation in a study".
The investigator must monitor the pregnant woman throughout her pregnancy or until the pregnancy is terminated, and must notify the sponsor of the outcome of the pregnancy using this form.
If the outcome of the pregnancy falls within the definition of a serious adverse event (miscarriage, pregnancy termination, fetal death, congenital abnormality, etc.), the investigator must follow the procedure for reporting SAEs.
The initial pregnancy notification, the SAE follow-up reports, and any other documents will be sent to the sponsor according to the same procedures specified herein.
If it was the father who was exposed, the investigator must obtain the pregnant woman's permission before collecting information about the pregnancy.

10.3.3 Role of the sponsor

The sponsor, represented by its Safety Department, shall continuously, throughout the trial, assess the safety of each investigational medicinal product throughout the study.

10.3.3.1 Analysis and declaration of serious adverse events

The sponsor assesses:

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1. the **seriousness** of all the adverse events reported
2. the **causal relationship** between these events and each investigational medicinal product and any other treatments,
   All serious adverse events which the investigator and/or the sponsor reasonably believe may have a causal relationship with the investigational medicinal product are classed as suspected serious adverse reactions.
3. the **expected or unexpected nature** of the serious adverse reactions
   Any serious adverse reaction whose nature, severity, frequency or outcome is inconsistent with the safety information described in the summary of product characteristics, or in the investigator's brochure if the product is not authorized, is considered unexpected.
   The sponsor, represented by its Safety Department, assesses the expected/unexpected nature of a serious adverse reaction based on the information described below**.**

For serious adverse events likely to be related to the investigational medicinal products, refer to the following documents:

- COMIRNATY® Summary of Product Characteristics (SmPC): The EMA site will be regularly consulted and that the most up-to-date COMIRNATY® SmPC will be taken into account throughout the duration of the trial: https://www.ema.europa.eu/en/documents/product-information/comirnaty-epar-product-information_en.pdf
- Sanofi Pasteur / GSK CoV2 preS dTM-AS03 adjuvanted vaccine (D614) and Investigator's Brochure version 10.0 dated 03/08/2021
- Sanofi Pasteur / GSK CoV2 preS dTM-AS03 adjuvanted vaccine (B.1.351) Investigator's Brochure version 10.0 dated 03/08/2021

For studies in healthy volunteers, the sponsor will report without delay all serious adverse events and all expected and unexpected serious adverse reactions to the ANSM (French Health Products Safety Agency).
For adverse events deemed "medically significant" and AESI that do not strictly meet the definition of a serious adverse event, the sponsor will declare them within 48h to the ANSM

Any suspected unexpected serious adverse reaction must also be declared electronically using the Eudravigilance European adverse drug reactions database managed by the European Medicines Agency (EMA).

The sponsor must notify all the investigators involved about any information that could adversely affect the safety of the research participants.

10.3.3.2 Analysis and declaration of other safety data

This means any new information that prompts a reassessment of the risk/benefit ratio of the trial or of the product under investigation, or which could be sufficient to consider changes to the use of the product, the trial procedures or trial documentation, or the suspension, cancellation or amendment of the research trial or of other similar trials. For trials involving the first administration or use of a health product in healthy volunteers: any serious adverse reaction.

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The sponsor will inform the competent authority and the Research Ethics Committee without delay upon knowledge of any emerging safety issue and, if applicable, describe what measures have been taken.

The sponsor will inform the regional healthcare authority (*Agence Régionale de Santé*) without delay of any emerging safety issues relating to healthy volunteers taking part in a clinical study and of any measures that have been taken.

Following the initial declaration of any emerging safety issue, the sponsor will address to competent authorities any additional relevant information about the emerging safety issue in the form of a follow-up report, which must be sent no later than 8 days after learning of the information.

10.3.3.3 Annual safety report

Once a year for the duration of the clinical study, the sponsor must produce an annual safety report (Development Safety Update Report - DSUR) which includes, in particular:

1. a safety analysis for the research participants,
2. a description of the patients included in the study (demographic profile etc.)
3. a list of all the suspected serious adverse reactions that occurred during the period covered by the report,
4. summary tables of all the serious adverse events that have occurred since the start of the study,

The report must be delivered no later than 60 days after the anniversary of the date on which the ANSM authorized the trial.

10.3.4 Data Safety Monitoring Board (DSMB)

As the study is classified as risk D, a DSMB will be constituted for this trial. The Data Safety Monitoring board will be composed of three independent experts in infectious diseases, vaccinology, and a methodologist. They will regularly review the safety data gathered all along the study and advise the sponsor on the actions to be taken for the continuation of the study. The scientific committee will meet periodically, in accordance with the DSMB charter.

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11 DATA MANAGEMENT

11.1 *Data collection procedures*

Information required by the protocol should be reported in the eCRF and a justification provided for missing data. Data should be reported in the eCRF when available, for clinical, para-clinical and immunological data.
Correction of non-compliant data on the eCRF will be requested through queries.
The anonymization of the participants will be ensured by an anonymization number reported on each document used in the research, or by deleting nominative/directly identifying data on the copies of the source documents.

11.2 *Identification of data recorded directly in the CRFs which will be considered as source data*

No data collected directly on the eCRF is considered source data.

11.3 *Right to access data and source documents*

11.3.1 Data access

In accordance with GCPs:

- the sponsor is responsible for ensuring all parties involved in the study agree to guarantee direct access to all locations where the study will be carried out, the source data, the source documents and the reports, for the purposes of the sponsor's quality control and audit procedures or inspections by the competent authority
- the investigators will ensure the persons in charge of monitoring, quality control and auditing or inspecting the interventional study involving human participants have access to the documents and personal data strictly necessary for these tasks, in accordance with the statutory and regulatory provisions in force (Articles L.1121-3 and R.5121-13 of the French Public Health Code)

Source Data Verification (SDV) will be done remotely and also on site, using the Investigator Cloud Case® (ICC) software, developed by MultiHealth Group. For data monitoring by the sponsor (AP-HP), the investigator or investigation team scans and uploads the source documents (consent form, medical records…) from the patient file, directly into the ICC® platform. The monitoring CRA is then notified by e-mail and is able to perform the monitoring by comparing the source documents with the data entered into the eCRF. The uploaded documents are permanently deleted when the monitoring is completed, or automatically permanently deleted after a predefined period (5 days by default), even if the monitoring has not been performed.

ICC® complies with FDA, EMA and GDPR requirements. As required by GDPR, the software is hosted in France on a server certified as “Health Data Hosting” in a fully secure environment that complies with all the current regulations (CEGEDIM).

11.3.2 Source documents

Source documents are defined as any original document or item that can prove the existence or accuracy of a data or a fact recorded during the study. These documents will be kept in

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accordance with the regulations by the investigator or by the hospital in the case of a hospital medical file.

The following documents are considered as source documents:

- Medical records
- Self-monitoring diary
- Pharmacy dispensing records and vaccination sheet
- Biological data

11.3.3 Data confidentiality

The persons responsible for the quality control of clinical studies (Article L.1121-3 of the *Code de la Santé Publique* [French Public Health Code]) will take all necessary precautions to ensure the confidentiality of information relating to the investigational medicinal products, the study, the study participants and in particular their identity and the results obtained.
These persons, as well as the investigators themselves, are bound by professional secrecy (in accordance with the conditions set out in Articles 226-13 and 226-14 of the *Code Pénal* [French Criminal Code]).
During and after the research involving human participants, all data collected concerning the participants and sent to the sponsor by the investigators (or any other specialised collaborators) will be rendered non-identifying.
Under no circumstances shall the names and addresses of the participants involved be shown. Only the participant's initials will be recorded, accompanied by an encoded number specific to the study indicating the order of enrolment.
The sponsor will ensure that each participant has given written permission for any personal information about him or her which is strictly necessary for the quality control of the study to be accessed.

11.4 Data processing and storage of research documents and data

11.4.1 Identification of the data processing manager and location(s)

Data processing and statistical analysis will be performed by URC Est (AP-HP), Paris.

11.4.2 Data entry

Non-identifying data will be entered electronically via a web browser.

11.5 Data ownership

AP-HP is the owner of the data. The data cannot be used or disclosed to a third party without its prior permission.

12 STATISTICAL ASPECTS

12.1 Description of statistical methods to be used including the timetable for the planned interim analyses

A detailed analysis plan will be a priori defined.

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Analysis will be performed by a statistician from URC-Est using SAS® software version 9.4 (or updated version) (SAS Institute Inc.). Partial data base locks will be performed for data from randomization to D28 to assess primary and secondary endpoints at D28, at M3 to assess M3 secondary endpoints. Final data base lock will be at the end of the trial to assess secondary M12 secondary endpoints.

A flow chart will be drawn according to consort statement. The proportion of eligible participants who refused to participate in the research or who did not come to the scheduled consultation will be described.

Baseline characteristics of patients will be described overall and per group.
Continuous variables will be summarized using descriptive statistics, i.e. number of subjects, mean, standard deviation (SD), median, inter quartile range, minimum and maximum depending on the variable distribution. Qualitative variables will be summarized by frequency and percentage.

Primary endpoint assessment

The main analysis will be performed on the per protocol population.
For each viral strains (D614 and B.1.351), proportion of subjects with an increase rate in neutralizing antibody titers against SARS-CoV-2 of at least 10 fold between D0 and D28 will be calculated with it 2-sided 95% confidence interval (95%CI) using the exact Clopper-Pearson method.

Secondary endpoints assessment

- Rate of increase in neutralizing antibody titers against SARS-CoV-2 D614 and B.1.351 viral strains measured by a microneutralisation technique between 0 and 28 days after the booster dose in each group of randomisation and in each age group (18-64 years and 65 years or more) will be described.

- Anti-Spike (D614) IgG levels, expressed in BAU/ml, according to WHO recommendations D28 after the booster dose mRNA or adjuvanted subunit vaccine, and their persistence at 3 and 12 months will be described as geometric means with 95% confidence intervals (by logarithmic transformation of the data, calculation of the arithmetic mean and its confidence interval and anti-log transformation of these mean and limits of the confidence interval).

- Anti-RBD (D614 and B.1.351) IgG levels up to 28 days after the booster dose mRNA or adjuvanted subunit vaccine and their persistence at 3 and 12 months will be described as geometric means with 95% confidence intervals (by logarithmic transformation of the data, calculation of the arithmetic mean and its confidence interval and anti-log transformation of these mean and limits of the confidence interval). Differences in Anti-Spike (D614) and anti-RBD (D614 and B.1.351) IgG levels between D3 and D0 and between 12 months and D0 will be estimated with 95% confidence intervals.

- For each vaccine, the antibody titers will be described at each time of measurement as geometric means with 95% confidence intervals (by logarithmic transformation of the data, calculation of the arithmetic mean and its confidence interval and anti-log

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transformation of these mean and limits of the confidence interval). Evolution between D0, M1, M3 and M12 will be described using graphs.

- Associated factors and determinants of boost response (neutralizing antibody titers against D614, alpha, gamma, and delta variants) in individuals previously vaccinated with 2 doses of mRNA vaccine will be studied.

- ELISpot IFN CD4 and CD8 response will be described. (*ancillary-analysis*)

Safety assessment

Safety assessment will be analysed among safety population.

- Proportions of 1) local adverse events and 2) systemic adverse events of any grade (assessed from the list of solicited adverse events) occurring up to 7 days after each injection will be described globally and by randomization group. Intensity will also be described.
- Quantity and intensity of unsolicited local and systemic events up to 28 days will also be described by randomization group.

12.2 Calculation hypotheses for the number of participants required and the result

The sample size calculation is performed to estimate the proportion of subjects with a sufficient rate of increase in neutralizing antibody titers and its 95% confidence interval with a given precision.
Due to the lack of available data on the Pfizer-BioNTech vaccine, the sample size calculation is based on published data on the Moderna vaccine (Wu, 2021(ref)) in which an increase rate of neutralizing antibody titer against historical SARS-CoV-2 (D 614 G) after Moderna boost at D15 of 23 and 32 for the B.1.351 variant is described. Using a conservative approach, we consider neutralizing activity to be sufficient if the increase rate is at least 10 at D28.

We assume a proportion of subjects with an increase rate of at least 10 between D0 and D28 of 85% in subjects aged 18-64 years and 75% in subjects aged 65 years and older.

Fifty subjects per age group will allow an estimation of the proportion in subjects aged 18 to 64 years of 85% with a half width of 95% confidence interval of 9.9% and in patients aged 65 years and older of 75% with a half width of 95% confidence interval of 12%.

Thus, a total of 300 volunteers will be randomized: 100 per group, 50 per age group.

12.3 Anticipated level of statistical significance

All tests will be two-sided, and a p-value of < 0.05 will be considered significant.

12.4 Statistical criteria for termination of the study.

Not applicable.

12.5 Method for taking into account missing, unused or invalid data

Missing data for the primary endpoint will be replaced by the geometric mean value of antibody levels observed in the group of the concerned subject.
Censored data reported as below the lower limit of detection/quantification will be imputed with a value equal to half of the threshold before transformation.
Other missing data will not be replaced.

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12.6 Management of modifications made to the analysis plan for the initial strategy.

All modification made to the analysis plan for the initial strategy will be documented in the analysis report.

12.7 Choice of individuals to be included in the analyses

Intent to treat population (ITT): all patients as randomized, regardless of the strategy received by the patient.

Per protocol (PP) population: all patients as randomized, treated without major protocol violations/deviations. Pre-defined major protocol violations/deviations are:

- Non-respect of eligibility criteria
- Non-respect of the randomized treatment allocation and/or duration (wrong vaccine received, second dose not received)
- Missing data for the primary efficacy endpoint

Major protocol deviation will be classified during a blinded data review before final data base lock.

Safety population: All patients as randomized who have received the boost dose of vaccine.

13 QUALITY CONTROL AND ASSURANCE

Every research project involving human participants managed by AP-HP is ranked according to the projected risk incurred by study participants using the classification system specific to AP-HP sponsored interventional research involving human participants.

13.1 *General organization*

The sponsor must ensure the safety and respect of individuals who have agreed to participate in the study. The sponsor must implement a quality assurance system to best monitor the implementation of the study in the investigation centers.

For this purpose, the sponsor shall assign Clinical Research Associates (CRA) whose primary role is to carry out regular follow-up visits on site whenever possible, or remotely using the ICC® software, after having carried out the initial visits.
The purpose of remote-monitoring the study is the same as on-site visits; as defined in Good Clinical Practices (GCP section 5.18.1), is to verify that:

- the rights, safety and protection of the research participants are met
- the data reported are exact, complete and consistent with the source documents
- the study is carried out in accordance with the protocol in force, the GCPs and the statutory and regulatory provisions in force

13.1.1 Strategy for center opening

The strategy for opening the centers established for this study is determined using the appropriate monitoring plan.

A feasibility questionnaire was sent to the pre-selected study sites in advance, in order to assess the feasibility of the study in terms of personnel, logistics and enrollment potential.

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13.1.2 Scope of center monitoring

In the case of this D risk study the appropriate monitoring level has been determined based on the complexity, the impact and the budget for the study. Therefore, in agreement with the coordinating investigator, the sponsor has determined the logistical score and impact, resulting in a study monitoring level to be implemented: level high

13.2 Quality control

The investigator and the members of the investigator's team agree to make themselves available during regular Quality Control remote visits carried out by the Clinical Research Associate. During these visits, the following elements will be reviewed depending on the monitoring level:

- written consent
- compliance with the study protocol and with the procedures defined therein
- quality of the data collected in the case report form: accuracy, missing data, consistency of the data with the "source" documents (medical files, appointment books, original copies of laboratory results, etc.)
- management of the treatments used

A Clinical Research Associate (CRA) appointed by the sponsor will be responsible for the good completion of the study, for collecting, documenting, recording and reporting all handwritten data, in accordance with the Standard Operating Procedures applied within the DRCI (Clinical Research and Innovation Department) and in accordance with Good Clinical Practices as well as the statutory and regulatory requirements. In the context of the covid-19 pandemic, monitoring of center data will be done on site and/or remotely using the Investigator Cloud Case® (ICC) software, developed by MultiHealth Group. The investigator with the help of its team will scan and upload the source documents (consent form, medical records…) from the patient file, directly into the ICC® platform. The monitoring CRA is then notified by e-mail and is able to perform the monitoring by comparing the source documents with the data entered into the eCRF. The uploaded documents are permanently deleted when the monitoring is completed, or automatically permanently deleted after a predefined period (5 days by default), even if the monitoring has not been performed. ICC® complies with FDA, EMA and GDPR requirements. As required by GDPR, the software is hosted in France on a server certified as "Health Data Hosting" in a fully secure environment that complies with all the current regulations (CEGEDIM).

13.3 Case report forms

Electronic CRF (eCRF):

All information required by the protocol must be entered in the case report forms. The data must be collected as and when they are obtained, and clearly recorded in these case report forms. Any missing data must be coded.

Every site will have access to the electronic case report forms via a web-based data collection system. Investigators will be given a document offering guidance on using this tool.

When the investigators complete the case report form via the Internet, the CRA can view the data quickly and remotely. The investigator is responsible for the accuracy, quality and

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relevance of all the data entered. In addition, the data are immediately verified as they are entered, thanks to consistency checks. To this end, the investigator must validate any changes to the values in the case report form. An audit trail will be kept of all changes. A justification can be added when applicable, as a comment.
A print-out, authenticated (signed and dated) by the investigator, will be requested at the end of the study. The investigator must archive a copy of the authenticated document that was issued to the sponsor.

13.4 Management of non-compliances

Any events that occur as a result of non-compliance – by the investigator or any other individual involved in running the study – with the protocol, standard operating procedures, good clinical practices or statutory and regulatory requirements must be recorded in a declaration of non-compliance and sent to the sponsor.

These non-compliances will be managed in accordance with the sponsor's procedures.

13.5 Audits/inspections

The investigators agree to consent to the quality assurance audits carried out by the sponsor as well as the inspections carried out by the competent authorities. All data, documents and reports may be subject to regulatory audits and inspections. These audits and inspections cannot be refused on the grounds of medical secrecy.

An audit can be carried out at any time by individuals appointed by the sponsor and independent of those responsible for the research. The aim of the audits is to ensure the quality of the study, the validity of the results and compliance with the legislation and regulations in force.

The persons who manage and monitor the study agree to comply with the sponsor's requirements and with the competent authority regarding study audits or inspections.

The audit may encompass all stages of the study, from the development of the protocol to the publication of the results, including the storage of the data used or produced as part of the study.

13.6 Principal Investigator's commitment to assume responsibility

Before starting the study, each investigator will give the sponsor's representative a copy of his/her updated personal *curriculum vitæ*, signed and dated less than one year, with his/her RPPS number (*Répertoire Partagé des Professionnels de Santé*, Collective Database of Health Professionals). The CV must include any previous involvement in clinical research and related training.

Each investigator will commit to comply with legislation and to conduct the study in line with GCP, in accordance with the Declaration of Helsinki.

The Principal Investigator at each participating site will sign a commitment of responsibility (standard DRCI document) which will be sent to the sponsor's representative.

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The investigators and their staff will sign a delegation of duties form specifying each person's role and will provide their CVs.

13.7 Pharmacist's commitment of responsibility

Before the start of the study, each pharmacist will provide the sponsor or the sponsor's representative a copy of their updated Curriculum Vitae, signed and dated less than one year. The CV must include their previous involvement in clinical research / clinical trials, as well as the related training.

Each pharmacies will commit to comply with legislation and to conduct the study in line with GCPs, in accordance with the Declaration of Helsinki.

The pharmacists will sign a delegation of duties form, specifying each person's role during the study.

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14 ETHICAL AND LEGAL CONSIDERATIONS

14.1 Methods for informing research participants and obtaining their consent

In accordance with Article L1122-1-1 of the Code de la Santé Publique (French Public Health Code), no interventional research involving human participants can be carried out on a person without his/her freely given and informed consent, obtained in writing after the person has been given the information specified in Article L.1122-1 of the aforementioned Code.

A reflection period is given to the individual between the time when they are informed and when they sign the consent form.

The person's freely-given, written, informed consent will be obtained by the principal investigator or a physician representing the investigator before the person is enrolled in the study at the inclusion visit.

A copy of the information note and consent form, signed and dated by the research participant and by the principal investigator or the physician representing the investigator will be given to the individual prior to their participation in the study. The principal investigator or the physician representing him/her will keep a copy.

At the end of the study, one copy will be placed in a tamper-proof sealed envelope containing all the consent forms. This envelope will be archived by the sponsor.

In addition, the investigator will specify in the person's medical file the person's participation in the research, the procedures for obtaining his/her consent, as well as the methods used for providing information for the purpose of collecting it. The investigator will retain one copy of the signed and dated consent form.

Special circumstances: Mention of the possibility for the investigator of withholding certain information relating to the diagnosis, as applicable, in accordance with paragraph 4 of Article L1122-1.

14.2 Prohibition from participating in another clinical study or exclusion period set after the study

No exclusion period of participation after the participant has finished this study is defined in the context of this research.
The participant may not enroll in another interventional study protocol involving human participants for the duration of his or her participation without consulting with the physician monitoring him or her in the context of the study.
The participants can however participate in other non-interventional studies.

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14.3 Compensation for participants

A compensation is planned for the participants in this research: 100€ for vaccination visit, and 50€ for each follow-up visit, for a total of 300€ per participant. The compensations will be paid according to the following schedule:

- 200€ (100€ for V1 + 50€ for V2 + 50€ for V3) will be paid after V3 completion
- 100€ (50€ for V4 + 50€ for V5) will be paid after V5 completion

A compensation corresponding to the reimbursement of the transport costs is also planned for this study, at a fixed amount of 20€ per visit.

Subjects taking part in the ancillary study will receive additional compensation of 50€ for the additional D3 follow-up visit.

14.4 Registration on the National Register of study participants to studies involving human participants concerning the products mentioned in Article L. 5311-1 of the *Code de la Santé Publique*

As the subjects enrolled in this study are healthy, volunteer to participate and receive a compensation for participating, in accordance with Art. L.1121-16 of the Code de la Santé Publique (French Public Health Code), they will be registered on the National Register of Study Participants ("VRB") after signing the Informed Consent Form, and before any study procedure.

14.5 Authorization for the research location

Units participating in the study must have specific authorization for the location, because the study requires the enrollment of healthy volunteers.

14.6 Legal obligations

14.6.1 Role of the sponsor

Assistance Publique - Hôpitaux de Paris (AP-HP) is the sponsor of this study and, by delegation, the DRCI (Clinical Research and Innovation Department) carries out the study's missions in accordance with Article L.1121-1 of the *Code de la Santé Publique (French Public Health Code)*. Assistance Publique - Hôpitaux de Paris reserves the right to halt the study at any time for medical or administrative reasons. In this case, notification will be sent to the investigator.

14.6.2 Request for approval from the CPP (Research Ethics Committee)

Prior to starting the study, AP-HP, as sponsor, must obtain for this interventional study involving human participants concerning a medicinal product for human use, approval from the appropriate CPP (Research Ethics Committee), within the scope of its authority and in accordance with in force legislation and regulatory requirements.

14.6.3 Request for authorization from ANSM

Prior to starting the study, AP-HP, as sponsor, must obtains authorization from the ANSM (French Health Products Safety Agency) for the interventional study involving human

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participants concerning a medicinal products for human use, within the scope of the ANSM's authority and in accordance with in force legislation and regulatory requirements.

14.6.4 Procedures relating to data protection regulations

The computer file used for this research is implemented in accordance with French (amended "Informatique et Libertés" law governing data protection) and European (General Data Protection Regulation – GDPR) regulations.

This research does not fall under the scope of the CNIL "Reference Methodology" (MR-001) because the monitoring of consents and patient files will be performed remotely via the ICC® software from the MultiHealth Group for study sites outside AP-HP.
However, with regards to the current health context and exceptional circumstances, the CNIL considers, as a derogation and on a strictly temporary basis, that it is not necessary to file an application for authorization to the CNIL, if the implementation of remote monitoring is the only point of non-compliance with the MRs, on the strict condition that all the requirements set out below are met, depending of the selected solution.

14.6.5 Amendments to the research

Any substantial modification to the protocol by the coordinating investigator must be sent to the sponsor for approval. After approval is given, the sponsor must obtain approval from the CPP (Research Ethics Committee) and authorization from the ANSM within the scope of their respective authorities, before the amendment can be implemented.
The information note and the consent form can be revised if necessary, in particular in case of a substantial amendment to the study or if adverse reactions occur.

14.6.6 Final study report

The final report for the research involving human participants referred to in Article R1123-67 of the *Code de la Santé Publique* (French Public Health Code) is written and signed by the sponsor and the investigator. A report summary drafted according to the reference plan of the competent authority must be sent to the competent authority within a period of one year following the end of the study, i.e., the end of the participation of the last participant in the study.

14.6.7 Archiving

Specific documents for an interventional study involving human participants concerning a medicinal product for human use will be archived by the investigator and the sponsor for fifteen years after the end of the research.

This indexed archiving includes, in particular:

- A sealed envelope for the investigator containing a copy of all the information notes and consent forms signed by all individuals at the centre who participated in the study;
- A sealed envelope for the sponsor, containing a copy of all the information notes and consent forms signed by all individuals at the centre who participated in the study;
- "Study" binders for the Investigator and the sponsor, including (non-exhaustive list) :
    - the successive versions of the protocol (identified by the version number and its date), and any appendices
    - the ANSM authorizations and CPP (Research Ethics Committee) decisions

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- any correspondence
- the enrolment list or register
- the appendices specific to the research
- final study report

- The data collection documents

15 FUNDING AND INSURANCE

15.1 *Funding sources*

The present study will be funded by xxxxx.

15.2 *Insurance*

For the duration of the study, the Sponsor will take out an insurance policy covering the sponsor's own public liability, as well as the public liability for all the physicians involved in the study. The sponsor will also provide full compensation for any damages caused by the study to the participant enrolled and their beneficiaries, unless the sponsor can prove that the harm is not the fault of the sponsor or any collaborator. Compensation cannot be refused on the grounds of a third-party act or the voluntary withdrawal of the person who initially consented to participate in the study.

Assistance Publique - Hôpitaux de Paris (AP-HP) has taken out insurance with HDI-GLOBAL SE through the insurance broker BIOMEDIC-INSURE for the full study period, which covers its own public liability and that of any collaborator (physician or research staff), in accordance with Article L.1121-10 of the *Code de la Santé Publique* (French Public Health Code).

16 PUBLICATION RULES

The Scientific Committee must be informed within a reasonable delay prior to each submission of any communication (abstract; written publication, other) regarding this trial.
A copy of the publication must be sent to the sponsor.
The first signatories of publications will be individuals who actually took part in the preparation and conduct of the protocol, the analysis and interpretation of the results, and the writing up and/or revision of the manuscript. Authorship definitions will follow the Vancouver rules.

For the other contributors, the order of authors will be allocated according to the number of participants included in the study site compared to the expected participants and their usable data. The next-to-last one will be reserved for the study coordinators.

The URC Est must be acknowledged for implementation, monitoring and data management in the "Acknowledgment" section.

The AGEPS will be also acknowledged in the "Acknowledgment" section.

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Sanofi-Pasteur and GSK will be acknowledged for providing the experimental vaccines, in the "Acknowledgment" section.

16.1 Mention of AP-HP affiliation for projects sponsored by AP-HP

Each author affiliation must appear and must be identified by an address and separated by a semicolon (;).
In case an author has multiple affiliations, each affiliation should appear. The order in which the institution (AP-HP; University; INSERM) is quoted has no importance.
For AP-HP members, the terms “Assistance Publique-Hôpitaux de Paris” or “AP-HP” must appear first in the authors’ address as follows AP-HP, hospital, department, city, postcode, France.

16.2 Mention of the sponsor AP-HP (DRCI) in the acknowledgements of the text

“The sponsor was Assistance Publique – Hôpitaux de Paris (Délégation à la Recherche Clinique et à l’Innovation)”

16.3 Mention of the financial backer in the acknowledgements of the text

“The study was funded by XXXXX”

This study has been registered on the website http://clinicaltrials.gov/ under number NCTXXXXXX

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17 REFERENCES

1. Avis n° 2021.0061/AC/SEESP du 23 août 2021 du collège de la HAS relatif à la définition des populations à cibler par la campagne de rappel vaccinal chez les personnes ayant eu une primovaccination complète contre la Covid-19 [Internet]. Haute Autorité de Santé. [cité 20 oct 2021]. Disponible sur: https://www.has-sante.fr/jcms/p_3283044/fr/avis-n-2021-0061/ac/seesp-du-23-aout-2021-du-college-de-la-has-relatif-a-la-definition-des-populations-a-cibler-par-la-campagne-de-rappel-vaccinal-chez-les-personnes-ayant-eu-une-primovaccination-complete-contre-la-covid-19

2. Haute Autorité de Santé. Stratégie de vaccination contre la Covid-19 - Place d'un rappel par le vaccin à ARNm COMIRNATY® [Internet]. Haute Autorité de Santé. 2021 [cité 20 oct 2021]. Disponible sur: https://www.has-sante.fr/jcms/p_3290614/fr/strategie-de-vaccination-contre-la-covid-19-place-d-un-rappel-par-le-vaccin-a-arnm-comirnaty

3. Pfizer and BIONTech Provide Update on Booster Program in Light of the Delta-Variant [Internet]. 2021. Disponible sur: https://www.sec.gov/Archives/edgar/data/1776985/000156459021036101/bntx-ex991_7.htm

4. Liu J, Liu Y, Xia H, Zou J, Weaver SC, Swanson KA, et al. BNT162b2-elicited neutralization of B.1.617 and other SARS-CoV-2 variants. Nature [Internet]. 10 juin 2021 [cité 5 août 2021]; Disponible sur: http://www.nature.com/articles/s41586-021-03693-y

5. Schmidt T, Klemis V, Schub D, Mihm J, Hielscher F, Marx S, et al. Immunogenicity and reactogenicity of heterologous ChAdOx1 nCoV-19/mRNA vaccination. Nat Med [Internet]. 26 juill 2021 [cité 11 août 2021]; Disponible sur: http://www.nature.com/articles/s41591-021-01464-w

6. Barros-Martins J, Hammerschmidt SI, Cossmann A, Odak I, Stankov MV, Morillas Ramos G, et al. Immune responses against SARS-CoV-2 variants after heterologous and homologous ChAdOx1 nCoV-19/BNT162b2 vaccination. Nat Med. 14 juill 2021;1-5.

7. Shaw RH, Stuart A, Greenland M, Liu X, Nguyen Van-Tam JS, Snape MD. Heterologous prime-boost COVID-19 vaccination: initial reactogenicity data. Lancet Lond Engl. 2021;397(10289):2043-6.

8. Sanofi. Sanofi: Press Releases, Thursday, May 27, 2021 [Internet]. https://www.sanofi.com/en/media-room/press-releases/2021/2021-05-27-07-30-00-2236989. Disponible sur: https://www.sanofi.com/media-room/press-releases/2021/2021-05-27 07-30-00 2236989

9. VaccinTracker Covid19 : nombre de français vaccinés [Internet]. CovidTracker. [cité 6 août 2021]. Disponible sur: https://covidtracker.fr/vaccintracker/

10. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med. 31 déc 2020;383(27):2603-15.

11. Haute Autorité de Santé. Stratégie de vaccination contre la Covid-19 - Place du vaccin à ARNm COMIRNATY (BNT162b2) dans la stratégie. 2020;102.

12. Dagan N, Barda N, Kepten E, Miron O, Perchik S, Katz MA, et al. BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Mass Vaccination Setting. N Engl J Med. 15 avr 2021;384(15):1412-23.

13. Lopez Bernal J, Andrews N, Gower C, Gallagher E, Simmons R, Thelwall S, et al. Effectiveness of Covid-19 Vaccines against the B.1.617.2 (Delta) Variant. N Engl J Med. 21 juill 2021;NEJMoa2108891.

14. Pfizer. Pfizer Second Qarter 2021 Teleconference. 2021.

This document is the property of DRCI/AP-HP. All reproduction is strictly prohibited.

Version 4.0 dated 31/05/2019

15. Sanofi Press Release. Sanofi and GSK COVID-19 vaccine candidate demonstrates strong immune responses across all adult age groups in Phase 2 trial. Sanofi Press Release [Internet]. https://www.sanofi.com/en/media-room/press-releases/2021/2021-05-17-07-30-00-2230312. 2021 [cité 5 août 2021]. Disponible sur: https://www.sanofi.com/media-room/press-releases/2021/2021-05-17 07-30-00 2230312

16. Sanofi Pasteur, a Sanofi Company. Immunogenicity and Safety of SARS-CoV-2 Recombinant Protein Vaccines With AS03 Adjuvant in Adults 18 Years of Age and Older as a Primary Series and Immunogenicity and Safety of a Booster Dose of SARS-CoV-2 Adjuvanted Recombinant Protein Vaccines (Two Monovalent and One Bivalent) [Internet]. clinicaltrials.gov; 2021 août [cité 9 août 2021]. Report No.: NCT04762680. Disponible sur: https://clinicaltrials.gov/ct2/show/NCT04762680

17. GSK Press Release. Sanofi and GSK initiate global Phase 3 clinical efficacy study of COVID-19 vaccine candidate [Internet]. 2021 [cité 5 août 2021]. Disponible sur: https://www.gsk.com/en-gb/media/press-releases/sanofi-and-gsk-initiate-global-phase-3-clinical-efficacy-study-of-covid-19-vaccine-candidate/

18. Haute Autorité de Santé. Stratégie de vaccination contre la Covid-19 - Place du vaccin à ARNm COMIRNATY® chez les 12–15 ans. 2 juin 2021;123.

19. Comirnaty - Summary of Product Characteristics FR [Internet]. Disponible sur: https://www.ema.europa.eu/en/documents/product-information/comirnaty-epar-product-information_fr.pdf

20. ANSM. Point de situation sur la surveillance des vaccins contre la COVID-19 - Période du 16/07/2021 au 22/07/2021 [Internet]. 2021. Disponible sur: https://ansm.sante.fr/actualites/point-de-situation-sur-la-surveillance-des-vaccins-contre-la-covid-19-periode-du-16-07-2021-au-22-07-2021

21. Sarkanen T, Alakuijala A, Julkunen I, Partinen M. Narcolepsy Associated with Pandemrix Vaccine. Curr Neurol Neurosci Rep. juill 2018;18(7):43.

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LIST OF ADDENDA

Each addendum and the log of addenda versions are attached, independently of the protocol. Each addendum can be modified (change of addendum version) without modifying the protocol version.

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17.1 List of investigators

Address of the study location	Title	First name SURNAME	Telephone/E-mail/Fax
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17.2 Serious Adverse Events notification form

Direction de la Recherche Clinique et de l'Innovation (DRCI)	ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS **Formulaire de notification d'un Evènement Indésirable Grave (EIG) survenant au cours d'une recherche impliquant la personne humaine portant sur un Médicament ou produit assimilé**	**PARTIE RESERVEE AU PROMOTEUR** **REFERENCE VIGILANCE :** Référence GED : REC-DTYP-0192

Dès la prise de connaissance de l'EIG par l'investigateur, ce formulaire doit être dûment complété (3 pages), signé et retourné sans délai au secteur Vigilance de la DRCI par mail (eig-vigilance.drc@aphp.fr).

NB : Il est également possible d'envoyer ce formulaire par fax to +33 (0)1 44 84 17 99 uniquement en cas de tentative infructueuse d'envoi par mail (pour éviter les doublons).

Notification initiale ☐ **Suivi d'EIG** ☐ **N° du suivi** |__|__|

1. Identification de la recherche

Acronyme : **COVIBOOST**

Code de la Recherche : APHP211184

Risque : D

Date de notification : |__|__| |__|__| |2|0|__|__| (jj mm aaaa)

Date de prise de connaissance de l'EIG par l'investigateur : |__|__| |__|__| |2|0|__|__| (jj mm aaaa)

Titre complet de la recherche :
Immunogenicity and reactogenicity following a booster dose of a COVID-19 mRNA vaccine (Pfizer-BioNTech) and two adjuvanted sub-unit vaccines (SP/GSK) administered in adults who received 2 doses of Pfizer-BioNTech mRNA vaccine as a primary vaccination: a randomized, single-blinded, multicenter clinical trial.

2. Identification du centre investigateur

Nom de l'établissement : .....
Ville et code postal : .....
Service : .....

Investigateur (nom/prénom) : .....

Tél : ..... Fax : .....
Mail : .....

3. Identification et antécédents de la personne se prêtant à la recherche

Référence de la personne : |__|__|__| - |__|__|__|__|__| - |__| - |__|
(n°centre - n° ordre de sélection - initiale nom - initiale prénom)

Sexe : ☐ M ☐ F

Poids : |__|__|__| kg
Taille : |__|__|__| cm

Date de naissance : |__|__| |__|__|__|__| (mm aaaa)

Age : |__|__|__|ans

Date de signature du consentement : |__|__| |__|__| |2|0|__|__| (jj mm aaaa)

Date de signature d'inclusion : |__|__| |__|__| |2|0|__|__| (jj mm aaaa)

Antécédents médicaux-chirurgicaux/familiaux pertinents pour l'évaluation du cas (joindre un CRH anonymisé le cas échéant) :
.....
.....
.....
.....
.....
.....
.....

Date de randomisation : |__|__| |__|__| |2|0|__|__| (jj mm aaaa)

Participation à la sous-étude (analyses complémentaires) :
☐ Oui ☐ Non

☐ Groupe 1 (mRNA Pfizer) ☐ Groupe 2 (SP-GSK D614)
☐ Groupe 3 (SP-GSK B.1.351)

N° randomisation : R |__|__|__|__|

4. Médicament(s) expérimental(aux) (ME) [préciser le(s)quel(s)] avant la survenue de l'EIG

(barrer l'encadré si traitement non débuté)

Nom commercial (de préférence) ou Dénomination Commune Internationale	Voie(1)	Posologie (préciser l'unité ex : mL)	Date de début *(jj/mm/aaaa)*	En cours(2)	Date de fin *(jj/mm/aaaa)*
Comirnaty® mRNA vaccine (Pfizer-BioNTech) ☐ NA	IM	.....	|__|__| |__|__| |2|0|__|__|	☐	|__|__| |__|__| |2|0|__|__|
Sanofi/GSK sub-unit adjuvanted vaccine D.614 ☐ NA	IM	.....	|__|__| |__|__| |2|0|__|__|	☐	|__|__| |__|__| |2|0|__|__|

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Sanofi/GSK sub-unit adjuvanted vaccine B.1.351 ☐ NA	IM	.....	|__|__| |__|__| |_2_|_0_|__|__|	☐	|__|__| |__|__| |_2_|_0_|__|__|

5. Procédures et actes ajoutés par la recherche *(barrer l'encadré si procédures et actes non réalisés)*	Date de réalisation *(jj/mm/aaaa)*	Volume de sang (mL)	Volume de sang cumulé (mL)	Chronologie	
				Avant la survenue de l'EIG	Après la survenue de l'EIG
Prélèvement nasal pour PCR	|__|__| |__|__| |_2_|_0_|__|__|	NA	NA	☐	☐
Prise de sang (préciser la plus récente)	|__|__| |__|__| |_2_|_0_|__|__|			☐	☐

Acronyme :

Référence de la personne se prêtant à la recherche : \|__\|__\|__\| - \|__\|__\|__\|__\| - \|__\| - \|__\|
n°centre - n° ordre de sélection - initiale nom - initiale prénom

6. Médicament(s) <u>concomitant(s)</u> au moment de l'EIG, à l'exclusion de ceux utilisés pour traiter l'événement indésirable ***(compléter le tableau ci-après et si nécessaire l'annexe relative aux médicaments concomitants ou barrer l'encadré si non applicable)***

➪ **Annexe jointe au présent formulaire :** ☐ Oui ☐ Non

Nom commercial (de préférence) ou Dénomination Commune Internationale	Voie(1)	Posologie (préciser l'unité ex : mg/j)	Dates d'administration *(du jj/mm/aa au jj/mm/aa)*	En cours (2)	Indication	***Action prise*** *0 : poursuite sans modification de la posologie 1 : arrêt 2 : diminution de la posologie 3 : augmentation de la posologie 4 : ne sais pas*	***Causalité de l'EIG*** *0 : non lié au médicament 1 : lié au médicament 2 : ne sais pas*
			du |__|__| |__|__| |__|__| au |__|__| |__|__| |__|__|	☐			
			du |__|__| |__|__| |__|__| au |__|__| |__|__| |__|__|	☐			

(1) Voie d'administration : VO=voie orale ; IM=Intramusculaire ; IV=intraveineuse ; SC=sous-cutanée ou autre (à préciser) (2) En cours au moment de la survenue de l'EIG

7. Evènement indésirable grave [EIG]

<u>Diagnostic</u> : ☐ Définitif ☐ Provisoire

.....

.....

.....

<u>Date de survenue des premiers symptômes</u> : \|__\|__\| \|__\|__\| \|_2_\|_0_\|__\|__\|

Préciser lesquels :

.....

<u>Organe(s) concerné(s)</u> :

.....

.....

.....

.....

.....

<u>Date d'apparition</u> de l'EIG :

\|__\|__\| \|__\|__\| \|_2_\|_0_\|__\|__\|

jj mm aaaa

Heure de survenue : \|__\|__\| hh \|__\|__\| min

☐ *donnée manquante*

<u>Délai</u> entre la date d'administration du ME et la date de survenue de l'EIG :

\|__\|__\| / \|__\|__\| \|__\|__\|

jj hh min

<u>Critères de gravité</u> :

☐ Nécessite ou prolonge l'hospitalisation :

du \|__\|__\| \|__\|__\| \|_2_\|_0_\|__\|__\|

au \|__\|__\| \|__\|__\| \|_2_\|_0_\|__\|__\| ☐ *en cours*

☐ Décès

☐ Mise en jeu du pronostic vital

☐ Incapacité ou handicap important ou durable

☐ Anomalie ou malformation congénitale

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

.....

.....

L'évènement a-t-il conduit à :

☐ aucune mesure prise concernant le ME

☐ arrêt définitif du ME le \|__\|__\| \|__\|__\| \|_2_\|_0_\|__\|__\|

☐ arrêt transitoire du ME, date de reprise : \|__\|__\| \|__\|__\| \|_2_\|_0_\|__\|__\|

☐ ne sais pas

Récidive de l'EIG après ré-administration : ○ Non ○ Oui Date : \|__\|__\| \|__\|__\| \|_2_\|_0_\|__\|__\|

○ Non applicable

Des mesures symptomatiques ont-elles été prises ?

☐ Non ☐ Oui Date : \|__\|__\| \|__\|__\| \|_2_\|_0_\|__\|__\| Préciser : .....

L'évènement a-t-il conduit à une <u>levée d'insu</u> ?

☐ Non ☐ Oui Date : \|__\|__\| \|__\|__\| \|_2_\|_0_\|__\|__\| ☐ Non applicable

<u>Degré de sévérité (OMS)</u>

☐ Léger ☐ Modéré ☐ Sévère

ou

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L'évènement fait-il suite à :				**Echelle de classement de la toxicité CTCAE**
- une erreur médicamenteuse ?	☐ Non	☐ Oui	Date : |__|__| |__|__| |_2_|_0_|__|__|	☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5
- un surdosage ?	☐ Non	☐ Oui	Date : |__|__| |__|__| |_2_|_0_|__|__|	ou
- un mésusage ?	☐ Non	☐ Oui	Date : |__|__| |__|__| |_2_|_0_|__|__|	**Echelle de classement de la toxicité FDA**
- autre (préciser) : ……	☐ Non	☐ Oui	Date : |__|__| |__|__| |_2_|_0_|__|__|	☐ Grade 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4

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PARTIE RESERVEE AU PROMOTEUR
REFERENCE VIGILANCE :

Référence GED : REC-DTYP-0192

Acronyme :

Référence de la personne se prêtant à la recherche : |__|__|__| - |__|__|__|__| - |__| - |__|
n°centre - n° ordre de sélection - initiale nom - initiale prénom

Evolution de l'événement

☐ **Décès** Date : |__|__| |__|__| |_2_|_0_|__|__|
○ sans relation avec l'EIG jj mm aaaa
○ en relation avec l'EIG

☐ **Sujet non encore rétabli**, préciser :
○ Etat stable ○ Amélioration ○ Aggravation

☐ **Résolu :** Date : |__|__| |__|__| |_2_|_0_|__|__|
○ sans séquelles jj mm aaaa
○ avec séquelles, préciser lesquelles : |__|__| |__|__|
hh min

☐ **Evolution inconnue**

8. Autre(s) étiologie(s) envisagée(s)

☐ Non ☐ Oui Si oui, préciser : .....
.....
.....

9. Examen(s) complémentaire(s) réalisé(s)

☐ Non ☐ Oui Si oui, préciser date, nature et résultats : [joindre les bilans anonymisés].....
.....
.....

10. Selon l'investigateur, l'événement indésirable grave est (plusieurs cases possibles)

Lié à la recherche :

☐ **Oui :** ☐ **au(x) médicament(s)/produit(s) assimilé(s) de la recherche : le(s)quel(s) ?**
- ☐ Comirnaty®
- ☐ SP-GSK D614
- ☐ SP-GSK B.1.351

☐ **à la (aux) procédure(s)/acte(s) de la recherche : la/le(s)quel(les) ?**
- ☐ prélèvement nasal pour PCR
- ☐ prise de sang

☐ **Non :** ☐ **à la progression de la maladie faisant l'objet de la recherche : (à compléter)**
☐ **à un (ou plusieurs) médicament(s) concomitant(s) administré(s), le(s)quel(s) : .....**
☐ **à une maladie intercurrente, laquelle : .....**
☐ **autre, préciser : .....**

Notificateur	**Investigateur**	Tampon du service :
Nom et fonction : Signature	Nom : Signature	

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17.3 Pregnancy notification form

Direction de la Recherche Clinique et de l'Innovation (DRCI)	ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS ***Notification et suivi d'une grossesse apparue au cours d'une recherche portant sur un Médicament ou produit assimilé***	**PARTIE RESERVEE AU PROMOTEUR** **REFERENCE INTERNE :** Référence GED : REC-DTYP-0185

Ce formulaire doit être dûment complété (3 pages), signé et retourné sans délai au secteur Vigilance de la DRCI par mail (eig-vigilance.drc@aphp.fr).

NB : Il est également possible d'envoyer ce formulaire par fax to +33 (0)1 44 84 17 99 uniquement en cas de tentative infructueuse d'envoi par mail (pour éviter les doublons).

1. Identification de la recherche

Acronyme : **COVIBOOST**
Code de la recherche : **APHP211184**

Notification initiale ☐ **Suivi de notification** ☐ **N° du suivi** |__|__|

Date de notification : |__|__| |__|__| |2|0|__|__| (jj mm aaaa)

Date de prise de connaissance de la grossesse par l'investigateur : |__|__| |__|__| |2|0|__|__| (jj mm aaaa)

Titre complet de la Recherche :
Immunogenicity and reactogenicity following a booster dose of a COVID-19 mRNA vaccine (Pfizer-BioNTech) and two adjuvanted sub-unit vaccines (SP/GSK) administered in adults who received 2 doses of Pfizer-BioNTech mRNA vaccine as a primary vaccination: a randomized, single-blinded, multicenter clinical trial.

2. Identification du centre investigateur

Nom de l'établissement : .....
Ville et code postal : .....
Service : .....

Investigateur (nom/prénom) : .....
Tél : Fax :
Mail :

3. Identification de la personne présentant une grossesse

Référence de la personne : |__|__|__| - |__|__|__|__| - |__| - |__|
(n°centre - n° ordre de sélection - initiale nom - initiale prénom)

Date de naissance (mm/aaaa) : |__|__| |__|__|__|__|
Age : |__|__|__|ans

Date d'inclusion : |__|__| |__|__| |2|0|__|__|
Date de randomisation : |__|__| |__|__| |2|0|__|__|
Numéro de randomisation : R |__|__|__|__|

Groupe de randomisation :
☐ Groupe 1 (mRNA Pfizer)
☐ Groupe 2 (SP-GSK D614)
☐ Groupe 3 (SP-GSK B.1.351)

Date des dernières règles : |__|__| |__|__| |2|0|__|__|
Et/ou date début de grossesse : |__|__| |__|__| |2|0|__|__|

Cas particulier d'une exposition paternelle : ☐ Oui ☐ Non

Référence de la personne : |__|__|__| - |__|__|__|__| - |__| - |__|
(n°centre - n° ordre de sélection - initiale nom - initiale prénom)

Date de naissance (mm/aaaa) : |__|__| |__|__|__|__|
Age : |__|__|__|ans

Date d'inclusion : |__|__| |__|__| |2|0|__|__|
Date de randomisation : |__|__| |__|__| |2|0|__|__|
Numéro de randomisation : R |__|__|__|__|

Groupe de randomisation :
☐ Groupe 1 (mRNA Pfizer)
☐ Groupe 2 (SP-GSK D614)
☐ Groupe 3 (SP-GSK B.1.351)

Expositions au cours de la grossesse :

Tabac :	☐ non	☐ oui (préciser nombre de paquets/année) :	☐ arrêt (préciser date) :	☐ poursuite
Alcool :	☐ non	☐ oui (préciser unités OH) :	☐ arrêt (préciser date) :	☐ poursuite
Drogue :	☐ non	☐ oui (préciser substance) :	☐ arrêt (préciser date) :	☐ poursuite
Autre (préciser) :				

4. Antécédents maternels

Médicaux :	**Chirurgicaux :**

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Obstétricaux : |__|__| geste |__|__| pare
Préciser si fausse couche, grossesse extra-utérine, interruption de grossesse (médicale ou volontaire), mort *in utero*, malformation congénitale, pathologie congénitale/néonatale non malformative, … (*nombre, date et nature/raison si applicable).*

Acronyme :

PARTIE RESERVEE AU PROMOTEUR
REFERENCE INTERNE :
REC-DTYP-0192

Référence de la personne : |__|__|__| - |__|__|__|__|__| - |__| - |__|
n°centre – n° ordre de sélection – initiale nom – initiale prénom

5. Médicament(s) expérimental (aux) administré(s) ou non pendant la grossesse ou s'il s'agit une exposition paternelle

Nom commercial (de préférence) ou Dénomination Commune Internationale	Date de première administration Ou non administré	Date de dernière administration Ou en cours	Voie (1)	Posologie / 24h
Comirnaty® mRNA vaccine (Pfizer-BioNTech) ☐ **NA**	|__|__| |__|__| |_2_|_0_|__|__| ☐ Non administré	|__|__| |__|__| |_2_|_0_|__|__| ☐ En cours	**IM**	
Sanofi/GSK sub-unit adjuvanted vaccine D.614 ☐ **NA**	|__|__| |__|__| |_2_|_0_|__|__| ☐ Non administré	|__|__| |__|__| |_2_|_0_|__|__| ☐ En cours	**IM**	
Sanofi/GSK sub-unit adjuvanted vaccine B.1.351 ☐ **NA**	|__|__| |__|__| |_2_|_0_|__|__| ☐ Non administré	|__|__| |__|__| |_2_|_0_|__|__| ☐ En cours	**IM**	

(1) Voie d'administration : VO=voie orale ; IM=Intramusculaire ; IV=intraveineuse ; SC=sous-cutanée ou autre (à préciser)

6. Procédures et actes ajoutés par la recherche ***(barrer l'encadré si procédures et actes non réalisés)***	Date de réalisation *(jj/mm/aaaa)*	Volume de sang (mL)	Volume de sang cumulé (mL)	Chronologie	
				Avant la grossesse	Au cours de la grossesse
Prélèvement nasal pour PCR	|__|__| |__|__| |_2_|_0_|__|__|	NA	NA	☐	☐
Prise de sang (préciser la plus récente)	|__|__| |__|__| |_2_|_0_|__|__|			☐	☐

7. Médicament(s) concomitants administré(s) dans le cadre du soin
(Cf. annexe « Liste relative aux médicaments concomitants » complétée : ☐ ***Oui*** ☐ ***Non applicable)***

Nom commercial (de préférence) ou Dénomination Commune Internationale	Date de première administration	Date de dernière administration Ou en cours	Voie d'administration(1)	Posologie / 24h
	|__|__| |__|__| |_2_|_0_|__|__|	|__|__| |__|__| |_2_|_0_|__|__| ☐ En cours		
	|__|__| |__|__| |_2_|_0_|__|__|	|__|__| |__|__| |_2_|_0_|__|__| ☐ En cours		
	|__|__| |__|__| |_2_|_0_|__|__|	|__|__| |__|__| |_2_|_0_|__|__| ☐ En cours		

(1) Voie d'administration : VO=voie orale ; IM=Intramusculaire ; IV=intraveineuse ; SC=sous-cutanée ou autre (à préciser)

8. Suivi de la grossesse

☐ Echographiques. Date(s) et résultats à préciser *(joindre les CR anonymisés)* :

☐ Autres examens. Date(s) et résultats à préciser *(joindre les CR anonymisés)* :

9. Grossesse en cours ou issue de la grossesse
☐ (envoyer par mail un nouveau formulaire complété à l'issue de la grossesse pour le suivi de la notification initiale)
☐ (compléter ci-dessous)

Date : |__|__| |__|__| |_2_|_0_|__|__| Terme : |__|__| SA |__|__| J

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☐ Fausse couche
→ Examen anatomo-pathologique disponible : ☐ Non ☐ Oui, précisez le résultat :

☐ Grossesse extra-utérine
→ Examen anatomo-pathologique disponible : ☐ Non ☐ Oui, précisez le résultat :

☐ Interruption de grossesse → Raison :
→ Examen anatomo-pathologique disponible : ☐ Non ☐ Oui, précisez le résultat :

☐ Accouchement : ☐ Spontané ☐ Provoqué ☐ Voie basse ☐ Césarienne

Naissance multiple : ☐ Non ☐ Oui, précisez le nombre :
Souffrance fœtale : ☐ Non ☐ Oui, précisez :
Mort-né : ☐ Non ☐ Oui, précisez :
Placenta normal : ☐ Oui ☐ Non, précisez :
Liquide amniotique : ☐ Clair ☐ Autre, précisez :
Anesthésie : ☐ Générale ☐ Péridurale ☐ Rachianesthésie ☐ Aucune

Acronyme :

PARTIE RESERVEE AU PROMOTEUR
REFERENCE INTERNE :
REC-DTYP-0192

Référence de la personne : |__|__|__| - |__|__|__|__|__| - |__| - |__|
n°centre – n° ordre de sélection – initiale nom – initiale prénom

10. Nouveau-né (Si naissance multiple, compléter les parties 1, 2, 3, 9 et 10 d'un nouveau formulaire et l'envoyer par mail)

Sexe : ☐ Masculin ☐ Féminin

Poids : |__|__|__|__| grammes Taille : |__|__|__| cm Périmètre crânien : |__|__|__| cm

APGAR : 1 minute : _____ 5 minutes : _____ 10 minutes : _____

Malformation(s) congénitale(s) : ☐ Non ☐ Oui, précisez :

Pathologie(s) congénitale(s)/néonatale(s) non malformative(s) : ☐ Non ☐ Oui, précisez :

Le nouveau-né a-t-il bénéficié d'un suivi particulier à la naissance : ☐ Non ☐ Oui, précisez : ☐ Non applicable

Notificateur	**Investigateur**	Tampon du service :
Nom et fonction : Signature :	Nom : Signature :	

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Immunogenicity and reactogenicity following a booster dose of a COVID-19 mRNA vaccine (Pfizer-BioNtech) and two adjuvanted sub-unit vaccines (SP/GSK) administered in adults who received 2 doses of Pfizer-BioNTech mRNA vaccine as a primary vaccination : A Randomized, single-blinded multicenter clinical trial

COVIBOOST

INTERVENTIONAL RESEARCH PROTOCOL INVOLVING HUMAN PARTICIPANTS CONCERNING A MEDICINAL PRODUCT FOR HUMAN USE

Version N°5.0 dated 03/01/2022
Project Code: APHP211184/ EUDRACT no: 2021-004550-33

Coordinating Investigator: Pr Odile LAUNAY
Centre d'Investigation Clinique Cochin Pasteur (CIC1417),
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27, rue du Faubourg Saint-Jacques,
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Scientific and Methodology Director: Pr Tabassome SIMON
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Mail: tabassome.simon@aphp.fr

Sponsor: Assistance Publique – Hôpitaux de Paris (AP-HP)
and by delegation: Délégation à la Recherche Clinique et à l'Innovation - DRCI (Clinical Research and Innovation Department)
Hôpital Saint-Louis
1, avenue Claude Vellefaux
DRCI-Head Office project advisor: Eunice NUBRET
Tel. +33 (0)1 44 84 17 08
Mail: eunice.nubret@aphp.fr

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Entity responsible for monitoring and management of the study:	Unité de Recherche Clinique (URC-Est) 184 rue du Faubourg Saint Antoine 75012 PARIS Project Manager DRCI-URC : Amel TOUATI Tel: +33 (0)1 49 28 22 02 Mail: amel.touati@aphp.fr
Entity responsible for safety:	Safety department - Hôpital Fernand Widal 200, rue du Faubourg Saint-Denis 75010 Paris Dr Sarra DALIBEY (head of Safety department) Safety assessor : Katya TOUAT Tel: +33 (0)1 40 27 55 56 Mail: expertisecsi.drc@aphp.fr
Entity responsible for relations with the sites and Covireivac network:	Centre d'Investigation Clinique Cochin-Pasteur CIC-1417 Hôpital Cochin - Bâtiment Lavoisier 27 rue du Faubourg Saint Jacques 75679 Paris cedex 14 Clinical coordinator: Laureen CURCI Tel: +33 (0)1 58 41 23 11 Courriel : laureen.curci@aphp.fr
Pharmaceutical coordination:	AGEPS – Département Essais Cliniques 7, rue du Fer à Moulin, 75 005 Paris, France Referent pharmacist : Jean-Roch FABREGUETTES Pharmaceutical coordinator: Florence CAPELLE Tel: +33 (0)1 46 69 14 67 Mail: florence.capelle@aphp.fr

Core labs:

For humoral analyses:	UMR190, IHU Méditerranée Infection 19-21 Boulevard Jean Moulin 13005 Marseille Coordinator: Pr Xavier de Lamballerie Mail: xavier.de-lamballerie@univ-amu.fr
For cellular analyses:	Laboratoire d'immunologie Biologique Hôpital Européen Georges Pompidou AP-HP 20 Rue Leblanc 75015 Paris Coordinator: Pr Eric Tartour Mail: eric.tartour@aphp.fr
For mucosal analyses	Laboratoire d'immunologie CHU Saint-Etienne, Pavillon de Biologie Avenue Albert Raymond 42270 Saint-Priest en Jarez Coordinator : Pr Stéphane Paul Mail: stephane.paul@chu-st-etienne.fr

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Network	I-REIVAC/COVIRIEIVAC Platform Launched in October 2020, the COVIREIVAC platform coordinated by Inserm & F-CRIN, in partnership with 32 university hospitals and a network of 11 immunology labs, is dedicated to clinical vaccine research in France.

Délégation à la Recherche Clinique et à l'Innovation - DRCI (Clinical Research and Innovation Department)
Hôpital Saint Louis 75010 PARIS

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SIGNATURE page for a research PROTOCOL

Research code number: APHP211184

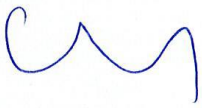
Title: **Immunogenicity and reactogenicity following a booster dose of COVID-19 mRNA vaccine (Pfizer-BioNtech) and two adjuvanted sub-unit vaccines (SP/GSK) administered in adults who received 2 doses of Pfizer-BioNTech mRNA vaccine as a primary vaccination: A Randomized, single-blinded multicenter, clinical trial - CoviBoost**

Version no. 5.0 dated: 03/01/2022

The study will be carried out in accordance with the protocol, with current good practices and with statutory and regulatory requirements.

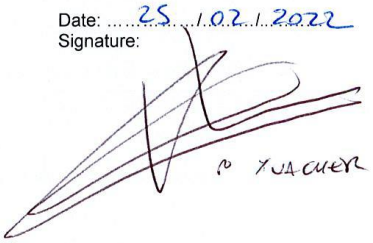
Coordinating Investigator:
Pr Odile LAUNAY
CIC-1417 Cochin Pasteur, Hôpital Cochin
Assistance Publique-Hôpitaux de Paris
27, rue du Faubourg Saint-Jacques,
75679 PARIS

Date: 04/01/2022
Signature:



Sponsor
Assistance Publique – Hôpitaux de Paris
Délégation à la Recherche Clinique et à l'Innovation - DRCI (Clinical Research and Innovation Department)
Hôpital Saint Louis
1 avenue Claude Vellefaux
75010 PARIS

Date: 25/02/2022
Signature:



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18 SUMMARY

Full title	Immunogenicity and reactogenicity following a booster dose of COVID-19 mRNA vaccine (Pfizer-BioNtech) and two adjuvanted sub-unit vaccines (SP/GSK) administered in adults who received 2 doses of Pfizer-BioNTech mRNA vaccine as a primary vaccination: A randomized, single-blinded multicenter clinical trial
Acronym/reference	CoviBoost
Coordinating investigator	Pr Odile LAUNAY CIC-1417 Cochin Pasteur, Hôpital Cochin Assistance Publique-Hôpitaux de Paris 27, rue du Faubourg Saint-Jacques, 75679 PARIS
Scientific and Methodology Director	Pr Tabassome SIMON Platform URC-EST/CRC/CRB Saint-Antoine Hospital, AP-HP Tel: +33 (0)1 40 01 13 58 Mail: tabassome.simon@aphp.fr
Sponsor	Assistance Publique – Hôpitaux de Paris
Scientific justification	The efficacy of COVID 19 vaccines for reducing the risk of severe COVID-19 infection has now been demonstrated in real life. In France, the vaccination campaign started on December 27th, 2020 and was launched rapidly for healthcare professionals and for individuals at risk of severe COVID on January 2021. On August 5th 30th, 2021, approximately 60% of the population (> 12 years) had already received complete vaccination. Out of approximately 74,3 million doses of vaccine administered, 58 million doses are Pfizer BioNTech vaccine (78%). Data currently available on the persistence of immunity on the one hand and the appearance of viral variants with reduced sensitivity to vaccine immunity on the other, raise the need to administer further additional dose at an interval from the primary vaccination that remains to be defined, possibly different according to age and co-existing diseases. Currently, the only data published are related to the administration of a third dose as booster of the same vaccine as the one used for primary vaccination. However, some vaccines developed more recently could be an interesting alternative for booster dose in terms of

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	reactogenicity, availability, cost and acceptance. Moreover heterologous vaccination could be more immunogenic than homologous scheme. The vaccine developed by Sanofi Pasteur is based on a conventional adjuvanted recombinant protein approach. Two candidate vaccines are under development, one based on the Spike protein of the SARS CoV-2 D614 strain, the other on the B.1.351 strain. Their interest as booster vaccines needs to be investigated. The objective of this trial is to assess the response induced by a booster dose of either recombinant protein-based subunit vaccine (targeting D614 strain or B.1.351 strain) or by a booster dose of Pfizer-BioNTech mRNA vaccine (targeting Wuhan strain) in individuals previously vaccinated with 2 doses of Pfizer-BioNTech mRNA vaccine. These results will provide important information for booster vaccination recommendations.
Main objective and primary endpoint	Main objective: To assess the immunogenicity of a booster dose of an adjuvanted subunit vaccine (SP vaccine) as between D614 or B.1.351 and a mRNA vaccine (Pfizer BioNTech) in adults who were primarily vaccinated with 2 doses of mRNA vaccine (Pfizer BioNTech) with the 2nd dose of vaccine received between 3 months and 7 months prior to the booster dose. Primary endpoint: Increased rate of at least 10 fold between D0 and D15 after the booster dose in neutralizing antibody titers against SARS-CoV-2 D614 and B.1.351 viral strains, measured by a microneutralisation technique in each group.
Secondary objectives and endpoints	Secondary objectives: 10. To compare the increase in neutralization antibody titers with regard to age groups (18-64 years old and >65 years or older) 11. To evaluate the local and general safety and tolerability of a booster dose of mRNA vaccine or adjuvanted subunit vaccine up to 28 days after administration; 12. To assess the humoral immune response by ELISA of a booster dose of mRNA vaccine or adjuvanted subunit vaccine at 15 and 28 days;

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	13. To assess the persistence of the immune response at 3 and 12 months after the booster dose of mRNA vaccine or adjuvanted subunit vaccine; 14. To evaluate the immunogenicity of the 3 vaccines on variants of interest ; 15. To describe the associated factors and determinants of boost response in individuals previously vaccinated with 2 doses of mRNA vaccine 16. To assess the mucosal immunity following a booster dose of mRNA vaccine or adjuvanted subunit vaccine 17. To assess the early humoral response by ELISA of a booster dose of mRNA vaccine or subunit adjuvanted vaccine at 3 days (*ancillary analysis*) 18. To explore CD4 and CD8 cellular response induced by a booster dose of mRNA vaccine or adjuvanted subunit vaccine *(ancillary analysis)* <u>Secondary endpoints</u>: 10. Rate of increase in neutralizing antibody titers against SARS-CoV-2 D614 and B.1.351 viral strains, measured by a microneutralisation technique between 0 and 28 days after the booster dose in each group. 11. Quantity and intensity of local and systemic events of any grade occurring up to 7 days after boost injection (assessed from the list of solicited adverse events); Quantity and intensity of unsolicited local and systemic events up to 28 days; 12. Anti-Spike (D614) and anti-RBD (D614 and B.1.351) IgG levels, expressed in BAU/ml, according to WHO recommendations D15 and D28 after the booster dose mRNA or adjuvanted subunit vaccine; 13. Difference in Anti-Spike (D614) and anti-RBD (D614 and B.1.351) IgG levels between M3 and D0 and between M12 and D0; 14. Neutralizing antibody titers against variants of interest at 28 days, 3 months and 12 months; 15. Factors of interest are age, gender, time interval between 2nd dose and boost dose, and vaccine boost type;

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	16. Mucosal SARS-CoV-2 specific antibodies via the measure of IgA in saliva by ELISA and PRNT assays at D0, D28 and D90 ; 17. Anti-Spike (D614) and anti-RBD (D614 and B.1.351) IgG levels, expressed in BAU/ml, according to WHO recommendations D3 after the booster dose mRNA or adjuvanted subunit vaccine (*ancillary analysis*) 18. ELISpot IFN CD4 and CD8 response at 28 days, 3 months and 12 months (*ancillary analysis*);
Design of the study	Randomized, single-blinded, multicenter, trial with three parallel arms stratified on age groups: **ARM 1 receiving Pfizer-BioNTech vaccine** - Group 1.A: 18-64 years old - Group 1.B: 65 years and older **ARM 2 receiving SP/GSK subunit D614 vaccine** - Group 2.A: 18-64 years old - Group 2.B: 65 years and older **ARM 3 receiving SP/GSK subunit B.1.351 vaccine** - Group 3.A: 18-64 years old - Group 3.B: 65 years and older
Population of study participants	Adult who previously received two doses of mRNA vaccine (Pfizer-BioNTech), with the second dose received between 3 months and 7 months prior to the administration of the booster dose.
Inclusion criteria	9. Age ≥ 18 years 10. Adult in a healthy condition or with a stable health status if pre-existing medical history. Stable health status is defined as an existing disease that has not required a significant change in treatment or hospitalization for worsening in the 3 months before enrollment, and for which neither a significant change in treatment or hospitalization for worsening is expected in the near future 11. For women of childbearing age: a negative highly sensitive pregnancy urinary test during the inclusion visit AND use of an effective contraceptive method at least 4 weeks prior to vaccination and until at least 12 weeks after the vaccination 12. Who has received 2 doses of mRNA vaccine (Pfizer-BioNTech) with an interval of 3 to 6 weeks 13. Second dose of mRNA vaccine (Pfizer-BioNTech) administered between 3 months and 7 months before the booster dose

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	14. Understands and agrees to comply with the study procedures 15. Written informed consent signed by both the participant and the investigator 16. Subject affiliated to the French Social Security System.
Exclusion criteria	15. Acute febrile infection (body temperature ≥ 38.0°C) within the previous 72 hours and/or presenting symptoms suggestive of COVID-19 within the previous 28 days or having been in contact with an infected individual for the last 14 days before the inclusion visit; 16. Virologically documented history of COVID-19 (PCR or serology); 17. Immunosuppressive therapy such as corticosteroids > 10 mg prednisone equivalent/day (excluding topical preparations and inhalers) within 3 months prior to inclusion or within 6 months for chemotherapies; 18. Treatment with immunoglobulins or other blood derivatives within 3 months prior to inclusion or scheduled administration of immunoglobulins or blood derivatives before the end of the study; 19. Known HIV, HCV or HBV infection; 20. Any medical condition, such as cancer, that might impair the immune response; 21. Use of experimental immunoglobulins, experimental monoclonal antibodies or convalescent plasma is not permitted during the study; 22. Pregnancy or breastfeeding currently ongoing, or positive pregnancy test at enrolment visit; 23. History of severe adverse events following vaccine administration including anaphylactic reaction and associated symptoms such as rash, breathing problems, angioedema, and abdominal pain, or a history of allergic reaction that could be triggered by a component of the SARS-COV-2 vaccine at the time of the first vaccine injection; 24. Participant who has received BCG (tuberculosis) vaccine within the previous year; 25. Has received a vaccine within 2 weeks prior to the boost injection or is scheduled to receive a registered vaccine 2 weeks after the boost injection 26. Any bleeding disorder considered as a contraindication to an intramuscular injection, previous phlebotomy, or receipt of anticoagulants

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	27. Participation in other research involving humans (French classification Jardé 1 or Jardé 2) within 4 weeks prior to the inclusion visit, or participation in any other vaccine trial 28. Subject under legal protection (e.g. guardianship, tutorship)
Investigational medicinal product(s)	**Pfizer/bioNTech BNT132b2 (Comirnaty®)** mRNA vaccine, intramuscular administration. **Sanofi-Pasteur / GSK** recombinant protein vaccines, intramuscular administration : - Recombinant protein vaccine targeting SARS-CoV-2 D614 Spike protein - Recombinant protein vaccine targeting SARS-CoV-2 B.1.351 Spike protein
Interventions added for the study	Diary for local and general adverse events to be completed by the participant.
Expected benefits for the participants and for society	Individual and collective benefit: This study will allow participants to be informed about their antibody titers (ELISA and neutralization) in accordance with the vaccine received. The study will provide the opportunity to evaluate the reactogenicity and immunogenicity of a booster dose of mRNA or subunit vaccine.
Risks and burdens added by the study	The risk level of the study is **D** (AP-HP classification) Risks added by the study: - Risks related to blood sampling, similar to those of a routine blood test - Risks related to the vaccine injection, including additional risks related to the recombinant protein vaccines that have not yet been licensed and are still experimental
Practical process	Inclusion and randomization (D0) will be performed at each study site by the investigator, though CleanWeb e-CRF (Telemedecine Technologies, S.A.S) The booster dose will be administered at D0, then 4 follow-up visits will be performed at D15, D28, M3 and M12. At each visit, a blood sample of 5ml will be taken for humoral analysis and biobanking. Ancillary analysis: For 26 participants in each arm there will be additional samples for cell analysis (3 x 6 ml) and blood count (3ml) at V1, V2, V3, V4 and V5. Subjects involved in the ancillary analysis will also attend an additional visit at D3 during which a 5ml blood sampling for serological analysis will be performed.

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	In total there will be minimum 5 visits and maximum 6 visits per participant.
Number of participants included	300 participants (100 per vaccine group)
Number of centres	12 study centers in France.
Duration of the study	- inclusion period: 1 month and 5 days - participation period (treatment + follow-up): 12 months - immunological analysis: 6 months - total duration: 19 months and 5 days
Number of enrolments expected per site and per month	25 participants per study site in one month
Statistical analysis	The analysis will be performed in four stages: at D15 (primary and secondary D15 endpoint), then at D28, M3 and M12 (secondary endpoints).
Funding sources	Soutien exceptionnel à la recherche et à l'innovation 2021
Study will have a Data Safety Monitoring Board	A DSMB is required for this study.

19 SCIENTIFIC JUSTIFICATION FOR THE STUDY

19.1 Hypothesis for the study

The efficacy of COVID 19 vaccines for reducing the risk of severe COVID-19 infection has now been demonstrated in real life. In France, the vaccination campaign started on December 27th, 2020 and was launched rapidly for healthcare professionals and for individuals at risk of severe COVID on January 2021. On August 5th, 2021, approximately 60% of the population (> 12 years) had already received complete vaccination. Out of approximately 74.3 million doses of vaccine administered, 58 million doses are Pfizer BioNTech vaccine (78%).

Data currently available on the persistence of immunity on the one hand and the appearance of viral variants with reduced sensitivity to vaccine immunity on the other, raise the need to administer additional doses at an interval from the primary vaccination that remains to be defined, possibly different according to age and co-existing diseases.

Since June 18th, new evidence supports the need for a third dose of COVID 19 vaccine, especially for people with immunodeficiency. The need of a booster dose in general population, particularly healthcare workers, is probable, given the increasingly active circulation of new variants since the beginning of summer 2021, and evidence of reduced protection against them. Recommendations for a booster dose are pending but some countries have already began the boost campaign for elderly and frail patients (for example people more than 60 years in Israel since the beginning of August 2021); in France, on August 23, 2021, the french Haute Autorité de Santé (HAS) has recommended an additional administration of the vaccine for persons aged 65 years and over, and fragile populations(1). On October 5, 2021, the HAS has extended this recommendation to health professionals, social care workers in contact with

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patients, health transport professionals, and people over 18 years old in contact with immunocompromised people (cocooning strategy)(2).

The French authorities do not currently support a mandatory administration of a booster dose outside the vulnerable/elderly individuals. However they highlight the need for studies in order to have data on the assessment of the impact or necessity of such a booster shot. It is thus essential to evaluate as soon as possible the efficacy of booster dose on viral variants, and their potential benefits in the general population.

This booster dose is meant to provide strengthened immune protection to individuals who have already received two doses. Currently, the only published data are related to the administration of a third dose as booster by the same vaccine used in primary vaccination. Official press releases from Pfizer and BioNTech regarding their ongoing study, estimate that a booster dose administered 6 months after the second dose has a consistent tolerability profile while generating high neutralization titers against the wild type and Beta variant, which are 5 to 10 times higher than after two primary doses(3). Furthermore, data from a recent publication in Nature shows that sera obtained two to four weeks after the second dose of the two-dose primary series of BNT162b2 present high neutralization titers (1:40 and higher) against the Delta B.1.617.2 variant. Thus, a booster dose should increase antibody titers even further, in the same way that the booster dose acts on the Beta B.1.351 variant(4).

However some vaccines which were developed more recently might offer an interesting alternative in terms of reactogenicity, accessibility, cost and acceptability. Furthermore boosting with another vaccine than the vaccine used for the primo vaccination could be more immunogenic as it is showed with heterologous vaccination. Some studies have already investigated an heterologous scheme with AstraZeneca/Oxford (Vaxzevira®) and Pfizer-BioNTech (Comirnaty®): the results showed increased anti-spike (S) IgG and IgA in both groups, but heterologous vaccination led to a significant 11.5-fold increase for anti-S IgG compared to a 2.9-fold increase after AstraZeneca/Oxford homologous vaccination, as well as a higher CD8+ and equivalent CD4 T cell production. One of the studies also found that homologous vaccination (AstraZeneca/Oxford) provided an increase neutralization of the B.1.1.7 variant in some individuals, but showed no effect against the P1 and B.1.351 variant; in contrast, heterologous vaccination provided neutralizing antibodies against the B.1.1.7, P1 and B.1.351 in almost all participants, as well as a higher neutralization capacity against the Wuhan strain (5,6). Adverse reactions were reported in heterologous and homologous schedules, with similar hematology and biochemistry profiles. Heterologous regimens induced slightly higher systemic reactogenicity: 34% of participants reported feverishness (versus 10% for homologous vaccination), and similar data was observed for chills, fatigue, headache, joint pain, and muscle ache, for participants aged < 50 years. All observed symptoms were short lived(7).

The vaccines developed by Sanofi Pasteur are based on a traditional recombinant protein approach adjuvant with the AS03 adjuvant from GSK. Two vaccine candidates are currently under development, the first one based on the SARS CoV-2 D614 Spike protein, the second one based on the B.1.351 strain(8). Their interest as boosters need to be evaluated.

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The objective of this trial is to assess the immune response induced by a booster dose of either recombinant protein-based subunit vaccine (D614 strain or B.1.351 strain) or by a booster dose of Pfizer-BioNTech mRNA vaccine in individuals previously vaccinated with 2 doses of Pfizer-BioNTech mRNA vaccine in two categories 18-64 years old and more than 64 years old. These results will provide important information for authorities, scientific communities, and the general population regarding the recommendations on booster vaccination.

Also, SARS-CoV2 is most commonly transmitted by the nasal or oral route and infects mucosal cells of the respiratory tract. Although serum antibodies may provide a correlate of protection against COVID-19, mucosal antibodies, especially IgA, may directly prevent or limit acquisition of the virus via the nasal, oral and conjunctival routes. To date, no data are available on the protective potential of the post-vaccination IgA response. We propose in this study to also measure the salivary anti-spike IgA response in order to evaluate its ability to predict vaccine efficacy.

19.2 Description of current knowledge related to COVID-19 and vaccines

Since the beginning of the pandemic, the SARS-CoV-2 virus has infected more than 200 million people worldwide (https://covid19.who.int/, data from August 5th, 2021) and more than 4 million of them have died. The most recent data from the World Health Organization (WHO) reports 6,168,252 confirmed cases of SARS-CoV-2 infection and 110,969 deaths in France (https://covid19.who.int/, data from August 5th, 2021).

The SARS-CoV-2 surface protein Spike (S), which contains the receptor-binding domain (RBD), is the predominant target of antibodies generated by natural infection. As a result, and according to WHO recommendations, most of the vaccine candidates against SARS-CoV-2 express the Spike protein or its RBD domain.

Therefore, it is possible that mutations affecting the Spike protein domain may interfere with the efficacy of either vaccine or natural immunity against SARS-CoV-2. Higher antibody titles have been demonstrated to increase neutralization of these variants, and potentially the protection against them.
Besides, several vaccine candidates targeting more specifically these variants are currently under development; hence, it is necessary to evaluate in parallel these new vaccines in the context of a “boost” regimen (homologous booster with a vaccine against the wild strain, or heterologous booster with a variant-targeted vaccine), to determine which would be more effective.

According to WHO, more than 100 vaccine candidates are currently under clinical development and more than 180 are being tested in preclinical phases. Several vaccines have been licensed worldwide, using many different vaccine platforms. However, mRNA vaccines such as Pfizer or Moderna’s remain the most widely used, especially in Europe and United States. In France, Pfizer’s COMIRNATY® vaccine is by far the most widely used, regardless of the age group.(9)

Since May 2021, the vaccine developed by Sanofi-Pasteur is undergoing clinical trials to evaluate its efficacy, immunogenicity and potential side effects.

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19.3 Summary of relevant pre-clinical experiments and clinical trials

19.3.1 BNT162b2 vaccine (COMIRNATY®) – Pfizer/BioNTech

This vaccine is composed of a single-stranded mRNA encoding the entire SARS-CoV-2 Spike (S) protein in a pre-fusion configuration, encapsulated in a lipid nanoparticle to protect it and facilitate its incorporation into the cell. The efficacy, immunogenicity and safety of two 30µg doses of BNT162b2 vaccine administered 21 days apart for the prevention of COVID-19 in individuals aged 16 years or older were evaluated in a 1:1 randomized, placebo-controlled, phase II/III study involving approximately 43,500 participants. The primary endpoint of the study was the incidence of a symptomatic COVID-19 infection from 7 days after the first vaccine injection in participants with no evidence of SARS-CoV-2 infection, until 7 days after the second dose.
An initial interim analysis of the study results, conducted in November 2020 (cut-off 14-Nov-2020) and published in December 2020 reported the following results(10,11):

4. **Vaccine efficacy**: among 43500 participants with no history of SARS-CoV-2 infection, 8 cases of COVID-19 were reported within 7 days after the second dose among the vaccine cohort (n = 18,198) while 162 cases were observed among placebo recipients (n = 18,235), corresponding to a vaccine efficacy of 95.0%. Among participants with and without evidence of prior SARS-CoV-2 infection, 9 cases of COVID-19 were observed 7 days after the 2nd dose in vaccine recipients, versus 169 cases in placebo recipients, corresponding to an efficacy of 94,6%.
5. **Local reactogenicity**: results from the sub-cohort of approximately 8000 subjects with a 7-day post-injection follow-up reported a significantly higher rate of local reactions among vaccine recipients – including mild to moderate pain at the injection site – with 71% of participants 55 years and older reporting local pain after the first dose and 66% after the second dose, versus 83% and 78% reported respectively in participants under 55 years old. Severe local reactions were reported in the BNT162b2 group with a frequency of less than 0.6%.
6. **Systemic reactogenicity**: systemic reactions in vaccine recipients were reported more frequently by younger subjects (16 – 55 years old) and more often after the second dose than after the first. The most commonly reported reactions were fatigue (62%), headache (55%), muscle pain (38%), chills (32%), joint pain (23%) and pyrexia (14%); most of these reactions were mild to moderate and resolved within a few days, regardless of the age group.

Real life data from the Israeli vaccination campaign, published in The New England Journal of Medicine, show an efficacy of 92% after the second dose, a result that is very close to the data observed in the phase III trial(12).

More recent data, published in the New England Journal of Medicine in July 2021 suggests however that the effectiveness of two doses of BNT162b2 vaccine was slightly reduced to 93.7% among patients with the Alpha variant and 88.0% among those with the delta variant (13). These data supports in parallel Pfizer's announcements, stating that a third dose as booster might be needed within 6 to 12 months after full vaccination, to maintain the highest level of protection, either against the wild strain or the variants(14).

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19.3.2 Sanofi-Pasteur / GSK CoV2 preS dTM-AS03 adjuvanted vaccine (product code No. 549 and 561)

The vaccines developed by Sanofi-Pasteur and GSK are recombinant protein-based adjuvanted vaccines, based on the same technology as the one used by Sanofi for one of its seasonal flu vaccines. It uses the truncated form of SARS-CoV-2 protein, deleted of its trans-membranary domain and stabilized on its pre-fusion configuration, as an antigen to support the immune system's ability to identify and fight the virus upon infection. The adjuvant used to enhance the immunological response produced by this vaccine is "AS03", a squalene-based immunologic adjuvant manufactured by GSK, and already used in several other vaccine products (such as Pandemrix® H1N1 flu vaccine).

On May 2021, results from **Sanofi and GSK phase II trial**, presented in their press release,(15,16) have shown that the recombinant COVID-19 vaccine candidate with GSK adjuvant induced high levels of neutralizing antibodies in non-naïve subjects who were previously affected by COVID-19 in all adult age groups. The study was conducted in 722 participants in the United States and Honduras, and assessed the safety, reactogenicity, and immunogenicity of 3 different doses of the adjuvanted vaccine, administered as 2 injections, 21 days apart.

Preliminary results (21 days post 2nd dose) reported 95% to 100% seroconversion following a second injection in all age groups (18 to 95 years) and for all doses; there were no death, no AEs leading to study discontinuation, and no AESIs reported during this period.

- **Solicited local reactions** within 7 days after each injection were mostly grade 1 and 2 intensity, with a higher frequency after the 2nd dose. The most frequently reported reactions were pain at the injection site, erythema and swelling. Grade 3 reactions were reported by 2.2% of the participants after the first dose, and 7.2% after the 2nd dose.
- **Solicited systemic reactions** within 7 days after each injection were also mostly grade 1 and 2: headache, myalgia and malaise were the most frequent. Grade 3 reactions were reported by 2.8% of the participants after the 1st dose and 16.9% after the 2nd.
- **Unsolicited adverse events** within 21 days after any injection occurred mainly 3 days after, were mostly Grade 1 and 2, and resolved within 7 days or less; the most commonly reported SOC AEs (≥ 5.0%) were "General disorders and administration site conditions", "gastrointestinal disorders", and "nervous system disorders"; PTs AEs (≥ 2.0%) reported reactogenicity-like events (i.e. fatigue, injection site pruritus, nausea, diarrhea).

Preliminary immunogenicity data based on the primary objective, determining the neutralizing antibody profile against the D614 variant, showed that, at 14 days post second injection (D36), the proportion of responders against the D614 variant with ≥ 4-fold rise GMT were 90% in both younger and older adult age groups (18-59 years and ≥ 60 years) in all dose groups. This proportion was similar between the subgroups of participants with and without a high-risk medical condition.

Interim primary analysis from this study showed that, in naïve participants, the proportion of participants having 2-fold and 4-fold or greater rise in neutralizing antibodies against D614 variant, at D36, was > 95% in the 18-59 years age group, and > 90% in the 60 years age group. In non-naïve participants, an increase in GMTs was observed 21 days after the first injection (D22); GMTs were higher in the 18-59 age group compared to the > 60 years age group.

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Overall, the encouraging results have allowed the two companies to start the phase III trial in May 2021(15).

The international, randomized, double-blind, placebo-controlled, multi-stage approach Phase III (CT registration No. PACTR202011523101903) study will enroll more than 35,000 participants. The primary endpoint is the prevention of symptomatic forms of Covid-19 in naïve adults. Prevention of severe forms and prevention of asymptomatic disease will also be evaluated. The study will investigate the potential of two different formulations, one targeting the original strain (D614 virus) and a second stage will include the B.1.351 variant (Bivalent vaccine with the B.1.351 variant) (17).

19.4 Description of the population to be studied and justification for the choice of participants

This trial will include men and women aged 18-64 years and over 65 years.
To be enrolled, participants must have previously received two doses of the BNT162b2 mRNA vaccine (COMIRNATY®, Pfizer/BioNTech). They will receive a booster dose of either a recombinant protein vaccine (Sanofi/GSK) or a BNT162b2 mRNA vaccine boost, between 3 months and 7 months after the second dose.

In order to optimize the interpretation of the immune response induced by the vaccine regimen studied, individuals with diseases/conditions that may compromise the immune response (such as autoimmune disease, cancer, HIV/HBV/HCV infection, or immunosuppressive therapy) will not be allowed to participate in this study.

19.5 Identification and description of the investigational medication or medications

The vaccines that will be evaluated in this study are:

3. A licensed vaccine: the Pfizer/BioNTech BNT162b2 mRNA vaccine (COMIRNATY®)
4. Two experimental vaccines: CoV2 preS dTM-AS03 adjuvanted vaccine: D614 recombinant protein vaccine, and B.1.351 recombinant protein vaccine, both developed by Sanofi-Pasteur/GSK

See section 7 for more details.

19.5.1 BNT162b2 mRNA vaccine (COMIRNATY®) from Pfizer/BioNTech

Comirnaty® is an mRNA (modified nucleoside) vaccine, indicated for active immunization for the prevention of Covid-19 caused by SARS-CoV-2, in individuals aged 12 years and older(18). The MA was obtained in Europe on December 21, 2020.

19.5.2 CoV2 preS dTM-AS03 adjuvanted vaccine from Sanofi-Pasteur/GSK

The two Sanofi-GSK vaccines are recombinant protein-based adjuvanted vaccines. Studies are currently being conducted to evaluate them. Depending on positive results and regulatory approvals, the vaccine candidate could receive marketing authorization by Q4 2021.

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19.6 Description and justification of the dosage, route of administration, administration schedule and treatment duration

Investigational products will be administered intra-muscularly into the deltoid muscle. Injection of a booster dose of recombinant protein-based subunit vaccine or mRNA vaccine in individuals previously vaccinated with two doses of BNT162b2 mRNA between 3 months and 7 months) after the 2nd dose and before the booster dose.

See section 7 for more details.

19.7 Summary of the known and foreseeable benefits and risks for the research participants

Individual benefit: This study will allow participants to be informed about their antibody titers (ELISA and neutralization) in accordance with the vaccine received.

Collective benefit: The study will provide the opportunity to evaluate the reactogenicity and immunogenicity of a booster dose of mRNA or subunit vaccine.

There are limited risks associated with the blood collections: like any routine blood draw, it may causes pain, bruising, bleeding, and less frequently, a weakness or fainting.

General risks related to vaccination

In general, IM injection may cause local itching, pain, tenderness, erythema/redness, swelling, bruising, as well as systemic symptoms such as fever, chills, rash, myalgia, nausea, fatigue and dizziness. These reactions are usually short-term and will be monitored throughout the study.

As with any vaccine injection, allergic reactions may occur, causing a rash, urticarial, and less frequently, anaphylaxis. Therefore, participants with a known history of anaphylaxis or serious adverse reaction following a vaccine administration, or a known allergy to any of the excipients, will be not be allowed to participate in the study.

After the injection of the booster dose, participants will be under surveillance during 30 minutes at the study site, in order to detect any acute reactions. In addition, periodic phone calls from the medical staff will be conducted, from 48 hours to 28 days after the booster dose injection to check if adverse reactions occurred.

Risks related to Comirnaty® mRNA vaccine (Pfizer-BioNTech):

The following adverse reactions have been reported after the injection of Pfizer-BioNTech's Comirnaty® vaccine during post-approval surveillance in persons 12 years of age and older(19):

- Very common: pain at the injection site, fatigue, headache, diarrhea, muscle pain, chills, joint pain, fever and swelling at the injection site
- Common: Nausea, vomiting, redness at the injection site
- Uncommon: Lymphadenopathy, hypersensitivity reactions (rash, urticaria...), insomnia, pain in the extremities, discomfort, itching at the injection site
- Rare and undetermined frequency: acute peripheral facial paralysis, anaphylaxis, myocarditis, pericarditis, extensive swelling of vaccinated limb, facial swelling.

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Since the marketing authorization, 36,512 cases of adverse reactions have been reported, 73% of which were non-serious(20). The effects reported are as follows: general disorders and abnormalities at the injection site, nervous system, gastrointestinal, musculoskeletal, skin and cutaneous tissue disorders, vascular, hematological and lymphatic, respiratory and thoracic disorders, cardiac disorders, ear and labyrinth disorders.

Risks related to CoV2 preS dTM adjuvanted vaccine (Sanofi-Pasteur/GSK):
Available data from the previous studies reported the following adverse reactions (the majority were grade 1 and 2) after one or two injections of the vaccine in adults:

- Injection site reactions: injection site pain, erythema, swelling, pruritus, upper limb edema
- Systemic reactions: fatigue, nausea, diarrhea, fever, headache, malaise, myalgia, arthralgia and chills were the most common. Isolated cases of blood pressure elevation were reported and self-resolved.

As other COVID-91 vaccines, some AESIs need to be considered even if they were not observed during previous clinical trials: generalized convulsion, thrombocytopenia, Guillain-Barré Syndrome, acute disseminated encephalomyelitis, thrombo-embolic events.

Narcolepsy being part of Potential immune-mediated diseases (pIMDs) is included in the list of Adverse Event of Special Interests (AESIs). Potential immune-mediated diseases are a subset of adverse events that include autoimmune diseases and other inflammatory and/or neurologic disorders of interest which may or may not have an autoimmune etiology.

Potential risks associated with AS03 adjuvant:
Increased risk of narcolepsy (2- to 7- fold in adults) was observed in some cases after the Pandemrix® H1N1 flu vaccination campaign(21) .

20 OBJECTIVES

20.1 Primary objective

To assess the immunogenicity of a booster dose of an adjuvanted subunit vaccine (SP vaccine) as between D614 or B.1.351 and a mRNA vaccine (Pfizer BioNTech) in adults who were primarily vaccinated with 2 doses of mRNA vaccine (Pfizer BioNTech) and received the 2nd dose of vaccine between 3 months and 7 months before the booster dose.

20.2 Secondary objectives

10. To compare the increase in neutralization antibody titers with regard to age groups (18-64 years old and >65 years or older)
11. To evaluate the local and general safety and tolerability of a booster dose of mRNA vaccine or adjuvanted subunit vaccine up to 28 days after administration;
12. To assess the humoral immune response by ELISA of a booster dose of mRNA vaccine or adjuvanted subunit vaccine at 15 and 28 days;
13. To assess the persistence of the immune response at 3 and 12 months after the booster dose of mRNA vaccine or adjuvanted subunit vaccine;

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14. To evaluate the immunogenicity of the 3 vaccines on variants of interest;
15. To describe the associated factors and determinants of boost response in individuals previously vaccinated with 2 doses of mRNA vaccine
16. To assess the mucosal immunity following a booster dose of mRNA vaccine or adjuvanted subunit vaccine
17. To assess the early humoral response by ELISA of a booster dose of mRNA vaccine or subunit adjuvanted vaccine at 3 days (*ancillary analysis*)
18. To explore CD4 and CD8 cellular response induced by a booster dose of mRNA vaccine or adjuvanted subunit vaccine *(ancillary analysis)*

21 STUDY DESIGN

21.1 *Study endpoints*

21.1.1 Primary endpoint

Increased rate of at least 10 fold between D0 and D15 after the booster dose in neutralizing antibody titers against SARS-CoV-2 D614 and B.1.351 viral strains, measured by a microneutralisation technique in each group.

21.1.2 Secondary endpoints

10. Rate of increase in neutralizing antibody titers against SARS-CoV-2 D614 and B.1.351 viral strains, measured by a microneutralisation technique between 0 and 28 days after the booster dose in each group.
11. Quantity and intensity of local and systemic events of any grade occurring up to 7 days after boost injection (assessed from the list of solicited adverse events); Quantity and intensity of unsolicited local and systemic events up to 28 days;
12. Anti-Spike (D614) and anti-RBD (D614 and B.1.351) IgG levels, expressed in BAU/ml, according to WHO recommendations D15 and D28 after the booster dose mRNA or adjuvanted subunit vaccine;
13. Difference in Anti-Spike (D614) and anti-RBD (D614 and B.1.351) IgG levels between M3 and D0 and between M12 and D0;
14. Neutralizing antibody titers against variants of interest at 28 days, 3 months and 12 months;
15. Factors of interest are age, gender, time interval between 2nd dose and boost dose, and vaccine boost type;
16. Mucosal SARS-CoV-2 specific antibodies via the measure of IgA in saliva by ELISA and PRNT assays at D0, D28 and D90 ;
17. Anti-Spike (D614) and anti-RBD (D614 and B.1.351) IgG levels, expressed in BAU/ml, according to WHO recommendations D3 after the booster dose mRNA or adjuvanted subunit vaccine (*ancillary analysis*);
18. ELISpot IFN CD4 and CD8 response at 28 days, 3 months and 12 months (*ancillary analysis*);

21.2 *Description of research methodology*

21.2.1 Design of the study

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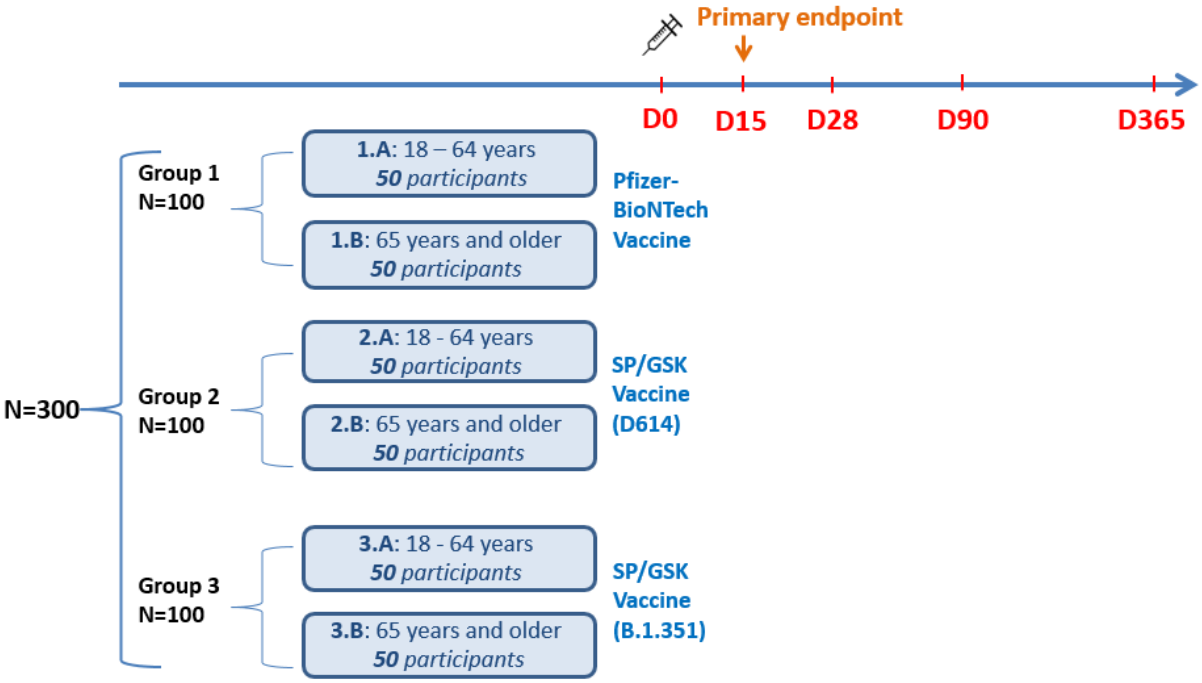
Randomized, single-blinded, multicenter trial in France to evaluate the immunogenicity and reactogenicity of a booster dose of a COVID-19 mRNA vaccine (Pfizer/BioNTech) or an adjuvanted subunit vaccine (SP/GSK strain D614 or strain B.1.351).

Randomization with a 1:1:1 ratio between the three different parallel arms will be applied with age stratification ([18-64] years or ≥ 65 years).



21.2.2 Number of participating sites

The study will be conducted in Clinical Investigation Centers (CIC), Clinical Research Centers (CRC) and hospital departments of the COVIREIVAC Network (French vaccine clinical research network COVID-19, INSERM) and in hospital vaccination centers.

- **Recruitment centres**

There will be 12 recruitment centers in France.

21.2.3 Identification of participants

The participants in this research will be identified as follows:

- Site number (3 digits)
- Sequential enrolment number for the site (4 digits)
- Surname initial – first name initial

This reference number is unique and will be used for the entire duration of the study.

A randomization number will also be assigned when the participant is randomized. This number will have the following format: RXXXX.

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21.2.4 Randomization

Participants who fulfill all eligibility criteria for the study and have signed informed consent will be enrolled and randomized in a 1:1:1 ratio between the 3 different parallel arms.

Randomization will be stratified on center and age group ([18-64] years or ≥ 65 years).

A statistician from the Clinical Research Unit (URC-EST), independent of the research, will edit the randomization list.

Randomization will be performed by the site staff using the centralized tool in the e-CRF just prior to the vaccine injection on D0 visit.

21.2.5 Blinding methods and measures put in place to protect blinding

The study will be performed in a single-blinded manner.

The healthcare professional administrating the vaccine will be aware of the treatment arm due to the differences between the vaccines, regarding their preparation: not only does the Sanofi-GSK vaccine require the mixing of two different vials (antigen and adjuvant), but also the amount to be withdrawn per syringe is different. Therefore, the injection will be carried out by a person external to the study.

Only the investigating physician will not be aware of which treatment the volunteer has received.

The central laboratories performing antibodies analyses will also be blinded, in order to limit measurement bias.

Sponsor blinding:
The sponsor staff (clinical research associates) who will perform the monitoring at the study site will be blinded. The staff who will perform the monitoring at the pharmacy will not be blinded.

21.2.6 Unblinding procedures

Unblinding will be requested for occurrence of SAEs requiring knowledge of the experimental product to determine the therapeutic course to be taken
by calling upon:

- **In emergency cases** at the poison control centre at Fernand Widal Hospital, Telephone: **+33 (0)1 40 05 48 48.**
- **Apart from an emergency situation** at the DRCI (Clinical Research and Innovation Department) to the DRCI project advisor whose contact informations are listed on the protocol cover page

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22 IMPLEMENTATION OF THE STUDY

Before any examination or intervention related to the study may be carried out, the investigator must obtain the *freely given, informed and written consent of the participant, or of his/her legal representative* where applicable.
Individuals liable to participate in studies stipulated in line 1° of article L. 1121-1 of the *Code de la Santé Publique* (French Public Health Code) benefit from a preliminary medical examination adapted to the study.

A single administration of COVID-19 vaccine will be performed at D0: Pfizer/BioNTech mRNA vaccine (Comirnaty®), or adjuvanted subunit vaccine (Sanofi-Pasteur/GSK strain D 614 or strain B.1.351), depending on randomization.
Four follow-up visits will be conducted at D15, D28, M3 and M12. An additional follow-up visit will be conducted at D3 for subjects participating in the ancillary study.

Study days should be calculated based on the date of the first vaccination (Day 0).
Visit at D3 and D15 should be performed ± 1 day compared to reference visit (D0), D28 should be performed ± 3 days from D0, visit at M3 ± 5 days from D0, and visit M12 ± 10 days from D0.

During the inclusion visit, participants will receive a self-report diary, which will be the baseline document for follow-up.
The diary will be reviewed and collected by the investigator at M1. The participants will report their temperature everyday for 7 days after vaccine administration, and collect safety information for 28 days after vaccine administration, including local (pain/swelling at the injection site) and systemic (temperature rise, headache, muscle pain, etc.) reactions, as well as concomitant treatments.

The diary will be collected at V3 and kept at the site until the last visit. The information collected in the diary will be used as a basis for the safety assessment performed by the investigator to determine if an adverse event (AE) has occurred between the three visits.

At the end of the third visit (D28), participants will be provided a memo to help them collect reactions that might occur between two visits. The memo will be reviewed at V4 and V5 and will be collected at the end of the last visit.

At the end of the first visit, participants will be provided with a ruler for daily measurement of the size of local reactions at vaccination site, and with a thermometer for daily measurement of temperature.

After the end of the first visit, the participant will be provided with a health pass that complies with current French regulations. The request for the health pass will be carried out by the investigating team, and will require the signature of a specific consent form by the participant.

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22.1 *Screening visit*

Participants will be recruited mainly from the COVIREIVAC volunteer platform, but they can also be recruited in collaboration with hospital vaccination centers, and traditional means of communication (poster, announcement on social networks, mailing lists).

A phone contact will be made by the investigator or a clinical research associate to explain the study (objectives, benefits and risks, and answer participants' questions), to inform the participant that his participation is voluntary and that he will be free to withdraw his consent at any time, without justification.

If the participant agrees on-principle to participate, a copy of the information notice will be sent to them for reading and having further information about the study, so that they can take the time to read it, and have enough time to make their decision.

After the patient has consented to participate to the study, the baseline visit will be planned.

Whose consent must be obtained	**Who informs the individuals and collects their consent**	**At what point the individuals are informed**	**At what point the consent is obtained**
The individual willing to participate in the study	The principal investigator or collaborating physician declared and trained in the study	Screening visit (by phone) and at the beginning of the inclusion visit	*Inclusion visit*

22.2 Baseline visit and randomization visit – V1 = D0

During this visit, investigator or authorized study staff will:

- Ensure that the participant has had enough time to take freely their decision, to read and understand the informed consent form
- Review all inclusion and non-inclusion criteria for eligibility of the participant. In the event that the participant is deemed ineligible for participation in the study, they will be considered as a “screen failure”. The reason for screen failure has to be documented on the screening log and into the eCRF.
- Obtain ICF signed by both the participant and the investigator
- Collect demographic data (including age and sex) and information about the medical history of the participant:
    - Any condition or medical history that may interfere with the participant’s eligibility or participation in the study, such as previous vaccinations, concomitant treatments initiated within the last month, previous or ongoing diseases
    - Any significant medical condition or history that may impair the assessment of the study or be relevant to the analyses of the immunological data
- Perform a clinical examination with measurement of vital signs (temperature, blood pressure, heart rate)
- Randomized the participant after verification of the eligibility criteria by entering the data collected into the eCRF

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- Perform, before the injection of the vaccine:
    - Urinary pregnancy test for women of childbearing potential
    - Naso pharyngeal SARS-CoV-2 PCR
    - Saliva sampling (3 ml) for assessment of mucosal immunity
    - Blood sampling for :
        - Humoral analysis and biobank (5 ml) for all participants
        - For 26 participants per group
            - Blood count (3 ml)
            - Cellular analyses (3 x 6 ml)
- Perform injection of mRNA or recombinant subunit vaccine (without waiting for the SARS-CoV-2 PCR result)
- Perform a 30-min follow-up after the administration, including a measurement of the vital signs (temperature, blood pressure, heart rate) and a recording of any significant medical event
- Report all the data into eCRF.
- Submit the request for the participant's health pass

<u>At the end of the visit, the investigator or authorized staff will</u>:

- Deliver to the participant:
    - A self-monitoring diary that should be filled until the next visit
    - A ruler to measure any skin reactions
    - A digital thermometer
    - A participant card that must constantly be kept with the participant
- Explain to the participant how and how often the diary should be completed
- Schedule the appointment for the V2 visit

22.3 Telephone contact between V1 and V3

During the first month of participation, participants will be followed-up via periodic telephone calls from the investigation team, in order to monitor post-vaccination adverse events:

- 48 to 72 hours after boost vaccine administration, except for subjects involved in the ancillary study.
- Then D7 and D21

22.4 Follow-up visits: V2 = D15 (± 1 day), V3 = D28 (± 3 days) / V4 = M3 (D90 (± 5 days)) / V5 = M12 (D365 (± 10 days))

During this visit, investigator or authorized study staff will:

- Ask the participant about medical history since last visit, intercurrent events and current treatments,
- V2 and V3: review and collect (collection at V3 only) the self-monitoring diary
- Perform a clinical examination, including vital signs (temperature, blood pressure and heart rate)

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- Perform a saliva sampling (3 ml) for assessment of mucosal immunity, **at V3 and V4 only**
- Perform a blood sampling for :
    - Humoral analysis and biobank (5 ml) for all participants
    - For 26 participants per group:
        - Blood count (3 ml)
        - Cellular analyses (3 x 6 ml)
- Provides memo to the participant
- Report all the data into eCRF

After each visit, an appointment is scheduled for the next visit.

22.5 Ancillary analysis additional visit: VX = D3 (± 1 day)

This visit only apply to the participants involved in the ancillary analysis. During this visit, investigator or authorized study staff will:

- Ask the participant about post-vaccination adverse events
- Perform a blood sampling for humoral analysis and biobank (5ml)
- Report all the data into eCRF

22.6 Expected length of participation and description of the chronology and duration of the study.

The inclusion period will be 1 month and 5 days , the duration of participation for each participant will be 12 months, and the total duration of the research will be 19 months and 5 days including the analysis.

Inclusion period	1 month and 5 days
Participation period, including : – Treatment duration – Follow-up duration	 1 day 12 months
Immunological analyses :	6 months
Total duration of the research :	19 months and 5 days

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22.7 Table summarizing the chronology of the study

	Inclusion + boost vaccination **V1**	Safety phone call	Early follow-up (*ancillary analysis*)[a] VX	Follow-up V2	Follow-up **V3**	Follow-up **V4**	Follow-up **V5**
	D0	**48 to 72h[b] post D0 then D7 and D21**	**D3**	**D15**	**D28 (M1)**	**D90 (M3)**	**D365 (M12)**
Authorized visit interval (days)		*+/- 1 d*	*+/- 1 d*	*+/- 1 d*	*+ / -3 d*	*+/-5 d*	*+/-10 d*
Informed consent	x						
Verification of inclusion and non-inclusion criteria	x						
Clinical examination	x		x	x	x	x	x
Medical history	x						
Concomitant therapy	x		x	x	x	x	x
Naso pharyngeal SARS-CoV-2 PCR	x						
Saliva (3 ml)	x				x	x	
Blood sampling for humoral analysis and biobanking (5mL)	x		x	x	x	x	x
CBC (3 mL) [a]	x			x	x	x	x
Blood sampling for cellular analysis (3x6mL) [a]	x			x	x	x	x
Urinary pregnancy test (U)	x (U)						
Adminisatration of the vaccine Pfizer-BioNTech / SP-GSK							
Post-vaccination follow-up (30 minutes)	x						
Delivery of the self-monitoring diary (C) / Memo (A)	x (C)				x (A)		
Review of the self-monitoring diary (C) / Memo (A)			x (C)	x (C)	x (C)	x (A)	x (A)
Adverse events	x	x	x	x	x	x	x
Blood volume (mL)	**5**		**5**	**5**	**5**	**5**	**5**
Blood volume (mL) for sub-analysis (CBC and cellular analyses) [a]	***21***			***21***	***21***	***21***	***21***
Cumulative blood volume (mL)	**5**			**10**	**15**	**20**	**25**
Cumulative blood volume (mL) with sub-analysis [a]	***26***		***31***	***57***	***83***	***109***	***135***

[a]: on a sub-population of 26 participants per group.
[b] the telephone call at 48-72h will not be performed for participants in the ancillary study, who will be seen at the study site (VX).

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22.8 Pregnancy test

A urine pregnancy test will be performed on women of childbearing potential before vaccination. They will be asked to keep using their contraception during the study.
The contraception used must be considered "highly effective", i.e. one of the following methods of contraception: Oral/intra-vaginal/transdermal hormonal contraception; Intrauterine device or intrauterine hormone delivery system; Bilateral occlusion/ligation of the fallopian tubes; Partner vasectomy; Abstinence (when consistent with subject's preferred lifestyle).
Periodic abstinence (e.g., calendar, thermal...), and withdrawal are not acceptable methods of contraception.

Note: The subject undertakes to use an effective contraceptive method (or the investigating physician ensures that effective contraception has been put in place at least 4 weeks prior to the vaccination and until at least 12 weeks after the last vaccination according to the recommendations "Recommendations for Contraception and Pregnancy Tests in Clinical Trials - Clinical Trials Facilitation and Coordination Group CTFG version 1.1 (21-Sept-2020)".

22.9 Biological samples circuit

At each visit, blood samples collected from the participant will be technically processed (decantation, centrifugation, aliquoting) at each study site (laboratory, CRB, CIC, CRC...) and stored temporary as described in the laboratory manual.

The samples will be periodically sent from the study sites to the CRB APHP.SU (central biological resources center). After verification, the CRB APHP.SU will ship the samples for analysis to the following laboratories:

- For humoral analyses: Unité des Virus Emergents, UMR190, IHU Méditerranée Infection, under the supervision of Pr De Lamballerie
- For cellular analyses: Laboratoire d'Immunologie Biologique, Hôpital Européen Georges Pompidou, under the supervision of Pr Tartour.
- For mucosal analyses: Laboratoire d'immunologie, CHU Saint Etienne, under the supervision of Pr Paul.

During the study, the samples will be sent from the investigation sites to the CRB APHP.SU and then to the corresponding laboratories at 4 separate timepoints:

- a shipment of all V1, VX and V2 after the last V2 visit
- a shipment of all V3 samples after the last V3 visit
- a shipment of all V4 samples after the last V4 visit
- a shipment of all V5 samples after the last V5 visit

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22.10 Biological samples collection

At each visit, an aliquot will be stored as biological sample collection. During the study the sample collection(s) will be stored at the laboratory CRB SAT APHP.SU (site Hôpital St Antoine) under the supervision of Pr Tabassome Simon.

At the end of the study, the samples may be used throughout a period of 3 years for further analysis not described in the initial protocol but which may be useful for investigation about COVID-19 infection related to SARS-CoV-2 virus, in light of advances in scientific knowledge, provided the participant is informed and does not oppose this, as stated in the information note/consent form. If the samples are kept at the end of the study, the sample collection will be declared to the ministry of research and to the director of the competent regional healthcare authority (Article L. 1243-3 of the *Code de la Santé Publique* [French Public Health Code]).

22.11 Distinction between standard care and study

TABLE: "Standard care" vs. "additional interventions" required specifically for the study

Interventions, procedures and treatments carried out for research purposes	**Interventions, procedures and treatments associated with standard care**	**Interventions, procedures and treatments added for research purposes**
Treatments	None	Vaccination at D0
Visits	None	4 follow-up visits at D15, M1, M3 and M12
Blood samples	None	Blood samples taken at each visit
Saliva sample	None	3ml saliva sample taken at D0, D28 and D90
Urinary sample	None	Urinary pregnancy test at D0 (females of childbearing potential only)

23 ELIGIBILITY CRITERIA

23.1 Inclusion criteria

9. Age ≥ 18 years
10. Adult in a healthy condition or with a stable health status if pre-existing medical history. Stable health status is defined as an existing disease that has not required a significant change in treatment or hospitalization for worsening in the 3 months before enrollment, and for which neither a significant change in treatment or hospitalization for worsening is expected in the near future
11. For women of childbearing age: a negative highly sensitive pregnancy urinary test during the inclusion visit AND use of an effective contraceptive method at least 4 weeks prior to vaccination and until at least 12 weeks after the vaccination
12. Who has received 2 doses of mRNA vaccine (Pfizer-BioNTech) with an interval of 3 to 6 weeks
13. Second dose of mRNA vaccine (Pfizer-BioNTech) administered between 3 months and 7 months before the booster dose
14. Understands and agrees to comply with the study procedures
15. Written informed consent signed by both the participant and the investigator

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16. Subject affiliated to the French Social Security System

23.2 Exclusion criteria

15. Acute febrile infection (body temperature ≥ 38.0°C) within the previous 72 hours and/or presenting symptoms suggestive of COVID-19 within the previous 28 days or having been in contact with an infected individual for the last 14 days before the inclusion visit;
16. Virologically documented history of COVID-19 (PCR or serology);
17. Immunosuppressive therapy such as corticosteroids > 10 mg prednisone equivalent/day (excluding topical preparations and inhalers) within 3 months prior to inclusion or within 6 months for chemotherapies;
18. Treatment with immunoglobulins or other blood derivatives within 3 months prior to inclusion or scheduled administration of immunoglobulins or blood derivatives before the end of the study;
19. Known HIV, HCV or HBV infection;
20. Any medical condition, such as cancer, that might impair the immune response;
21. Use of experimental immunoglobulins, experimental monoclonal antibodies or convalescent plasma is not permitted during the study;
22. Pregnancy or breastfeeding currently ongoing, or positive pregnancy test at enrolment visit;
23. History of severe adverse events following vaccine administration including anaphylactic reaction and associated symptoms such as rash, breathing problems, angioedema, and abdominal pain, or a history of allergic reaction that could be triggered by a component of the SARS-COV-2 vaccine at the time of the first vaccine injection;
24. Participant who has received BCG (tuberculosis) vaccine within the previous year
25. Has received a vaccine within 2 weeks prior to the boost injection or is scheduled to receive a registered vaccine 2 weeks after the boost injection
26. Any bleeding disorder considered as a contraindication to an intramuscular injection, previous phlebotomy or receipt of anticoagulants
27. Participation in other research involving humans (French classification Jardé 1 or Jardé 2) within 4 weeks prior to the inclusion visit, or participation in any other vaccine trial
28. Subject under legal protection (e.g. guardianship, tutorship)

23.3 Recruitment procedure

The study will be conducted in Clinical Investigation Centers (CIC), Clinical Research Centers (CRC) and hospital departments of the national vaccine clinical research network COVID-19 COVIREIVAC (Inserm).

The recruitment of participants will be carried out mainly by phone using the COVIREIVAC platform, but also in relation with the vaccination campaign coordinators of the Hospital Groups (GH) involved. An informative e-mail will be sent to all hospital staff. Posters will be displayed in the hospitals. A diffusion via social networks (Twitter, Facebook...) can be carried out.

	Number of participants
Total number of participants to be included	*300*

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Number of centres	*12*
Enrollment period (months)	*1month and 5 days*
Number of participants/centre	*25*
Number of participants/centre/month	***25***

In order to ensure the overcome the recruitment issues in the ≥ 65 years group, inclusions of subjects in the 18-64 years group may exceed 150.

23.4 Termination rules

23.4.1 Criteria and procedures for premature withdrawal of a participant from the study

- Participants may exit the study at any time and for any reason.
- The investigator can temporarily or permanently withdraw a participant from the study for any safety reason or if it is in the participant's best interests.
- Participant lost to follow-up: the participant cannot be located. The investigator must make every effort to reconnect with the participant (and document his attempts in the source file), at least to determine whether the participant is alive or dead

If a participant exits the study prematurely or withdraws consent, any data collected prior to the date of premature exit may still be used.
- In case of serious adverse events, see the corresponding section on vigilance.

The case report form must list the various reasons why the participant has discontinued the study:
- Lack of efficacy
- Adverse reaction
- Another medical issue
- Personal reasons of the participant
- Explicit withdrawal of consent
- Lost to follow-up

23.4.2 Procedures for replacing participants

Participants who signed the informed consent form but were not randomized may be replaced. Participants who discontinued participation or withdrew their consent after V1 will not be replaced.

23.4.3 Full or partial discontinuation of the study

AP-HP as sponsor or the Competent Authority (ANSM) can prematurely discontinue all or part of the study, temporarily or permanently, if suspected unexpected serious adverse reactions (SUSARs) are observed in one of the treatment arms or if there is a discrepancy in the serious adverse reactions between the treatment arms, requiring a reassessment of the benefit-risk ratio for the study.

Similarly, AP-HP, as the sponsor, or the Competent Authority (ANSM) may decide to prematurely discontinue the study due to unforeseen issues or new information about the product, in light of which the objectives of the study or clinical program are unlikely to be achieved.

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AP-HP as sponsor reserves the right to permanently suspend enrolment at any time if it appears that the inclusion objectives are not met.

If the study is prematurely discontinued for safety reasons, the decision and justification will be provided by the sponsor (AP-HP) to the Competent Authority (ANSM) and to the CPP (Research Ethics Committee) within a period of 15 days.

24 TREATMENT ADMINISTERED TO STUDY PARTICIPANTS

24.1 *Description of the investigational medicinal products*

24.1.1 Pfizer-BioNTech COVID-19 mRNA vaccine (COMIRNATY®)

Pfizer-BioNTech COVID-19 (COMIRNATY®) vaccine is a lipid nanoparticle dispersion (LNP) of a 5'-capped single-stranded mRNA produced by cell-free in vitro transcription from the corresponding DNA templates and encoding the SARS-CoV-2 viral Spike (S) protein.

Indications:
The vaccine is indicated for active immunization for the prevention of COVID-19 caused by SARS-CoV-2 virus, in individuals aged 12 years and older. Pfizer-BioNTech COVID-19 vaccine received conditional marketing authorization (MA) in Europe on December 21st, 2020 for “active immunization against COVID-19 caused by SARS-CoV-2 virus in persons aged 16 years and older," with an extension of the indication to teenagers from 12 to 15 years old on May 28th, 2021.
The vaccine is administered by intra-muscular (IM) injection, using a 2-dose schedule with a minimum interval of 3 weeks after the first dose.

Product description:
The product is supplied in a multi-dose vial and must be diluted before use. The vial can be stored at a temperature between +2°C and +8°C during one month, otherwise it must be stored at a temperature of -80°C. The shipment of the vial can be done at -20°C.
One vial (0.45 mL) contains 6 doses of 0.3 mL after dilution.
One dose (0.3 mL) contains 30 micrograms of COVID-19 mRNA vaccine (encapsulated in lipid nanoparticles).

Product composition:

Active substance: The vaccine contains a nucleoside-modified messenger RNA encoding the SARS-CoV-2 spike virus glycoprotein (S).

Excipients:
- ALC-0315 = ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate)
- ALC-0159 = 2-[(polyethylene glycol)-2000]-N,N-ditradecylacetamide
- 1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC)
- Cholesterol
- Potassium chloride
- Monopotassium phosphate
- Sodium chloride

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- Disodium phosphate dihydrate
- Sucrose
- Water for injection

24.1.2 Sanofi Pasteur / GSK COVID-19 recombinant protein vaccines (SARS-CoV-2 D614 or B.1.351 Spike protein)

CoV2 preS dTM-AS03 adjuvanted vaccines (product code No. 549 and 567) are candidate vaccines consisting both of a stabilized pre-fusion trimer of the SARS-CoV-2 Spike (S) protein, and including the AS03 α-tocopherol and squalene oil/water emulsion adjuvant manufactured by GSK, to optimize the immune response.

Administration:
One of these vaccines is administered by intra-muscular (IM) injection.

Product description:
The product is a liquid formulation made of recombinant protein, placed in a formulation buffer and stored in glass vials at +2°C to +8°C. The product should be stored in a place protected from light.
The CoV2 preS dTM vaccine has to be mixed with equal volumes of adjuvant AS03 at the study site before administration.
One vial contains 10 doses of 0.5ml and can be used up to 12 hours after reconstitution.

Product composition:
- CoV2 preS dTM vaccine contains phosphate-buffered saline (PBS) buffer, residual amount of baculovirus and *Spodoptera frugiperda* cell proteins, baculovirus and cellular DNA. It **does not** contain egg protein, antibiotics, or preservatives.
- AS03 adjuvant contains α-tocopherol, squalene and polysorbate.

24.2 *Description of traceability elements accompanying the investigational medicinal product(s)*

The pharmaceutical circuit and the storage/dispensing methods will be described in a specific procedure (see SOP Pharmacy Manual).

The reference documents for each vaccines used in this study are:
- COMIRNATY® Summary of Product Characteristics (SmPC), the most up-to-date version. The EMA site will be regularly consulted and the most up-to-date COMIRNATY® SmPC will be taken into account throughout the duration of the trial: https://www.ema.europa.eu/en/documents/product-information/comirnaty-epar-product-information_en.pdf
- Sanofi Pasteur / GSK CoV2 preS dTM-AS03 adjuvanted vaccine (D614) Investigator's Brochure version 10.0 dated 03/08/2021
- Sanofi Pasteur / GSK CoV2 preS dTM-AS03 adjuvanted vaccine (B.1.351) Investigator's Brochure version 10.0 dated 03/08/2021

A vaccination certificate will be provided to the participant after vaccination.

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24.3 *Authorized and prohibited treatments (medicinal, additional medicinal, surgical), including rescue medications*

24.3.1 Authorized treatments

All treatments are authorized, they will be reported in the eCRF.

24.3.2 Prohibited treatments

- Any other COVID-19 vaccine, including non-specific vaccines used in a clinical trial to evaluate their effectiveness against COVID-19 infection (e.g. BCG vaccine)
- Licensed vaccine within 2 weeks before and after the boost injection
- Immunosuppressive therapies, such as corticosteroids at a dose > 10mg prednisone equivalent per day (excluding topical preparations and inhaled products), within 3 months prior to inclusion, or within 6 months for chemotherapies
- Treatment with immunoglobulins or any other derived blood product within 3 months prior to inclusion, or planned administration before the study completion.
- Experimental immunoglobulins, experimental monoclonal antibodies, convalescent plasma.

24.4 *Methods for monitoring compliance with the study procedures*

A self-monitoring diary will be provided to the participant after the boost injection. This diary will be completed by the participant in order to record all the adverse events that occurred between D0 and D28.

25 EFFICACY ASSESSMENT

25.1 *Description of efficacy endpoints assessment parameters*

- **Anti SARS-CoV-2 antibodies anti-Spike, anti-RBD and anti-NP (Pr X. De Lamballerie, IHU Méditerrannée, Marseille, France)**

The ELISA kit from Euroimmun® (Luebeck, Germany) targets anti-SARS-CoV-2 IgG antibodies directed against the S1 domain of the virus' Spike protein. It is used according to the recommendations given by the manufacturer.

- **Neutralizing antibodies against European strain of SARS-CoV-2 and variants of interest (Pr X. De Lamballerie, IHU Méditerrannée, Marseille, France)**

The microneutralization test is performed according to the published protocol (Gallian P. et al, 2002). The test uses a clinical strain of SARS-CoV-2 (100 TCID50/well), VeroE6 cells and a readout by the reading of the cytopahic effect (CPE) at 5 days post-infection.
It is a VNT100 (100% of wells lysed in quadruplicate format).
Its performance is very close to a PRNT90 test. The test is automated in the NSB3 laboratory for all dilution and distribution steps and for the reading of the CPE.
The dilutions tested are 20, 40, 80, 160, 320, 640, 1280. The range is extended if a titre of 1280 is observed at first intension.

- **ELISpot IFN CD4 and CD8 (Pr E. Tartour, laboratoire d'immunologie biologique, Hôpital Européen Georges Pompidou, APHP, Paris, France)**

This test will be performed for 26 participants in each group. ELISpot uses a commercially available kit from Mabtech or C.T.L. The peptides are purchased for JPT technologies. This technique has been accredited by the French accreditation agency Cofrac.

- **Anti SARS-CoV-2 IgA anti-spike (Pr S. Paul, CHU Saint-Etienne, France)**

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The measurement of anti-spike secretory IgA will be performed by ELISA technique and the measurement of the neutralizing activity of salivary IgA will be performed by PRNT technique.

25.2 *Anticipated methods and timetable for measuring, collecting and analyzing the efficacy data*

Blood samples for humoral and cellular analyses will be taken before the boost dose, 15 days after, at D28, at M3 and at M12.The follow-up of the adverse events post-vaccination will be carried out immediately during 30 minutes after the administration of the boost dose, then at D15, D28, M3 and M12.

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26 SPECIFIC STUDY COMMITTEES

26.1 *Steering Committee*

The steering committee is composed of the coordinating investigator and coordinating team.

- Committee members: Odile Launay, Laureen Curci, Amel Touati, Alexandra Rousseau, Laurence Bérard, Tabassome Simon, Florence Capelle, Fatiha Djennaoui, and principal investigators from the study sites.

- Roles: Define the overall structure of the study, coordinate information, determine the initial methodology and oversee the study

- Operating procedures: the steering committee will meet:
  - Before the first inclusion
  - When 50% of participants are enrolled
  - When 100% of participants are enrolled
  - When 100% of the visits have been completed
  - An additional meeting could be scheduled in case of unexpected problem

27 SAFETY ASSESSMENT - RISKS AND BURDEN ADDED BY THE STUDY

27.1 *Description of Safety endpoints assessment parameters*

Vaccines will be monitored for reactogenicity and safety.
The term "reactogenicity" refers to selected signs and symptoms occurring immediately after vaccination or in the days following vaccination, which are recorded by the participant for seven consecutive days in their self-monitoring diary.

27.2 *Anticipated methods and timetable for measuring, collecting and analyzing the safety endpoints*

Vaccine safety will be monitored by collecting the following data:

- Vaccine-related adverse events (AEs) of any grade:
  - Any adverse event occurring within 30 minutes following the boost injection
  - Solicited local (pain, erythema/redness, itching, swelling, bruising) and systemic (pyrexia, chills, headache, fatigue, arthralgia, myalgia, nausea/vomiting, faintness, insomnia, pain in the extremities, lymph nodes) adverse events, routinely collected within the 7 days post-vaccination, and reported in the diary.
  - Unsolicited events, or events occurring after the 7 self-monitoring days, up to 28 days after the boost injection
  - AEs of grade ≥ 4, reported by the participant at the next visit

- Serious adverse events occurring throughout the entire study period.

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27.3 *Recording and reporting adverse events*

27.3.1 Definitions

According to Article R.1123-46 of the *Code de la Santé Publique* (French Public Health Code):

- **Adverse event**

Any untoward medical occurrence in a study participant, which does not necessarily have a causal relationship with the study or with the product subject to the study.

- **Adverse reaction**

An adverse event occurring in a study involving human participants when this event is related to the study or to the product being studied.

- **Adverse reaction to an investigational medicinal product**

Any untoward and unwanted reaction to an investigational medication regardless of the dose administered.

- **Serious adverse event or reaction**

Any adverse event or reaction that results in death, threatens the life of the participant enrolled in the study, requires hospitalization or prolongs existing hospitalization, causes a severe or long-term disability or handicap, or results in a congenital abnormality or deformity, and in the case of a medication, regardless of the dose administered.

- **Unexpected adverse reaction to an investigational medicinal product**

Any adverse reaction to the product whose nature, severity, frequency or outcome is inconsistent with the standard safety information described in the summary of the product characteristics, or in the investigator's brochure if the product is not authorized.

According to Article R.1123-46 of the Code de la Santé Publique and the guidelines for sponsors of clinical trials (ANSM):

- **Emerging safety issue**

Any new information that may lead to a reassessment of the risk/benefit ratio of the trial or of the product under investigation, modifications in the investigational medicinal product use, the conduct of the clinical trial or the clinical trial documents, or a suspension, interruption or modification of the clinical trial or of similar trials.
For studies involving the first administration of a health product in healthy volunteers: any serious adverse reaction.

Examples:

- any clinically significant increase in the frequency of an expected serious adverse reaction;

  any new fact relating to the conduct of the clinical trial or the development of the investigational medicinal product, if the new fact is likely to affect participant safety.
  For example:
  - a serious adverse event that may be related to the trial's interventions and diagnostic procedures and which may impact the conduct of the clinical trial, if this event could affect the safety of the participants,
  - a significant risk for the trial participants such as a lack of efficacy of the investigational medicinal product used in the treatment of a life-threatening disease,
  - significant safety results from a recently completed research on animals (such as a carcinogenicity research),

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- the premature termination, or temporary suspension for safety reasons, of a trial conducted in another country by the same sponsor using the same investigational medicinal product
- a serious adverse event related to a auxilliary medicinal product required to conduct the trial and without interaction with the investigational medicinal product, if this event could affect the safety of the participants (e.g.: challenge agents, emergency treatment)

- recommendations from the Data Safety Monitoring Board (SMB), wherever applicable, if they are relevant to the safety of the participants

- for clinical trial conducted on an advanced therapy medicinal product for human use, any relevant information about safety (e.g.: about the supply and cell donation).

- any unexpected serious adverse reaction with the IMP reported to the sponsor by spontaneous notifications, by publications or health authorities, if this adverse reaction could affect the safety of the participants of the clinical trial conducted by the sponsor.
For example:
- adverse reactions occurring in a clinical trial, partially or entirely, conducted in European Union (EU), by another sponsor,
- adverse reactions occurring in a third-party country not involved in a clinical trial, caused by a medicinal product commercialized in this third-party country but exclusively used in EU as an IMP.

Solicited *versus* unsolicited adverse events:
Solicited and unsolicited adverse events must be recorded in the electronic case report form (eCRF).

- **Solicited adverse events following vaccination**

Solicited adverse events are a list of events/symptoms that participants are specifically asked to record for the week after vaccination.

Local solicited adverse events are:
- Injection site pain
- Injection site erythema (redness)
- Injection site swelling/induration (hardness)
- Injection site itching

Systemic solicited adverse events are:
- Axillary (underarm) swelling or tenderness ipsilateral to the side of injection
- Lymphadenopathy
- Headache
- Fatigue
- Malaise
- Nausea/vomiting
- Diarrhea
- Insomnia
- Chills
- Fever
- Myalgia (muscle aches all over body)
- Arthralgia (joint aches in several joints)
- Pain in the extremities

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- **Unsolicited adverse events**

The solicited symptoms can also occur after the diary-keeping period – as well as unexpected adverse events that aren't on the solicited list, or any safety issues that people are asked to watch out for and notify. Those are grouped into unsolicited adverse events time-limited to the month after vaccination.

27.3.2 The role of the investigator

The investigator must **assess the seriousness of each adverse event** and record all serious and non-serious adverse events in the electronic case report form (eCRF).

The investigator must **document** serious adverse events **as thoroughly as possible** and provide a definitive medical diagnosis, if possible.

The investigator must **assess the intensity** of the adverse events:

- Either by using the toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (Modified FDA scale / September 2007) here below:

Reaction	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4* Potentially Life Threatening
Injection site pain	None	Does not interfere with activity	Repeated use of over-the-counter pain reliever > 24 hours or interferes with activity	Any use of prescription pain reliever or prevents daily activity	Requires emergency room visit or hospitalization
Injection site erythema (redness)	< 25 mm/ < 2.5 cm	25 - 50 mm/ 2.5 - 5 cm	51 - 100 mm/ 5.1 - 10 cm	> 100 mm/ > 10 cm	Necrosis or exfoliative dermatitis
Injection site swelling/induration (hardness)	< 25 mm/ < 2.5 cm	25 - 50 mm/ 2.5 - 5 cm	51 - 100 mm/ 5.1 - 10 cm	> 100 mm/ > 10 cm	Necrosis
Axillary (underarm) swelling or tenderness ipsilateral to the side of injection*	None	No interference with activity	Repeated use of over-the-counter (non-narcotic) pain reliever > 24 hours or some interference with activity	Any use of prescription (narcotic) pain reliever or prevents daily activity	Emergency room visit or hospitalization
Headache	None	No interference with activity	Repeated use of over-the-counter pain reliever > 24 hours or some	Significant; any use of prescription pain reliever or	Requires emergency room visit or hospitalization

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			interference with activity	prevents daily activity	
Fatigue	None	No interference with activity	Some interference with activity	Significant; prevents daily activity	Requires emergency room visit or hospitalization
Myalgia (muscle aches all over body)	None	No interference with activity	Some interference with activity	Significant; prevents daily activity	Requires emergency room visit or hospitalization
Arthralgia (joint aches in several joints)	None	No interference with activity	Some interference with activity	Significant; prevents daily activity	Requires emergency room visit or hospitalization
Nausea/vomiting	None	No interference with activity or 12 episodes/ 24 hours	Some interference with activity or > 2 episodes/24 hours	Prevents daily activity, requires outpatient intravenous hydration	Requires emergency room visit or hospitalization for hypotensive shock
Chills	None	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	Requires emergency room visit or hospitalization
Fever (oral)	< 38.0°C < 100.4°F	38.0 – 38.4°C 100.4 – 101.1°F	38.5 – 38.9°C 101.2 – 102.0°F	39.0 – 40.0°C 102.1 – 104.0°F	> 40.0°C > 104.0°F

Table : Modified from final US FDA guidance: Toxicity Grading Scale for Healthy Adult and Adolescent Subjects Enrolled in Preventive Vaccine Clinical Trials (September 2007)

- Or by using
- Common Terminology Criteria for Adverse Events [National Cancer Institute]
- general terms if the above-mentioned scale cannot be used for a specific case:
    - *Mild: tolerated by the patient, does not interfere with daily activities*
    - *Moderate: sufficiently uncomfortable to affect daily activities*
    - *Serious: prevents daily activities*

The investigator must **assess the causal relationship** between serious adverse events and the investigational medicinal products.

The method used by the investigator uses the following 2 causality terms:

3. Reasonable possibility
4. No reasonable possibility

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27.3.2.1 Serious adverse events that require the investigator to notify the sponsor without delay

As per article R.1123-49 of the *Code de la Santé Publique* (French Public Health Code), the investigator notifies the sponsor without delay on the day the investigator becomes aware of any serious adverse event which occurs during a study that meets the description in line 1° of Article L.1121-1 of the Code de la Santé Publique, with the exception of any event which is listed in the protocol and, if applicable, in the investigator's brochure as not requiring notification.

A serious adverse event is any untoward medical occurrence that:

- results in death
- is life-threatening to the participant enrolled in the study
- requires hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect

27.3.2.2 Specific features of the protocol

27.3.2.2.1 Other events that require the investigator to notify without delay the sponsor

The investigator must notify the sponsor without delay on the day the investigator becomes aware of these adverse events described here-below, in the same manner and within the same deadline as for serious adverse events (see above).

- **Adverse events deemed "medically significant"**

  - Solicited adverse events **grade ≥4 according to FDA modified scale** following vaccination up to D7:
    Local solicited adverse events are:
    - Injection site pain
    - Injection site erythema (redness)
    - Injection site swelling/induration (hardness)

    Systemic solicited adverse events are:
    - Axillary (underarm) swelling or tenderness ipsilateral to the side of injection
    - Headache
    - Fatigue
    - Nausea/vomiting
    - Chills
    - Fever
    - Myalgia (muscle aches all over body)
    - Arthralgia (joint aches in several joints)

  - Zona

  - Uncontrolled diabetes in contexts of reactogenicity.

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- Acute pancreatitis.

- Rheumatoid arthritis.

- Neuroinflammatory disorders:
  - Cranial nerve neuropathy, including paralysis and paresis (eg, Bell's palsy).
  - Optic neuritis.
  - Multiple sclerosis.
  - Transverse myelitis.
  - Myasthenia gravis, including Lambert-Eaton myasthenic syndrome.
  - Demyelinating peripheral neuropathies including:
    - Chronic inflammatory demyelinating polyneuropathy.
    - Multifocal motor neuropathy.
    - Polyneuropathies associated with monoclonal gammopathy.
  - Narcolepsy.

- **Adverse events of special interest (AESIs)**

Adverse Event of Special Interest (AESI) is further defined in Council for International Organizations of Medical Sciences (CIOMS)VII as:
"An adverse event of special interest (serious or non-serious) is one of scientific and medical concern specific to the sponsor's product or program, for whichongoing monitoring and rapid communication by the investigator to the sponsor could be appropriate. Such an event might require further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial sponsor to other parties (e.g., regulators) might also be warranted."

As other COVID-91 vaccines, some AESIs need to be considered, they are listed in the table n°1 here below:

Table n°1: Adverse Events of Special Interest

Body system	AESIs type
Neurologic	Generalized convulsion
	Guillain-Barré Syndrome (GBS)
	Acute disseminated encephalomyelitis (ADEM)
	Aseptic meningitis
	Anosmia, ageusia
Hematologic	Thrombocytopenia
	Thrombo-embolic events
Immunologic	Anaphylaxis
	Vasculitides
	Arthritis
	Enhanced disease following immunization
Repiratory	Acute respiratory distress syndrome (ARDS)
Cardiac	Acute cardiac injury including: • Microangiopathy • Heart failure and cardiogenic shock • Stress cardiomyopathy • Coronary artery disease • Arrhythmia • Myocarditis, pericarditis
Renal	Acute kidney injury
Dermatologic	Chiblain-like lesions

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	Single organ cutaneous vasculitis
	Erythema multiforme
Other	Serious local/systemic adverse event following immunization Potential Immune-mediated Diseases with the adjuvanted vaccines

- ✓ **Collection, documentation and monitoring of Potential Immune-mediated Diseases (pIMDs) with adjuvanted vaccines**

- **Potential Immune-mediated Diseases (pIMDs)**

To date there are no guidelines for collection, documentation and monitoring of pIMDs reported in the course of clinical trials with adjuvanted vaccines (20).

Potential immune-mediated diseases are a subset of AEs that include autoimmune diseases and other inflammatory and/or neurologic disorders of interest which may or may not have an autoimmune etiology. AEs that need to be recorded and reported as pIMDs include those listed in table n°2.

However, the investigator will exercise their medical and scientific judgement in deciding whether other diseases have an autoimmune origin (that is pathophysiology involving systemic or organ-specific pathogenic autoantibodies) and should also be recorded as a pIMD.

When there is enough evidence to make any of the diagnoses mentioned in table n°2, the AE must be reported as a pIMD. Symptoms, signs or conditions which might (or might not) represent the above diagnoses, should be recorded and reported as AEs but not as pIMDs until the final or definitive diagnosis has been determined, and alternative diagnoses have been eliminated or shown to be less likely.

Once a pIMD is diagnosed (serious or non-serious) in a study subject, the investigator must notify the sponsor without delay on the day the investigator becomes aware of these adverse events, in the same manner and within the same deadline as for serious adverse events (see above).

Table N°2: List of Potential Immune-mediated Diseases *(adapted from suggested list of pIMDs of interest for possible evaluation in clinical vaccine studies (20))*

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Neuroinflammatory disorders	Musculoskeletal disorders	Skin disorders
• Cranial nerve neuropathy, including paralysis and paresis (eg, Bell's palsy). • Optic neuritis. • Multiple sclerosis. • Transverse myelitis. • Guillain-Barré syndrome, including Miller Fisher syndrome and other variants. • Acute disseminated encephalomyelitis, including site specific variants, eg, noninfectious encephalitis, encephalomyelitis, myelitis, myeloradiculoneuritis. • Myasthenia gravis, including Lambert-Eaton myasthenic syndrome. • Demyelinating peripheral neuropathies including: - Chronic inflammatory demyelinating polyneuropathy. - Multifocal motor neuropathy. - Polyneuropathies associated with monoclonal gammopathy. • Narcolepsy.	• Systemic lupus erythematosus and associated conditions. • Systemic scleroderma (systemic sclerosis), including: - Diffuse scleroderma. - CREST syndrome. • Idiopathic inflammatory myopathies, including: - Dermatomyositis. - Polymyositis. • Anti-synthetase syndrome. • Rheumatoid arthritis and associated conditions including: - Juvenile idiopathic arthritis. - Still's disease. • Polymyalgia rheumatica. • Spondyloarthropathies, including: - Ankylosing spondylitis. - Reactive arthritis (Reiter's syndrome). - Undifferentiated spondyloarthritis. - Psoriatic arthritis. - Enteropathic arthritis. • Relapsing polychondritis. • Mixed connective tissue disorder. • Gout.	• Psoriasis. • Vitiligo. • Erythema nodosum. • Autoimmune bullous skin diseases (including pemphigus, pemphigoid, and dermatitis herpetiformis). • Lichen planus. • Sweet's syndrome. • Localized scleroderma (morphea).
Vasculitis	**Blood disorders**	**Others**
• Large vessels vasculitis including: - Giant cell arteritis (temporal arteritis). - Takayasu's arteritis. • Medium sized and/or small vessels vasculitis including:	• Autoimmune hemolytic anemia. • Autoimmune thrombocytopenia. • Antiphospholipid syndrome. • Pernicious anemia.	• Autoimmune glomerulonephritis including: - IgA nephropathy. - Glomerulonephritis rapidly progressive. - Membranous glomerulonephritis.

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- Polyarteritis nodosa. - Kawasaki's disease. - Microscopic polyangiitis. - Wegener's granulomatosis (granulomatosis with polyangiitis). - Churg–Strauss syndrome (allergic granulomatous angiitis or eosinophilic granulomatosis with polyangiitis). - Buerger's disease (thromboangiitis obliterans). - Necrotizing vasculitis (cutaneous or systemic). - Antineutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified). - Henoch-Schonlein purpura (IgA vasculitis). - Behcet's syndrome. - Leukocytoclastic vasculitis.	• Autoimmune aplastic anemia. • Autoimmune neutropenia. • Autoimmune pancytopenia.	- Membranoproliferative glomerulonephritis. - Mesangioproliferative glomerulonephritis. - Tubulointerstitial nephritis and uveitis syndrome. • Ocular autoimmune diseases including: - Autoimmune uveitis. - Autoimmune retinitis. • Autoimmune myocarditis. • Sarcoidosis. • Stevens-Johnson syndrome. • Sjögren's syndrome. • Alopecia areata. • Idiopathic pulmonary fibrosis. • Goodpasture syndrome. • Raynaud's phenomenon.
Liver disorders	**Gastrointestinal disorders**	**Endocrine disorders**
• Autoimmune hepatitis. • Primary biliary cirrhosis. • Primary sclerosing cholangitis. • Autoimmune cholangitis.	• Inflammatory bowel disease, including: - Crohn's disease. - Ulcerative colitis. - Microscopic colitis. - Ulcerative proctitis. • Celiac disease. • Autoimmune pancreatitis.	• Autoimmune thyroiditis (Hashimoto thyroiditis). • Grave's or Basedow's disease. • Diabetes mellitus type 1. • Addison's disease. • Polyglandular autoimmune syndrome. • Autoimmune hypophysitis.

- ***In utero* exposure**

  The investigator must notify the sponsor without delay on the day the investigator becomes aware of any pregnancy that occurs during the study, even if it is not associated with an adverse event.

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If the investigational medicinal product is genotoxic, every case of maternal or paternal exposure must be notified.

27.3.2.2.2 Serious adverse events that do not require the investigator to notify the sponsor without delay

These serious adverse events are only recorded in the electronic case report form (eCRF).

- *Special circumstances*

- Hospitalization for a pre-existing illness or condition
- Hospitalization for a medical or surgical treatment scheduled prior to the study
- Admission for social or administrative reasons
- Emergency care (< 12 hours)

- *Adverse events potentially related to treatments prescribed as part of the care provided during the study follow-up*

The investigator must report these adverse events to the relevant regional pharmacovigilance centre, Centre Régional de Pharmacovigilance (CRPV):

- *Confirmed COVID-19 infections <u>that do not meet</u> at least one of the seriousness criteria.*
- *Solicited adverse events grade <4 according to FDA modified scale following vaccination up to D7.*

27.3.2.3 Period during which SAEs must be notified without delay by the investigator to the sponsor

The investigator must notify the sponsor without delay of any serious adverse events as defined in the corresponding section:

- from the date on which the participant signs the consent form / begins treatment with the investigational medicinal product,
- throughout the whole follow-up period required for the trial
- indefinitely, if the SAE is likely to be due to the investigational medicinal product or to the study interventions (e.g. serious reactions that could appear long after exposure to the medication, such as cancers or congenital abnormalities)

27.3.2.4 Procedures and deadlines for notifying the sponsor

The initial notification of an SAE must be provided in a written report signed by the investigator using a SAE notification form specific to the study and intended for this purpose (in the case report form).

Each item in this form must be completed by the investigator so that the sponsor can carry out the appropriate analysis.

The initial notification to the sponsor of a serious adverse event must be quickly followed by an additional detailed written report (or reports) so that the case outcome may be monitored by the Safety Department or to provide further information.

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Whenever possible, the investigator will provide the sponsor with any documents that may be useful (medical reports, laboratory test results, results from additional examinations, etc.). These documents must be non-identifying. In addition, the documents must include the following: study acronym, number and participant's initials.

Any adverse event will be monitored until fully resolved (stabilization at a level considered acceptable by the investigator, or return to the previous state) even if the participant has left the study.

The initial notification, the SAE follow-up reports and all other documents must be sent to the sponsor's Safety Department by email (eig-vigilance.drc@aphp.fr). It should be noted that it is possible to send SAE reports to the Safety Department by fax to +33 (0)1 44 84 17 99 only in the event of a failed attempt to send the SAE report by email (in order to avoid duplication).

As the study uses an e-CRF:

- the investigator completes the SAE notification form in the e-CRF, then validates, prints, and signs the form before sending it by email;
- if it is not possible to connect to the e-CRF, the investigator should complete, sign, and send the SAE notification form to the Safety Department. As soon as the connection is restored, the SAE notification form in the e-CRF must be duly completed.

The investigator must respond to all requests from the sponsor for additional information.
For all questions relating to the notification of an adverse event, the Safety Department can be contacted via email: vigilance.drc@aphp.fr.

For cases of *in utero* exposure, the investigator will complete the Notification and Follow-up form for a pregnancy occurring during participation in a study".
The investigator must monitor the pregnant woman throughout her pregnancy or until the pregnancy is terminated, and must notify the sponsor of the outcome of the pregnancy using this form.
If the outcome of the pregnancy falls within the definition of a serious adverse event (miscarriage, pregnancy termination, fetal death, congenital abnormality, etc.), the investigator must follow the procedure for reporting SAEs.
The initial pregnancy notification, the SAE follow-up reports, and any other documents will be sent to the sponsor according to the same procedures specified herein.
If it was the father who was exposed, the investigator must obtain the pregnant woman's permission before collecting information about the pregnancy.

27.3.3 Role of the sponsor

The sponsor, represented by its Safety Department, shall continuously, throughout the trial, assess the safety of each investigational medicinal product throughout the study.

27.3.3.1 Analysis and declaration of serious adverse events

The sponsor assesses:

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4. the **seriousness** of all the adverse events reported
5. the **causal relationship** between these events and each investigational medicinal product and any other treatments,

   All serious adverse events which the investigator and/or the sponsor reasonably believe may have a causal relationship with the investigational medicinal product are classed as suspected serious adverse reactions.
6. the **expected or unexpected nature** of the serious adverse reactions

   Any serious adverse reaction whose nature, severity, frequency or outcome is inconsistent with the safety information described in the summary of product characteristics, or in the investigator's brochure if the product is not authorized, is considered unexpected.

   The sponsor, represented by its Safety Department, assesses the expected/unexpected nature of a serious adverse reaction based on the information described below**.**

For serious adverse events likely to be related to the investigational medicinal products, refer to the following documents:

- COMIRNATY® Summary of Product Characteristics (SmPC): The EMA site will be regularly consulted and that the most up-to-date COMIRNATY® SmPC will be taken into account throughout the duration of the trial: https://www.ema.europa.eu/en/documents/product-information/comirnaty-epar-product-information_en.pdf
- Sanofi Pasteur / GSK CoV2 preS dTM-AS03 adjuvanted vaccine (D614) and Investigator's Brochure version 10.0 dated 03/08/2021
- Sanofi Pasteur / GSK CoV2 preS dTM-AS03 adjuvanted vaccine (B.1.351) Investigator's Brochure version 10.0 dated 03/08/2021

For studies in healthy volunteers, the sponsor will report without delay all serious adverse events and all expected and unexpected serious adverse reactions to the ANSM (French Health Products Safety Agency).
For adverse events deemed "medically significant" and AESI that do not strictly meet the definition of a serious adverse event, the sponsor will declare them within 48h to the ANSM

Any suspected unexpected serious adverse reaction must also be declared electronically using the Eudravigilance European adverse drug reactions database managed by the European Medicines Agency (EMA).

The sponsor must notify all the investigators involved about any information that could adversely affect the safety of the research participants.

27.3.3.2 Analysis and declaration of other safety data

This means any new information that prompts a reassessment of the risk/benefit ratio of the trial or of the product under investigation, or which could be sufficient to consider changes to the use of the product, the trial procedures or trial documentation, or the suspension, cancellation or amendment of the research trial or of other similar trials. For trials involving the first administration or use of a health product in healthy volunteers: any serious adverse reaction.

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The sponsor will inform the competent authority and the Research Ethics Committee without delay upon knowledge of any emerging safety issue and, if applicable, describe what measures have been taken.

The sponsor will inform the regional healthcare authority (*Agence Régionale de Santé*) without delay of any emerging safety issues relating to healthy volunteers taking part in a clinical study and of any measures that have been taken.

Following the initial declaration of any emerging safety issue, the sponsor will address to competent authorities any additional relevant information about the emerging safety issue in the form of a follow-up report, which must be sent no later than 8 days after learning of the information.

27.3.3.3 Annual safety report

Once a year for the duration of the clinical study, the sponsor must produce an annual safety report (Development Safety Update Report - DSUR) which includes, in particular:

5. a safety analysis for the research participants,
6. a description of the patients included in the study (demographic profile etc.)
7. a list of all the suspected serious adverse reactions that occurred during the period covered by the report,
8. summary tables of all the serious adverse events that have occurred since the start of the study,

The report must be delivered no later than 60 days after the anniversary of the date on which the ANSM authorized the trial.

27.3.4 Data Safety Monitoring Board (DSMB)

As the study is classified as risk D, a DSMB will be constituted for this trial. The Data Safety Monitoring board will be composed of three independent experts in infectious diseases, vaccinology, and a methodologist. They will regularly review the safety data gathered all along the study and advise the sponsor on the actions to be taken for the continuation of the study. The scientific committee will meet periodically, in accordance with the DSMB charter.

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28 DATA MANAGEMENT

28.1 *Data collection procedures*

Information required by the protocol should be reported in the eCRF and a justification provided for missing data. Data should be reported in the eCRF when available, for clinical, para-clinical and immunological data.
Correction of non-compliant data on the eCRF will be requested through queries.
The anonymization of the participants will be ensured by an anonymization number reported on each document used in the research, or by deleting nominative/directly identifying data on the copies of the source documents.

28.2 *Identification of data recorded directly in the CRFs which will be considered as source data*

No data collected directly on the eCRF is considered source data.

28.3 *Right to access data and source documents*

28.3.1 Data access

In accordance with GCPs:

- the sponsor is responsible for ensuring all parties involved in the study agree to guarantee direct access to all locations where the study will be carried out, the source data, the source documents and the reports, for the purposes of the sponsor's quality control and audit procedures or inspections by the competent authority
- the investigators will ensure the persons in charge of monitoring, quality control and auditing or inspecting the interventional study involving human participants have access to the documents and personal data strictly necessary for these tasks, in accordance with the statutory and regulatory provisions in force (Articles L.1121-3 and R.5121-13 of the French Public Health Code)

Source Data Verification (SDV) will be done remotely and also on site, using the Investigator Cloud Case® (ICC) software, developed by MultiHealth Group. For data monitoring by the sponsor (AP-HP), the investigator or investigation team scans and uploads the source documents (consent form, medical records…) from the patient file, directly into the ICC® platform. The monitoring CRA is then notified by e-mail and is able to perform the monitoring by comparing the source documents with the data entered into the eCRF. The uploaded documents are permanently deleted when the monitoring is completed, or automatically permanently deleted after a predefined period (5 days by default), even if the monitoring has not been performed.

ICC® complies with FDA, EMA and GDPR requirements. As required by GDPR, the software is hosted in France on a server certified as “Health Data Hosting” in a fully secure environment that complies with all the current regulations (CEGEDIM).

28.3.2 Source documents

Source documents are defined as any original document or item that can prove the existence or accuracy of a data or a fact recorded during the study. These documents will be kept in

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accordance with the regulations by the investigator or by the hospital in the case of a hospital medical file.

The following documents are considered as source documents:

- Medical records
- Self-monitoring diary
- Pharmacy dispensing records and vaccination sheet
- Biological data

28.3.3 Data confidentiality

The persons responsible for the quality control of clinical studies (Article L.1121-3 of the *Code de la Santé Publique* [French Public Health Code]) will take all necessary precautions to ensure the confidentiality of information relating to the investigational medicinal products, the study, the study participants and in particular their identity and the results obtained.
These persons, as well as the investigators themselves, are bound by professional secrecy (in accordance with the conditions set out in Articles 226-13 and 226-14 of the *Code Pénal* [French Criminal Code]).
During and after the research involving human participants, all data collected concerning the participants and sent to the sponsor by the investigators (or any other specialised collaborators) will be rendered non-identifying.
Under no circumstances shall the names and addresses of the participants involved be shown. Only the participant's initials will be recorded, accompanied by an encoded number specific to the study indicating the order of enrolment.
The sponsor will ensure that each participant has given written permission for any personal information about him or her which is strictly necessary for the quality control of the study to be accessed.

28.4 Data processing and storage of research documents and data

28.4.1 Identification of the data processing manager and location(s)

Data processing and statistical analysis will be performed by URC Est (AP-HP), Paris.

28.4.2 Data entry

Non-identifying data will be entered electronically via a web browser.

28.5 Data ownership

AP-HP is the owner of the data. The data cannot be used or disclosed to a third party without its prior permission.

29 STATISTICAL ASPECTS

29.1 Description of statistical methods to be used including the timetable for the planned interim analyses

A detailed analysis plan will be a priori defined.

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Analysis will be performed by a statistician from URC-Est using SAS® software version 9.4 (or updated version) (SAS Institute Inc.). Partial data base locks will be performed for data from randomization to D15 to assess primary endpoint and secondary endpoints at D15, at D28 to assess D28 secondary endpoint, M3 to assess M3 secondary endpoints. Final data base lock will be at the end of the trial to assess secondary M12 secondary endpoints.

A flow chart will be drawn according to consort statement. The proportion of eligible participants who refused to participate in the research or who did not come to the scheduled consultation will be described.

Baseline characteristics of patients will be described overall and per group.
Continuous variables will be summarized using descriptive statistics, i.e. number of subjects, mean, standard deviation (SD), median, inter quartile range, minimum and maximum depending on the variable distribution. Qualitative variables will be summarized by frequency and percentage.

Primary endpoint assessment

The main analysis will be performed on the per protocol population.
For each viral strains (D614 and B.1.351), proportion of subjects with an increase rate in neutralizing antibody titers against SARS-CoV-2 of at least 10 fold between D0 and D15 will be calculated with it 2-sided 95% confidence interval (95%CI) using the exact Clopper-Pearson method.

Secondary endpoints assessment

- Rate of increase in neutralizing antibody titers against SARS-CoV-2 D614 and B.1.351 viral strains measured by a microneutralisation technique between 0 and 28 days after the booster dose in each group of randomisation and in each age group (18-64 years and 65 years or more) will be described.

- Anti-Spike (D614) IgG levels, expressed in BAU/ml, according to WHO recommendations up to D28 after the booster dose mRNA or adjuvanted subunit vaccine, and their persistence at 3 and 12 months will be described as geometric means with 95% confidence intervals (by logarithmic transformation of the data, calculation of the arithmetic mean and its confidence interval and anti-log transformation of these mean and limits of the confidence interval).

- Anti-RBD (D614 and B.1.351) IgG levels up to 28 days after the booster dose mRNA or adjuvanted subunit vaccine and their persistence at 3 and 12 months will be described as geometric means with 95% confidence intervals (by logarithmic transformation of the data, calculation of the arithmetic mean and its confidence interval and anti-log transformation of these mean and limits of the confidence interval). Differences in Anti-Spike (D614) and anti-RBD (D614 and B.1.351) IgG levels between D3 and D0 and between 12 months and D0 will be estimated with 95% confidence intervals.

- For each vaccine, the antibody titers will be described at each time of measurement as geometric means with 95% confidence intervals (by logarithmic transformation of the data, calculation of the arithmetic mean and its confidence interval and anti-log

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transformation of these mean and limits of the confidence interval). Evolution between D0, D15, M1, M3 and M12 will be described using graphs.

- Associated factors and determinants of boost response (neutralizing antibody titers against variants of interest) in individuals previously vaccinated with 2 doses of mRNA vaccine will be studied.

- ELISpot IFN CD4 and CD8 response will be described. (*ancillary-analysis*)

Safety assessment

Safety assessment will be analysed among safety population.

- Proportions of 1) local adverse events and 2) systemic adverse events of any grade (assessed from the list of solicited adverse events) occurring up to 7 days after each injection will be described globally and by randomization group. Intensity will also be described.
- Quantity and intensity of unsolicited local and systemic events up to 28 days will also be described by randomization group.

29.2 Calculation hypotheses for the number of participants required and the result

The sample size calculation is performed to estimate the proportion of subjects with a sufficient rate of increase in neutralizing antibody titers and its 95% confidence interval with a given precision.
Due to the lack of available data on the Pfizer-BioNTech vaccine, the sample size calculation is based on published data on the Moderna vaccine (Wu, 2021(ref)) in which an increase rate of neutralizing antibody titer against historical SARS-CoV-2 (D 614 G) after Moderna boost at D15 of 23 and 32 for the B.1.351 variant is described. Using a conservative approach, we consider neutralizing activity to be sufficient if the increase rate is at least 10 at D15.

We assume a proportion of subjects with an increase rate of at least 10 between D0 and D15 of 80%.

One hundred subjects per group will allow an estimation of the proportion of 80% with a half width of 95% confidence interval of 7.8%.

Thus, a total of 300 volunteers will be randomized: 100 per group.

29.3 Anticipated level of statistical significance

All tests will be two-sided, and a p-value of < 0.05 will be considered significant.

29.4 Statistical criteria for termination of the study.

Not applicable.

29.5 Method for taking into account missing, unused or invalid data

Missing data for the primary endpoint will be replaced by the geometric mean value of antibody levels observed in the group of the concerned subject.
Censored data reported as below the lower limit of detection/quantification will be imputed with a value equal to half of the threshold before transformation.
Other missing data will not be replaced.

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29.6 Management of modifications made to the analysis plan for the initial strategy.

All modification made to the analysis plan for the initial strategy will be documented in the analysis report.

29.7 Choice of individuals to be included in the analyses

Intent to treat population (ITT): all patients as randomized, regardless of the strategy received by the patient.

Per protocol (PP) population: all patients as randomized, treated without major protocol violations/deviations, except participants presenting a positive NP serology at D0 or D15 and lost to follow-up participants.
Pre-defined major protocol violations/deviations are:

- Non-respect of eligibility criteria
- Non-respect of the randomized treatment allocation and/or duration (wrong vaccine received, second dose not received)
- Missing data for the primary efficacy endpoint

Major protocol deviation will be classified during a blinded data review before final data base lock.

Safety population: All patients as randomized who have received the boost dose of vaccine.

30 QUALITY CONTROL AND ASSURANCE

Every research project involving human participants managed by AP-HP is ranked according to the projected risk incurred by study participants using the classification system specific to AP-HP sponsored interventional research involving human participants.

30.1 *General organization*

The sponsor must ensure the safety and respect of individuals who have agreed to participate in the study. The sponsor must implement a quality assurance system to best monitor the implementation of the study in the investigation centers.

For this purpose, the sponsor shall assign Clinical Research Associates (CRA) whose primary role is to carry out regular follow-up visits on site whenever possible, or remotely using the ICC® software, after having carried out the initial visits.
The purpose of remote-monitoring the study is the same as on-site visits; as defined in Good Clinical Practices (GCP section 5.18.1), is to verify that:

- the rights, safety and protection of the research participants are met
- the data reported are exact, complete and consistent with the source documents
- the study is carried out in accordance with the protocol in force, the GCPs and the statutory and regulatory provisions in force

30.1.1 Strategy for center opening

The strategy for opening the centers established for this study is determined using the appropriate monitoring plan.

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A feasibility questionnaire was sent to the pre-selected study sites in advance, in order to assess the feasibility of the study in terms of personnel, logistics and enrollment potential.

30.1.2 Scope of center monitoring

In the case of this D risk study the appropriate monitoring level has been determined based on the complexity, the impact and the budget for the study. Therefore, in agreement with the coordinating investigator, the sponsor has determined the logistical score and impact, resulting in a study monitoring level to be implemented: level high

30.2 Quality control

The investigator and the members of the investigator's team agree to make themselves available during regular Quality Control remote visits carried out by the Clinical Research Associate. During these visits, the following elements will be reviewed depending on the monitoring level:

- written consent
- compliance with the study protocol and with the procedures defined therein
- quality of the data collected in the case report form: accuracy, missing data, consistency of the data with the "source" documents (medical files, appointment books, original copies of laboratory results, etc.)
- management of the treatments used

A Clinical Research Associate (CRA) appointed by the sponsor will be responsible for the good completion of the study, for collecting, documenting, recording and reporting all handwritten data, in accordance with the Standard Operating Procedures applied within the DRCI (Clinical Research and Innovation Department) and in accordance with Good Clinical Practices as well as the statutory and regulatory requirements. In the context of the covid-19 pandemic, monitoring of center data will be done on site and/or remotely using the Investigator Cloud Case® (ICC) software, developed by MultiHealth Group. The investigator with the help of its team will scan and upload the source documents (consent form, medical records…) from the patient file, directly into the ICC® platform. The monitoring CRA is then notified by e-mail and is able to perform the monitoring by comparing the source documents with the data entered into the eCRF. The uploaded documents are permanently deleted when the monitoring is completed, or automatically permanently deleted after a predefined period (5 days by default), even if the monitoring has not been performed. ICC® complies with FDA, EMA and GDPR requirements. As required by GDPR, the software is hosted in France on a server certified as "Health Data Hosting" in a fully secure environment that complies with all the current regulations (CEGEDIM).

30.3 Case report forms

Electronic CRF (eCRF):

All information required by the protocol must be entered in the case report forms. The data must be collected as and when they are obtained, and clearly recorded in these case report forms. Any missing data must be coded.

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Every site will have access to the electronic case report forms via a web-based data collection system. Investigators will be given a document offering guidance on using this tool.
When the investigators complete the case report form via the Internet, the CRA can view the data quickly and remotely. The investigator is responsible for the accuracy, quality and relevance of all the data entered. In addition, the data are immediately verified as they are entered, thanks to consistency checks. To this end, the investigator must validate any changes to the values in the case report form. An audit trail will be kept of all changes. A justification can be added when applicable, as a comment.
A print-out, authenticated (signed and dated) by the investigator, will be requested at the end of the study. The investigator must archive a copy of the authenticated document that was issued to the sponsor.

30.4 Management of non-compliances

Any events that occur as a result of non-compliance – by the investigator or any other individual involved in running the study – with the protocol, standard operating procedures, good clinical practices or statutory and regulatory requirements must be recorded in a declaration of non-compliance and sent to the sponsor.

These non-compliances will be managed in accordance with the sponsor's procedures.

30.5 Audits/inspections

The investigators agree to consent to the quality assurance audits carried out by the sponsor as well as the inspections carried out by the competent authorities. All data, documents and reports may be subject to regulatory audits and inspections. These audits and inspections cannot be refused on the grounds of medical secrecy.

An audit can be carried out at any time by individuals appointed by the sponsor and independent of those responsible for the research. The aim of the audits is to ensure the quality of the study, the validity of the results and compliance with the legislation and regulations in force.

The persons who manage and monitor the study agree to comply with the sponsor's requirements and with the competent authority regarding study audits or inspections.

The audit may encompass all stages of the study, from the development of the protocol to the publication of the results, including the storage of the data used or produced as part of the study.

30.6 Principal Investigator's commitment to assume responsibility

Before starting the study, each investigator will give the sponsor's representative a copy of his/her updated personal *curriculum vitæ*, signed and dated less than one year, with his/her RPPS number (*Répertoire Partagé des Professionnels de Santé*, Collective Database of Health Professionals). The CV must include any previous involvement in clinical research and related training.

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Each investigator will commit to comply with legislation and to conduct the study in line with GCP, in accordance with the Declaration of Helsinki.

The Principal Investigator at each participating site will sign a commitment of responsibility (standard DRCI document) which will be sent to the sponsor's representative.
The investigators and their staff will sign a delegation of duties form specifying each person's role and will provide their CVs.

30.7 Pharmacist's commitment of responsibility

Before the start of the study, each pharmacist will provide the sponsor or the sponsor's representative a copy of their updated Curriculum Vitae, signed and dated less than one year. The CV must include their previous involvement in clinical research / clinical trials, as well as the related training.

Each pharmacies will commit to comply with legislation and to conduct the study in line with GCPs, in accordance with the Declaration of Helsinki.

The pharmacists will sign a delegation of duties form, specifying each person's role during the study.

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31 ETHICAL AND LEGAL CONSIDERATIONS

31.1 Methods for informing research participants and obtaining their consent

In accordance with Article L1122-1-1 of the Code de la Santé Publique (French Public Health Code), no interventional research involving human participants can be carried out on a person without his/her freely given and informed consent, obtained in writing after the person has been given the information specified in Article L.1122-1 of the aforementioned Code.

A reflection period is given to the individual between the time when they are informed and when they sign the consent form.

The person's freely-given, written, informed consent will be obtained by the principal investigator or a physician representing the investigator before the person is enrolled in the study at the inclusion visit.

A copy of the information note and consent form, signed and dated by the research participant and by the principal investigator or the physician representing the investigator will be given to the individual prior to their participation in the study. The principal investigator or the physician representing him/her will keep a copy.

At the end of the study, one copy will be placed in a tamper-proof sealed envelope containing all the consent forms. This envelope will be archived by the sponsor.

In addition, the investigator will specify in the person's medical file the person's participation in the research, the procedures for obtaining his/her consent, as well as the methods used for providing information for the purpose of collecting it. The investigator will retain one copy of the signed and dated consent form.

Special circumstances: Mention of the possibility for the investigator of withholding certain information relating to the diagnosis, as applicable, in accordance with paragraph 4 of Article L1122-1.

31.2 Prohibition from participating in another clinical study or exclusion period set after the study

No exclusion period of participation after the participant has finished this study is defined in the context of this research.
The participant may not enroll in another interventional study protocol involving human participants for the duration of his or her participation without consulting with the physician monitoring him or her in the context of the study.
The participants can however participate in other non-interventional studies.

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31.3 Compensation for participants

A compensation is planned for the participants in this research: 100€ for vaccination visit, and 50€ for each follow-up visit, for a total of 300€ per participant. The compensations will be paid according to the following schedule:

- 200€ (100€ for V1 + 50€ for V2 + 50€ for V3) will be paid after V3 completion
- 100€ (50€ for V4 + 50€ for V5) will be paid after V5 completion

A compensation corresponding to the reimbursement of the transport costs is also planned for this study, at a fixed amount of 20€ per visit.

Subjects taking part in the ancillary study will receive additional compensation of 50€ for the additional D3 follow-up visit.

31.4 Registration on the National Register of study participants to studies involving human participants concerning the products mentioned in Article L. 5311-1 of the *Code de la Santé Publique*

As the subjects enrolled in this study are healthy, volunteer to participate and receive a compensation for participating, in accordance with Art. L.1121-16 of the Code de la Santé Publique (French Public Health Code), they will be registered on the National Register of Study Participants ("VRB") after signing the Informed Consent Form, and before any study procedure.

31.5 Authorization for the research location

Units participating in the study must have specific authorization for the location, because the study requires the enrollment of healthy volunteers.

31.6 Legal obligations

31.6.1 Role of the sponsor

Assistance Publique - Hôpitaux de Paris (AP-HP) is the sponsor of this study and, by delegation, the DRCI (Clinical Research and Innovation Department) carries out the study's missions in accordance with Article L.1121-1 of the *Code de la Santé Publique (French Public Health Code)*. Assistance Publique - Hôpitaux de Paris reserves the right to halt the study at any time for medical or administrative reasons. In this case, notification will be sent to the investigator.

31.6.2 Request for approval from the CPP (Research Ethics Committee)

Prior to starting the study, AP-HP, as sponsor, must obtain for this interventional study involving human participants concerning a medicinal product for human use, approval from the appropriate CPP (Research Ethics Committee), within the scope of its authority and in accordance with in force legislation and regulatory requirements.

31.6.3 Request for authorization from ANSM

Prior to starting the study, AP-HP, as sponsor, must obtains authorization from the ANSM (French Health Products Safety Agency) for the interventional study involving human

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participants concerning a medicinal products for human use, within the scope of the ANSM's authority and in accordance with in force legislation and regulatory requirements.

31.6.4 Procedures relating to data protection regulations

The computer file used for this research is implemented in accordance with French (amended "Informatique et Libertés" law governing data protection) and European (General Data Protection Regulation – GDPR) regulations.

This research does not fall under the scope of the CNIL "Reference Methodology" (MR-001) because the monitoring of consents and patient files will be performed remotely via the ICC® software from the MultiHealth Group for study sites outside AP-HP.
However, with regards to the current health context and exceptional circumstances, the CNIL considers, as a derogation and on a strictly temporary basis, that it is not necessary to file an application for authorization to the CNIL, if the implementation of remote monitoring is the only point of non-compliance with the MRs, on the strict condition that all the requirements set out below are met, depending of the selected solution.

31.6.5 Amendments to the research

Any substantial modification to the protocol by the coordinating investigator must be sent to the sponsor for approval. After approval is given, the sponsor must obtain approval from the CPP (Research Ethics Committee) and authorization from the ANSM within the scope of their respective authorities, before the amendment can be implemented.
The information note and the consent form can be revised if necessary, in particular in case of a substantial amendment to the study or if adverse reactions occur.

31.6.6 Final study report

The final report for the research involving human participants referred to in Article R1123-67 of the *Code de la Santé Publique* (French Public Health Code) is written and signed by the sponsor and the investigator. A report summary drafted according to the reference plan of the competent authority must be sent to the competent authority within a period of one year following the end of the study, i.e., the end of the participation of the last participant in the study.

31.6.7 Archiving

Specific documents for an interventional study involving human participants concerning a medicinal product for human use will be archived by the investigator and the sponsor for fifteen years after the end of the research.

This indexed archiving includes, in particular:

- A sealed envelope for the investigator containing a copy of all the information notes and consent forms signed by all individuals at the centre who participated in the study;
- A sealed envelope for the sponsor, containing a copy of all the information notes and consent forms signed by all individuals at the centre who participated in the study;
- "Study" binders for the Investigator and the sponsor, including (non-exhaustive list) :
    - the successive versions of the protocol (identified by the version number and its date), and any appendices
    - the ANSM authorizations and CPP (Research Ethics Committee) decisions

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- any correspondence
- the enrolment list or register
- the appendices specific to the research
- final study report

- The data collection documents

32 FUNDING AND INSURANCE

32.1 *Funding sources*

The present study will be funded by Soutien exceptionnel à la recherche et à l'innovation 2021 from Health Ministry.

32.2 *Insurance*

For the duration of the study, the Sponsor will take out an insurance policy covering the sponsor's own public liability, as well as the public liability for all the physicians involved in the study. The sponsor will also provide full compensation for any damages caused by the study to the participant enrolled and their beneficiaries, unless the sponsor can prove that the harm is not the fault of the sponsor or any collaborator. Compensation cannot be refused on the grounds of a third-party act or the voluntary withdrawal of the person who initially consented to participate in the study.

Assistance Publique - Hôpitaux de Paris (AP-HP) has taken out insurance with HDI-GLOBAL SE through the insurance broker BIOMEDIC-INSURE for the full study period, which covers its own public liability and that of any collaborator (physician or research staff), in accordance with Article L.1121-10 of the *Code de la Santé Publique* (French Public Health Code).

33 PUBLICATION RULES

The Scientific Committee must be informed within a reasonable delay prior to each submission of any communication (abstract; written publication, other) regarding this trial.
A copy of the publication must be sent to the sponsor.
The first signatories of publications will be individuals who actually took part in the preparation and conduct of the protocol, the analysis and interpretation of the results, and the writing up and/or revision of the manuscript. Authorship definitions will follow the Vancouver rules.

For the other contributors, the order of authors will be allocated according to the number of participants included in the study site compared to the expected participants and their usable data. The next-to-last one will be reserved for the study coordinators.

The URC Est must be acknowledged for implementation, monitoring and data management in the "Acknowledgment" section.

The AGEPS will be also acknowledged in the "Acknowledgment" section.

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Sanofi-Pasteur and GSK will be acknowledged for providing the experimental vaccines, in the "Acknowledgment" section.

33.1 Mention of AP-HP affiliation for projects sponsored by AP-HP

Each author affiliation must appear and must be identified by an address and separated by a semicolon (;).
In case an author has multiple affiliations, each affiliation should appear. The order in which the institution (AP-HP; University; INSERM) is quoted has no importance.
For AP-HP members, the terms “Assistance Publique-Hôpitaux de Paris” or “AP-HP” must appear first in the authors’ address as follows AP-HP, hospital, department, city, postcode, France.

33.2 Mention of the sponsor AP-HP (DRCI) in the acknowledgements of the text

“The sponsor was Assistance Publique – Hôpitaux de Paris (Délégation à la Recherche Clinique et à l’Innovation)”

33.3 Mention of the financial backer in the acknowledgements of the text

“The study was funded by XXXXX”

This study has been registered on the website http://clinicaltrials.gov/ under number NCT05124171.

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34 REFERENCES

1. Avis n° 2021.0061/AC/SEESP du 23 août 2021 du collège de la HAS relatif à la définition des populations à cibler par la campagne de rappel vaccinal chez les personnes ayant eu une primovaccination complète contre la Covid-19 [Internet]. Haute Autorité de Santé. [cité 20 oct 2021]. Disponible sur: https://www.has-sante.fr/jcms/p_3283044/fr/avis-n-2021-0061/ac/seesp-du-23-aout-2021-du-college-de-la-has-relatif-a-la-definition-des-populations-a-cibler-par-la-campagne-de-rappel-vaccinal-chez-les-personnes-ayant-eu-une-primovaccination-complete-contre-la-covid-19

2. Haute Autorité de Santé. Stratégie de vaccination contre la Covid-19 - Place d'un rappel par le vaccin à ARNm COMIRNATY® [Internet]. Haute Autorité de Santé. 2021 [cité 20 oct 2021]. Disponible sur: https://www.has-sante.fr/jcms/p_3290614/fr/strategie-de-vaccination-contre-la-covid-19-place-d-un-rappel-par-le-vaccin-a-arnm-comirnaty

3. Pfizer and BIONTech Provide Update on Booster Program in Light of the Delta-Variant [Internet]. 2021. Disponible sur: https://www.sec.gov/Archives/edgar/data/1776985/000156459021036101/bntx-ex991_7.htm

4. Liu J, Liu Y, Xia H, Zou J, Weaver SC, Swanson KA, et al. BNT162b2-elicited neutralization of B.1.617 and other SARS-CoV-2 variants. Nature [Internet]. 10 juin 2021 [cité 5 août 2021]; Disponible sur: http://www.nature.com/articles/s41586-021-03693-y

5. Schmidt T, Klemis V, Schub D, Mihm J, Hielscher F, Marx S, et al. Immunogenicity and reactogenicity of heterologous ChAdOx1 nCoV-19/mRNA vaccination. Nat Med [Internet]. 26 juill 2021 [cité 11 août 2021]; Disponible sur: http://www.nature.com/articles/s41591-021-01464-w

6. Barros-Martins J, Hammerschmidt SI, Cossmann A, Odak I, Stankov MV, Morillas Ramos G, et al. Immune responses against SARS-CoV-2 variants after heterologous and homologous ChAdOx1 nCoV-19/BNT162b2 vaccination. Nat Med. 14 juill 2021;1-5.

7. Shaw RH, Stuart A, Greenland M, Liu X, Nguyen Van-Tam JS, Snape MD. Heterologous prime-boost COVID-19 vaccination: initial reactogenicity data. Lancet Lond Engl. 2021;397(10289):2043-6.

8. Sanofi. Sanofi: Press Releases, Thursday, May 27, 2021 [Internet]. https://www.sanofi.com/en/media-room/press-releases/2021/2021-05-27-07-30-00-2236989. Disponible sur: https://www.sanofi.com/media-room/press-releases/2021/2021-05-27 07-30-00 2236989

9. VaccinTracker Covid19 : nombre de français vaccinés [Internet]. CovidTracker. [cité 6 août 2021]. Disponible sur: https://covidtracker.fr/vaccintracker/

10. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med. 31 déc 2020;383(27):2603-15.

11. Haute Autorité de Santé. Stratégie de vaccination contre la Covid-19 - Place du vaccin à ARNm COMIRNATY (BNT162b2) dans la stratégie. 2020;102.

12. Dagan N, Barda N, Kepten E, Miron O, Perchik S, Katz MA, et al. BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Mass Vaccination Setting. N Engl J Med. 15 avr 2021;384(15):1412-23.

13. Lopez Bernal J, Andrews N, Gower C, Gallagher E, Simmons R, Thelwall S, et al. Effectiveness of Covid-19 Vaccines against the B.1.617.2 (Delta) Variant. N Engl J Med. 21 juill 2021;NEJMoa2108891.

14. Pfizer. Pfizer Second Qarter 2021 Teleconference. 2021.

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Version 4.0 dated 31/05/2019

15. Sanofi Press Release. Sanofi and GSK COVID-19 vaccine candidate demonstrates strong immune responses across all adult age groups in Phase 2 trial. Sanofi Press Release [Internet]. https://www.sanofi.com/en/media-room/press-releases/2021/2021-05-17-07-30-00-2230312. 2021 [cité 5 août 2021]. Disponible sur: https://www.sanofi.com/media-room/press-releases/2021/2021-05-17 07-30-00 2230312

16. Sanofi Pasteur, a Sanofi Company. Immunogenicity and Safety of SARS-CoV-2 Recombinant Protein Vaccines With AS03 Adjuvant in Adults 18 Years of Age and Older as a Primary Series and Immunogenicity and Safety of a Booster Dose of SARS-CoV-2 Adjuvanted Recombinant Protein Vaccines (Two Monovalent and One Bivalent) [Internet]. clinicaltrials.gov; 2021 août [cité 9 août 2021]. Report No.: NCT04762680. Disponible sur: https://clinicaltrials.gov/ct2/show/NCT04762680

17. GSK Press Release. Sanofi and GSK initiate global Phase 3 clinical efficacy study of COVID-19 vaccine candidate [Internet]. 2021 [cité 5 août 2021]. Disponible sur: https://www.gsk.com/en-gb/media/press-releases/sanofi-and-gsk-initiate-global-phase-3-clinical-efficacy-study-of-covid-19-vaccine-candidate/

18. Haute Autorité de Santé. Stratégie de vaccination contre la Covid-19 - Place du vaccin à ARNm COMIRNATY® chez les 12–15 ans. 2 juin 2021;123.

19. Comirnaty - Summary of Product Characteristics FR [Internet]. Disponible sur: https://www.ema.europa.eu/en/documents/product-information/comirnaty-epar-product-information_fr.pdf

20. ANSM. Point de situation sur la surveillance des vaccins contre la COVID-19 - Période du 16/07/2021 au 22/07/2021 [Internet]. 2021. Disponible sur: https://ansm.sante.fr/actualites/point-de-situation-sur-la-surveillance-des-vaccins-contre-la-covid-19-periode-du-16-07-2021-au-22-07-2021

21. Sarkanen T, Alakuijala A, Julkunen I, Partinen M. Narcolepsy Associated with Pandemrix Vaccine. Curr Neurol Neurosci Rep. juill 2018;18(7):43.

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LIST OF ADDENDA

Each addendum and the log of addenda versions are attached, independently of the protocol. Each addendum can be modified (change of addendum version) without modifying the protocol version.

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34.1 List of investigators

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CIC-1404 Rouen CHU de Rouen, Hôpital Ch. Nicolle 1 Rue de Germont 76031 ROUEN	Pr	Marie-Pierre TAVOLACCI	+33 (0)2 32 88 88 62 mp.tavolacci@chu-rouen.fr
CIC-1414 Rennes CHU Rennes, Hôpital Pontchaillou Rue Henri Le Guilloux 35033 RENNES	Pr	Fabrice LAINE	+33 (0)2 99 28 91 99 fabrice.laine@chu-rennes.fr
Service de Maladies Infectieuses et Tropicales Lyon Hôpital de la Croix Rousse 103 Grande Rue de la Croix Rousse 69004 LYON	Pr	Christian CHIDIAC	+33 (0)4 72 07 11 07 christian.chidiac@chu-lyon.fr
CIC-1434 Strasbourg Hôpitaux Universitaires de Strasbourg / Nouvel Hôpital Civil 1, place de l'hôpital 67091 STRASBOURG Cedex	Dr	Catherine MUTTER	+33 (0)3 69 55 13 63 catherine.mutter@chru-strasbourg.fr
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34.2 Serious Adverse Events notification form

Direction de la Recherche Clinique et de l'Innovation (DRCI)	ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS **Formulaire de notification d'un Evènement Indésirable Grave (EIG) survenant au cours d'une recherche impliquant la personne humaine portant sur un Médicament ou produit assimilé**	**PARTIE RESERVEE AU PROMOTEUR** **REFERENCE VIGILANCE :** Référence GED : REC-DTYP-0192

Dès la prise de connaissance de l'EIG par l'investigateur, ce formulaire doit être dûment complété (3 pages), signé et retourné sans délai au secteur Vigilance de la DRCI par mail (eig-vigilance.drc@aphp.fr).

NB : Il est également possible d'envoyer ce formulaire par fax to +33 (0)1 44 84 17 99 uniquement en cas de tentative infructueuse d'envoi par mail (pour éviter les doublons).

Notification initiale ☐ **Suivi d'EIG** ☐ **N° du suivi** |__|__|

1. Identification de la recherche

Acronyme : **COVIBOOST**

Code de la Recherche : APHP211184

Risque : D

Date de notification : |__|__| |__|__| |2|0|__|__| (jj mm aaaa)

Date de prise de connaissance de l'EIG par l'investigateur : |__|__| |__|__| |2|0|__|__| (jj mm aaaa)

Titre complet de la recherche :
Immunogenicity and reactogenicity following a booster dose of a COVID-19 mRNA vaccine (Pfizer-BioNTech) and two adjuvanted sub-unit vaccines (SP/GSK) administered in adults who received 2 doses of Pfizer-BioNTech mRNA vaccine as a primary vaccination: a randomized, single-blinded, multicenter clinical trial.

2. Identification du centre investigateur

Nom de l'établissement : .....
Ville et code postal : .....
Service : .....

Investigateur (nom/prénom) : .....
Tél : ..... Fax : .....
Mail : .....

3. Identification et antécédents de la personne se prêtant à la recherche

Référence de la personne : |__|__|__| - |__|__|__|__|__|__| - |__| - |__|
(n°centre - n° ordre de sélection - initiale nom - initiale prénom)

Sexe : ☐ M ☐ F

Poids : |__|__|__| kg
Taille : |__|__|__| cm

Date de naissance : |__|__| |__|__|__|__| (mm aaaa)
Age : |__|__|__|ans

Date d'inclusion et de randomisation : |__|__| |__|__| |2|0|__|__| (jj mm aaaa)

Participation à la sous-étude (analyses complémentaires) :
☐ Oui ☐ Non

Antécédents médicaux-chirurgicaux/familiaux pertinents pour l'évaluation du cas (joindre un CRH anonymisé le cas échéant) :
.....
.....
.....
.....
.....
.....
.....

☐ Groupe 1 (mRNA Pfizer) ☐ Groupe 2 (SP-GSK D614)
☐ Groupe 3 (SP-GSK B.1.351) ☐ NA (en aveugle)

N° randomisation : R |__|__|__|__|

4. Médicament(s) expérimental(aux) (ME) [préciser le(s)quel(s)] avant la survenue de l'EIG

(barrer l'encadré si traitement non débuté)

Nom commercial (de préférence) ou Dénomination Commune Internationale	Voie(1)	Posologie (préciser l'unité ex : mL)	Date de début *(jj/mm/aaaa)*	En cours(2)	Date de fin *(jj/mm/aaaa)*
Comirnaty® mRNA vaccine (Pfizer-BioNTech) ☐ NA	IM	.....	|__|__| |__|__| |2|0|__|__|	☐	|__|__| |__|__| |2|0|__|__|
Sanofi/GSK sub-unit adjuvanted vaccine D.614 ☐ NA	IM	.....	|__|__| |__|__| |2|0|__|__|	☐	|__|__| |__|__| |2|0|__|__|
Sanofi/GSK sub-unit adjuvanted vaccine B.1.351 ☐ NA	IM	.....	|__|__| |__|__| |2|0|__|__|	☐	|__|__| |__|__| |2|0|__|__|

5. Procédures et actes ajoutés par la recherche ***(barrer l'encadré si procédures et actes non réalisés)***	Date de réalisation *(jj/mm/aaaa)*	Volume de sang (mL)	Volume de sang cumulé (mL)	Chronologie	
				Avant la survenue de l'EIG	Après la survenue de l'EIG
Prélèvement nasal pour PCR	|__|__| |__|__| |2|0|__|__|	NA	NA	☐	☐
Prise de sang (préciser la plus récente)	|__|__| |__|__| |2|0|__|__|			☐	☐

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PARTIE RESERVEE AU PROMOTEUR
REFERENCE VIGILANCE :

Référence GED : REC-DTYP-0192

Acronyme : **COVIBOOST**

Référence de la personne se prêtant à la recherche : |__|__|__| - |__|__|__|__| - |__| - |__|
n°centre - n° ordre de sélection - initiale nom - initiale prénom

6. Médicament(s) concomitant(s) au moment de l'EIG, à l'exclusion de ceux utilisés pour traiter l'événement indésirable *(compléter le tableau ci-après et si nécessaire l'annexe relative aux médicaments concomitants ou barrer l'encadré si non applicable)*

⇨ **Annexe jointe au présent formulaire :** ☐ Oui ☐ Non

Nom commercial (de préférence) ou Dénomination Commune Internationale	Voie(1)	Posologie (préciser l'unité ex : mg/j)	Dates d'administration *(du jj/mm/aa au jj/mm/aa)*	En cours (2)	Indication	***Action prise*** *0 : poursuite sans modification de la posologie 1 : arrêt 2 : diminution de la posologie 3 : augmentation de la posologie 4 : ne sais pas*	***Causalité de l'EIG*** *0 : non lié au médicament 1 : lié au médicament 2 : ne sais pas*
			du |__|__| |__|__| |__|__| au |__|__| |__|__| |__|__|	☐			
			du |__|__| |__|__| |__|__| au |__|__| |__|__| |__|__|	☐			

(1) Voie d'administration : VO=voie orale ; IM=Intramusculaire ; IV=intraveineuse ; SC=sous-cutanée ou autre (à préciser) (2) En cours au moment de la survenue de l'EIG

7. Evènement indésirable grave [EIG]

Diagnostic : ☐ Définitif ☐ Provisoire

.....

.....

.....

Date de survenue des premiers symptômes : |__|__| |__|__| |_2_|_0_|__|__|

Préciser lesquels :

.....

Organe(s) concerné(s) :

.....

.....

.....

.....

.....

.....

Date d'apparition de l'EIG :

|__|__| |__|__| |_2_|_0_|__|__|

jj mm aaaa

Heure de survenue : |__||__| hh |__||__| min

☐ *donnée manquante*

Délai entre la date d'administration du ME et la date de survenue de l'EIG :

|__||__||__| / |__||__| |__||__|

jj hh min

Critères de gravité :

☐ Nécessite ou prolonge l'hospitalisation :

du |__|__| |__|__| |_2_|_0_|__|__|

au |__|__| |__|__| |_2_|_0_|__|__| ☐ *en cours*

☐ Décès

☐ Mise en jeu du pronostic vital

☐ Incapacité ou handicap important ou durable

☐ Anomalie ou malformation congénitale

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

.....

.....

L'évènement a-t-il conduit à :

☐ aucune mesure prise concernant le ME

☐ arrêt définitif du ME le |__|__| |__|__| |_2_|_0_|__|__|

☐ arrêt transitoire du ME, date de reprise : |__|__| |__|__| |_2_|_0_|__|__|

☐ ne sais pas

Récidive de l'EIG après ré-administration : ○ Non ○ Oui Date : |__|__| |__|__| |_2_|_0_|__|__|

○ Non applicable

Des mesures symptomatiques ont-elles été prises ?

☐ Non ☐ Oui Date : |__|__| |__|__| |_2_|_0_|__|__|Préciser : .....

L'évènement a-t-il conduit à une levée d'insu ?

☐ Non ☐ Oui Date : |__|__| |__|__| |_2_|_0_|__|__| ☐ Non applicable

L'évènement fait-il suite à :

- une erreur médicamenteuse ? ☐ Non ☐ Oui Date : |__|__| |__|__| |_2_|_0_|__|__|
- un surdosage ? ☐ Non ☐ Oui Date : |__|__| |__|__| |_2_|_0_|__|__|
- un mésusage ? ☐ Non ☐ Oui Date : |__|__| |__|__| |_2_|_0_|__|__|
- autre (préciser) : ..... ☐ Non ☐ Oui Date : |__|__| |__|__| |_2_|_0_|__|__|

Degré de sévérité (OMS)

☐ Léger ☐ Modéré ☐ Sévère

ou

Echelle de classement de la toxicité CTCAE

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

ou

Echelle de classement de la toxicité FDA

☐ Grade 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4

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PARTIE RESERVEE AU PROMOTEUR
REFERENCE VIGILANCE :

Référence GED : REC-DTYP-0192

Acronyme :

Référence de la personne se prêtant à la recherche : |__|__|__| - |__|__|__|__| - |__| - |__|
n°centre - n° ordre de sélection - initiale nom - initiale prénom

Evolution de l'événement

☐ **Décès**
○ sans relation avec l'EIG
○ en relation avec l'EIG
Date : |__|__| |__|__| |_2_|_0_|__|__|
jj mm aaaa

☐ **Sujet non encore rétabli**, préciser :
○ Etat stable ○ Amélioration ○ Aggravation

☐ **Résolu :**
○ sans séquelles
○ avec séquelles, préciser lesquelles :
Date : |__|__| |__|__| |_2_|_0_|__|__|
jj mm aaaa
|__|__| |__|__|
hh min

☐ **Evolution inconnue**

8. Autre(s) étiologie(s) envisagée(s)

☐ Non ☐ Oui Si oui, préciser : .....
.....
.....

9. Examen(s) complémentaire(s) réalisé(s)

☐ Non ☐ Oui Si oui, préciser date, nature et résultats : [joindre les bilans anonymisés].....
.....
.....

10. Selon l'investigateur, l'événement indésirable grave est (plusieurs cases possibles)

Lié à la recherche :

☐ **Oui (Reasonable possibility) :**
- ☐ **au(x) médicament(s)/produit(s) assimilé(s) de la recherche : le(s)quel(s) ?**
  - ☐ Comirnaty®
  - ☐ SP-GSK D614
  - ☐ SP-GSK B.1.351
  - ☐ NA (en aveugle)
- ☐ **à la (aux) procédure(s)/acte(s) de la recherche : la/le(s)quel(les) ?**
  - ☐ prélèvement nasal pour PCR
  - ☐ prise de sang

☐ **Non (No reasonable possibility) :**
- ☐ **à un (ou plusieurs) médicament(s) concomitant(s) administré(s), le(s)quel(s) : .....**
- ☐ **à une maladie intercurrente, laquelle : .....**
- ☐ **autre, préciser : .....**

Notificateur	**Investigateur**	Tampon du service :
Nom et fonction : Signature	Nom : Signature	

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34.3 Pregnancy notification form

Direction de la Recherche Clinique et de l'Innovation (DRCI)	ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS ***Notification et suivi d'une grossesse apparue au cours d'une recherche portant sur un Médicament ou produit assimilé***	**PARTIE RESERVEE AU PROMOTEUR** **REFERENCE INTERNE :** Référence GED : REC-DTYP-0185

Ce formulaire doit être dûment complété (3 pages), signé et retourné sans délai au secteur Vigilance de la DRCI par mail (eig-vigilance.drc@aphp.fr).

NB : Il est également possible d'envoyer ce formulaire par fax to +33 (0)1 44 84 17 99 uniquement en cas de tentative infructueuse d'envoi par mail (pour éviter les doublons).

1. Identification de la recherche

Acronyme : **COVIBOOST**
Code de la recherche : **APHP211184**

Notification initiale ☐ **Suivi de notification** ☐ **N° du suivi** |__|__|

Date de notification : |__|__| |__|__| |2|0|__|__| (jj mm aaaa)

Date de prise de connaissance de la grossesse par l'investigateur : |__|__| |__|__| |2|0|__|__| (jj mm aaaa)

Titre complet de la Recherche :
Immunogenicity and reactogenicity following a booster dose of a COVID-19 mRNA vaccine (Pfizer-BioNTech) and two adjuvanted sub-unit vaccines (SP/GSK) administered in adults who received 2 doses of Pfizer-BioNTech mRNA vaccine as a primary vaccination: a randomized, single-blinded, multicenter clinical trial.

2. Identification du centre investigateur

Nom de l'établissement : .....
Ville et code postal : .....
Service : .....

Investigateur (nom/prénom) : .....
Tél : Fax :
Mail :

3. Identification de la personne présentant une grossesse

Référence de la personne : |__|__|__| - |__|__|__|__| - |__| - |__| (n°centre - n° ordre de sélection - initiale nom - initiale prénom)

Date de naissance (mm/aaaa) : |__|__| |__|__|__|__|
Age : |__|__|__|ans

Date d'inclusion et de randomisation : |__|__| |__|__| |2|0|__|__| (jj mm aaaa)

Numéro de randomisation : R |__|__|__|__|

Groupe de randomisation :
☐ Groupe 1 (mRNA Pfizer)
☐ Groupe 2 (SP-GSK D614)
☐ Groupe 3 (SP-GSK B.1.351)
☐ NA (en aveugle)

Date des dernières règles : |__|__| |__|__| |2|0|__|__|
Et/ou date début de grossesse : |__|__| |__|__| |2|0|__|__|

Cas particulier d'une exposition paternelle : ☐ Oui ☐ Non

Référence de la personne : |__|__|__| - |__|__|__|__| - |__| - |__| (n°centre - n° ordre de sélection - initiale nom - initiale prénom)

Date de naissance (mm/aaaa) : |__|__| |__|__|__|__|
Age : |__|__|__|ans

Date d'inclusion et de randomisation: |__|__| |__|__| |2|0|__|__|
Numéro de randomisation : R |__|__|__|__|

Groupe de randomisation :
☐ Groupe 1 (mRNA Pfizer)
☐ Groupe 2 (SP-GSK D614)
☐ Groupe 3 (SP-GSK B.1
☐ NA (en aveugle)

Expositions au cours de la grossesse :

Tabac :	☐ non	☐ oui (préciser nombre de paquets/année) :	☐ arrêt (préciser date) :	☐ poursuite
Alcool :	☐ non	☐ oui (préciser unités OH) :	☐ arrêt (préciser date) :	☐ poursuite
Drogue :	☐ non	☐ oui (préciser substance) :	☐ arrêt (préciser date) :	☐ poursuite

Autre (préciser) :

4. Antécédents maternels

Médicaux :	**Chirurgicaux :**

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Obstétricaux : |__|__| geste |__|__| pare

Préciser si fausse couche, grossesse extra-utérine, interruption de grossesse (médicale ou volontaire), mort *in utero*, malformation congénitale, pathologie congénitale/néonatale non malformative, … (*nombre, date et nature/raison si applicable).*

Acronyme : COVIBOOST

Référence de la personne : |__|__|__| - |__|__|__|__|__| - |__| - |__|
n°centre – n° ordre de sélection – initiale nom – initiale prénom

PARTIE RESERVEE AU PROMOTEUR
REFERENCE INTERNE :
REC-DTYP-0192

5. Médicament(s) expérimental (aux) administré(s) ou non pendant la grossesse ou s'il s'agit une exposition paternelle

Nom commercial (de préférence) ou Dénomination Commune Internationale	Date de première administration Ou non administré	Date de dernière administration Ou en cours	Voie (1)	Posologie / 24h
Comirnaty® mRNA vaccine (Pfizer-BioNTech) ☐ **NA**	|__|__| |__|__| |_2_|_0_|__|__| ☐ Non administré	|__|__| |__|__| |_2_|_0_|__|__| ☐ En cours	**IM**	
Sanofi/GSK sub-unit adjuvanted vaccine D.614 ☐ **NA**	|__|__| |__|__| |_2_|_0_|__|__| ☐ Non administré	|__|__| |__|__| |_2_|_0_|__|__| ☐ En cours	**IM**	
Sanofi/GSK sub-unit adjuvanted vaccine B.1.351 ☐ **NA**	|__|__| |__|__| |_2_|_0_|__|__| ☐ Non administré	|__|__| |__|__| |_2_|_0_|__|__| ☐ En cours	**IM**	

(1) Voie d'administration : VO=voie orale ; IM=Intramusculaire ; IV=intraveineuse ; SC=sous-cutanée ou autre (à préciser)

6. Procédures et actes ajoutés par la recherche ***(barrer l'encadré si procédures et actes non réalisés)***	Date de réalisation *(jj/mm/aaaa)*	Volume de sang (mL)	Volume de sang cumulé (mL)	Chronologie	
				Avant la grossesse	Au cours de la grossesse
Prélèvement nasal pour PCR	|__|__| |__|__| |_2_|_0_|__|__|	NA	NA	☐	☐
Prise de sang (préciser la plus récente)	|__|__| |__|__| |_2_|_0_|__|__|			☐	☐

7. Médicament(s) concomitants administré(s) dans le cadre du soin

(Cf. annexe « Liste relative aux médicaments concomitants » complétée : ☐ Oui ☐ Non applicable)

Nom commercial (de préférence) ou Dénomination Commune Internationale	Date de première administration	Date de dernière administration Ou en cours	Voie d'administration(1)	Posologie / 24h
	|__|__| |__|__| |_2_|_0_|__|__|	|__|__| |__|__| |_2_|_0_|__|__| ☐ En cours		
	|__|__| |__|__| |_2_|_0_|__|__|	|__|__| |__|__| |_2_|_0_|__|__| ☐ En cours		
	|__|__| |__|__| |_2_|_0_|__|__|	|__|__| |__|__| |_2_|_0_|__|__| ☐ En cours		

(1) Voie d'administration : VO=voie orale ; IM=Intramusculaire ; IV=intraveineuse ; SC=sous-cutanée ou autre (à préciser)

8. Suivi de la grossesse

☐ Echographiques. Date(s) et résultats à préciser *(joindre les CR anonymisés)* :

☐ Autres examens. Date(s) et résultats à préciser *(joindre les CR anonymisés)* :

9. Grossesse en cours ou issue de la grossesse

☐ (envoyer par mail un nouveau formulaire complété à l'issue de la grossesse pour le suivi de la notification initiale)
☐ (compléter ci-dessous)

Date : |__|__| |__|__| |_2_|_0_|__|__| Terme : |__|__| SA |__|__| J

☐ Fausse couche
→ Examen anatomo-pathologique disponible : ☐ Non ☐ Oui, précisez le résultat :

☐ Grossesse extra-utérine
→ Examen anatomo-pathologique disponible : ☐ Non ☐ Oui, précisez le résultat :

☐ Interruption de grossesse → Raison :
→ Examen anatomo-pathologique disponible : ☐ Non ☐ Oui, précisez le résultat :

☐ Accouchement : ☐ Spontané ☐ Provoqué ☐ Voie basse ☐ Césarienne

Naissance multiple : ☐ Non ☐ Oui, précisez le nombre :

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Souffrance fœtale :	☐ Non ☐ Oui, précisez :
Mort-né :	☐ Non ☐ Oui, précisez :
Placenta normal :	☐ Oui ☐ Non, précisez :
Liquide amniotique :	☐ Clair ☐ Autre, précisez :
Anesthésie :	☐ Générale ☐ Péridurale ☐ Rachianesthésie ☐ Aucune

Acronyme : COVIBOOST

PARTIE RESERVEE AU PROMOTEUR
REFERENCE INTERNE :
REC-DTYP-0192

Référence de la personne : |__|__|__| - |__|__|__|__|__| - |__| - |__|
n°centre – n° ordre de sélection – initiale nom – initiale prénom

10. Nouveau-né (Si naissance multiple, compléter les parties 1, 2, 3, 9 et 10 d'un nouveau formulaire et l'envoyer par mail)

Sexe : ☐ Masculin ☐ Féminin

Poids : |__|__|__|__| grammes Taille : |__|__|__| cm Périmètre crânien : |__|__|__| cm

APGAR : 1 minute : _____ 5 minutes : _____ 10 minutes : _____

Malformation(s) congénitale(s) : ☐ Non ☐ Oui, précisez :

Pathologie(s) congénitale(s)/néonatale(s) non malformative(s) : ☐ Non ☐ Oui, précisez :

Le nouveau-né a-t-il bénéficié d'un suivi particulier à la naissance : ☐ Non ☐ Oui, précisez : ☐ Non applicable

Notificateur	**Investigateur**	Tampon du service :
Nom et fonction : Signature :	Nom : Signature :	

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Summary of changes_CoviBOOST

Modification number	Description	Ethic committee approval	Competent authority authorization
1	Modification requested by theFrench competent authority ANSM; Modification of an exclusion criteria due to the beginning of flu vaccinnation; modification of the patient information sheet; modification of communication poster and email	09/11/2021	NSM
2	The main objective, which is the measurement of neutralizing antibody titers, is now evaluated on D15 instead of D28. Secondary objectives are not affected. Clarification of inclusion criterion no. 5 at the request of the DSMB: participants included in the study must have received their 2nd dose of mRNA vaccine within an interval of 6 months +/- 1 month preceding the injection of the boost dose; Modification of the sample transport schedule to the centralizing BRC and the analysis laboratories: addition of additional transport to allow the main analysis to be carried out on D15; Addition of details concerning the per-protocol population, at the request of the DSMB. Mention in the NIFC of the update of the health pass following the boost dose; Addition of additional visits in the documents intended for patients (patient card, communication document, self-monitoring notebook, memory aid). Revision of the Poster following the update of inclusion criterion n°5; Modification of the list of participating centres: Removal of CIC Bordeaux IP Pr Girodet and Addition of CIC Bichat IP Pr Duval; Typo correction.	29/11/2021	30/11/2021
3	Addition of a subject information sheet regarding the health pass	04/12/2021	NSM
4	Inclusion of subjects aged 18-64 beyond the 150 initially planned; typos correction; update of the patient information sheet health pass.	21/12/2021	NSM
5	inclusion of subjects between 3 and 7 months after the 2nd dose; addition of Omicron variant analysis.	29/12/2021	29/12/2021
6	Extension of the search for an additional week.	06/01/2022	NSM

NSM : Non Substantial Modification

Original statistical analysis plan

See chapter 12 STATISTICAL ASPECTS of final protocol (V5.0 2022/01/03)

12 STATISTICAL ASPECTS

12.1 Description of statistical methods to be used including the timetable for the planned interim analyses

A detailed analysis plan will be a priori defined.

Analysis will be performed by a statistician from URC-Est using SAS® software version 9.4 (or updated version) (SAS Institute Inc.). Partial data base locks will be performed for data from randomization to D15 to assess primary endpoint and secondary endpoints at D15, at D28 to assess D28 secondary endpoint, M3 to assess M3 secondary endpoints. Final data base lock will be at the end of the trial to assess secondary M12 secondary endpoints.

A flow chart will be drawn according to consort statement. The proportion of eligible participants who refused to participate in the research or who did not come to the scheduled consultation will be described.

Baseline characteristics of patients will be described overall and per group.

Continuous variables will be summarized using descriptive statistics, i.e. number of subjects, mean, standard deviation (SD), median, inter quartile range, minimum and maximum depending on the variable distribution. Qualitative variables will be summarized by frequency and percentage.

Primary endpoint assessment

The main analysis will be performed on the per protocol population.

For each viral strains (D614 and B.1.351), proportion of subjects with an increase rate in neutralizing antibody titers against SARS-CoV-2 of at least 10 fold between D0 and D15 will be calculated with it 2-sided 95% confidence interval (95%CI) using the exact Clopper-Pearson method.

Secondary endpoints assessment

- Rate of increase in neutralizing antibody titers against SARS-CoV-2 D614 and B.1.351 viral strains measured by a microneutralisation technique between 0 and 28 days after the booster dose in each group of randomisation and in each age group (18-64 years and 65 years or more) will be described.

- Anti-Spike (D614) IgG levels, expressed in BAU/ml, according to WHO recommendations up to D28 after the booster dose mRNA or adjuvanted subunit vaccine, and their persistence at 3 and 12 months will be described as geometric means with 95% confidence intervals (by logarithmic transformation of the data, calculation of the arithmetic mean and its confidence interval and anti-log transformation of these mean and limits of the confidence interval).

- Anti-RBD (D614 and B.1.351) IgG levels up to 28 days after the booster dose mRNA or adjuvanted subunit vaccine and their persistence at 3 and 12 months will be

described as geometric means with 95% confidence intervals (by logarithmic transformation of the data, calculation of the arithmetic mean and its confidence interval and anti-log transformation of these mean and limits of the confidence interval). Differences in Anti-Spike (D614) and anti-RBD (D614 and B.1.351) IgG levels between D3 and D0 and between 12 months and D0 will be estimated with 95% confidence intervals.

- For each vaccine, the antibody titers will be described at each time of measurement as geometric means with 95% confidence intervals (by logarithmic transformation of the data, calculation of the arithmetic mean and its confidence interval and anti-log transformation of these mean and limits of the confidence interval). Evolution between D0, D15, M1, M3 and M12 will be described using graphs.

- Associated factors and determinants of boost response (neutralizing antibody titers against variants of interest) in individuals previously vaccinated with 2 doses of mRNA vaccine will be studied.

- ELISpot IFN CD4 and CD8 response will be described. (*ancillary-analysis*)

Safety assessment

Safety assessment will be analysed among safety population.

- Proportions of 1) local adverse events and 2) systemic adverse events of any grade (assessed from the list of solicited adverse events) occurring up to 7 days after each injection will be described globally and by randomization group. Intensity will also be described.
- Quantity and intensity of unsolicited local and systemic events up to 28 days will also be described by randomization group.

12.2 Calculation hypotheses for the number of participants required and the result

The sample size calculation is performed to estimate the proportion of subjects with a sufficient rate of increase in neutralizing antibody titers and its 95% confidence interval with a given precision.

Due to the lack of available data on the Pfizer-BioNTech vaccine, the sample size calculation is based on published data on the Moderna vaccine (Wu, 2021(ref)) in which an increase rate of neutralizing antibody titer against historical SARS-CoV-2 (D 614 G) after Moderna boost at D15 of 23 and 32 for the B.1.351 variant is described. Using a conservative approach, we consider neutralizing activity to be sufficient if the increase rate is at least 10 at D15.

We assume a proportion of subjects with an increase rate of at least 10 between D0 and D15 of 80%.

One hundred subjects per group will allow an estimation of the proportion of 80% with a half width of 95% confidence interval of 7.8%.

Thus, a total of 300 volunteers will be randomized: 100 per group.

12.3 Anticipated level of statistical significance

All tests will be two-sided, and a p-value of < 0.05 will be considered significant.

12.4 Statistical criteria for termination of the study.

Not applicable.

12.5 Method for taking into account missing, unused or invalid data

Missing data for the primary endpoint will be replaced by the geometric mean value of antibody levels observed in the group of the concerned subject.
Censored data reported as below the lower limit of detection/quantification will be imputed with a value equal to half of the threshold before transformation.
Other missing data will not be replaced.

12.6 Management of modifications made to the analysis plan for the initial strategy.

All modification made to the analysis plan for the initial strategy will be documented in the analysis report.

12.7 Choice of individuals to be included in the analyses

Intent to treat population (ITT): all patients as randomized, regardless of the strategy received by the patient.

Per protocol (PP) population: all patients as randomized, treated without major protocol violations/deviations, except participants presenting a positive NP serology at D0 or D15 and lost to follow-up participants.
Pre-defined major protocol violations/deviations are:

- Non-respect of eligibility criteria
- Non-respect of the randomized treatment allocation and/or duration (wrong vaccine received, second dose not received)
- Missing data for the primary efficacy endpoint

Major protocol deviation will be classified during a blinded data review before final data base lock.

Safety population: All patients as randomized who have received the boost dose of vaccine.

Statistical analysis plan (SAP)

Statistical analysis plan presented below has been revised before data base lock.
We do not expect modifications of the initial analysis strategy. However, in case of occurrence of such validated modifications after the SAP, a modified SAP would be issued. The original SAP as well as the modified SAP will be kept in the study files, with the justification for any modification.

Analysis will be performed by a statistician from URC-Est using SAS® software version 9.4 (or updated version) (SAS Institute Inc.), R freeware (version 3.6.3) and GraphPad Prism software (version 9.2.0, San Diego, California USA). Partial data base locks will be performed for data from randomization to D15 to assess primary endpoint and secondary endpoints at D15, at D28 to assess D28 secondary endpoints and at M3 to assess M3 secondary endpoints. Final data base lock will be at the end of the trial to assess secondary M12 secondary endpoints.

1 ANALYSIS PLAN

1.1 Selection of populations

Intent to treat population (ITT): all patients as randomized, regardless of the strategy received by the patient, except patient with positive or doubtful or missing NP antibodies at baseline.

Safety population: All patients as randomized who have received the boost dose of vaccine.

The per protocol (PP) population is defined as all patients randomized, treated without major protocol violations/deviations. Pre-defined major protocol violations/deviations are:

- Non-respect of eligibility criteria
- Non-respect of the randomized treatment allocation and/or duration (wrong vaccine received, second dose not received)
- Missing data for the primary efficacy endpoints
- Patient with positive or doubtful NP antibodies at baseline and/or D15 and those tested PCR + versus SARS Cov-2 from baseline to D15.

Major protocol deviation will be classified during a blinded data review before final data base lock.

Safety population is defined as all randomized patients who have received the second dose of vaccine.

1.2 Description of planned statistical methods

A flow chart will be drawn according to consort statement. The proportion of eligible participants who refused to participate in the research or who did not come to the scheduled consultation will be described.

Baseline characteristics of patients will be described overall and per group.
Continuous variables will be summarized using descriptive statistics, i.e. number of subjects, mean, standard deviation (SD), median, inter quartile range, minimum and maximum depending on the variable distribution. Qualitative variables will be summarized by frequency and percentage.

The proportion of patients having been in contact with the virus before baseline on the one hand and after baseline on the other hand will be calculated (contact with the virus defined as positive if anti-nucleocapsid Ig G assay measured by ELISA on baseline and D28 positive or doubtful).

<u>Primary endpoint assessment</u>

The main analysis will be performed on the per protocol population with an additional sensitivity analysis on the intention-to-treat population.
For each viral strains (D614 and B.1.351), proportion of subjects with an increase rate in neutralizing antibody titers against SARS-CoV-2 measured by a microneutralisation technique of at least 10 fold

between D0 and D15 will be calculated with it 2-sided 95% confidence interval (95%CI) using the exact Clopper-Pearson method.

Secondary endpoints assessment

1. Rate of increase in neutralizing antibody titers against SARS-CoV-2 D614 and B.1.351 viral strains measured by a microneutralisation technique between baseline and D28 after the booster dose in each group of randomisation and in each age group (18-64 years and 65 years or more) will be described.

2. Anti-Spike (D614) IgG levels, expressed in BAU/ml, according to WHO recommendations up to 15 days and D28 after the booster dose mRNA or adjuvanted subunit vaccine, and their persistence at 3 and 12 months will be described as geometric means with 95% confidence intervals (by logarithmic transformation of the data, calculation of the arithmetic mean and its confidence interval and anti-log transformation of these mean and limits of the confidence interval).
   Differences in Anti-Spike (D614) IgG levels between M3 and baseline and between 12 months and baseline will be estimated with 95% confidence intervals.
   Anti-Spike (D614) IgG levels, expressed in BAU/ml according to WHO recommendations, D3 after the booster dose mRNA or adjuvanted subunit vaccine will be analyzed as described above (ancillary analysis).

3. Anti-RBD (D614 and B.1.351) IgG levels up to 28 days after the booster dose mRNA or adjuvanted subunit vaccine and their persistence at 3 and 12 months will be described as geometric means with 95% confidence intervals (by logarithmic transformation of the data, calculation of the arithmetic mean and its confidence interval and anti-log transformation of these mean and limits of the confidence interval). Differences in Anti-Spike (D614) and anti-RBD (D614 and B.1.351) IgG levels between M3 and baseline and between 12 months and baseline will be estimated with 95% confidence intervals.
   Anti-RBD (D614 and B.1.351) IgG levels, expressed in BAU/ml according to WHO recommendations, D3 after the booster dose mRNA or adjuvanted subunit vaccine will be analyzed as described above (ancillary analysis).

4. For each vaccine, the neutralizing antibody titers measured by a microneutralisation technique against variants of interest (D614, B.1.351, Delta, Omicron) will be described at each time of measurement (baseline, D3 (ancillary analysis), D15, M1, M3 and M12) as geometric means with 95% confidence intervals (by logarithmic transformation of the data, calculation of the arithmetic mean and its confidence interval and anti-log transformation of these mean and limits of the confidence interval). Evolution between baseline, D15, M1, M3 and M12 will be described using graphs.

5. Associated factors and determinants of boost response (neutralizing antibody titers against variants of interest) in individuals previously vaccinated with 2 doses of mRNA vaccine will be studied.
   Factors of interest are age, gender, time interval between 2nd dose and boosterdose, and vaccine boost type. Linear generalized regression model adapted to the data distribution will be used.

6. Mucosal SARS-CoV-2 specific antibodies via the measure of IgA in saliva by ELISA and PRNT assays at baseline, D28 and D90 will be described as geometric means with 95% confidence intervals.

7. ELISpot IFN CD4 and CD8 response at D28, M3 and M12 will be described (ancillary-analysis).

Safety assessment

Safety assessment will be analysed among safety population.

Proportions of 1) local adverse events and 2) systemic adverse events of any grade (assessed from the list of solicited adverse events) occurring up to 7 days after each injection will be described globally and by randomization group. Intensity will also be described.
Quantity and intensity of unsolicited local and systemic events up to 28 days will also be described by randomization group.

1.3 Hypotheses for calculating the required number of subjects

The sample size calculation is performed to estimate the proportion of subjects with a sufficient rate of increase in neutralizing antibody titers and its 95% confidence interval with a given precision.
Due to the lack of available data on the Pfizer-BioNTech vaccine, the sample size calculation is based on published data on the Moderna vaccine (Wu, 2021(ref)) in which an increase rate of neutralizing antibody titer against historical SARS-CoV-2 (D 614 G) after Moderna boost at D15 of 23 and 32 for the B.1.351 variant is described. Using a conservative approach, we consider neutralizing activity to be sufficient if the increase rate is at least 10 at D15.

We assume a proportion of subjects with an increase rate of at least 10 between D0 and D15 of 80%.

One hundred subjects per group will allow an estimation of the proportion of 80% with a half width of 95% confidence interval of 7.8%.

Thus, a total of 300 volunteers will be randomized: 100 per group.

1.4 Anticipated level of statistical significance

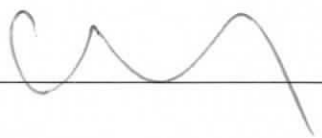
All tests will be two-sided, and a p-value of < 0.05 will be considered significant.
No adjustment will be planned for multiplicity except for comparisons between groups in pairs for which a Bonferroni correction will be used.

1.5 Statistical criteria for termination of the study

Not applicable.

1.6 Method for taking into account missing, unused or invalid data

Missing data for the primary endpoint will be replaced by the geometric mean value of antibody levels observed in the group of the concerned subject and at the concerned evaluation time.
Censored data reported as below the lower limit of detection/quantification will be imputed with a value equal to half of the threshold before transformation.
Other missing data will not be replaced.

	Coordinator	Biostatisticien / Coordinator data management and statistic
First name Name	O. Launay	N. Cachanado
Date	25/02/2022	25/02/2022
Signature		

Summary of changes to the statistical analysis plan (SAP)

Statistical analysis plan version	Cause of changes
Statistical analysis plan V1 (included in original protocol)	First release.
Statistical analysis plan V2	Review of SAP prior to final analyses, before data base lock.

Chapter of SAP V1	Statistical analysis plan V1	Chapter of SAP V2	Statistical analysis plan V2
12.1 Description of statistical methods to be used including the timetable for the planned interim analyses	A detailed analysis plan will be a priori defined. Analysis will be performed by a statistician from URC-Est using SAS® software version 9.4 (or updated version) (SAS Institute Inc.).	**Introduction**	*Addition of general precisions.* Statistical analysis plan presented below has been revised before data base lock. We do not expect modifications of the initial analysis strategy. However, in case of occurrence of such validated modifications after the SAP, a modified SAP would be issued. The original SAP as well as the modified SAP will be kept in the study files, with the justification for any modification. Analysis will be performed by a statistician from URC-Est using SAS® software version 9.4 (or updated version) (SAS Institute Inc.), R freeware (version 3.6.3) and GraphPad Prism software (version 9.2.0, San Diego, California USA).

Chapter of SAP V1	Statistical analysis plan V1	Chapter of SAP V2	Statistical analysis plan V2
12.1 Description of statistical methods to be used including the timetable for the planned interim analyses	The main analysis will be performed on the per protocol population. (…) between 0 and 28 days (…) Differences in Anti-Spike (D614) and anti-RBD (D614 and B.1.351) IgG levels between D3 and D0 and between 12 months and D0 will be estimated with 95% confidence intervals. Differences in Anti-Spike (D614) and anti-RBD (D614 and B.1.351) IgG levels between D3 and D0 and between 12 months and D0 will be estimated with 95% confidence intervals. For each vaccine, the antibody titers will be described at each time of measurement as	**1.2 Description of planned statistical methods**	*Addition:* The main analysis will be performed on the per protocol population with an additional sensitivity analysis on the intention-to-treat population. *Editorial amendment:* (…) between baseline and 28 days (…) *Editorial amendment:* Differences in Anti-Spike (D614) IgG levels between M3 and baseline and between 12 months and baseline will be estimated with 95% confidence intervals. *Addition:* Anti-Spike (D614) IgG levels, expressed in BAU/ml according to WHO recommendations, D3 after the booster dose mRNA or adjuvanted subunit vaccine will be analyzed as described above (ancillary analysis). *Editorial amendment:* Anti-RBD (D614 and B.1.351) IgG levels between M3 and baseline and between 12 months and baseline will be estimated with 95% confidence intervals. *Addition:* Anti-RBD (D614 and B.1.351) IgG levels, expressed in BAU/ml according to WHO recommendations, D3 after the booster dose mRNA or adjuvanted subunit vaccine will be analyzed as described above (ancillary analysis). *Addition of precisions:* For each vaccine, the neutralizing antibody titers measured by a microneutralisation technique against variants of interest (D614, B.1.351, Delta, Omicron) will be described at each time of measurement (baseline,

Chapter of SAP V1	Statistical analysis plan V1	Chapter of SAP V2	Statistical analysis plan V2
	geometric means with 95% confidence intervals (by logarithmic transformation of the data, calculation of the arithmetic mean and its confidence interval and anti-log transformation of these mean and limits of the confidence interval).		D3 (ancillary analysis), D15, M1, M3 and M12) as geometric means with 95% confidence intervals (by logarithmic transformation of the data, calculation of the arithmetic mean and its confidence interval and anti-log transformation of these mean and limits of the confidence interval). *Addition of precisions:* Factors of interest are age, gender, time interval between 2nd dose and boosterdose, and vaccine boost type. Linear generalized regression model adapted to the data distribution will be used. *Addition:* Mucosal SARS-CoV-2 specific antibodies via the measure of IgA in saliva by ELISA and PRNT assays at baseline, D28 and D90 will be described as geometric means with 95% confidence intervals.
12.3 Anticipated level of statistical significance		**1.4 Anticipated level of statistical significance**	*Addition of precisions:* No adjustment will be planned for multiplicity except for comparisons between groups in pairs for which a Bonferroni correction will be used.

Chapter of SAP V1	Statistical analysis plan V1	Chapter of SAP V2	Statistical analysis plan V2
12.5 Method for taking into account missing, unused or invalid data	Missing data for the primary endpoint will be replaced by the geometric mean value of antibody levels observed in the group of the concerned subject.	**1.6 Method for taking into account missing, unused or invalid data**	*Addition of precisions:* Missing data for the primary endpoint will be replaced by the geometric mean value of antibody levels observed in the group of the concerned subject and at the concerned evaluation time.
12.7 Choice of individuals to be included in the analyses	Intent to treat population (ITT): all patients as randomized, regardless of the strategy received by the patient. Per protocol (PP) population: all patients as randomized, treated without major protocol violations/deviations, except participants presenting a positive NP serology at D0 or D15 and lost to follow-up participants. Pre-defined major protocol violations/deviations are: - Non-respect of eligibility criteria - Non-respect of the randomized treatment allocation and/or duration (wrong vaccine received, second dose not received) - Missing data for the primary efficacy endpoint	**1.1 Selection of populations**	*Addition of an exclusion criterio, in ITT population definition:* Intent to treat population (ITT): all patients as randomized, regardless of the strategy received by the patient, except patient with positive or doubtful or missing NP antibodies at baseline. *Editorial amendment and addition of an exclusion criterion in PP population definition:* The per protocol (PP) population is defined as all patients randomized, treated without major protocol violations/deviations. Pre-defined major protocol violations/deviations are: - Non-respect of eligibility criteria - Non-respect of the randomized treatment allocation and/or duration (wrong vaccine received, second dose not received) - Missing data for the primary efficacy endpoints Patient with positive or doubtful NP antibodies at baseline and/or D15 and those tested PCR + versus SARS Cov-2 from baseline to D15.

Changes to the SAP after data base lock

Modifications made
Addition of a post hoc analyses: Primary outcome has been compared between groups using a Pearson Chi² test. In a sensitivity analysis, multiple imputation was performed to account for missing data. Multiple imputation was performed using the Full Conditional Specific Model of PROC MI (SAS/STAT version 14.3) and 15 data sets were created. For the primary endpoint, sensitivity analyses were performed on ITT population and on ITT population with available data. Proportions of patients with an increase of neutralizing antibodies of at least 4 times or at least 2 times between baseline and D15 was described for each strains by their number, frequency and 95% confidence interval calculated using the exact Clopper-Pearson method.
Addition of precisions: Association between factors of interest and an increase of at least 10 folds of neutralizing antibodies against the 4 strains was performed using a logistic regression model. Variables with a p-value <0.2 in the unadjusted analysis were retained for the adjusted analysis. For continuous variables, if the log-linearity was not respected, the variables were categorized.