Institut Pasteur

CONFIDENTIAL

A randomized, placebo-controlled trial, to evaluate the safety and immunogenicity of the COVID-19 vaccine, a measles vector-based vaccine candidate against COVID-19 in healthy volunteers consisting of an unblinded dose escalation and a blinded treatment phase

COVID-19-101

EudraCT: n°2020-002973-89

Sponsor:
INSTITUT PASTEUR
25-28 rue du Docteur Roux
75724 Paris Cedex 15

Sponsor ID: 2020-016

Version: V6F on March 2nd , 2021

Research regulatory framework : Phase I Clinical Trial
Keywords : COVID-19; vaccine, Measles vector

INTERNATIONAL INVESTIGATORS AND CONTACT INFORMATION	
INSTITUT PASTEUR (sponsor)	**Sponsor Representative** [redacted]
INSTITUT PASTEUR	**Vaccine Innovation Development** [redacted]
THEMIS Bioscience GmbH a subsidiary of Merck & Co., Inc., Kenilworth, New Jersey USA (vaccine developer)	[redacted]

SITE INVESTIGATORS AND CONTACT INFORMATION	
CIC-COCHIN - PASTEUR	
Site Principal Investigator (France)	[redacted]
Study Coordinator	[redacted]
Pharmacist	[redacted]

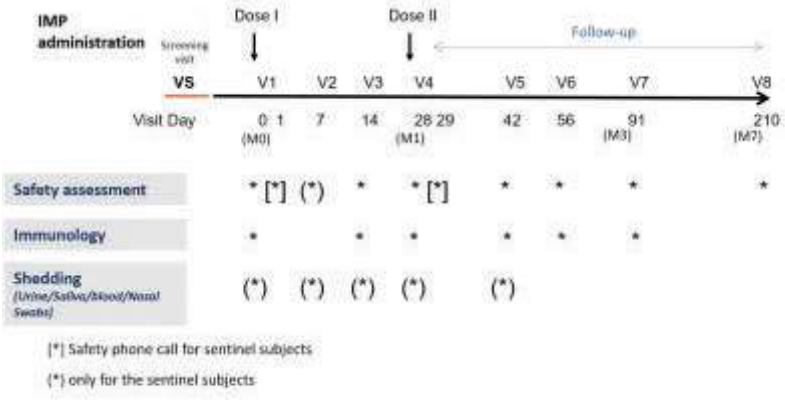
SGS LIFE SCIENCES, CLINICAL PHARMACOLOGY UNIT	
Site Principal Investigator (Belgium)	[redacted]
Study Coordinator	[redacted]
Pharmacist	[redacted]
CLINICAL TRIAL SUPPORT	
Methodologist	[redacted]
Data manager	SGS Life Sciences
Monitoring	
Pharmacovigilance	

VERSIONS LOG

Final Version	Date	Summary of amendments Date of approvals and authorizations
1d7	May 27th, 2020	Version submitted to IRB-Institut Pasteur
1F	June 17th, 2020	Version submitted to French and Belgian CA/EC
1F	July 1st, 2020	Version further to ANSM comments
1F	July 16th, 2020	Version further to ANSM additional comments
2F	July 20th, 2020	Version further to FAMHP comments
2F	August 14th, 2020	Version further to FAMHP additional comments Version 2 submitted to French EC and to ANSM
3F	September 11th, 2020	Version further to the change of the principal investigator at CPU (Belgian site)
4F	November 30th, 2020	Amended version submitted to French and Belgian CA/EC
5F	February 10th , 2021	Amended version submitted to French CA/EC
6F	March 2nd , 2021	Amended version submitted to French and Belgium CA/EC further to sponsor modification of version V5F

PROTOCOL SYNOPSIS

1. Full title	A randomized, placebo-controlled trial, to evaluate the safety and immunogenicity of the COVID-19 vaccine, a measles vector-based vaccine candidate against COVID-19 in healthy volunteers consisting of an unblinded dose escalation and a blinded treatment phase
2. Acronym or short title	COVID-19-101
3. Study Rational	Coronaviruses are a large family of viruses that mostly cause disease similar to the common cold in humans, but also epidemics of more severe diseases, such as Severe Acute Respiratory Syndrome (SARS) in 2003, and the Middle East Respiratory Syndrome (MERS) since 2012. A novel coronavirus infectious disease (COVID-19) was identified in 2019 in Wuhan, China, caused by the Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2). The ongoing outbreak of COVID-19 disease has been declared a Public Health Emergency of International Concern (PHEIC, WHO). By now, cases have been confirmed in 199 countries and territories. Human to human infection is now the main source of new infections (Chen and al; 2020 Infectious Disease). There is currently no specific treatment, only supportive care. The development of vaccines is an important tool to interrupt infection, reduce viral shedding and stop the spread of the disease. Attenuated strains of the measles virus are proven vaccine vectors and may be used as a backbone to express and present relevant antigens to promote a protective immunological response against infectious pathogens. This technology is already well advanced in clinical development. An MV-based candidate for chikungunya virus (MV-CHIK) is entering Phase III trials and has been shown to be well tolerated and highly immunogenic. Importantly, pre-existing anti-measles immunity does not impair the response. In addition, the higher doses tested resulted in seroconversion upon a single immunization in approximately 90% of subjects (Ramsauer et al, 2015, Lancet Inf. Dis.; Reisinger et al., 2018, Lancet), highlighting that one dose might be sufficient to gain clinical benefit, which is essential during an epidemic or outbreak. An MV-based SARS vaccine candidate, expressing the full-length Spike (S) protein was demonstrated to be efficacious in mice against SARS-CoV-1 (Escriou et al., 2014, Virology). Similarly, an MV-MERS candidate under development to enter clinical trials, based on the homologous S antigen from MERS-CoV, was also efficacious in mice against MERS (Malczyk et al., 2015, J. Virol). Therefore, there is an expectation that a measles vector candidate (MV-SARS-2) targeting the S protein of SARS-CoV-2 could be a promising approach to generating an effective vaccine against COVID-19.
4. Investigational product and matching placebo	COVID-19 vaccine, a live-attenuated recombinant measles vaccine virus vector expressing a modified surface glycoprotein of the novel Coronavirus (SARS-CoV-2) administered at two dosage levels (target concentration of 5 log 10 or 6 log 10 $TCID_{50}$) in a single or two injections (days 0 and 28) The vaccine is administered by i.m. injection

5. Placebo	Physiological saline solution (0.9% NaCl), administered by i.m. injection
6. Study design	This first in human clinical trial is planned to be conducted in Europe at two sites, one in France and one in Belgium with competitive recruitment. The purpose of the clinical trial will be to demonstrate vaccine safety and immunogenicity in healthy adult population. To achieve these objectives, 90 subjects will be included, 30 per cohort in three cohorts, each cohort comprising 24 vaccinees and 6 placebo recipients. Subjects will either receive a low dosage vaccine (2 immunizations) or a high dosage vaccine (1 or 2 immunizations) or placebo. Eight clinic visits (nine for the “Sentinel Groups”) are planned during the length of the study. Among those eight (nine for “Sentinel Groups”) visits, one is the screening visit, five (six for “Sentinel Groups”) are follow-up visits with blood samples and two correspond to injection visits. In addition, one safety phone call will be made 24hours after each injection (only for the “Sentinel Groups”).  After the screening visit, participants will be expected to return to investigational clinical site for visits on days 0, 7 (only for sentinel subjects), 14, 28, 42, and 56 for safety assessments and immunogenicity sample collection, and additionally on day 91 safety follow-up and for long-term immunogenicity sampling. Samples for shedding will only be collected from subjects of the “Sentinel Groups” (unblinded treatment in cohort A and B). Body fluids including saliva, nasal swab, urine and whole blood will be collected therefore at visit 1 (day 0), visit 2 (day 7 after the first immunization), visit 3 (day 14), visit 4 (day 28) and visit 5 (day 42).

Cohort	Treatment	Injection 1 D0	Injection 2 D28	Number of participants		
				COVID-19 vaccine **Sentinel**	COVID-19 vaccine **Main grp**	Placebo
A	COVID-19 low Dosage	Vaccine	Vaccine	3	21	6
B	COVID-19 high Dosage	Vaccine	Vaccine	3	21	6
C	COVID-19 high Dosage	Vaccine	Placebo	0	24	6

As safety precaution, the study will begin with the enrolment of a small group of sentinel subjects (3 subjects from cohort A and 3 subjects from cohort B), each of whom will receive the vaccine on days 0 and 28 in an unblinded and non-randomized manner. The enrolment of the "Sentinel Groups" will be conducted at one investigational site. The one located in the country where approval and authorization from Ethic Committee and Competent Authority will be obtained first

The first subject of the "Sentinel Groups" will be enrolled in cohort A and will receive the low dose vaccine on day 0. Twenty-four hours after the injection, the subject will be called to collect safety information related to the vaccination. The clinical investigator can then decide to move on with the vaccination of the second and third subject based on the absence of related severe AEs/SAEs (no less than 24hrs after the first subject received the first treatment and phone call).

The second and third subject of the "Sentinel Groups" will be enrolled the same day, with an interval of at least 3 hours, in cohort A and will receive the low dose vaccine on day 0. Twenty-four hours after the injection, the second and third subject will be called to collect safety information related to the vaccination. The clinical investigator can then decide to move on with the vaccination of the fourth subject based on the absence of related severe AEs/SAEs (no less than 24hrs after the second and third subject received the first treatment and phone call).

The fourth subject of the "Sentinel Groups" will be enrolled, in cohort B and will receive the high dose vaccine. Twenty-four hours after the injection, the subject will be called to collect safety information related to the vaccination. The clinical investigator can then decide to move on with the vaccination of the two last subjects based on the absence of related severe AEs /SAEs (no less than 24hrs after the fourth subject received the first treatment and phone call).

The fifth and sixth participants of the "Sentinel Groups" will be enrolled the same day, with an interval of at least 3 hours, in cohort B and will receive the high dose vaccine on day 0. Twenty-four hours after the injection, they will be called to collect safety information related to the vaccination.

Following the 14 day follow up of all sentinel subjects, the DSMB will review safety data after the first dose in these six participants, before giving a positive written recommendation for continuing with the double-blind, randomized treatment phase.

	Following the 42 day follow-up of all sentinel subject, a medical monitoring of safety data will be performed to evaluate safety of the second injection in these six participants. In case of any safety concern, an ad hoc DSMB meeting will be organized before giving a positive recommendation for continuing with the second injection of the double-blind, randomized cohorts ("main cohorts"). In case of any related severe AE or related SAE, Sponsor will be contacted and after the case has been discussed by the Sponsor and DSMB, it will be determined if study vaccination can be continued according to the protocol. Assays will include sero-neutralization, ELISA against SARS-CoV-2 antigens and measles antibodies, Intracellular Staining (ICS) to assess T cell responses and shedding assays (only for sentinel subjects).
7. Primary Objective	To assess the safety and tolerability of the COVID-19 vaccine following one or two consecutive intramuscular injections in healthy volunteers.
8. Secondary Objectives	To assess induction of SARS-CoV-2 spike protein-binding antibodies upon one or two administrations of the COVID-19 vaccine by means of ELISA up to study day 91. To assess induction of SARS-CoV-2 neutralizing antibodies upon one or two administrations of the COVID-19 vaccine by means of serum neutralization assay up to study day 91. To assess SARS-CoV-2 spike protein-specific, cell-mediated immune responses up to study day 91 induced by one or two doses of vaccine, by means of intracellular staining and flow cytometry. To assess potential measles virus shedding by means of RT-qPCR of saliva, nasal swab, urine, or blood samples in sentinel groups on day 0, 7, 14, 28 and 42
9. Exploratory objectives	To assess the anti-measles antibody levels at baseline, on day 28, and on day 56 by ELISA. To assess the natural exposure of the subjects to SARS-CoV-2 during the duration of the trial by means of N protein-specific immunoassay. To assess the occurrence of COVID-19 cases in study participants all along the duration of the study.
10. Primary evaluation criterion	• Rate of solicited Adverse Event up to 14 days after each injection. • Rate of unsolicited AE up to 28 days after each injection. • Rate of serious adverse events (SAEs), serious adverse reactions (SARs), suspected unexpected serious adverse reactions (SUSARs) and adverse events of special interest (AESI) all along the study period.
11. Secondary evaluation criteria	• Onset: SARS-CoV-2 specific antibodies up to study day 56 as measured by spike protein-specific ELISA and serum neutralization assay. • Durability: SARS-CoV-2 specific antibodies on day 91 for each cohort as measured by spike protein-specific ELISA and serum neutralization assay.

	• SARS-CoV-2 spike protein-specific cell-mediated immune response up to study day 91 induced by one or two doses as measured by intracellular staining and flow cytometry. • Occurrence of measles virus shedding as evidenced by a positive RT-PCR for saliva, nasal swab, urine, or blood sample in sentinel groups.
12. Exploratory	• Measles virus antibody levels as assessed by standard ELISA assays on day 0, day 28, and day 56. • SARS-CoV-2 N protein specific antibody up to study day 91 as measured by immunoassay to differentiate the response to the COVID-19 vaccine from infection • Occurrence of confirmed COVID-19 (i.e. asymptomatic, paucisymptomatic or symptomatic) cases in the study participant all along the study period.
13. Study population	Healthy volunteers – adults 18 to 55 years
14. Number of subjects	90
15. Inclusion criteria	1. Males and females between the ages of 18 and 55 years (at the time of consent). 2. Healthy participant, according to the investigator's clinical judgment, as established by medical history, vital signs, physical examination, and laboratory assessments 3. Participant with a body mass index (BMI) <30.0 kg/m^2 4. Provide written informed consent before initiation of any study procedures. 5. A female participant is eligible for this study if she is not pregnant, given by a negative serum pregnancy test at screening and a negative urine pregnancy test at V1 (1st injection), or breast feeding and 1 of the following: o Of non-childbearing potential (i.e., women who have had a hysterectomy or tubal ligation or are postmenopausal, as defined by no menses in greater than or equal to 1 year). o Of childbearing potential but has been and agrees to continue practicing highly effective contraception or abstinence (if this is the preferred and usual lifestyle of the participant) from 30 days prior to vaccination up to 6 months after the last injection (D210). o Highly effective methods of contraception include 1 or more of the following: ▪ male partner who is sterile (vasectomised) prior to the female participants entry into the study and is the sole sexual partner for the female participant; ▪ hormonal (oral, intravaginal, transdermal, implantable or injectable); ▪ an intrauterine hormone-releasing system (IUS);

	▪ an intrauterine device (IUD) with a documented failure rate of < 1%. 6. A female participant is eligible if she is willing to abstain from donating oocyte from the screening visit up to 6 months after the last injection (D210); 7. A male participant who is sexually active is eligible if he is willing to : o use a condom (with/without spermicidal product) from the screening visit up to 6 months after the last injection (D210) except if the male participant is sterile (e.g. vasectomised); the unique female sexual partner is postmenopausal (defined as no menses for 12 months without an alternative medical cause), is permanently sterilized (e.g. hysterectomy or tubal ligation), or use a highly effective methods of contraception; o not donate sperm from the screening visit up to 6 months after the last injection (D210); o not plan to father a child from the screening visit up to 6 months after the last injection (D210). 8. Negative HIV 1/2 antibody/antigen test, Hepatitis B surface antigen (HBsAg), and Hepatitis C virus (HCV) antibody. 9. Able to understand and comply with planned study procedures and willing to be available for all study-required procedures, visits and calls for the duration of the study. 10. Willing to abstain from donating whole blood or blood derivatives, tissue or organ all along the study. 11. Affiliated to a social security system, (except state medical aid) (Only for France). 12. Volunteer registered in the French Health Ministry computerized file and authorized to participate in a clinical trial (only for France).
16. Exclusion criteria	13. Subjects actively or previously infected by SARS-CoV-2, as determined by a positive RT-PCR and positive serology test. 14. Subject currently working with high risk of exposure to SARS-CoV-2 (e.g. health care worker, emergency response personnel, etc.) or considered at the investigator's discretion to be at increased risk to acquire SARS-CoV-2 for any other reason. 15. Previous vaccination with an investigational COVID-19 vaccine. 16. History of presence of pulmonary disorders (e.g. COPD, etc.) or asthma. 17. History or present of thrombocytopenia and/or bleeding disorders. 18. A positive serum pregnancy test at screening or urine pregnancy test prior to study injection, women who are planning to become pregnant during the study, or women who are breastfeeding. 19. Clinically relevant history of or current renal, hepatic, gastrointestinal, cardiovascular, respiratory, skin, hematological, endocrine, inflammatory, autoimmune, central nervous system or neurological diseases or clinically relevant abnormal laboratory values.

20. Use of immunosuppressive drugs like e.g. corticosteroids (excluding topical preparations and inhalers) within 3 months prior to the first vaccination or 6 months for chemotherapies and all along the study.
21. A diagnosis of schizophrenia, bipolar disease, or history of hospitalization for a psychiatric condition or previous suicide attempt.
22. A history of treatment for any other psychiatric disorder in the past 3 years that increases the risk to the subject in the opinion of the investigator.
23. Received immunoglobulin or other blood product within 3 months prior to enrollment or planned receipt of immunoglobulin or a blood product through study completion.
24. Vaccination within 4 weeks prior to first injection or planning to receive a licensed vaccine before D56 (*e.g. Inactivated influenza vaccine*).
25. Received measles-containing vaccine within 3 months prior to enrollment.
26. History of severe adverse reactions to vaccine administration, including anaphylaxis and related symptoms, such as urticaria, respiratory difficulty, angioedema and abdominal pain to vaccines, or history of known or suspected allergic reaction likely to be exacerbated by any component of the COVID-19 vaccine.
27. Participation in another investigational clinical study within four weeks before the screening visit or planned before the study completion.
28. Individuals who are living and/or working with severely immunocompromised people, pregnant women, lactating women, children under 12 months old, or any other individual that, in the judgment of the investigator, might be at increased risk.
29. Any condition that, in the opinion of the investigator, may interfere with the aim of the study or the safety or wellbeing of the subject.
30. Subjects with any condition associated with, or that might be associated with, an increased risk of severe illness from COVID-19 according to US CDC definition[1].
31. Subjects with confirmed or suspected immunodeficiency.
32. Exposure to an individual with confirmed COVID-19 or SARS-CoV-2 infection within the past 2 weeks prior to enrollment.
33. Subject with an acute disease and/or fever (body temperature ≥ 38°C) at the time of the 1st vaccination visit.
34. History of confirmed SARS-CoV or MERS-CoV infection.
35. Current heavy smoker defined as smoking at least 20 cigarettes (1 pack, or equivalent) per day or former heavy smoker who was an active heavy smoker within the last year prior to the screening visit or has a total smoking history of ≥ 1 pack per day for 10 years or more.
36. Current or history of alcohol or drug abuse during the previous 3 years.

[1] https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fneed-extra-precautions%2Fgroups-at-higher-risk.html

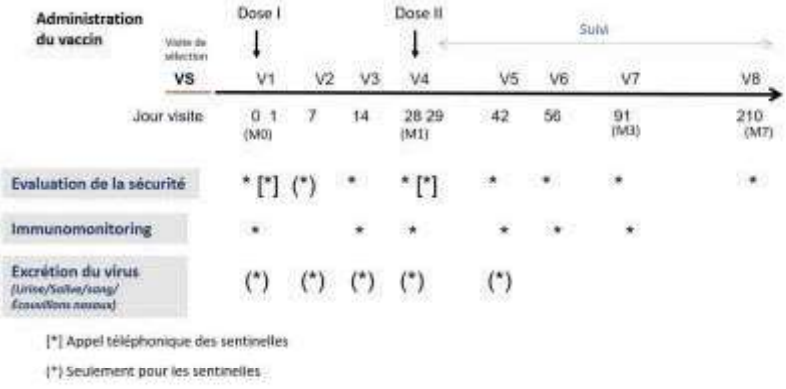
	37. Presence of tattoos that, in the opinion of the investigator, would preclude evaluation of the injection site.
17. DSMB	An independent DSMB will be installed to review accruing safety information, and if necessary, to determine whether study or individual participant halting rules have been met. The DSMB will review listings and summary tabulations of SAEs, deaths, AESIs, solicited AEs, unsolicited AEs and AEs leading to withdrawal from further vaccination. A DSMB meeting, to review the safety data to evaluate the safety of the unblinded sentinel subjects before giving a positive recommendation for continuing with the blinded treatment phase will be performed once all six participants enrolled in the unblinded COVID-19 vaccine groups completed day 14 (V3). A Medical review of safety data (Intermediate Report 2, IR2, see below) will be performed after all six sentinels subjects completed day 42 (V5 – 14 days after the second injection). In case of any safety concern, an ad hoc DSMB meeting will be organized before giving a positive recommendation for continuing with the second injection of the "main cohorts". Additionally, the intermediate and interim analysis reports prepared at the following time points and will be shared with the DSMB (excluding observing DSMB members who will only have access to blinded safety report) and with the vaccine developer: 1. Intermediate Report 1 (IR1): After all six sentinel subjects completed visit 4 (day 28) 2. Intermediate Report 2 (IR2): After all six sentinel subjects completed visit 5 (day 42), as outlined above 3. Intermediate Report 3 (IR3): After all (or at least 50% depending on the enrolment rate) subjects completed visit 4 (day 28) A final DSMB meeting will be organized after all subjects completed visit 8 (day 210) to be informed of the study global results. Upon Sponsor decision ad hoc DSMB meetings might be scheduled during the whole duration of the study. A written DSMB charter will be developed. DSMB recommendations will also be transmitted to the Competent Authorities, the vaccine developer's representative, and IRB-Institut Pasteur.
18. Study halting rules	The criteria for considering a contraindication or preventive action to the start of the treatment of the 2nd or 3rd cohort (increasing dosage) or administration of the COVID-19 vaccine to subsequent subjects in the current cohort will be: - A serious adverse reaction (i.e. a serious adverse event considered at least possibly related to the study vaccine) in one subject. - The occurrence of clinically significant severe (grade 3 or higher) non-serious adverse events considered as at least possibly related to the vaccine administration in two subjects in the same cohort, independent of within or not within the same system-organ-class. Both clinical and laboratory abnormalities are considered. - Any onset of AESI assessed as related to the vaccine by the investigator or by the sponsor.
19. Main personal data to be collected	- Age, sex - Physical examination, with height, weight - Personal medical history & vaccination history - Treatment history - Allergies

	- Pregnancy test results for women - Contraception methods - Safety Laboratory results (see Appendix 1) - ECG
20. Data collection, transfer, record and management	The trial data management plan will be issued before data collection begins and will describe all functions, processes, and specifications for data collection, cleaning and validation. The data management documents will describe captured methods, who is authorized to enter the data, decisions about ownership of data, source data storage, which data will be transferred (including timing of transfers), the origin and destination of the data and who will have access to the data at all times.
21. Statistical analysis	The Statistical Analysis Plan will be issued before any trial data are made available. The plan will determine all necessary data preparation steps (e.g. additional validations, generation of new variables), definitions (e.g. analysis sets) and statistical analyses (e.g. models, outputs such as tables and graphs). All participants entered into the study who receive at least one vaccination will be included in the safety analysis. For solicited local, solicited systemic and unsolicited AEs, the number and percentage of participants with AEs will be summarized for each cohorts, overall, by system organ class /preferred term, AE grade, and relatedness. Solicited (local and systemic) and unsolicited AEs will be analyzed descriptively. The secondary and exploratory immunogenicity endpoints will be analyzed within each group, using appropriate tests.
22. Interim Analysis	Intermediate reports (no database lock) and interim analysis (with database lock) including safety and some immunogenicity data will be performed: 1. Intermediate Report 1: After all six sentinel subjects completed visit 4 (day 28) 2. Intermediate Report 2: After all six sentinel subjects completed visit 5 (day 42) 3. Intermediate Report 3: After all (or at least 50% depending on the enrolment rate) subjects completed visit 4 (day 28) 4. Interim analysis for interim CSR after all subjects completed visit 7 (day 91) or the Early Termination visit (ET) The purpose of these intermediate analyses is to provide safety and some immunogenicity data for further SARS-CoV-2 vaccine development in outbreak situation. Intermediate analyses will also be presented to an independent data review monitoring board (DSMB). DSMB recommendations regarding further study conduct and/or protocol modifications will be considered by the sponsor. An interim analysis for the preparation of an interim CSR will be generated. Upon request, the DSMB members will have access to this interim CSR. The final analysis (final CSR) will be conducted once the last participant has completed the study.
23. Study Calendar	▪ Provisional start recruitment date: Q2 2020 ▪ Provisional start enrollment date : Q3 2020 ▪ Provisional inclusion duration: approximately 6 weeks ▪ Subject's participation duration: approximately 7 months ▪ Projected study duration: approximately 15 months ▪ Data archiving duration: 25 years after the completion of the study ▪ Biobanks duration: 15 years

24. Number of clinical investigational centers	2 clinical sites, one in France (CIC-Pasteur Cochin, Paris) and one in Belgium (SGS Life Sciences, Clinical Pharmacology Unit, Antwerp)

PROTOCOL SYNOPSIS (FRENCH VERSION)

1. Titre complet	Essai randomisé, contrôlé par placebo, pour évaluer la sécurité et l'immunogénicité d'un candidat vaccin (TMV-083) utilisant le vaccin de la rougeole comme vecteur contre la COVID-19 chez des volontaires sains, consistant en une escalade de dose en ouvert et une phase de traitement en aveugle
2. Acronyme ou titre court	COVID-19-101
3. Rationnel de l'étude	Les coronavirus sont une grande famille de virus qui, pour la plupart, causent des maladies similaires au rhume chez l'être humain, mais aussi des épidémies de maladies plus sévères, comme le syndrome respiratoire aigu sévère (SRAS) en 2003 et le syndrome respiratoire du Moyen-Orient (MERS) depuis 2012. Une nouvelle maladie infectieuse à coronavirus (COVID-19) a été identifiée en 2019 à Wuhan, en Chine, provoquée par le coronavirus du syndrome respiratoire aigu sévère 2 (SARS-CoV-2). L'épidémie de COVID-19 en cours a été déclarée urgence de santé publique de portée internationale (PHEIC, OMS). À l'heure actuelle, des cas ont été confirmés dans 199 pays et territoires. La transmission interhumaine est désormais la principale source des nouvelles infections (Chen et al., Infectious Disease 2020). Il n'existe actuellement aucun traitement spécifique, uniquement des soins de support. Le développement de vaccins est un outil essentiel pour mettre fin aux infections, réduire l'excrétion virale et stopper la propagation de la maladie. Les souches atténuées du virus de la rougeole sont des vecteurs de vaccination éprouvés et peuvent être utilisées comme squelette pour exprimer et présenter des antigènes pertinents afin de favoriser une réponse immunologique protectrice contre les pathogènes infectieux. Le développement clinique de cette technologie est déjà bien avancé. Un candidat vaccin utilisant le vecteur rougeole (MV) contre le virus chikungunya (MV-CHIK) est actuellement testé dans des essais de phase III et s'est avéré être bien toléré et hautement immunogène. Il est important de noter que l'immunité pré-existante contre la rougeole n'altère pas la réponse. De plus, les doses plus élevées testées ont entraîné une séroconversion après une seule immunisation chez environ 90 % des sujets (Ramsauer et al., 2015, Lancet Inf. Dis. ; Reisinger et al., 2018, Lancet), indiquant qu'une seule dose pourrait suffire pour obtenir un bénéfice clinique, ce qui est capital pendant une épidémie ou une flambée. Un vaccin contre le SRAS utilisant le vecteur rougeole (MV) et exprimant la protéine Spike (S) complète, a démontré son efficacité chez la souris contre le SARS-CoV-1 (Escriou et al., 2014, Virology). De même, un candidat vaccin MV-MERS-CoV en développement en vue d'essais cliniques, basé sur l'antigène S homologue du MERS-CoV, s'est lui aussi avéré efficace chez la souris contre le MERS (Malczyk et al., 2015, J. Virol). Par conséquent, on peut s'attendre à ce que le candidat vaccin utilisant le vecteur rougeole (MV-SARS-2) ciblant la protéine S du SARS-CoV-2 soit une approche prometteuse pour produire un vaccin efficace contre la COVID-19.

4. Produit expérimental et placebo correspondant	Vaccin contre la COVID-19, un vaccin recombinant basé sur le virus vivant atténué de la rougeole comme vecteur, exprimant une glycoprotéine de surface modifiée du nouveau coronavirus (SARS-CoV-2), administré à deux niveaux de dosage (à des concentrations cibles de 5 log 10 ou 6 log 10 $DICT_{50}$) en une ou deux injections (aux jours 0 et 28). Le vaccin est administré par injection intramusculaire (i.m).
5. Placebo	Sérum physiologique (NaCl à 0,9 %), administré par injection i.m.
6. Design de l'étude	Ce premier essai clinique chez l'Homme sera mené en Europe dans deux centres d'investigation, un en France et un en Belgique, avec un recrutement compétitif. L'objectif de cet essai clinique est de démontrer la sécurité et l'immunogénicité du vaccin chez une population adulte de volontaires sains. Pour atteindre ces objectifs, 90 sujets seront inclus, 30 par cohorte dans trois cohortes, chaque cohorte comprenant 24 sujets vaccinés et 6 sujets recevant le placebo. Les sujets recevront soit le vaccin à faible dosage (2 injections) soit le vaccin à fort dosage (1 ou 2 injections) ou le placebo. Huit visites (neuf pour les « groupes sentinelles ») sont prévues pendant la durée de l'étude. Parmi ces huit visites (neuf pour les « groupes sentinelles »), une correspond à la visite de sélection, cinq (six pour les « groupes sentinelles ») sont des visites de suivi avec la réalisation de prélèvements sanguins et deux correspondent aux visites d'injection. De plus, un appel téléphonique dit de sécurité sera effectué 24 heures après chaque injection (uniquement pour les « groupes sentinelles »).  [*] Appel téléphonique dit de sécurité auprès des sujets sentinelles (*) Uniquement pour les sujets sentinelles Après la visite de sélection, les participants devront revenir au centre d'investigation pour les visites aux jours 0, 7 (uniquement pour les sujets sentinelles), 14, 28, 42 et 56 pour des évaluations de sécurité et pour un recueil d'échantillons pour l'analyse de l'immunogénicité, puis aux jours 91 dans le cadre du suivi et pour la réalisation de prélèvement dans le cadre de l'analyse de l'immunogénicité à long terme. Des échantillons seront collectés uniquement sur les sujets des « groupes sentinelles » (traitement sans insu dans les cohortes A et B) pour l'étude de l'excrétion virale de la rougeole. Les liquides corporels, incluant la salive, un

écouvillonnage nasal, l'urine et le sang total, seront collectés à la visite 1 (jour 0), la visite 2 (jour 7 après la première injection), la visite 3 (jour 14), la visite 4 (jour 28) et la visite 5 (jour 42).

Cohorte	Traitement	Injection 1 J0	Injection 2 J28	Nombre de participants		
				Vaccin contre la COVID-19 **Groupe Sentinelles**	Vaccin contre la COVID-19 **Groupe Principal**	Placebo
A	COVID-19 à faible dosage	Vaccin	Vaccin	3	21	6
B	COVID-19 à fort dosage	Vaccin	Vaccin	3	21	6
C	COVID-19 à fort dosage	Vaccin	Placebo	0	24	6

Par mesure de précaution, l'étude commencera avec le recrutement d'un petit groupe de sujets dits « sentinelles » (3 sujets de la cohorte A et 3 sujets de la cohorte B), chacun d'entre eux recevra le vaccin aux jours 0 et 28 de manière non randomisée et en ouvert. Le recrutement des « groupes sentinelles » sera effectué dans un seul centre de recherche, celui situé dans le pays où l'avis favorable du Comité d'éthique et l'autorisation de l'Autorité compétente seront obtenus en premier.

Le premier sujet des « groupes sentinelles » sera recruté dans la cohorte A et recevra le vaccin à faible dosage au jour 0. Vingt-quatre heures après l'injection, le sujet sera contacté par téléphone afin de recueillir des informations de sécurité liées à la vaccination. L'investigateur clinique pourra ensuite décider de passer à la vaccination du deuxième et du troisième sujet en l'absence d'EI sévères/d'EIG liés au vaccin (pas moins de 24 heures après que le premier sujet a reçu la première injection et l'appel téléphonique).

Le deuxième et le troisième sujet des « groupes sentinelles » seront recrutés le même jour, avec un intervalle d'au moins 3 heures, dans la cohorte A, et recevront le vaccin à faible dosage au jour 0. Vingt-quatre heures après l'injection, le deuxième et le troisième sujet seront contactés par téléphone afin de recueillir des informations de sécurité liées à la vaccination. L'investigateur clinique pourra ensuite décider de passer à la vaccination du quatrième sujet en l'absence d'EI sévères/d'EIG liés au vaccin (pas moins de 24 heures après que le deuxième et le troisième sujet ont reçu la première injection et l'appel téléphonique).

Le quatrième sujet des « groupes sentinelles » sera recruté dans la cohorte B et recevra le vaccin à fort dosage. Vingt-quatre heures après l'injection, le sujet sera contacté par téléphone afin de recueillir des informations de sécurité liées à la vaccination. L'investigateur clinique pourra ensuite décider de passer à la vaccination des deux derniers sujets en l'absence d'EI sévères/d'EIG liés au vaccin (pas moins de 24 heures après que le quatrième sujet a reçu le premier traitement et l'appel téléphonique).

Le cinquième et le sixième participant des « groupes sentinelles » seront recrutés le même jour, avec un intervalle d'au moins 3 heures, dans la cohorte B, et recevront le vaccin à fort dosage au jour 0. Vingt-quatre heures après l'injection, ils seront contactés par téléphone afin de recueillir des informations de sécurité liées à la vaccination.

	Lorsque tous les sujets sentinelles auront réalisé leurs visites de suivi 14 jours post-vaccination, le Comité indépendant de surveillance et de suivi de l'étude (DSMB) examinera les données de sécurité faisant suite à la première injection réalisée chez ces six participants, avant de donner une recommandation (écrite) pour la poursuite de l'étude avec l'initiation de la phase randomisée en double aveugle. **Lorsque tous les sujets sentinelles** auront réalisé leurs visites de suivi 42 jours post-vaccination, une surveillance médicale des données de sécurité sera effectuée afin d'évaluer la sécurité de la seconde injection chez ces six participants. En cas de potentiel problème de sécurité, une réunion ad hoc du DSMB sera organisée avant de donner une recommandation positive pour la poursuite de la seconde injection dans les cohortes randomisées en double aveugle (« cohortes principales »). En cas d'EI sévères ou d'EIG liés au vaccin, le promoteur sera contacté par le DSMB et après discussion, il sera décidé si l'étude peut être poursuivie conformément au protocole. Les analyses prévues dans le cadre de cette étude incluront : des tests de séroneutralisation, des tests ELISA pour vérifier la présence d'anticorps anti-protéine S et N du SARS-CoV-2, des tests ELISA pour vérifier la présence d'anticorps contre la rougeole, des analyses de marquage intracellulaire pour évaluer les réponses des lymphocytes T et des analyses d'excrétion virale de la rougeole (uniquement pour les sujets sentinelles).
7. Objectif principal	Évaluer la sécurité et la tolérance du vaccin TMV-083 contre la COVID-19 après une ou deux injections intramusculaires consécutives chez des volontaires sains.
8. Objectifs secondaires	Évaluer l'induction d'anticorps anti-protéine Spike du SARS-CoV-2 après une ou deux administrations du vaccin contre la COVID-19 au moyen d'un test ELISA jusqu'au jour 91 de l'étude. Évaluer l'induction d'anticorps neutralisant le SARS-CoV-2 après une ou deux administrations du vaccin contre la COVID-19 au moyen d'un essai de séroneutralisation jusqu'au jour 91 de l'étude. Évaluer les réponses immunitaires à médiation cellulaire spécifiques à la protéine Spike du SARS-CoV-2, induites par une ou deux doses de vaccin, au moyen d'un marquage intracellulaire et d'une cytométrie en flux, jusqu'au jour 91 de l'étude. Évaluer, au moyen d'une RT-qPCR, l'excrétion potentielle du virus de la rougeole sur des échantillons de salive, d'urine, de sang ou sur un écouvillonnage nasal collectés chez les groupes sentinelles aux jours 0, 7, 14, 28 et 42.
9. Objectifs exploratoires	Évaluer, par l'intermédiaire d'un test ELISA, les taux d'anticorps contre la rougeole à l'inclusion, au jour 28 et au jour 56. Évaluer, au moyen d'un test d'immunoessai pour la protéine N, l'exposition naturelle des sujets au SARS-CoV-2 pendant la durée de l'essai. Évaluer l'apparition de cas de COVID-19 chez les participants à l'étude tout au long de l'étude.

10. Critère d'évaluation principal	• Taux d'événements indésirables sollicités jusqu'à 14 jours après chaque injection. • Taux d'EI non sollicités jusqu'à 28 jours après chaque injection. • Taux d'événements indésirables graves (EIG), de réactions indésirables graves (RIG), de suspicions d'effets indésirables graves inattendus (SEIGI) et d'événements indésirables d'intérêt particulier (EIIP) tout au long de l'étude.
11. Critères d'évaluation secondaires	• Apparition de l'immunité : présence d'anticorps spécifiques au SARS-CoV-2 jusqu'au jour 56 de l'étude mesurée par un test ELISA pour la protéine Spike et une analyse de séroneutralisation. • Durabilité de l'immunité : présence d'anticorps spécifiques au SARS-CoV-2 jusqu'aux jours 91 pour chaque cohorte, mesurée par un test ELISA pour la protéine Spike et une analyse de séroneutralisation. • Présence d'une réponse immunitaire à médiation cellulaire spécifique à la protéine Spike du SARS-CoV-2 jusqu'au jour 91 de l'étude, après une ou deux doses de vaccin, mesurée par un marquage intracellulaire et une cytométrie en flux. • Survenue de l'excrétion du virus de la rougeole, donnée par une RT-PCR positive sur les échantillons de salive, d'urine, de sang ou le prélèvement nasal dans les groupes sentinelles.
12. Critères d'évaluation exploratoires	• Taux d'anticorps au virus de la rougeole tels qu'évalués par des dosages ELISA standard au jour 0, au jour 28 et au jour 56. • Anticorps spécifiques à la protéine N du SARS-CoV-2 jusqu'au jour 91 de l'étude tels que mesurés par test d'immunoessai pour différencier la réponse au vaccin contre la COVID-19 d'une infection. • Apparition de cas de COVID-19 confirmés (c.-à-d. asymptomatiques, paucisymptomatiques ou symptomatiques) chez les participants à l'étude tout au long de l'étude.
13. Population de l'étude	Volontaires sains – adultes de 18 à 55 ans
14. Nombre de sujets	90
15. Critères d'inclusion	1. Hommes et femmes âgés de 18 à 55 ans (au moment du consentement). 2. Participant en bonne santé, selon l'avis clinique de l'investigateur, comme établi par les antécédents médicaux, les signes vitaux, l'examen physique et les analyses biologiques. 3. Participant présentant un indice de masse corporelle (IMC) < 30,0 kg/m^2). 4. Recueil d'un consentement éclairé écrit avant le début de toute procédure de l'étude. 5. Une participante est éligible à cette étude si elle n'est pas enceinte, confirmé par un test de grossesse sanguin négatif à la sélection et par un

test de grossesse urinaire négatif à la V1 (1re injection) ou si elle n'allaite pas, et si elle répond à l'un des critères suivants :

- Ne pouvant pas avoir d'enfant (c.-à-d., femme ayant subi une hystérectomie ou une ligature des trompes, ou femme ménopausée, à savoir n'ayant pas eu de règles depuis au moins 1 an).
- Pouvant avoir des enfants mais utilisant et acceptant de continuer à utiliser une contraception hautement efficace ou de pratiquer l'abstinence (si c'est le mode de vie choisi et habituel de la participante) 30 jours avant la vaccination et jusqu'à 6 mois après la dernière injection (J210).
- Les méthodes de contraception hautement efficaces incluent une ou plusieurs des méthodes suivantes :
  - partenaire masculin stérile (ayant subi une vasectomie) avant que la participante n'entre dans l'étude et étant le seul partenaire sexuel de la participante ;
  - contraception hormonale (orale, intravaginale, transdermique, implantable ou injectable) ;
  - système intra-utérin (SIU) à libération d'hormone ;
  - dispositif intra-utérin (DIU) avec un taux d'échec documenté < 1 %.

6. Une participante est éligible si elle accepte de ne pas faire de don d'ovocytes depuis la visite de sélection et jusqu'à 6 mois après la dernière injection (J210).
7. Un participant masculin qui est sexuellement actif est éligible s'il accepte :
   - d'utiliser des préservatifs (avec ou sans spermicide) depuis la visite de sélection et jusqu'à 6 mois après la dernière injection (J210) sauf si le participant est stérile (ex. vasectomie); l'unique partenaire sexuelle féminine est ménopausée (défini comme n'ayant pas eu de règles pendant 12 mois sans autre cause médicale), est stérile de façon permanente (ex. hystérectomie ou ligature des trompes) ou utilise une méthode de contraception très efficace ;
   - de ne pas faire de don de sperme depuis la visite de sélection et jusqu'à 6 mois après la dernière injection (J210) ;
   - de ne pas envisager de concevoir un enfant depuis la visite de sélection et jusqu'à 6 mois après la dernière injection (J210).
8. Sérologies négatives pour le VIH1/2 (anticorps/antigènes négatifs), pour l'hépatite B (AgHBs négatif) et pour l'hépatite C (Ac anti-VHC négatif).
9. En mesure de comprendre et de suivre les procédures prévues à l'étude et acceptant d'être disponible, pendant toute la durée de l'étude, pour la réalisation de toutes les procédures, visites et tous les appels requis pour l'étude.
10. Acceptant de ne pas faire de don de sang total ou de dérivés sanguins, de tissus ou d'organes pendant toute la durée de l'étude.

	11. Affilié(e) à un régime de sécurité sociale (sauf Aide médicale d'État) (uniquement pour la France). 12. Volontaire inscrit dans le registre informatisé du ministère français de la Santé et autorisé à participer à un essai clinique (uniquement pour la France).
16. Critères de non-inclusion	13. Sujets précédemment ou actuellement infectés par le SARS-CoV-2, donné par un résultat virologique positif par RT-PCR et par un résultat sérologique positif. 14. Sujet ayant un travail présentant un risque élevé d'exposition au SARS-CoV-2 (ex. professionnel de santé, personnel d'intervention d'urgence, etc.) ou considéré, de l'avis de l'investigateur, comme présentant un risque élevé de contracter le SARS-CoV-2 pour toute autre raison. 15. Précédemment vacciné avec un vaccin expérimental contre la COVID-19. 16. Antécédents de maladies pulmonaires (ex. BPCO, etc.) ou d'asthme. 17. Présence ou antécédent d'une thrombocytopénie et/ou de troubles hémorragiques. 18. Test de grossesse sérique positif lors de la sélection ou test de grossesse urinaire positif avant l'injection du vaccin à l'étude, femmes qui prévoient une grossesse pendant l'étude, ou femmes qui allaitent. 19. Présence ou antécédents cliniquement significatifs de maladie rénale, hépatique, gastro-intestinale, cardiovasculaire, respiratoire, cutanée, hématologique, endocrinienne, inflammatoire, auto-immune, du système nerveux central ou neurologique, ou de résultats d'analyses biologiques anormaux et cliniquement significatifs. 20. Prise de médicaments immunosuppresseurs, ex. corticostéroïdes, (sauf les préparations topiques et les inhalateurs) dans les 3 mois précédant la première vaccination ou dans les 6 mois pour les chimiothérapies et tout au long de l'étude. 21. Diagnostic de schizophrénie, de bipolarité ou antécédents d'hospitalisation pour une maladie psychiatrique ou pour une tentative de suicide. 22. Antécédents de traitement pour tout autre trouble psychiatrique au cours des 3 dernières années qui, de l'avis de l'investigateur, peut induire un risque pour le sujet. 23. Utilisation ou utilisation prévue d'immunoglobuline ou autre produit sanguin dans les 3 mois précédant l'inclusion ou pendant toute la période de l'étude. 24. Vaccination avec un vaccin commercialisé dans les 4 semaines précédant la première injection ou prévue avant le J56 (ex. vaccin de la grippe). 25. Ayant été vacciné(e) avec un vaccin contenant la rougeole dans les 3 mois précédant l'inclusion. 26. Antécédents de réactions indésirables sévères suite à l'administration d'un vaccin, anaphylaxie et symptômes associés, tels qu'urticaire, difficulté respiratoire, œdème de Quincke et douleur abdominale liés à des vaccins, ou antécédents connus ou suspectés de réaction allergique susceptible d'être exacerbée par tout composant du vaccin contre la COVID-19.

	27. Participation à une autre étude de recherche clinique dans les quatre semaines précédant la visite de sélection ou prévue avant la fin de l'étude. 28. Individus qui vivent et/ou travaillent avec des personnes sévèrement immunodéprimées, des femmes enceintes, des femmes qui allaitent, des enfants de moins de 12 mois, ou tout individu qui, de l'avis de l'investigateur, peut présenter un risque accru. 29. Maladie qui, de l'avis de l'investigateur, peut compromettre l'objectif de l'étude ou la sécurité ou le bien-être du sujet. 30. Sujets présentant une maladie associée ou pouvant être associée à un risque accru de COVID-19 sévère d'après la définition des CDC américains[2]. 31. Sujets présentant une immunodéficience confirmée ou suspectée. 32. Exposition à un individu ayant une COVID-19 ou une infection par le SARS-CoV-2 confirmée dans les 2 semaines précédant le recrutement. 33. Sujet présentant une maladie aiguë et/ou de la fièvre (température ≥ 38 °C) au moment de la visite de la 1re vaccination. 34. Antécédents d'infection par le SRAS ou le MERS-CoV confirmée. 35. Gros fumeur actuel, défini comme fumant au moins 20 cigarettes (1 paquet ou équivalent) par jour ou ancien gros fumeur qui a été un gros fumeur au cours de l'année précédant la visite de sélection ou qui un antécédent de consommation de cigarettes ≥ 1 paquet/jour pendant 10 ans ou plus. 36. Abus d'alcool ou de drogues actuel ou passé au cours des 3 années précédant l'inclusion. 37. Présence de tatouages qui, de l'avis de l'investigateur, empêcheraient l'évaluation du site d'injection.
17. DSMB	Un DSMB indépendant sera instauré pour examiner les informations de sécurité obtenues et, si nécessaire, pour déterminer si les règles d'arrêt de l'étude ou de retrait d'un participant spécifique ont été respectées. Le DSMB passera en revue les listes et les tableaux synthétiques d'EIG, de décès, d'EIIP, d'EI sollicités, d'EI non sollicités et d'EI conduisant à l'arrêt de toute nouvelle vaccination. Une réunion du DSMB pour examiner les données de sécurité afin d'évaluer la sécurité des sujets sentinelles sans insu (en ouvert) avant de donner une recommandation positive pour passer à la phrase de traitement en insu (en aveugle) aura lieu une fois que les six participants inclus dans les groupes du vaccin contre la COVID-19 sans insu auront tous effectué la visite du jour 14 (V3). Une revue médicale des données de sécurité sera effectuée une fois que les six sujets sentinelles auront tous effectué la visite du jour 42 (V5 – 14 jours après la seconde injection). En cas de potentiel problème de sécurité, une réunion ad hoc du DSMB sera organisée avant de donner une recommandation positive pour la poursuite de la seconde injection dans les « cohortes principales ».

[2] https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fneed-extra-precautions%2Fgroups-at-higher-risk.html

	Le DSMB (à l'exception des membres observateurs du DSMB qui n'auront accès qu'au rapport de sécurité en insu) recevra également des rapports et les analyses intermédiaires prévues au protocole : 1. Rapport intermédiaire 1 (RI1) : Lorsque les 6 sujets sentinelles auront effectué la visite 4 du jour 28, 2. Rapport intermédiaire 2 (RI2) : lorsque les 6 sujets sentinelles auront effectués la visite 5 du jour 42 comme indiqué ci-dessus 3. Rapport intermédiaire 3 (RI3) : Lorsque tous les sujets (ou au moins 50 % en fonction du taux de recrutement) auront effectué la visite 4 du jour 28. Une dernière réunion du DSMB sera organisée après que tous les sujets auront terminé la visite 8 (jour 210) pour être informé des résultats globaux de l'étude. Après la décision du promoteur, des réunions ad hoc du DSMB pourraient être prévues pendant toute la durée de l'étude. Une charte du DSMB sera rédigée. Les recommandations du DSMB seront également transmises aux Autorités compétentes, au représentant du développeur du vaccin, et à l'IRB Institut Pasteur.
18. Règles d'arrêt de l'étude	Les critères pour envisager une contre-indication ou une action préventive au démarrage du traitement dans la 2e ou la 3e cohorte (montée de dosage) ou à l'administration du vaccin contre la COVID-19 aux sujets suivants dans la même cohorte seront : - Une réaction indésirable grave (c.-à-d. un événement indésirable grave considéré comme au moins possiblement lié au vaccin à l'étude) chez un sujet. - La survenue d'événements indésirables non graves sévères (grade 3 ou plus) cliniquement significatifs, considérés comme possiblement liés à l'administration du vaccin chez deux sujets de la même cohorte, que ces EI concernent ou non la même classe de systèmes d'organes. Les anomalies cliniques et biologiques sont prises en compte. - Toute apparition d'événement indésirable d'intérêt particulier (EIIP) évalué comme lié au vaccin par l'investigateur ou par le promoteur.
19. Principales données à caractère personnel recueillies	- Âge, sexe - Examen physique, avec taille et poids - Antécédents médicaux personnels et antécédents de vaccination - Antécédents de traitement - Allergies - Résultats du test de grossesse pour les femmes - Méthodes de contraception - Résultats des analyses biologiques de sécurité (voir l'annexe 1) - ECG
20. Recueil, transfert, enregistre-ment et traitement des données	Le plan de gestion des données de l'essai sera publié avant que la collecte des données commence et décrira toutes les fonctions, procédures et spécifications pour la collecte, le nettoyage et la validation des données. Les documents de gestion des données décriront les méthodes de recueil, les personnes autorisées à saisir les données, les décisions sur la propriété des données, le stockage des données source, quelles données seront transférées (y compris le moment des transferts), l'origine et la destination des données et les personnes qui auront accès aux données à tout moment.
21. Analyse statistique	Le plan d'analyse statistique sera rédigé avant que les données de l'essai soient disponibles. Le plan déterminera toutes les étapes de préparation des données

	nécessaires (ex. validations supplémentaires, génération de nouvelles variables), définitions (ex. ensembles d'analyses) et analyses statistiques (ex. modèles, types de sorties tels que tableaux et graphiques). Tous les participants recrutés dans l'étude qui recevront au moins une vaccination seront inclus dans l'analyse de sécurité. Pour les EI locaux sollicités, les EI systémiques sollicités et les EI non sollicités, le nombre et le pourcentage de participants avec des EI seront résumés pour chaque cohorte, globalement, par classe de systèmes d'organes/terme préféré, grade d'EI et lien avec le vaccin expérimental. Les EI (locaux et systémiques) sollicités et les EI non sollicités seront analysés de manière descriptive. Les critères d'évaluation secondaires et exploratoires d'immunogénicité seront analysés dans chaque groupe, en utilisant les tests appropriés.
22. Analyse intermédiaire	Des analyses intermédiaires incluant les données de sécurité et certaines données d'immunogénicité seront réalisées : 1. Rapport intermédiaire 1 : Lorsque les 6 sujets sentinelles auront effectué la visite 4 du jour 28, 2. Rapport intermédiaire 2 : Lorsque les 6 sujets sentinelles auront effectué la visite 5 du jour 42 3. Rapport intermédiaire3 : Lorsque tous les sujets (ou au moins 50 % en fonction du taux de recrutement) auront effectué la visite 4 du jour 28, 4. Une analyse intermédiaire pour le rapport d'étude intermédiaire : lorsque tous les sujets auront effectué la visite 7 du jour 91 ou la visite de fin d'étude anticipée. L'objectif de ces analyses intermédiaires est de fournir des données de sécurité et certaines données d'immunogénicité pour le développement d'un vaccin contre le SARS-CoV-2 en situation d'épidémie. Pendant l'analyse intermédiaire, les données de sécurité seront aussi présentées à un Comité de surveillance et de suivi des données (DSMB) indépendant. Les recommandations du DSMB concernant la poursuite de l'étude et/ou des modifications du protocole seront prises en compte par le promoteur. Une analyse intermédiaire pour la préparation du rapport d'étude intermédiaire sera établie. Sur demande, les membres du DSMB auront accès au rapport d'étude intermédiaire. L'analyse finale (Rapport final de l'étude) sera effectuée une fois que le dernier participant aura terminé l'étude.
23. Calendrier de l'étude	▪ Date prévisionnelle de début de la phase de sélection : 2e trimestre 2020 ▪ Date prévisionnelle de début des inclusions : 3e trimestre 2020 ▪ Durée prévisionnelle des inclusions : environ 6 semaines ▪ Durée de participation du sujet : environ 7 mois ▪ Durée prévisionnelle de l'étude : environ 15 mois ▪ Durée de conservation des données : 25 ans après la fin de l'étude ▪ Durée des biobanques : 15 ans
24. Nombre de centres de recherche clinique	2 centres cliniques, un en France (CIC-Pasteur Cochin, Paris) et un en Belgique (SGS Life Sciences, unité de pharmacologie clinique, Anvers)

SIGNATURES PAGE

The sponsor undertakes to conduct this study in accordance with the approved protocol and the current legal and regulatory provisions.

Duly authorized representative of the Institut Pasteur

The sponsor undertakes to conduct this study in accordance with the approved protocol and the current legal and regulatory provisions.

Head of Vaccine Programs
[redacted]

Signature by the vaccine developer

The developer undertakes to conduct this study in accordance with the approved protocol and the current legal and regulatory provisions.

Duly authorized representative of the vaccine developer

Signature of investigators

I have carefully read this protocol and consider it contains all necessary details to undergo this study. I hereby confirm I will also conduct this study in accordance with the approved protocol and the current legal and regulatory provisions.

By my signature, I confirm that I am informed that identifiable data relating to my professional skills or the conduct of the research will be processed by the research sponsor or his representative in accordance with the provisions of the Data Protection Act and will be kept for a period of 5 years from the end of the research. In relation to these data, I have the right to access, modify, oppose and erase them by contacting the [redacted]

Coordinating - Investigator
Site Principal Investigator (France)
[redacted]

Signature of investigators

I have carefully read this protocol and consider it contains all necessary details to undergo this study. I hereby confirm I will also conduct this study in accordance with the approved protocol and the current legal and regulatory provisions.

By my signature, I confirm that I am informed that identifiable data relating to my professional skills or the conduct of the research will be processed by the research sponsor or his representative in accordance with the provisions of the Data Protection Act and will be kept for a period of 5 years from the end of the research. In relation to these data, I have the right to access, modify, oppose and erase them by contacting the [redacted]

Site Principal Investigator (Belgium)
[redacted]

TABLE OF CONTENTS

LIST OF FIGURES AND TABLES

ABBREVIATIONS

Ab:	Antibody
AE:	Adverse Event
AESI:	Adverse Event of Special Interest
Ag:	Antigen
ALT:	Alanine Aminotransferase (SGPT)
ANSM:	National Agency for the Safety of Medicines and Health Products (French CA)
AR:	Adverse Reaction
AST:	Aspartate Aminotransferase (SGOT)
BSL1:	Biosafety Level 1
BSL2:	Biosafety Level 2
BMI:	Body Mass Index
CA:	Competent Authority
CDC:	Centers for Disease Control and Prevention
CEPI:	Coalition for Epidemic Preparedness Innovations
CHIK:	Chikungunya
CIC:	Centre d 'Investigation Clinique (Investigational clinical site)
COVID-19:	Coronavirus Disease 2019
CPP:	French Research Ethic Committees
CPU:	Clinical Pharmacology Unit
CRA:	Clinical Research Associate
CRO:	Contract Research Organization
CRT-CC:	Centre for Translational Science – Clinical Core
eCRF:	(electronic) Case Report Form
CSR:	Clinical Study Report
DSMB:	Data Safety Monitoring Board
EC:	Ethics Committee
ECDC:	European Centre for Disease Prevention and Control
ECG:	Electrocardiogram
ELISA:	Enzyme Linked Immunosorbent Assay
ER:	Emergency Room
ET:	Early Termination Visit
FAMHP:	Federal Agency for Medicine and Health Products (Belgium CA)
GCP:	Good Clinical Practice
GMO:	Genetically Modified Organism
GMP:	Good Manufacturing Practice
GMT:	Geometric Mean Titer

GP:	General Practitioner
HBV:	Hepatitis B virus
HCV:	Hepatitis C virus
HIV:	Human immunodeficiency virus
IB:	Investigator's Brochure
ICF:	Informed Consent Form
ICH:	International Conference of Harmonization
ICS:	Intracellular Staining
ICU:	Intensive Care Unit
IgG:	Immunoglobulin G
IgM:	Immunoglobulin M
i.m:	Intramuscular
IMP:	Investigational Medical Product
ITT:	Intention to Treat
MedDRA:	Medical Dictionary for Regulatory Activities
MERS:	Middle East Respiratory Syndrome
MV:	Measles Vector
MSD:	Merck Sharp & Dohme Corp.
PBMC:	Peripheral blood mononuclear cells
PCR:	Polymerase Chain Reaction
PHEIC:	Public Health Emergency of International Concern
PI:	Principal Investigator
PP:	Per-Protocol
PT:	Prothrombin Time
RT-PCR:	Reverse Transcriptase Polymerase Chain Reaction
SAE:	Serious Adverse Event
SADR:	Serious Adverse Drug Reaction
SARS:	Severe Acute Respiratory Syndrome
SARS-CoV-2:	Severe Acute Respiratory Syndrome Coronavirus 2
SOP:	Standard Operating Procedure
SUSAR:	Suspected Unexpected Serious Adverse Reaction
$TCID_{50}$:	Tissue Culture Infective Dose 50%
TMV-083	COVID-19 Vaccine candidate
VNT:	Virus Neutralization Test
WHO:	World Health Organization

1. SCIENTIFIC JUSTIFICATION OF RESEARCH-

1.1. Background

1.1.1. The disease to be prevented

Coronaviruses are a large family of viruses that mostly cause common cold but are also known to be the cause of epidemics of severe diseases such as Severe Acute Respiratory Syndrome (SARS) in 2003 and the Middle East Respiratory Syndrome (MERS) since 2012. A novel coronavirus infectious disease (COVID-19) was identified in 2019 in Wuhan, China, and is caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). The World Health Organization (WHO) has declared the ongoing outbreak of COVID-19 a Public Health Emergency of International Concern (PHEIC) on 30 January 2020 and officially declared the COVID-19 outbreak a pandemic on 11 March 2020. On May 12 2020, the WHO reported approximately 4.1 million confirmed cases of COVID-19 infection and 280 thousand deaths globally, with numbers increasing daily (WHO, COVID-19 situation reports).

Whilst up to 40-50% of cases may be asymptomatic cases (CEBM, 2020), COVID-19 usually presents as a distinctive symptomatic illness. Common symptoms include fever, tiredness and dry cough, other symptoms may include shortness of breath, aches and pains, sore throat and reports of diarrhea early during infection are increasing. Less commonly observed are nausea and rhinorrhea (runny nose) (WHO, Coronavirus Symptoms). SARS-CoV-2 has an incubation period of 5-12 days and a mean reproductive number (R0) of 3.28 (ECDC, April 2020). The case fatality rate is approximately 1.5%. Hospitalization occurred in 32% (48 755 of 152 375) of cases reported from 26 countries (median country-specific estimate, interquartile range (IQR): 28%, 14–63%), severe illness (requiring intensive care unit [ICU] and/or respiratory support) accounted for 2,859 of 120,788 (2.4%) cases reported from 16 countries (median, IQR: 1.4%, 0–33%). Among hospitalized cases: severe illness was reported in 9.2% (3,567 of 38,960) of hospitalized cases from 19 countries (median, IQR: 15%, 3.8–35%). Death occurred in 1,005 of 9,368 (11%) hospitalized cases from 21 countries (median, IQR: 3.9%, 0–13%) (ECDC, April 2020). The median time from onset of symptoms to mortality is 18.8 days and to recovery is 22.6 days (Verity et al, 2020). The median time from onset to respiratory failure is 12 days (Zhou et al, 2020). As there currently is no approved specific treatment or vaccine against COVID-19 infection, patients can only be treated empirically. The development of vaccines and treatments is therefore of utmost importance and promising candidates should be progressed to clinical evaluation as quickly as possible.

1.1.2. Development of COVID-19 vaccine

A key effort to prevent and combat further spread of COVID-19 is the rapid development of an effective and safe vaccine. Estimates on the availability of a vaccine for use in the general population range from 12 to 18 months. According to the WHO draft landscape of COVID-19 candidate vaccines of 11 May 2020, 8 candidate vaccines are currently in clinical evaluation and 102 are in preclinical evaluation.

Institut Pasteur is developing COVID-19 vaccine, a promising vaccine candidate against SARS-CoV-2, based on the measles virus vaccine platform, in collaboration with Themis and the University of Pittsburgh. The consortium is funded by the Coalition for Epidemic Preparedness Innovations (CEPI), an organization set up to accelerate the development of

vaccines against emerging infectious threats like COVID-19. Further advancement of the vaccine candidate is already under discussion with CEPI and plans for advanced clinical trials are currently being developed. These will be aligned with clinical trial designs under development by WHO with the aim to harmonize global efforts or even to compare multiple candidates in the same trial (WHO Solidarity trial). The advanced trials of our program are envisioned to be triggered based on positive results of interim analyses of this Phase I trial. At the same time, CEPI's aim in response to the pandemic is to develop manufacturing in parallel with the clinical development of the vaccine, so that if the vaccine is proven to be safe and effective, it can be made available without delay. Thus, discussions to include a large manufacturer into our consortium are also ongoing. The aim of the consortium is to obtain the WHO Emergency Use Listing enabling its use during the public health emergency and/or to obtain WHO pre-qualification. CEPI's mission is to ensure equitable access which is very much aligned with Institut Pasteur's mission to improve Global Health. During the pandemic, CEPI, together with WHO, plans to set up a Global Allocation Mechanism with an Allocation Body having the authority to determine the geographies and populations with the vaccines will be provided (including high-income and low-and-middle-income countries, LMIC). Vaccines produced from CEPI-funded partners are designated to the mechanism. After the pandemic, CEPI will ensure access to the vaccine for LMIC.

1.1.3. Immune responses to SARS-CoV-2 infection

In most COVID-19 convalescent patients analyzed so far, SARS-CoV-2 infection elicited an antibody response to the virus (Zhao et al, 2020; WHO Immunity passports). There is experimental evidence highlighting the protective capacity of antibodies in the immune response against SARS-CoV-2. Polyclonal sera from mice immunized with SARS-CoV S protein prevented infection of cells by SARS-CoV-2 in vitro (Walls et al, 2020). Further, sera from COVID-19 patients containing SARS-CoV-2 specific IgG were able to neutralize SARS-CoV-2 in vitro. Lastly, administration of convalescent plasma containing neutralizing antibodies to 15 severe patients suffering from COVID-19, of which five were critically ill, led to considerable improvement in the clinical status of these patients in a preliminary uncontrolled case series (Shen et al, 2020, Duan et al, 2020). Taken together, these data strongly suggest that induction of antibodies will be highly important for protection. Some convalescent patients have low levels of neutralizing antibodies, suggesting that also cellular immunity may be important for recovery (Wu et al, 2020). A similar observation was made in patients infected with SARS-CoV. A Th1-type immune response was predominantly induced in convalescent patients after SARS-CoV infection, with the majority of T cell responses directed to the S protein, while in contrast, the risk of fatal infection with SARS-CoV has been linked to a Th2-type immune response (Li et al, 2008). These data suggest that induction of a Th1-type T cells response will further strengthen a protective response.

Despite this evidence pointing to an important role for antibody and T cell responses for protection, a correlate of protection against COVID-19 is not yet known and a definitive statement about the potential effectiveness of antibody or T cells response cannot yet be made.

1.1.4. The measles virus technology

The recombinant measles virus technology utilizes as vector the Schwarz measles vaccine, one of the live attenuated measles virus strains currently used as measles vaccine. The live attenuated measles vaccines are internationally widely used to prevent measles virus infection and are safe and effective. They have been used since the 1960s and have reached an 83% vaccine coverage of the world's population of children (WHO, 2020 b).

The extensive knowledge accumulated with live attenuated measles vaccines in the past 40 years renders this technology attractive for a new vaccine approach. Moreover, used the measles vaccine as a vector, offers a plug-and-play technology for rapid development of vaccine based on the following advantages:

- Great packaging ability for additional transcription units – multiple genes can be introduced into the measles vaccine backbone
- Replicating virus – strong and sustained immunogenicity
- Inducement of both humoral and cellular responses, no adjuvant needed
- Pre-existing vector immunity does not impact infectivity or replication – boosting possible

The most advanced measles vector-based candidate vaccine, a vaccine against chikungunya, MV-CHIK, is entering Phase III clinical trials, and has presented an excellent safety and immunogenicity record. Also, MV-Zika and MV-Lassa vaccine candidates are currently in Phase I trials.

1.1.5. The COVID-19 candidate vaccine under evaluation

The strategy chosen to generate the first COVID-19 vaccine candidate originated from the previous experience with an MV-based candidate against SARS-CoV (Escriou et al, 2014). Among several measles vector-based candidates, recombinant MV expressing the full-length membrane-anchored spike (S) protein of SARS-CoV induced the highest titers of neutralizing antibodies in hCD46+/--IFNAR-/- (hCD46-IFNAR) mice susceptible to measles virus, and protected immunized animals from intranasal infectious challenge with SARS-CoV. Similarly, a MV-based vaccine candidate carrying the full-length membrane-bound S of MERS-CoV, protected mice against challenge with MERS-CoV (Malczyk et al., 2015).

We thus constructed a recombinant COVID-19 vaccine candidate expressing the SARS-CoV-2 spike (S) glycoprotein in its full-length membrane anchored form. Specific modifications were introduced to further improve the immunogenicity of the S protein.

A human codon-optimized sequence encoding the SARS-CoV-2 spike glycoprotein was synthesized (GeneArt, ThermoFisher, Regensburg, Germany) and inserted into the 'additional transcription unit 3 (ATU3)' of the MV Schwarz vector using reverse genetics (Figure 1). The resulting virus, TMV-083 is rescued from a co-culture system of helper cells with a Vero cell line (Combredet et al., 2003). After rescue the vaccine candidate virus is propagated on Vero cells. A WHO-approved Vero cell line is also used for production.

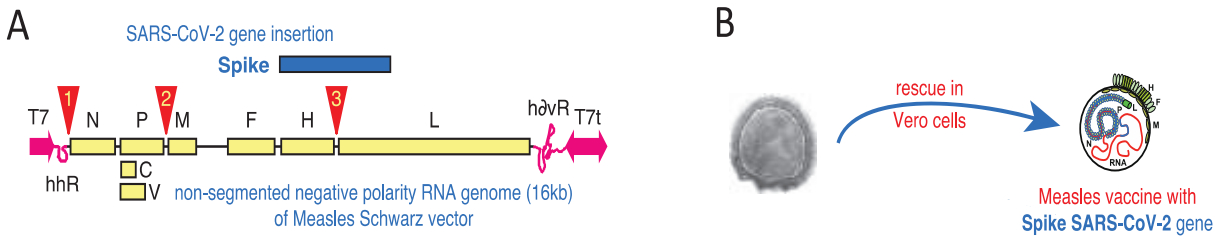


Figure 1: Schematic view of the COVID-19 vaccine candidate genome (A) and rescued vaccine virus TMV-083 (B).

A) The full-length viral antigenomic cDNA of the measles Schwarz vaccine was cloned into a plasmid under T7 promoter with the accessory DNA sequence of GGG motif, hammerhead, and hepatitis delta viral ribozyme to ensure the production of viral RNA in the cytoplasm. Three additional transcription units (ATUs, red arrows) were introduced at various sites of the genome. The ATUs are multiple-cloning site cassettes under the control of cis-acting promoters necessary for the transcription of the transgene, introduced at different positions to obtain high or low protein expression dependent on the insertion position (Combredet et al., 2003). COVID-19 vaccine candidate TMV-083 was generated by inserting an optimized gene encoding the spike protein of SARS-CoV-2 into ATU3. MV genes: N (nucleoprotein), PVC (phoshoprotein and V/C proteins), M (matrix), F (fusion), H (hemagglutinin), L (polymerase), T7 (T7 RNA polymerase promoter), hh (hammerhead ribozyme), T7t (T7 RNA polymerase terminator), ∂ (hepatitis delta virus ribozyme). B) Rescue of the recombinant virus (TMV-083) was performed using the helper-cell-based rescue method as previously described (Combredet et al., 2003)

The proposed mode of action is based on data generated with vaccine candidates of the measles vector (MV) platform. Upon vaccination with the COVID-19 vaccine candidate, the measles virus will deliver the SARS-CoV-2 spike antigen to antigen presenting cells susceptible to measles virus, including dendritic cells and monocytes, thereby inducing a SARS-CoV-2 specific cellular and humoral immune responses without the need for an additional adjuvant.

The immunogenicity of the COVID-19 vaccine candidate has been assessed in a measles vector-permissive mouse model (Mura at al, 2018). TMV-083 was shown to elicit high antibody titers and neutralizing antibodies to SARS-CoV-2 and a Th1-type immune response as assessed by a strong IgG2a to IgG1 response. Combined with the positive *in vitro* characteristics (growth, sequence stability, antigen expression), these data support taking TMV-083 into GMP manufacturing and clinical trials.

A detailed description of the vaccine construct and mechanism of action will be found in the Investigators' Brochure (IB).

1.2. Pre-clinical safety studies

The COVID-19 vaccine is based on Pasteur/Themis´ well-established MV platform. For the purpose of preparing clinical trials of the platform candidates, extensive preclinical testing has been performed with the vaccine candidates. MV-based vaccine candidates for Zika, Lassa, Dengue and Chikungunya are well tolerated, and no signs of systemic toxicity were noted. None of the heterologous antigens added to the measles vector changed the toxicology profile, biodistribution, shedding behavior or tropism. Biodistribution of MV-based vaccines was similar to that of the parental MV-Schwarz vaccine strain.

1.3. Pre-existing immunity against the Measles-vector

The impact of pre-existing immunity is a major point of interest for Measles-vectored vaccines, as large parts of the population have been vaccinated at least once, while some have undergone natural infections. In previous phase I (Ramsauer et al. 2015) and phase II (Reisinger et al. 2018) clinical trials we have shown that the immunogenicity of another vaccine using the same vector (MV-CHIK) is not influenced by the levels of Measles-specific serum IgG before vaccination. In addition, we found that the frequency of Adverse Events (AEs) in participants with low (< 200 iU/l) and participants with high (≥ 200 U/l) frequency of anti-Measles IgG is similar (p= 0.0658 when comparing unsolicited AEs, p= 1.0000 when comparing solicited AEs).

1.4. Study rationale

This phase I trial will be a first in human study, designed to investigate the safety, tolerability and immunogenicity of a novel vaccine candidate against SARS-CoV-2 infection. A randomized study design was chosen to enable an objective recording and assessment of all AEs occurring up to day 210. It will further allow, to evaluate two different concentrations of COVID-19 vaccine 5 log 10 or 6 log 10 (± 0.8 log) $TCID_{50}$ per dose regarding safety and tolerability. For a better legibility the manufacturing dependent window of (± 0.8 log) will be omitted in the rest of this document.

The vaccine dose was selected based on clinical outcome of the platform-based vaccine candidate MV-CHIK. A dose of $1x10^4$-$1x10^6$ (±1.0 log) $TCID_{50}$ was efficient to induce seroconversion rates of up to 100% in the study population after 2 immunizations. The higher dose induced seroconversion in approximately 90% of subjects already after the first immunization (Reisinger et al, 2018). The COVID-19 will be administered as single immunization or in prime/boost schedule at day 0 and 28.

In the pandemic context, two aspects are critical for vaccine development, the time required from immunization to the onset of clinical benefit and the feasibility of manufacturing hundreds of millions of doses quickly. For rapid onset of clinical benefit, a single immunization is preferred. Regarding this aspect and based on clinical experience with the MV-CHIK vaccine candidates (Ramsauer et al. 2015; Reisinger et al. 2018), the expectation is that a single immunization with the high dose of COVID-19 vaccine will be sufficient to elicit seroconversion as measured by neutralizing antibodies. This expectation is supported by preclinical data with the COVID-19 vaccine candidate in mice which showed substantial levels of neutralizing antibodies after one immunization (see IB). For use during the pandemic, it will important to understand not only the time to onset and initial magnitude of the immune response but also its duration after single immunization. While the onset of the immune response can be studied after the first immunization in the groups receiving two immunization, the persistence of such immune response needs to be addressed in a cohort receiving a single immunization. On the other hand, dependent on the yields of large-scale manufacturing, two immunizations with the low dose (approximately 10-fold lower) would allow immunizing 5 times as many people with the same manufacturing batch than using a single administration the high dose. But time to clinical benefit might be delayed with the low dose. To address the question which of these scenarios might be more beneficial, a cohort receiving a single immunization with the high dose and a cohort receiving two immunizations with the low dose will be studied. While the study size is not designed to allow a detailed comparison, it will provide an indication in case of large differences. In addition, two immunizations with the high dose will be evaluated. Based

on previous experience with MV-CHIK (Reisinger et al. 2018), this regimen is likely to be even more effective but would require an even larger manufacturing scale during the pandemic.

As a correlate of protection is not yet known, it is unclear at this time which magnitude of the immune response, and in particularly of which parameter, will be required. Thus, different parameters of the immune response, particularly neutralizing antibodies and T cell responses will be followed. In case a correlate of protection becomes available during the study, the efficacy of the different regimen will be evaluated based on the established correlate.

This study will address the immune response to COVID-19 vaccine on days 28 and 56 as well as the long-term durability of specific anti-SARS-CoV-2 antibody response up to day 91 after administration of two different dose levels.

A Virus Neutralizing Test (VNT) will be used to analyze functional anti-SARS-CoV-2 antibodies induced by COVID-19 vaccine throughout the entire study.

The induction of virus specific T-cells is known as a critical step in the generation of a functional immune response. For this purpose, the rate of SARS-CoV-2 virus-specific T cells will be determined for all timepoints of the study.

Additionally, Enzyme-linked immunosorbent assays (ELISAs) will be performed to obtain data on SARS-CoV-2 antibody (Ab) titer of all treatment groups starting with baseline up to D91, as well as on the development of measles antibody titer up to day 56 after the first treatment.

As mentioned before, a staggered unblinded dose-escalation design has been implemented to ensure careful observation on subjects' safety during the first treatments. In the unblinded dose-escalation phase the study safety data will be available for a subset of three sentinel subjects per dose level, 14 days following the first vaccinations in order to initiate the blinded randomization part of the study. Only after written favorable opinion of the DSMB, randomization to the blinded treatment phase will be initiated. Subjects will be followed closely by the investigators of both study sites. Individual as well as treatment halting rules have been implemented for safety monitoring.

In the Phase I study, healthy subjects 18-55 years of age will be enrolled which is a typical age group for a First-in-Human trial with the primary objective to confirm safety. Older age groups, who are most affected by COVID-19, are planned to be included in the advanced clinical trials.

Even in case the vaccine was not licensed for elderly, the elderly would benefit from the implementation of the vaccine. Immunization of a sufficiently large proportion of the population, 60% has been estimated for COVID-19, would result in herd immunity through which also the elderly would be protected.

This study was designed according to the Note for Guidance on Clinical Evaluation of New Vaccines (CHMP/VWP/164653/2005), where applicable, and will be conducted in compliance with the protocol, Good Clinical Practice (GCP) as set forth in the International Council on Harmonization (ICH) guidelines on GCP (ICH-E6(R2)), and applicable local regulatory requirements.

1.5. Benefit/Risk Assessment

Potential risks that are frequently associated with vaccination are the occurrence of local reactions such as edema, induration and erythema, transient local pain or tenderness at the injection site as well as mild to moderate headache, myalgia, flu-like symptoms or fatigue. As any other vaccine, the COVID-19 vaccine might induce allergic and anaphylactic reactions apart from reactions at the vaccination site and systemic flu-like reactions. In some cases, the

injection might lead to a syncope immediately after/during injection. Additionally, blood sampling by venipuncture may cause discomfort and/or local reactions.

The COVID-19 vaccine candidate is based on a recombinant live measles vaccine virus carrying the genetic sequence of the spike protein of SARS-CoV-2. No live SARS-CoV-2 virus is present in the vaccine. Therefore, induction of COVID-19-like symptoms is not expected. However, the participants will be closely monitored for occurrence of any adverse sign or symptom.

A theoretical risk that is discussed with in the scientific community and the International Coalition of Medicines Regulatory Authorities (ICMRA) is a theoretical risk of disease enhancement in SARS-CoV-2 infection after prior immunization. For SARS vaccine candidates, an immunopathology was observed in animal models after challenge with SARS-CoV, specifically after immunization with inactivated vaccine candidates. Such immunopathology was linked to a Th2-type T cell response or, more globally, to the absence of a Th1-type T cell response. Thus, it is recognized that the risk is mitigated if the vaccine technology is known to elicit a Th1-type immune response. For the standard measles vaccine and prior measles vector-based vaccine candidates, this is the case (Ovsyannikova et al, 2003; Escriou et al, 2014; Mateo et al, 2019). For the COVID-19 vaccine candidate, the Th1-type response has already been shown in the first mouse studies and will be further confirmed before staring the clinical trial. Importantly, first international results in non-human primates with a vaccine candidate formulation (alum adjuvanted inactivated vaccine) that would have been expected to trigger the disease enhancement if it occurred in the same way as it did with SARS vaccine candidates have not detected any immunopathology or risk related to COVID-19 vaccines (Gao et al, 2020).

As mentioned in section 1.1.2, there are data supporting that antibodies and T cells will be important for protection. Nevertheless, a correlate of protection is unknown and thus the immunogenicity outcomes of the study will not be predictive of protection against COVID-19.

Generally, the subjects cannot expect to directly benefit from study participation, except for potential boosting of measles immunity and for a free of charge SARS-CoV-2 screening (RT-PCR and serology).

2. STUDY OBJECTIVES AND OUTCOMES

2.1. Objectives

2.1.1. Primary Objective

The primary objective is:

- To assess the safety and tolerability of the COVID-19 vaccine following one or two consecutive intramuscular injections in healthy volunteers.

2.1.2. Secondary objectives

The secondary objectives are:

- To assess induction of SARS-CoV-2 spike protein-binding antibodies upon one or two administrations of the COVID-19 vaccine by means of ELISA up to study day 91.
- To assess induction of SARS-CoV-2 neutralizing antibodies upon one or two administrations of the COVID-19 vaccine by means of serum neutralization assay up to study day 91
- To assess SARS-CoV-2 spike protein-specific, cell-mediated immune responses up to study day 91 induced by one or two doses of vaccine, by means of intracellular staining and flow cytometry.
- To assess potential measles virus shedding by means of RT-qPCR of saliva, nasal swab, urine, or blood samples in sentinel groups on day 0, 7, 14, 28 and 42.

2.1.3. Exploratory objective

The explorative objective is:

- To assess the anti-measles antibody levels at baseline, on day 28, and on day 56 by ELISA.
- To assess the natural exposure of the subjects to SARS-CoV-2 infection during the duration of the trial by means of N protein-specific immunoassay.
- To assess the occurrence of COVID-19 cases in study participants all along the duration of the study.

2.2. Outcomes

2.2.1. Primary outcome measures

- Rate of solicited Adverse Event up to 14 days after each injection.
- Rate of unsolicited AE up to 28 days after each injection.
- Rate of serious adverse events (SAEs) serious adverse reactions (SARs), suspected unexpected serious adverse reactions (SUSARs) and adverse events of special interest (AESI) all along the study period.

Safety and tolerability will be assessed after each vaccination and participants will remain under observation at the study site for at least one hour for presence of any acute reactions and solicited events and by means of a diary completed by the participants for 14 days after each vaccination (from day 0 up to day 14 and from day 28 up to day 42). For each AE/SAE/AESI, the intensity and the relationship to vaccination will be reported and will be evaluated by the investigator.

2.3. Secondary outcome measures

- Onset: SARS-CoV-2 specific antibodies up to study day 56 as measured by spike protein-specific ELISA and serum neutralization assay.
- Durability: SARS-CoV-2 specific antibodies on day 91 for each cohort as measured by spike protein-specific ELISA and serum neutralization assay.
- SARS-CoV-2 spike protein-specific cell-mediated immune response up to study day 91 induced by one or two doses as measured by intracellular staining and flow cytometry.
- Occurrence of measles virus shedding as evidenced by a positive RT-PCR for saliva, nasal swab, urine or blood sample in sentinel groups.

2.4. Exploratory outcomes measures

- Measles virus antibody levels as assessed by standard ELISA assays on day 0, day 28, and day 56.
- SARS-CoV-2 N protein specific antibody up to study day 91 as measured by immunoassay to differentiate the response to the COVID-19 vaccine from infection
- Occurrence of confirmed COVID-19 (i.e. asymptomatic, paucisymptomatic or symptomatic) cases in the study participant all along the study period.

3. DESIGN AND METHODOLOGY

3.1. Overall study design

This is a prospective, interventional, randomized, phase I trial, comparing two different dose levels of COVID-19 vaccine and two different strategies (one vs. two injections of high dosage) to evaluate safety, tolerability and immunogenicity of this novel COVID-19 vaccine consisting of an unblinded dose escalation in two sentinel groups (three participants treated with the low dose and three participants treated with the high dose) and a double-blinded treatment phase (blinded cohorts).

The study will be conducted at two study sites: CIC Cochin Pasteur (Paris, France) and SGS Life Sciences, Clinical Pharmacology Unit (Antwerp, Belgium) and will be registered online under http://www.ClinicalTrials.gov and with the EudraCT number 2020-002973-89.

3.2. Unblinded / non-randomized sentinel groups

As safety precaution, the study will begin with the enrolment of a small group of sentinel subjects (“Sentinel Groups”), each of whom will receive the vaccine in an unblinded and non-randomized manner. The investigator, the pharmacist and site personnel performing study related assessments, all participants of the “Sentinel Groups”, as well as the sponsor’s representatives involved in the monitoring and conduct of the study will be unblinded. The enrolment of the “Sentinel Groups” will be conducted in one investigational site. The one located in the country where approval and authorization from Ethics Committee and Competent Authority will be obtained first.

Six sentinel subjects will be enrolled either in Cohort A (low dosage, vaccinations on days 0 and 28) or in cohort B (high dosage, vaccinations on day 0 and 28) according to the following scheme:

- The first subject of the “Sentinel Groups” will be enrolled in cohort A and will receive the low dose vaccine on day 0.
- Twenty-four hours after the injection, the subject will be called to collect safety information related to the vaccination.
- The clinical investigator can then decide to move on with the vaccination of the second and third subject based on the absence of related severe AEs/SAEs (no less than 24hrs after the first subject received the first treatment and phone call).
- The second and third subject of the “Sentinel Groups” will be enrolled, the same day with an interval of at least 3 hours, in cohort A and will receive the low dose vaccine on day 0.
- Twenty-four hours after the injection, the second and third subject will be called to collect safety information related to the vaccination.
- The clinical investigator can then decide to move on with the vaccination of the fourth subject based on the absence of related severe AEs/SAEs (no less than 24hrs after the second and third subject received the first treatment and phone call).
- The fourth subject of the “Sentinel Groups” will be enrolled in cohort B and will receive the high dose vaccine.
- Twenty-four hours after the injection, the subject will be called to collect safety information related to the vaccination.

- The clinical investigator can then decide to move on with the vaccination of the two last subjects based on the absence of related severe AEs /SAEs (no less than 24hrs after the fourth subject received the first treatment and phone call).
- The fifth and sixth participants of the “Sentinel Groups” will be enrolled, the same day with an interval of at least 3 hours, in cohort B and will receive the high dose vaccine on day 0. 24 hours after the injection, they will be called to collect safety information related to the vaccination.
- Following the 14 day follow up of all sentinel subjects, the DSMB will review safety data after the first dose in these six participants, before giving a positive written recommendation for continuing with the double-blind, randomized treatment phase.

Following the 42-day follow-up of all sentinel subject, a medical monitoring of safety data will be performed to evaluate safety of the second injection in these six participants. In case of any safety concern, an ad hoc DSMB meeting will be organized before giving a positive recommendation for continuing with the second injection of the double-blind, randomized cohorts (“main cohorts”). In case of any related severe AE or related SAE, Sponsor will be contacted and after the case has been discussed by the Sponsor and DSMB it will be determined if study vaccine can be continued according to the protocol.

All subjects included in the “Sentinel Groups” will be included in the shedding assessment. Body fluids including saliva, nasal swab, urine and whole blood will be collected therefore at visit 1 (day 0), visit 2 (day 7), visit 3 (day 14), visit 4 (day 28) and visit 5 (day 42).

3.3. Blinded / randomized cohorts

After DSMB review and positive recommendation, sponsor will decide to continue the study by the enrollment of the remaining 84 participants (“Main Cohorts”), in a blinded randomized manner, in the low dose group (cohort A) or in high dose groups (cohort B and C).

Table 1: **Treatment groups allocation**

Cohort	Treatment	Injection 1 D0	Injection 2 D28	Number of participants		
				COVID-19 vaccine **Sentinel**	COVID-19 vaccine **Main grp**	Placebo
A	COVID-19 low Dosage	Vaccine	Vaccine	3	21	6
B	COVID-19 high Dosage	Vaccine	Vaccine	3	21	6
C	COVID-19 high Dosage	Vaccine	Placebo	0	24	6

Participants will be observed closely for safety and immunogenicity from the first injection to the end of study.

The investigator, and site personnel performing study related assessments, all participants, as well as the sponsor’s representatives involved in the monitoring and conduct of the study will be blinded.

Only site personnel performing randomization, preparation of IMP and monitoring of the IMP handling process will be unblinded as well as the DSMB members (excluding observing DSMB members who will only have access to blinded safety report).

During the follow up phase (after all subjects have completed V6), the head of vaccine programs of Institut Pasteur and a project manager from the vaccine developer (Themis Bioscience GmbH a subsidiary of Merck & Co., Inc., Kenilworth, New Jersey USA,) will have access to the unblinded data for the purpose of immunogenicity assessment. In the current pandemic, rapid assessment of the potential of the vaccine, including the balance of safety and immunogenicity is required to move promising candidates forward as quickly as possible. All data will be stored on a secured server accessible with a login and password to which only the unblinded person has access. The risk of impact on the study is minimized as unblinding will occur when the treatment phase will have been completed, the analyses have been defined, and the unblinded personnel is not involved in the clinical evaluation and management of the participants.

3.4. Schematic overview of the study design

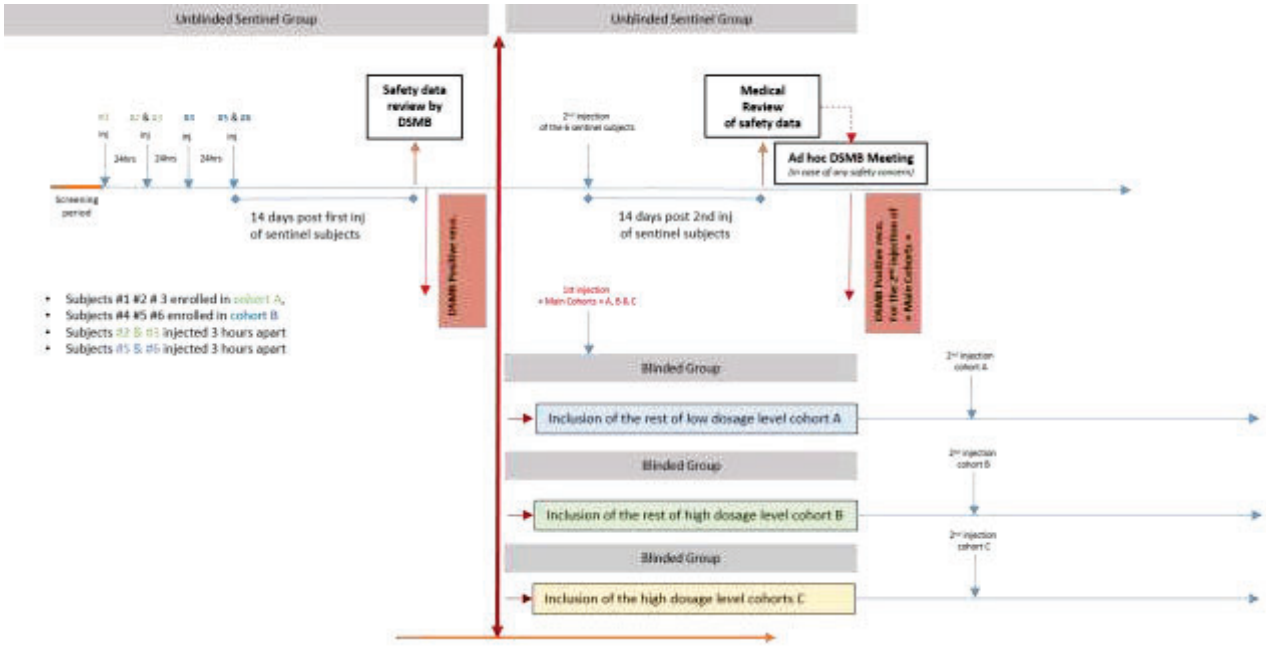


Figure 2: Schematic overview of the study design

3.5. Justification of doses

Multiple vaccines based on the same Measles Schwarz strain platform have undergone clinical evaluation and dose finding has repeatedly demonstrated that higher vaccine doses induce more robust neutralizing antibody responses (see for instance Reisinger et al 2018). The clinically most advanced candidate MV-CHIK has been administered to trial participants up to a dose of $1x10^6$ $TCID_{50}$ per vaccination without any significant safety findings and has been well tolerated in pre-clinical repeated dose toxicity testing in NHPs up to $2.51 \times 10^7 TCID_{50}$ per dose. The selection of low and high dose used throughout this study was based on these findings.

4. STUDY POPULATION

4.1. Number of subjects

This study will be conducted in 90 healthy adults, who have fulfilled the following inclusion and exclusion criteria.

4.2. Inclusion criteria

The volunteer must fulfill the following criteria to be eligible for the study:

1. Males and females between the ages of 18 and 55 years (at the time of consent).
2. Healthy participant, according to the investigator's clinical judgment, as established by medical history, vital signs, physical examination, and laboratory assessments
3. Participant with a body mass index (BMI) <30.0 kg/m^2
4. Provide written informed consent before initiation of any study procedures.
5. A female participant is eligible for this study if she is not pregnant given by a negative serum pregnancy test at screening and a negative urine pregnancy test at V1 (1st injection) or breast feeding and 1 of the following:
    - Of non-childbearing potential (i.e., women who have had a hysterectomy or tubal ligation or are postmenopausal, as defined by no menses in greater than or equal to 1 year).
    - Of childbearing potential but has been and agrees to continue practicing highly effective contraception or abstinence (if this is the preferred and usual lifestyle of the participant) from 30 days prior to vaccination up to 6 months after the last injection (D210).
    - Highly effective methods of contraception include 1 or more of the following:
        - male partner who is sterile (vasectomised) prior to the female participants entry into the study and is the sole sexual partner for the female participant;
        - hormonal (oral, intravaginal, transdermal, implantable or injectable);
        - an intrauterine hormone-releasing system (IUS);
        - an intrauterine device (IUD) with a documented failure rate of < 1%.
6. A female participant is eligible if she is willing to abstain from donating oocytes from the screening visit up to 6 months after the last injection (D210).
7. A male participant who is sexually active is eligible if he is willing to :
    - use a condom (with/without spermicidal product) from the screening visit up to 6 months after the last injection (D210) except if the male participant is sterile (e.g. vasectomised); the unique female sexual partner is postmenopausal (defined as no menses for 12 months without an alternative medical cause), is permanently sterilized (e.g. hysterectomy or tubal ligation), or use a highly effective methods of contraception;
    - not donate sperm from the screening visit up to 6 months after the last injection (D210);

- not plan to father a child from the screening visit up to 6 months after the last injection (D210).

8. Negative HIV 1/2 antibody/antigen test, Hepatitis B surface antigen (HBsAg), and Hepatitis C virus (HCV) antibody.
9. Able to understand and comply with planned study procedures and willing to be available for all study-required procedures, visits and calls for the duration of the study.
10. Willing to abstain from donating whole blood or blood derivatives, tissue or organ all along the study.
11. Affiliated to a social security system, (except state medical aid) (Only for France).
12. Volunteer registered in the French Health Ministry computerized file and authorized to participate in a clinical trial (only for France).

4.3. Exclusion criteria

Participants will not be enrolled in this study if they meet any of the exclusion criteria:

13. Subjects actively or previously infected by SARS-CoV-2, as determined by a positive RT-PCR and positive serology test.
14. Subject currently working with high risk of exposure to SARS-CoV-2 (e.g. health care worker, emergency response personnel, etc.…) or considered at the investigator's discretion to be at increased risk to acquire SARS-CoV-2 for any other reason.
15. Previous vaccination with an investigational COVID-19 vaccine.
16. History of or presence of pulmonary disorders (e.g. COPD, etc.) or asthma.
17. History or present of thrombocytopenia and/or bleeding disorders.
18. A positive serum pregnancy test at screening or urine pregnancy test prior to study injection, women who are planning to become pregnant during the study, or women who are breastfeeding.
19. Clinically relevant history of or current renal, hepatic, gastrointestinal, cardiovascular, respiratory, skin, hematological, endocrine, inflammatory, autoimmune, central nervous system or neurological diseases or clinically relevant abnormal laboratory values.
20. Use of immunosuppressive drugs like e.g. corticosteroids (excluding topical preparations and inhalers) within 3 months prior to the first vaccination or 6 months for chemotherapies and all along the study.
21. A diagnosis of schizophrenia, bipolar disease, or history of hospitalization for a psychiatric condition or previous suicide attempt.
22. A history of treatment for any other psychiatric disorder in the past 3 years that increases the risk to the subject in the opinion of the investigator.
23. Received immunoglobulin or other blood product within 3 months prior to enrollment or planned receipt of immunoglobulin or a blood product through study completion.
24. Vaccination within 4 weeks prior to first injection or planning to receive a licensed vaccine before D56 (*e.g. Inactivated influenza vaccine*).
25. Received measles-containing vaccine within 3 months prior to enrollment.

26. History of severe adverse reactions to vaccine administration, including anaphylaxis and related symptoms, such as urticaria, respiratory difficulty, angioedema and abdominal pain to vaccines, or history of known or suspected allergic reaction likely to be exacerbated by any component of the COVID-19 vaccine.
27. Participation in another investigational clinical study within four weeks before the screening visit or planned before the study completion.
28. Individuals who are living and/or working with severely immunocompromised people, pregnant women, lactating women, children under 12 months old, or any other individual that, in the judgment of the investigator, might be at increased risk.
29. Any condition that in the opinion of the investigator, may interfere with the aim of the study or the safety or wellbeing of the subject.
30. Subjects with any condition associated with, or that might be associated with, an increased risk of severe illness from COVID-19 according to US CDC definition[3].
31. Subjects with confirmed or suspected immunodeficiency.
32. Exposure to an individual with confirmed COVID-19 or SARS-CoV-2 infection within the past 2 weeks prior to enrollment.
33. Subject with an acute disease and/or fever (body temperature > 38°C) at the time of the 1st vaccination visit.
34. History of confirmed SARS-CoV or MERS-CoV infection.
35. Current heavy smoker defined as smoking at least 20 cigarettes (1 pack, or equivalent) per day or former heavy smoker who was an active heavy smoker within the last year prior to the screening visit or has a total smoking history of ≥ 1 pack per day for 10 years or more.
36. Current or history of alcohol or drug abuse during the previous 3 years.
37. Presence of tattoos that, in the opinion of the investigator, would preclude evaluation of the injection site.

4.4. Screening failure

Participants who are not fulfilling inclusion/exclusion criteria at any stage during the screening period (D-28 to D-1) will be defined as screen failures. All screen failures will be documented in source data, on the screening log and in the eCRF. The screening log will be kept in the Investigators Site File.

4.5. Removal / Early Withdrawal

Participants are free to discontinue their participation in the study at any time, without prejudice and with any obligation to give his/her reason(s) and without any change in their treatment related to safety follow-up. The Investigator must withdraw any participant from the study if he/she requests to be withdrawn, or if it is determined that continuing would result in a significant safety risk or may affect the well-being of the participant.

[3] https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fneed-extra-precautions%2Fgroups-at-higher-risk.html

In addition, the participant may withdraw/be withdrawn for any of the following reasons:

- Administrative decision by the investigator / sponsor
- Ineligibility (identified at any time during the study) 'in the case it is considered to be in the best interest of the subject's health'
- Significant protocol deviation
- Non-compliance with study procedures/requirements
- Occurrence of an AE, which at the opinion of the investigator requires discontinuation of the participant or results in inability to continue to comply with study procedures/requirements
- Participant (Female) who become pregnant during the study
- Lost to follow-up

The reason for withdrawal, in case provided, will be recorded in the participant's source data and in the e-CRF. If withdrawal is due to an AE, appropriate follow-up visits or medical care will be arranged, with the agreement of the participants, until the AE has resolved or stabilized.

In case of lost to follow-up, at least 2 contacts attempts must be made within 1 week to contact any participant lost to follow-up prior to the last scheduled visit. All attempted contacts (e.g. phone contact, post mail, email) will be documented in the participant's source data.

4.6. Handling of Withdrawals

If a participant is withdrawn from the study at his/her request or further to the Investigator's decision, information and reason of withdraw will be documented in the participant's source data and recorded in the eCRF.

Upon withdrawal from the study, any time after first vaccination has taken place, the participant will be encouraged to attend an Early Termination visit (ET) (see section 7.2.13). All relevant investigations scheduled should be performed if the participant agrees. If, however, for any reason the participant does not agree to return to the investigational site for the Early Termination visit, this will be documented in the participant's source data and recorded in the e-CRF.

If a participant is withdrawn from the study at his/her request, his/her coded data and biological materials stored in the study biobank may be erased/destroyed further to his/her request. However, some data and biological materials previously collected may not be erased/destroyed if their deletion/destruction is likely to render impossible or seriously compromise the achievement of the study objectives or to satisfy a legal or regulatory obligation.

4.7. Replacement Rules

Participants who are discontinued before randomization will be regarded as screening failures and screening will be continued until 90 participants will be enrolled and randomized. Screen failed participants may be eligible for re-screening once.

Participants who withdraw or are withdrawn after enrollment and randomization will not be replaced. This may result in a decreased number of participants in the predefined sample size.

4.8. Individual participants halting rules

The following are specific criteria for discontinuing individual participants from further vaccination, but not from completing scheduled follow-up assessments, unless the participant is explicitly withdrawn from the study:

- Participants who experienced a Serious Adverse Reaction (i.e. a Serious Adverse Event considered at least possibly related to vaccine).
- Participants who experienced a severe (grade 3 or higher) non-serious adverse event considered as at least possibly related to the vaccine
- Participants who develop a medical condition for which continued participation, in the opinion of the investigator, would pose a risk to the participant or would be likely to confound interpretation of the results
- Participants with a confirmed SARS CoV-2 infection given by a positive RT-PCR or a positive serology.
- Participants who donate whole blood or blood derivatives, tissue or organ all along the study.
- Participants who become pregnant during the treatment phase of the study.
- Participants not using a reliable method of contraception
- Participants who experience hypersensitivity reaction such as anaphylaxis within 24 hours or generalized urticaria within 72 hours after administration of the study vaccine
- Participants who use immunosuppressive drugs
- Participants who receive immunoglobulin or other blood product before study completion.
- Participants who live and/or work with severely immunocompromised people, pregnant women, lactating women, children under 12 months old, or any other individual that, in the judgment of the investigator, might be at increased risk from the first vaccination (D0) up to 28 days after the second vaccination (D56).

If any of these occur, appropriate measures to treat the participant will be taken and the participant will be asked to perform an ET visit if the participant is withdrawn (for any reason) from the study. The sponsor will be notified immediately.

4.9. Study halting rules, early study termination, end of study

4.9.1. Study halting rules

The study could be temporally suspended, pending a full DSMB safety review. The criteria for considering a contraindication or preventive action to the start of the treatment of cohort B and C (increasing dosage) or administration of the COVID-19 vaccine to subsequent subjects in the current cohort will be:

- A serious adverse reaction (i.e. a serious adverse event considered at least possibly related to the study vaccine) in one subject.
- The occurrence of clinically significant severe (grade 3 or higher) non-serious adverse events considered as at least possibly related to the vaccine administration in two subjects in the same cohort, independent of within or not within the same system-organ-class. Both clinical and laboratory abnormalities are considered.

- Any onset of AESI assessed as related to the vaccine by the investigator or by the sponsor.

After complete safety review by the DSMB and taking into account its recommendation, sponsor will decide if the study (i.e. new inclusion and/or new injection) should be discontinued, continued after protocol modifications or resumed according to the protocol.

In case of study discontinuation, the Competent Authorities (CA) and Ethics Committees (EC) will be informed and all participants still in follow-up will be contacted for attending an Early Termination visit (see section 7.2.13).

4.9.2. Early study termination

The study in its entirety may be discontinued prematurely by the Sponsor, Competent Authorities or Ethics Committees with oversight responsibilities at any time, and/or participant may terminate their participation prematurely, or have their participation be terminated by the Investigator. Participants shall be asked to perform all procedures as defined for the early termination visit.

4.9.3. End of Study

The end of study will be defined as the date of the last visit of the last participant. The study will then be stopped. A final study report will be sent to CAs, ECs, the DSMB (excluding observing DSMB members who will only have access to blinded safety report), the vaccine developer's representative, and IRB-Institut Pasteur.

4.10. Source of Recruitment and Available expertise

CIC-Cochin / Pasteur (France)

The Clinical Investigation Center Cochin Pasteur (CIC 1417) is a public research center located in the Cochin Hospital, as a part of AP-HP (Assistance Publique des Hôpitaux de Paris) and the only French investigation center dedicated to vaccinology, it is ISO 9001:2015 certified. The strengths and the opportunities offered by the CIC Cochin Pasteur 1417 are an expertise in designing, implementing and regulating phase I-IV national and international clinical trials in the fields of vaccinology in healthy volunteers (children and adults) and specific populations. Since 2005, around 65 vaccine clinical trials (12 phase 1) such as A/H1N1 2009 Influenza pandemic, EBOVAC2 and STOPENTERICS have been conducted in CIC Cochin Pasteur. It also has a large database of volunteers who agreed to participate to clinical trials, thus allowing a rapid and secured recruitment based on administrative criteria.

In the frame of this study, participants will be recruited through:

- An electronic database recording all administrative data, such as age, sex, address and previous participation to a clinical study.
- Advertisement: flyers which have been approved by the Ethical Committee in France.
- CIC1417 website: www.cicvaccinologie.com

A first contact with the volunteer will be made by phone with a site investigator who will:

- present briefly the study
- ask for their participation agreement
- schedule an appointment for the screening visit

- send the information sheet form either by mail or email at least 48 hr before the screening visit. This step is to give a period of reflection to the volunteer prior the screening visit and signature of the informed consent

SGS – Clinical Pharmacology Unit (Belgium)

The Clinical Pharmacology Unit Antwerpen (CPU) is an independent research center located in the ZNA Stuivenberg hospital, as a part of Ziekenhuis Netwerk Antwerpen. The strengths offered by the CPU are an expertise in complex phase I-II clinical trials settings in a variety of fields in both healthy and specific populations. Since years, several vaccine trials have been conducted at CPU, such as H3N2 Influenza A trials.

The CPU has a large database of active volunteers who are participating on a regular base in clinical trials which allows a fluent and secured recruitment based on administrative criteria.

For this trial, participants can be recruited by:

- the above mentioned electronic database, recording all administrative data, such as age, sex, address and previous participation to a clinical study
- advertisements, after approval by the Ethical Committee in Belgium
- the dedicated CPU website where trials can be published

Volunteers receive a recruitment letter which contains in-/exclusion criteria (eg: age and BMI, study specific restrictions and information on how to subscribe for this trial) and a study/cohort specific planning.

This recruitment letter is a template, pre-approved by the Ethical committee, which is updated with trial specific data.

After subscribing, volunteers are contacted by the CPU to schedule an appointment for a screening visit. Any specific restrictions such as fasted state etc. are at that stage discussed with the potential participant to determine if they can attend the screening visit.

4.11. Allocation of Subjects to Treatment groups

- **Unblinded/non randomized – "Sentinel Groups"**
  The 6 first participants enrolled in the study will be treated sequentially in an unblinded and non-randomized manner. Three from cohort A and three from cohort B will received the low and high dose, respectively.

- **Blinded/randomized - Cohort A (low dose or placebo, two injections)**
  21 subjects treated with low dose on days 0 + 28 and 6 subjects treated with placebo on days 0 + 28.

- **Blinded/randomized - Cohort B (high dose or placebo, two injections)**
  21 subjects treated with high dose on days 0 + 28 and 6 subjects treated with placebo on days 0 + 28.

- **Blinded/randomized - Cohort C (high dose or placebo, two injections)**
  24 subjects treated with high dose on day 0 and with placebo on day 28 and 6 subjects treated with placebo on days 0 + 28.

4.11.1. Randomization procedures

A total of 84 participants will each be randomly assigned to one of three different cohorts, receiving either one or two COVID-19 vaccinations or one or two placebo injections at the allocation ratio 7: 2 for cohort A and B and 4: 1 for cohort C.

4.11.2. Blinding procedure

During the unblinded dose escalation phase, the investigator and site personnel performing study related assessments, all participants, as well as the sponsor's representatives involved in the data monitoring and conduct of the study and the one involved in the monitoring of IMP accountability will be unblinded to which vaccine was administered.

During the blinded phase, the investigator and site personnel performing study related assessments, all participants, as well as the sponsor's representatives involved in the data monitoring and conduct of the study will be blinded to which vaccine was administered.

In addition, the lab tests for both safety and immunogenicity outcomes will be carried out in a blinded manner by the lab technicians. Moreover, a randomization procedure will be used to eliminate selection bias. Randomization will be via computer generated random vaccine assignments. The randomization number will be assigned to subject by allocation of the next available randomization entry in the randomization list. The randomization list will be established before the start of the study.

The pharmacist, all pharmacy personnel who will be responsible for vaccine preparation, the sponsor's representative (i.e. pharmacy monitor) involved in the IMP accountability and the sponsor's and vaccine developer's representatives will be unblinded to the study vaccine allocation. The unblinded pharmacist involved in the IMP accountability and the sponsor's and vaccine developer's representatives will have access to the unblinded randomization list through a secure electronic platform accessible with a login and password. This randomization list will contain the specific treatment assignments for the participants, allowing unblinded pharmacy team to know what treatment each new subject should receive.

In summary, except the pharmacist, the sponsor and vaccine developer's representative involved the IMP accountability, none of the individuals involved in the study will have access to treatment assignment. Data will be unblinded after all subjects completed visit 7 (day 91) or the Early Termination visit (ET) (after the interim database lock) for the interim analysis as part of the interim CSR, for DSMB analysis or in case of emergency.

Please note that this code-breaking should only be done by the investigator if the knowledge of the participant´s treatment influences the decision on further procedures. If unblinding would not make any difference for further treatment, the study team should remain blinded.

4.11.3. Unblinding procedure

Unblinding is the process by which the allocation code is broken so that the Investigator, clinical staff and/or the trial statistician become aware of the study product assignment for a participant in a clinical trial.

An emergency decoding possibility, computer-based, will be available/accessible to the Investigator and his/her delegates and to designated persons acting as the Sponsor. Breaking of the blinding for individual participants in emergency situations is an Investigator responsibility.

Unblinding in emergency situations is only permitted in case of a suspected, unexpected serious adverse reaction (SUSAR) or other important adverse events, when the knowledge of the cohort allocation is required for therapeutic decisions to treat the concerned subject(s). The need to break the blinding will be agreed by the Investigator and the Sponsor with the exception of an extreme emergency situation that would require immediate intervention. The Investigator or his/her delegate, who unblinds the participant study product assignment, must record the reason and date for unblinding before the treatment code can be broken. The Investigator must record the event of unblinding in the participant's source data, including the reason for unblinding. In case of accidental unblinding, the same documentation as for emergency unblinding must be provided.

Information on whether the blinding has been broken for any participants must be collected before the database is declared clean and is released to the statistician.

Data will be unblinded after all subjects completed visit 7 (day 91) or the Early Termination visit (ET) and the database lock for visits 1 to 7 was completed in order to allow the preparation of the interim CSR.

A final database lock will be performed after all subjects completed visit 8 (day 210) or the Early Termination visit (ET) for the preparation of the final CSR.

The investigator will inform the subject of the treatment assignment once the final database lock was completed and data are ready to be published.

4.12. Data Safety Monitoring Board (DSMB)

A DSMB will be established in the framework of this trial. The DSMB is an expert advisory group with the responsibility of evaluating, primarily, cumulative safety data before starting randomization of blinded participants and at regular intervals thereafter. During the conduct of the study, the responsibilities of the DSMB will be:

- To periodically review listings and summary tabulations of SAEs, deaths, AESIs, solicited AEs, unsolicited AEs, AEs leading to withdrawal from further vaccination and all AEs reported.
- To determine whether study or individual participant halting rules have been met.
- To make recommendations to the Sponsor regarding study conduct and possible study modifications.

A DSMB meeting will be organized to review the safety data to evaluate the safety of the unblinded low and high dosage before giving a positive recommendation for continuing with the blinded treatment phase once all six sentinel subject enrolled in the unblinded COVID-19 vaccine "Sentinel Groups" completed day 14. Following the 42-day follow-up of all sentinel subject, medical monitoring of safety data will be performed (Intermediate Report 2, IR2) to evaluate safety of the second injection in these six participants. In case of any safety concern, an ad hoc DSMB meeting will be organized before giving a positive recommendation for continuing with the second injection of the double-blind, randomized cohorts ("main cohorts").

A final DSMB meeting will be organized after all subjects completed visit 8 (D210) to be informed of the study global results.

Additionally, the intermediate analysis reports prepared at the following time points and the final study report will be shared with the DSMB (excluding observing DSMB members who will only have access to blinded safety report) and with the vaccine developer:

1. Intermediate Report 1 (IR1): After all six sentinel subjects completed visit 4 (day 28)
2. Intermediate Report 2 (IR2): After all six sentinel subjects completed visit 5 (day 42)
3. Intermediate Report 3 (IR3): After all (or at least 50% depending on the enrolment rate) subjects completed visit 4 (day 28)

Upon Sponsor decision ad hoc DSMB meetings might be scheduled during the whole duration of the study.

Besides, in the event of any unexpected safety concern, an unscheduled meeting could be organized at any time further to the sponsor or DSMB requests.

DSMB recommendations will also be transmitted to the Competent Authorities, the vaccine developer's representative, and IRB-Institut Pasteur.

The DSMB will be composed of at least a methodologist, a physician and a clinician with expertise in immunity to vaccines. A DSMB charter will be prepared and signed prior to enrolment of the first subject.

4.13. Intermediate reports and interim analysis

Intermediate reports and an interim analysis including safety and some immunogenicity data will be performed:

1. Intermediate Report 1 (IR1): After all six sentinel subjects completed visit 4 (day 28)
2. Intermediate Report 2 (IR2): After all six sentinel subjects completed visit 5 (day 42)
3. Intermediate Report (IR3): After all (or at least 50% depending on the enrolment rate) subjects completed visit 4 (day 28)
4. Interim analysis for interim CSR after all subjects completed visit 7 (day 91) or the Early Termination visit (ET)

The purpose of these intermediate analyses is to provide safety and some immunogenicity data for further SARS-CoV-2 vaccine development in outbreak situation.

Intermediate analyses will also be presented to an independent data review monitoring board (DSMB). DSMB recommendations regarding further study conduct and/or protocol modifications will be considered by the sponsor.
An interim analysis for the preparation of an interim CSR will be generated. Upon request, the DSMB members will have access to interim CSR.

The final analysis (final CSR) will be conducted once the last participant has completed the study.

5. INVESTIGATIONAL PRODUCT

5.1. Description of the active vaccine

The COVID-19 vaccine candidate is a live attenuated recombinant viral vectored vaccine for the prevention of COVID-19 disease. The spike protein of SARS-CoV-2 was selected as target antigen. Specific mutations were introduced to keep the protein in its pre-fusion conformation. Nucleotide sequences encoding the modified SARS-CoV-2 surface protein Spike (S) were codon-optimized for the expression in mammalian cells, chemically synthesized and inserted into the Schwarz vaccine strain of measles virus to produce the candidate COVID-19 vaccine, TMV-083 on Vero 10-87 cells. A detailed description of the vaccine construct and mechanism of action will be found in the Investigators' Brochure (IB).

The COVID-19 vaccine will be provided by Themis as a liquid frozen suspension of viral particles for single use IM injection in two different concentrations. The vaccine is contained in standard 2R clear glass vials labeled as TMV-083. The vaccine when thawed is presented as a liquid, clear to slightly turbid, colorless to whitish suspension. No adjuvants are added.
The target concentration of the vaccine is $1x10^5$ $TCID_{50}$/dose for the low dose vaccine and $1x10^6$ $TCID_{50}$/dose for the high dose vaccine. The vaccine dosages are liable to the manufacturing dependent window of ± 0.8 log steps. For ease of reading, this manufacturing dependent window will not be given in the other parts of this study protocol

5.2. Description of the placebo

Sterile physiological saline solution will be used as placebo as a control to enable comparison of treatment reactions within the different cohorts (A, B and C).

The physiological saline solution (ampoule of NaCl 0.9% for injection) is a clear colorless solution ready to use, stored according to the label and provided by the local pharmacy. The volume of placebo injected will be of 0.5 mL.

5.3. Packaging and Labeling

An individual cardboard box will contain a single 2 mL clear glass vials, containing liquid frozen COVID-19 vaccine. The labels on vials and boxes will be in English language.

After preparation, the ready to use IMP syringe will be administered directly by the study site personnel and therefore labelling of the ready to use IMP syringe will be done according to the site SOPs. For further details of IMP labelling, please refer to the study specific IMP-Manual.

5.4. Receipt, Storage and Preparation

5.4.1. Receipt

All IMPs should arrive at the pharmacy of the investigational site in sufficient time to enable dispensing and dosing as scheduled.

The Sponsor must notify the Principal Investigator prior to dispatch of drug supplies, with the anticipated date of their arrival. The IMP supplies will be addressed to:

French investigation site

Dr Corinne Guerin (PH –essais cliniques-ATU- Rétrocession)

PUI site Cochin - Hôpital Cochin - Bat Jean-Dausset

27 rue du Faubourg Saint Jacques

75014 Paris (France)

Belgium investigation site

Emma Van Roeyen, Senior Clinical Trial Pharmacist

SGS, Clinical Pharmacology Unit Antwerp

Pesthofstraat Poort 5

2060 Antwerpen (Belgium)

For further details of IMP reception, please refer to the study specific IMP-Manual.

5.4.2. Storage

The COVID-19 vaccine must be received by a designated and trained person at the study site, handled and stored safely and properly.

The IMP has to be stored under continuously temperature-controlled condition in a lockable room, or lockable freezer with limited access.

The minimum and maximum temperature will be recorded daily in the temperature logs.

In case the freezer is connected to an alarm system and corresponding copies of the readout can be filed, a min/max temperature does not need to be recorded daily. It is acceptable to use a site-specific temperature log, which covers all the required information.

The COVID-19 vaccine has to be kept in the outer package to be protected from light.

The liquid frozen formulation of the COVID-19 vaccine will be stored and transported at or below -65°C and shall be administered within 30 min after preparation when kept at room temperature. The ready to use syringe can be stored refrigerated at 2 to 8°C for up to one hour.

The 0.9% saline solution will be stored according to instruction leaflet. It is under the site's responsibility to ensure the storage conditions according to the summary product characteristics.

After administration, all used containers properly labelled with participant ID and appropriate visit identifier (e.g. visit number, date of administration) will be stored at site until checked by an unblinded monitor.

5.4.3. IMP Preparation

The pharmacist and all pharmacy personnel who will be responsible for vaccine preparation will be unblinded to the study vaccine allocation and otherwise not involved in the conduct of the trial after randomization.

COVID-19 is assessed as a biosafety level 1 (BSL1) product. Preparation of the COVID-19 vaccine for injection will be performed in a dedicated lab appropriate for handling of GMOs applying biosafety level 1 (BSL1) standards. The COVID-19 vaccine and placebo will be exclusively used for the present clinical trial and will only be administered to participants enrolled in the study.

Remove the COVID-19 vaccine vials containing frozen drug product from the freezer (stored at -65°C or below in the outer carton to protect from light) and allow to reach ambient temperature for max. 30 minutes.

Gently invert the vial 3-5 times. The drug product is presented as clear colorless to transparent white solution without any visible particulates. The thawed vaccine should be inspected visually for any foreign particulate matter and/or abnormal physical appearance prior to administration. In the event of either being observed, contact the sponsor or sponsor´s representative and do not use the vaccine. IMP should be put under quarantine until further advice from sponsor or sponsor´s representative.

The vaccine must be administered within another 30 minutes when kept at room temperature (in total within 60 minutes after removal from the freezer) or within 60 minutes when kept at 2-8°C (in total within 90 minutes after removal from the freezer).

All participants will receive IM injections of the COVID-19 vaccine or placebo in the deltoid region of the arm. Proper documentation of the injection site arm is required.

After administration, all used containers properly labelled with participant ID and appropriate visit identifier (e.g. visit number, date of administration) will be stored at site until checked by an unblinded monitor.

The COVID-19 vaccine and placebo will be exclusively used for the present clinical trial and will only be administered to participants enrolled in the study. For further instructions about study treatment storage, handling, preparation and destruction, please refer to the IMP Manual provided for the study.

5.4.4. Vaccine Administration

Only participants who fulfill inclusion/exclusion criteria of the study may receive the Investigational medical product. The day of first injection will be designated 'Day 0' (V1), the second injection will be designed 'Day 28' (V4). The IMP will be administered, in the presence of a blinded study physician, as a single intramuscular injection to the deltoid muscle of the arm. The volume of vaccine injected will be of 0.5 mL.

Vaccine administration will be documented in the participant’s source data, in the eCRF and in applicable logs.

Importantly, Intensive care Unit (ICU) and Emergency Room (ER) will be informed of the conduct of the study in the facility prior the first injection.

5.4.5. Vaccine Accountability

IMP accountability will be performed throughout the entire study, starting with the initial receipt of medication.

The authorized, unblinded study staff members will confirm the number and condition of received vials, by signing and dating an IMP receipt form.

Upon receipt an IMP inventory log will be kept current by the site and pharmacy, detailing the batch numbers, dates and quantity of IMP obtained, used for administration on a per participant basis and destroyed or returned to the sponsor. This documentation will only be available to an unblinded monitor verifying drug accountability during the study.

At the end of the study, all unused and used COVID-19 vials (marked with participant ID) will be returned to the manufacturer or destroyed by the pharmacist of the investigational site in a confidential manner, after final reconciliation and confirmation of correctness of drug accountability by the sponsor.

5.4.6. Management of genetically modified organisms (GMO)

The COVID-19 vaccine is a genetically modified organism (GMO) requiring BSL1 standards. Needles and syringes that have been in contact with the COVID-19 vaccine, as well as all other potentially contaminated materials, will be collected in dedicated containers and will be destroyed in a safe manner. This study will be conducted under regulations for contained use of a GMO.

6. STUDY RESTRICTION

6.1. Concomitant Medication

6.1.1. Permitted Prior and Concomitant Therapy

Should be documented any prior vaccination within the last three years prior screening and any medication within 30 days prior screening. Oral contraceptives are permitted and should be continued in a stable fashion as prescribed from the screening visit and up to visit 8 (D210).

Any medication taken during study participation up to the last visit (day 210) has to be reported to the investigator and will be documented.

Additionally, any treatment that will be considered necessary for the participant´s welfare may be given at the discretion of the Investigator. All concomitant medications must be reported in the participant's source data and in the eCRF along with dosage information, dates of administration, and reasons for use. Generic names for concomitant medication should be preferred, if possible. All concomitant medications will be coded using the WHO Drug Dictionary.

6.1.2. Forbidden Prior and Concomitant Therapy

Table 2: forbidden prior and concomitant therapy

Any treatment with licensed vaccines	Within four weeks prior to the first vaccination at visit 1 until 28 days after the second vaccination (D56)
Use of immunosuppressive drugs like corticosteroids (excluding topical preparations and inhalers)	within 3 months prior to the first vaccination or 6 months for chemotherapies and all along the study

Receipt of blood products or immunoglobulins	Within 3 months prior to enrollment or anticipated receipt of any blood product or immunoglobulin before completion of study participation (day 210)

6.1.3. Additional restrictions

- Women of childbearing potential must have a negative serum β-human chorionic gonadotropin (β-hCG) test on screening (and negative consecutive urine tests during the study) and be willing and able to use an acceptable method of birth control (e.g. contraceptives, intrauterine device, etc.) from the screening visit up to 6 months after the last injection (D210), or declare that they are abstaining from heterosexual intercourse, or be surgically sterile (bilateral tubal ligation, bilateral oophorectomy, or hysterectomy) or post-menopausal (menstruation ceased for 12 consecutive months prior to signing of the informed consent form).
- A male participant who is sexually active must use a condom (with/without spermicidal product); not donate sperm; not plan to father a child from the screening visit up to 6 months after the last injection (D210).
- Subjects must refrain from donating blood, blood derivatives, tissue or organ throughout the study period (up to D210)
- Subjects must not be in contact (Living or working) with severely immunocompromised people, pregnant women, lactating women, children under 12 months old, or any other individual that, in the judgment of the investigator might be at increased risk up to 28 days after each injection.

7. STUDY PROCEDURE AND ASSESSMENTS

7.1. Study procedures

See table next page

Visit	S	1	24hrs	2	3	4	24hrs	5	6	7	8	#
Visit Type	**Screening**	**1st Vaccination**	**Phone Call 1↟**	**FU "Sentinel groups"**	**FU1**	**2nd Vaccination**	**Phone call 2↟**	**FU2**	**FU3 End of treatment phase**	**LTFU1**	**LTFU2 EOS**	***Unscheduled visit***
Day	**-28 to -1**	**0**	**1***	**7±1**	**14±1**	**28±3**	**29***	**42±3**	**56±3**	**91±7**	**210±14**	***N/A***
Signed informed consent	✓											
Inclusion/exclusion criteria	✓	✓										
Individual halting rules			✓↟	✓↟	✓	✓	✓↟	✓	✓	✓		
Medical history & vaccination	✓											
Prior & Concomitant Medication (including immunization⌖)	✓	✓	✓↟	✓↟	✓	✓	✓↟	✓	✓	✓	✓	✓
Demographic (1)	✓					✓			✓			✓
Physical examination(2)	✓	✓		✓↟	✓	✓			✓		✓	✓
Vital Signs (3)	✓	✓		✓↟	✓	✓		✓	✓	✓	✓	✓
12-lead ECG	✓											
Randomization / Group allocation		✓										
COVID-19 vaccine/ Placebo		✓				✓						
Recording all AEs, AESIs and SAEs	✓	✓	✓↟	✓↟	✓	✓	✓↟	✓	✓	✓	✓	✓
Local reaction (Tolerability)		✓	✓↟	✓↟	✓	✓	✓↟	✓	✓			✓
Participant diary (4)		✓		✓↟	✓	✓		✓				
Pregnancy test	✓ (5)	✓ (6)				✓ (6)			✓ (6)	✓ (6)	✓ (6)	
Blood Safety Analysis (7)	✓			✓↟	✓	✓			✓		✓	✓
Breath alcohol and urine drug tests	✓	✓⌖				✓						
Viral Serology (HBV, HCV, HIV)	✓											
SARS-CoV-2 PCR and serology	✓											✓(8)
PBMC collection for immunological assessments (9)		✓			✓	✓		✓	✓	✓		
Serum collection for immunological assessments (9)		✓			✓	✓		✓	✓	✓		
Measles-Ab (ELISA)		✓				✓			✓			
Measles Shedding (10) (Blood, urine, saliva, nasal swab)		✓↟		✓↟	✓↟	✓↟		✓↟				

(1) Demographic: Weight, Height (only at VS), BMI;
(2) Physical examination: a complete physical examination (including assessment of general appearance, ears / nose / throat; skin; lymph nodes; musculoskeletal/extremities; abdomen; cardiovascular; respiratory; neurological body systems) will be performed at VS, V8. A directed physical examination (i.e. the examination will only be done on one or several body system such as general appearance, ears / nose / throat; skin; lymph nodes; musculoskeletal/extremities; abdomen; cardiovascular; respiratory; neurological body systems in case of symptoms) will be performed at V1, V2 (only for the "Sentinel Groups"), V3, V4, and V6.
(3) Vital Signs: HR, BP, RR (at rest) and body temperature;
(4) Participant diary: provided at V1 and V4, filled in up to 14±1 days after each vaccination, retrieved at V3 and V5.
(5) Pregnancy test: Serum β-human chorionic gonadotropin (β-HCG)
(6) Urine pregnancy spot test
(7) Safety analysis: See Appendix 1
(8) In case of presence of COVID-19 symptoms, SARS-CoV-2 PCR should be performed.
(9) Parameters that will be assessed: SARS-CoV-2 specific serum antibodies, neutralizing antibodies, staining panel for T cell characterization: (anti-CD3, CD4, CD8, CD45RA, CCR7, INF-γ, TNF-α, IL-5, IL-13, Granzym B).
(10) Only the 6 subjects of the "Sentinel Groups" will be part of shedding assessment. Samples (saliva, nasal swab, urine and whole blood) will be collected.

⌖ ***Including history of measles infection or measles immunization***
♦ ***Only for "Sentinel Groups"***
* ***A time window of ± 3 hours is allowed***
⌖ ***only if the screening visit (VS) took place more than 7 days prior to V1***

Visit	Type of Tubes	S	1	2	3	4	5	6	7	8	#
Visit Type		Screening	1st Vaccination	FU Sentinel group	FU1	2nd Vaccination	FU2	FU3	LTFU1	LTFU2 EOS	Unscheduled visit
Day		-28 to -1	0	7±1	14±1	28±3	42±3	56±3	91±7	210±14	N/A
Blood Safety Analysis : Hematology	EDTA	3 to 4.5 mL	-	3 to 4.5 mL	3 to 4.5 mL	3 to 4.5 mL	-	3 to 4.5 mL	-	3 to 4.5 mL	As needed
Blood Safety Analysis : biochemistry (*)	Serum or Lithium heparin	3 to 8 mL	-	3 to 8 mL	3 to 8 mL	3 to 8 mL	-	3 to 8 mL	-	3 to 8 mL	As needed
Viral Serology (HBV, HCV, HIV) from biochemistry sample	Serum	6 mL	-	-	-	-	-	-	-	-	
Blood Safety Analysis : coagulation	Citrate	3 to 3.5 mL	-	3 to 3.5 mL	3 to 3.5 mL	3 to 3.5 mL	-	3 to 3.5 mL	-	3 to 3.5 mL	As needed
Urine Safety analysis	container	5 to 8.5 mL	-	5 to 8.5 mL	5 to 8.5 mL	5 to 8.5 mL	-	5 to 8.5 mL	-	5 to 8.5 mL	As needed
Blood Pregnancy test	serum	4.5mL	-	-	-	-	-	-	-	-	
Urine Pregnancy test	Urine dipstick	-	1	-	-	1	-	1	1	1	
SARS-CoV 2 PCR	Swab	1	-	-	-	-	-	-	-	-	As needed
SARS-CoV 2 serology	serum	5 mL	-	-	-	-	-	-	-	-	As needed
PBMC collection	Heparin	-	100 to 120 mL♦		50 mL	100 to 120 mL♦	50 mL	100 to 120 mL♦	50 mL		
Serum collection for immunological assessments (including Measles-Ab when applicable)	Serum or dry tube		16 mL		16mL	16 mL	16 mL	16mL	16 mL		
Blood Measles virus shedding test	Whole blood	-	5 mL	5 mL	5 mL	5 mL	5 mL	-	-	-	
Urine Measles virus shedding test	container	-	5 mL	5 mL	5 mL	5 mL	5 mL	-	-	-	
Saliva Measles virus shedding test	container	-	1	1	1	1	1	-	-	-	
Nasal shedding test	Swab	-	2	2	2	2	2	-	-	-	
Max. blood volume drawn "Sentinel Groups"		31,5 mL	141 mL	21mL	87 mL	157 mL	71 mL	152 mL	66 mL	16 mL	As needed
Max. blood volume drawn "Main Cohorts"		31,5 mL	136ml	-	82 mL	152 mL	66 mL	152 mL	66 mL	16 mL	As needed
Max. urine volume collected "Sentinel Groups"		8.5 mL	5 mL	13,5 mL	13,5 mL	13,5 mL	5 mL	13,5 mL	-	8.5 mL	As needed
Max. urine volume collected "Main Cohorts"		8.5 mL	-	-	8.5 mL	8.5 mL	-	8.5 mL	-	8.5 mL	As needed

*For Belgian site: β-HCG included, 2mL on Na Fluoride for glucose dosage; ♦ Blood volume collected will be adjusted to body weight according to 3HREC guideline for maximum paediatric blood volumes for research purpose" and will not exceed 120mL.

Table 3: **total volume of blood and urine drawn/collected during the study**

7.2. Study Visits

7.2.1. Screening visit (VS) (28 to 1 days before randomization)

After providing information on objectives, procedure and potential risk of the study, a sufficient time will be let to healthy volunteers (participant) for questions and answers and reflection as to whether or not he/she wishes to participate. Those willing to participate will be invited to sign an informed consent form and will be assessed for their eligibility to participate in the study. Screening tests will start only after the participant and Investigator have signed the informed consent form (ICF). Screening will take place from 28 days to 1 days prior to injection for the “Sentinel Groups” and to randomization/injection for the “Main Cohorts”.

The following screening assessments will be performed for each participant

- Participant identification
- Record of medical and surgery history (including history of measles infection)
- Record of prior and concomitant therapy (including history of measles immunization)
- Demographics: including Sex; month and year of birth; Height; Weight; BMI (calculated as Kg/m^2)
- A complete physical examination
- Vital signs: blood pressure and heart rate (in sitting or supine position*), respiration rate (RR), body temperature,
- 12-lead ECG
- Laboratory safety screens as outlined in Appendix 1 (including blood pregnancy test for female subjects)
- Breath alcohol and urine drug tests (as outlined in Appendix 1)
- HBV; HCV and HIV serology**
- SARS-CoV-2 PCR and serology
- Compliance with inclusion/exclusion criteria

* Vital signs can be measured in sitting or supine position as well as long as within 1 patient the measurements are always done in the same position.

** Results of HBV, HCV and HIV serology will be communicated to participant unless he/she expresses the wish, via the Informed consent form, not to be informed.

At the end of the screening visit, the next visit (Visit 1) will be scheduled and confirmed (once results of laboratory safety test will be available and assess).

During the time window authorized for the screening visit, the Investigator may order a re-test of the following parameters: demographics (Height, weight and BMI), vital signs (HR, RR, BP, body temperature), 12-lead ECG, laboratory safety screen tests, breath alcohol and/or urine drug tests evaluated during the initial screening visit, if they need to evaluate the evolution of that parameter(s) or to confirm the value

observed. Results of this re-test must be available prior to the first administration of the investigational product. The result of the re-test will be considered for subject eligibility.

7.2.2. Visit 1 - Randomization/ first injection (Day 0)

Participant will arrive at the Investigational clinical site of the randomization/vaccination day.

The following assessments will be performed for each participant before first injection for the “Sentinel Groups” and before randomization / first injection for “Main Cohorts”:

- Re-check record of medical and surgery history
- Recording of any changes in the concomitant medications or medical status since screening visit.
- Re-check compliance with inclusion/exclusion criteria
- A directed physical examination
- Vital signs (BP, HR, respiratory rate, and body temperature) measurement in sitting or supine position*
- Urine pregnancy test (for Females)
- Breath alcohol and urine drug tests** (as outlined in Appendix 1)
- Blood sample will be drawn for immunomonitoring analysis
- Collection of saliva, urine, nasal swab and blood for shedding assessment (only for “Sentinel Groups”)

** Vital signs can be measured in sitting or supine position as well as long as within 1 patient the measurements are always done in the same position.*

*** only if the screening visit (VS) took place more than 7 days prior to V1*

If all criteria are fulfilled, no significant change in the participant’s health, he/she will receive the vaccine for the “Sentinel Groups” or be assigned a study randomization number (see section 4.11) for the “Main Cohorts”. Then, he/she will receive the first intramuscular injection into the deltoid muscle. The time and the arm (left or right) in which the vaccine was injected will be recorded in the participant’s source data and in the eCRF.

After injection, the participants will remain in the Investigational clinical site for medical supervision and monitoring. If they belong to:

- the "Sentinel Groups" for a minimum of 1 hour post-injection.
- the "Main Cohorts" for a minimum of 1 hour post-injection.

The following assessment / activities will be performed after vaccine administration:

For “Sentinel Groups”: at 1 hour (±15 min) after injection

- Vital signs (BP, HR, respiratory rate, body temperature).
- Assessment of Local reaction of the injection site and general reaction (see Appendix 2) by a study physician, or his/her delegate.

For "Main Cohorts": at 1 hour (±15 min) after injection

- Vital signs
- Local reaction of the injection site and general reaction.

During the visit, the Investigator may order one re-test of the following parameters: vital signs (HR, RR, BP, body temperature), urine pregnancy test (for Females), breath alcohol and/or urine drugs test, if they need to evaluate the evolution of that parameter(s) or to confirm the value observed. The reason of this re-test will be documented in the participant's source data. Results of this re-test must be available prior to the first administration of the investigational product. The results of the re-test will be considered for subject eligibility. The reason and results of this re-test will be documented in the participant's source data and in the eCRF.

Participant will be provided with a diary, a ruler and a thermometer and they will receive instructions on how to measure temperature and record adverse events during the subsequent 14±1 days after the injection. The diary will be returned on the next visit at investigational clinical site.

Subject will be given an emergency card with a phone number to call in case of questions or upon occurrence of any AE.

At the end of the visit, which lasts approximately 1 hour 30 min in the "Sentinel Groups" and in the "Main Cohorts", once the study physician has determined that he/she is fit to be released, the participant will be discharged from the investigational clinical site. The appointment for the phone call (24 hours±3) and for the Visit 2 (day 7±1) for the "Sentinel Groups" and for Visit 3 (Day 14±1) for the "Main Cohorts" will be scheduled and confirmed with the participant.

7.2.3. Phone call 1 - "Sentinel Groups" (Day 1 - 24 hours ± 3 hours after the 1st injection)

Twenty-four hours (±3 hours) after the first injection, participants of the "Sentinel Groups" will be contacted by phone for the monitoring of AE; AESI and SAE. Any changes in the concomitant medications, medical status and occurrence of AE since the previous visit will be checked and recorded in the participant's source data and in the eCRF. In case of AE corresponding to the definition of SAE or AESI, an unscheduled visit will be organized in the investigational clinical site. At the end of the phone call, appointment for the visit 2 (day 7±1) will be confirmed with the participant of the "Sentinel Groups".

7.2.4. Visit 2 – "Sentinel Groups" (Day 7±1 after injection)

This visit will take place 7±1 after the first vaccination for participants of the "Sentinel Groups". Participants will be interviewed by a physician, or his/her delegate, of the investigational clinical site about any changes in their medical status, concomitant medications and/or occurrence of any AEs, AESI an SAE since the last contact. Diaries will be reviewed and all AEs will be documented in participant's source data and in the eCRFs.

The following assessment / activities will be performed during this visit

- Check if participant has met any individual halting rule
- Examination of the site of injection and assessment of local reaction.
- A directed physical examination

- Record of vital signs in sitting or supine position*
- Safety laboratory evaluations (blood and urine)
- Collection of saliva, urine, nasal swab and blood for shedding assessment

** Vital signs can be measured in sitting or supine position as well as long as within 1 patient the measurements are always done in the same position.*

During the visit, the Investigator may order one re-test of the following parameters: vital signs (HR, RR, BP, body temperature), safety laboratory tests, if they need to evaluate the evolution of that parameter(s) or to confirm the value observed. The reason and results of this re-test will be documented in the participant's source data and in the eCRF.

At the end of the visit, the next visit (Visit 3) will be scheduled and confirmed with the participants of the "Sentinel Groups".

7.2.5. Visit 3 - Follow-up 1 (Day 14±1)

This visit will take place 14±1 days after the first vaccination. Participants will be interviewed by a physician, or his/her delegate, of the investigational clinical site about any changes in their medical status, concomitant medications and/or occurrence of any AEs, AESI an SAE since the last visit/contact. Diaries will be collected, reviewed and all AEs will be documented in participant's source data and in the eCRFs.

The following assessment / activities will be performed during this visit

- Check if participant has met any individual halting rule
- Examination of the site of injection and assessment of local reaction.
- Record of vital signs in sitting or supine position*.
- A directed physical examination.
- Safety laboratory evaluations (blood and urine).
- A blood sample will be drawn for immunomonitoring analysis.
- Saliva, Urine, nasal swab and an additional blood sample will be collected/drawn in the "Sentinel Groups" for shedding assessment.

** Vital signs can be measured in sitting or supine position as well as long as within 1 patient the measurements are always done in the same position*

During the visit, the Investigator may order one re-test of the following parameters: vital signs (HR, RR, BP, body temperature), safety laboratory tests, if they need to evaluate the evolution of that parameter(s) or to confirm the value observed. The reason and results of this re-test will be documented in the participant's source data and in the eCRF.

At the end of the visit, the next visit (Visit 4) will be scheduled and confirmed with the participants.

7.2.6. Visit 4 - Second injection (Day 28±3)

This visit will take place 28±3 days after the first vaccination. Participants will be interviewed by a physician, or his/her delegate, of the investigational clinical site about any changes in their medical status, concomitant medications and/or occurrence of any AEs, AESI an SAE since the last visit.

The following assessment / activities will be performed during this visit and before the second injection

- Check if participant has met any individual halting rule
- Record of demographics (*only weight and BMI*).
- A directed physical examination.
- Record of vital signs in sitting or supine position*.
- Safety laboratory evaluations (blood and urine).
- Urine pregnancy test (For Females).
- Breath alcohol and urine drug tests (as outlined in Appendix 1)
- A blood sample will be drawn for immunomonitoring analysis.
- Saliva, Urine, nasal swab and an additional blood sample will be collected/drawn in the “Sentinel Groups” for shedding assessment.

** Vital signs can be measured in sitting or supine position as well as long as within 1 patient the measurements are always done in the same position*

During the visit, the Investigator may order one re-test of the following parameters: demographics (Weight and BMI), vital signs (HR, RR, BP, body temperature), safety laboratory tests, urine pregnancy test (for females), breath alcohol and/or urine drug tests, if they need to evaluate the evolution of that parameter(s) or to confirm the value observed. Results of this re-test must be available prior to the second administration of the investigational product. The reason and results of this re-test will be documented in the participant’s source data and in the eCRF.

If, no significant change in the participant’s health since the last visit, he/she will receive the second intramuscular injection into the deltoid muscle of the opposite arm of the first injection ideally. The time and the arm (left or right) in which the vaccine was injected will be recorded in the participant’s source data and in the eCRF.

In case of presence of a clinically significant acute disease at the time of vaccination or presence of fever defined by a body temperature ≥ 38.0°C 24 hours prior to the visit or at the time of vaccination, the participant may be vaccinated at a later date, at the discretion of the Investigator or withdrawn from the study if he/she has met an individual halting rules (see section 4.8). The subject must be followed until resolution of the event.

After injection, the participants will remain in the Investigational clinical site for medical supervision and monitoring for a minimum of 1 hour after injection.

The following assessment / activities will be performed 1 hour (±15 min) after the second injection:

- Vital signs in sitting or supine position*.
- Local reaction of the injection site.

Participant will be provided with a new diary for the 14±1 following days. At the end of the visit, which lasts approximately 2 hours and once the study physician has determined that he/she is fit to be released, the participant will be discharged from the Investigational clinical site. The appointment for the phone call 2 will be scheduled and confirmed with the participants of the "Sentinel Groups and the appointment for the Visit 5 (Day 42) will be scheduled and confirmed with the participants of the "Main Cohorts.

7.2.7. Phone call 2 - "Sentinel Groups" (Day 29 - 24 hours ±3 hours after 2nd injection)

Twenty-four hours (±3 hours) after the second injection, participants of the "Sentinel Groups" will be contacted by phone for the monitoring of AE; AESI and SAE. Any changes in the concomitant medications, medical status and occurrence of AEs, AESI and SAE since the previous visit will be checked and recorded in the participant's source data and in the eCRF. In case of AE corresponding to the definition of SAE or AESI, an unscheduled visit will be organized at the investigational clinical site. Appointment for the visit 5 (day 42) will be confirmed with the participant.

7.2.8. Visit 5 - Follow-up 2 (Day 42±3)

This visit will take place 42±3 days after the first injection. Participants will be interviewed by a physician, or his/her delegate, of the investigational clinical site about any changes in their medical status, concomitant medications and/or occurrence of AEs, AESI and SAE since the last contact. Diaries will be collected, reviewed and all AEs will be documented in participant's source data and in the CRFs.

The following assessment / activities will be performed during this visit

- Check if participant has met any individual halting rule
- Examination of the site of injection and assessment of local reaction.
- Record of vital signs in sitting or supine position*.
- A blood sample will be drawn for immunomonitoring analysis

** Vital signs can be measured in sitting or supine position as well as long as within 1 patient the measurements are always done in the same position.*

During the visit, the Investigator may order one re-test of the following parameters: vital signs (HR, RR, BP, body temperature), if they need to evaluate the evolution of that parameter(s) or to confirm the value observed. The reason and results of this re-test will be documented in the participant's source data and in the eCRF

Saliva, Urine, nasal swab and an additional blood sample will be collected/drawn in the "Sentinel Groups" for shedding assessment.

At the end of the visit, the next visit (Visit 6) will be scheduled and confirmed.

7.2.9. Visit 6 - Follow-up 3/ End of Treatment phase (Day 56±3)

This visit will take place 56±3 days after the first injection. Participants will be interviewed by a physician, or his/her delegate, of the investigational clinical site about any changes in their medical status, concomitant medications AEs, AESI and SAE since the last visit.

The following assessment / activities will be performed during this visit

- Check if participant has met any individual halting rule
- Examination of the site of injection and assessment of local reaction.
- Record of demographics (*only weight and BMI*)
- A directed physical examination
- Record of vital signs in sitting or supine position*.
- Safety laboratory evaluations (blood and urine)
- Urine pregnancy test (For Females)
- A blood sample will be drawn for immunomonitoring analysis

** Vital signs can be measured in sitting or supine position as well as long as within 1 patient the measurements are always done in the same position.*

During the visit, the Investigator may order one re-test of the following parameters: Demographics (Weight and BMI), vital signs (HR, RR, BP, body temperature), safety laboratory tests, urine pregnancy test (for females) if they need to evaluate the evolution of that parameter(s) or to confirm the value observed. The reason and results of this re-test will be documented in the participant's source data and in the eCRF.

At the end of the visit, the next visit (Visit 7) will be scheduled and confirmed with the participant.

7.2.10. Visit 7 – Long Term Follow-up 1 (Day 91±7)

This visit will take place 91±7 days after the first injection. Participants will be interviewed by a physician, or his/her delegate, of the investigational clinical site about any changes in their medical status, concomitant medications and/or occurrence of any AEs, AESI and SAE since the last visit and will be documented in participant's source data and in the eCRFs and assessed.

The following assessment / activities will be performed during this visit

- Check if participant has met any individual halting rule
- Record of vital signs in sitting or supine position*.
- Urine pregnancy test (For Females)
- A blood sample will be drawn for immunomonitoring analysis

** Vital signs can be measured in sitting or supine position as well as long as within 1 patient the measurements are always done in the same position.*

During the visit, the Investigator may order one re-test of the following parameters: vital signs (HR, RR, BP, body temperature), urine pregnancy test (for females), if they need to evaluate the evolution of that parameter(s) or to confirm the value observed. The reason and results of this re-test will be documented in the participant's source data and in the eCRF.

At the end of the visit, the next visit (Visit 8) will be scheduled and confirmed with the participant.

7.2.11. Visit 8 – Long Term Follow-up 2 / End of Study (Day 210±14)

This visit will take place 210±14 days after the first injection. Participants will be interviewed by a physician, or his/her delegate, of the investigational clinical site about any changes in their medical status, concomitant medications and/or occurrence of any AEs, AESI and SAE since the last visit and will be documented in participant's source data and in the eCRFs and assessed.

The following assessment / activities will be performed during this visit

- A complete physical examination
- Record of vital signs in sitting or supine position*.
- Safety laboratory evaluations (blood and urine)
- Urine pregnancy test (For Females)

** Vital signs can be measured in sitting or supine position as well as long as within 1 patient the measurements are always done in the same position.*

During the visit, the Investigator may order one re-test of the following parameters: vital signs (HR, RR, BP, body temperature), safety laboratory tests, if they need to evaluate the evolution of that parameter(s) or to confirm the value observed. The reason and results of this re-test will be documented in the participant's source data and in the eCRF.

7.2.12. Early Termination visit (ET)

Participants, who are withdrawn from the study (for any reason) or wish to stop (for any reason) his/her participation prematurely, will be invited to attend an Early Termination visit (ET).

If the withdrawn or study discontinuation occur between D0 (first vaccination) and D56 (28 days after the second vaccination), the subjects will be invited to perform the following assessment / activities during this Early termination visit:

- Examination of the site of injection and assessment of local reaction.
- Record of vital signs in sitting or supine position*
- Safety laboratory evaluations (blood and urine)

A blood sample could also be drawn for immunomonitoring analysis.

** Vital signs can be measured in sitting or supine position as well as long as within 1 patient the measurements are always done in the same position.*

During the visit, the Investigator may order one re-test of the following parameters: vital signs (HR, RR, BP, body temperature), safety laboratory tests, if they need to evaluate the evolution of that parameter(s) or to confirm the value observed. The reason and results of this re-test will be documented in the participant's source data and in the eCRF.

If the withdrawn or study discontinuation occur after D56, participant will be asked to participate in a phone follow-up call at D91 and D210 for assessing occurrence of any AEs since the visit D56.

If the withdrawn or study discontinuation is related to an AE, the participant will be contacted by phone, at the discretion of the investigator, up to resolution or stabilization of the event. This will be documented in the participant's source data and in the eCRF.

7.2.13. Unscheduled Visit(s)

An unscheduled visit may be performed at any time during the study at the participant's request or as required by the Investigator due to medical considerations including suspicion or confirmed SARS-CoV-2 infection (see section 9.1.11).

A participant in contact, according to ECDC definition[4], with a SARS-CoV-2 confirmed case or a participant with suspected or confirmed SARS-Co-V-2 infection will be managed according to the following local procedure:

For the Belgium site:

If a participant notices a contact with a confirmed case or typical COVID-19 symptoms (see section 9.1.11) while he/she is present at CPU, an ad hoc nasal swabbing for a SARS-CoV-2 PCR will be performed. If the PCR result is negative, a physical examination, vital signs measurement (including body temperature, BP, HR, Oxygen saturation), will be performed. If the PCR result is positive, the General Practitioner (GP) will be contacted and contact with CPU staff will be limited.

If the contact with a confirmed case or symptoms are noticed at home, the CPU staff will advise the participant to get tested, within 3 days, at their GP and to send the result of the SARS-CoV-2 PCR to the investigator. If the participant is tested positive, he/she will be excluded from further visits at CPU for two weeks in order to prevent him/her contaminating the unit and he/she will be withdrawn from dosing (if applicable). A telephone follow-up will be organized with the participant up to 14 days after testing and further follow-up will be discussed with the GP. If no visits are planned two weeks after the positive PCR and if the subject is not hospitalized because of COVID-19, an unscheduled visit will be planned with the participant for a post-infection follow-up.

For the French site:

If a participant notices a contact with a confirmed case or experiences typical COVID-19 symptoms (see section 9.1.11) while he/she is present at CIC-Cochin-Pasteur, the following examinations will be performed: ad hoc physical examination, vital signs measurement (including body temperature, BP, HR, Oxygen saturation), nasal swabbing for SARS-CoV-2 PCR, blood samples for laboratory tests, including cell blood count, and ionogram with CRP. Blood culture will also be performed if body temperature is > 38°C. If the contact with a confirmed case or symptoms are noticed at home, the participant will be invited to attend an unscheduled visit within 3 days after notification of a contact with a confirmed case or onset of symptoms. The same tests as described above in case of contact or the subject notices the symptoms

[4] https://www.ecdc.europa.eu/sites/default/files/documents/Public-health-management-persons-contact-novel-coronavirus-cases-2020-03-31.pdf

while at the site will be performed. In case of suspected severe forms, the participant will be sent to the ICU of the Cochin Teaching hospital where the recruiting center is affiliated.

The date and reason for the unscheduled visit will be recorded in the participant's source data and in the eCRF. AE monitoring and concomitant medication recording will be performed by the Investigator. Other procedures and evaluations will be completed as deemed necessary by the Investigator and may include (but not limited to) safety laboratory tests, vital signs and physical examination.

7.3. Blood Volume justification

Blood will be taken at each visit for safety laboratory assessments and immunologic assays (See table 3). Based on our calculation, the maximum blood volume taken within 28 days period is compliant with "*HREC guideline for maximum paediatric blood volumes for research purpose*"[5]. Additional blood sampling may occur at unscheduled visits, if needed, for safety laboratory tests.

8. SAFETY ASSESSMENTS

8.1. Adverse Events (AEs) and Concomitant Medications

8.1.1. Adverse Events (AEs)

AEs, either observed by the study physician (or his/her delegate) or reported by the participants (orally or in the participant diary), will be collected and assessed all along the study from the screening visit (VS) through the last long-term Follow-up/EOS visit (V8), in participants who have been enrolled.

AEs reported prior to first injection will be recorded in the participant's source data and in the eCRF and will be considered as non-treatment emergent AEs. Any new systemic effect that occurs between scheduled visits should be brought to the attention of the Investigator and recorded in the participant's source data and in the eCRF.

The severity of the general systemic symptoms will be graded according to the "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" (Appendix 2).

8.1.2. Concomitant Medications

Use of concomitant medication will be recorded continuously starting from signing the ICF until the EOS visit (V8).

8.1.3. Vital signs

Vital signs (sitting or supine* BP, HR, RR, and body temperature) will be measured with the participant at rest at following visits:

5 https://www.sun.ac.za/english/faculty/healthsciences/rdsd/Documents/Ethics/HREC%20(2016).%20HREC%20guideline%20for%20maximum%20paediatric%20blood%20volumes%20for%20research%20purposes.pdf

- Screening visit (VS),
- 1st injection visit (V1)
    - For “Sentinel Groups”: before injection and 1 hour (±15 min) after vaccine injection
    - For “Main Cohorts”: before injection and 1 hour (±15 min) after vaccine/placebo injection
- Day 7 (V2) for “Sentinel Groups”
- 2nd injection visit (V4): before injection and 1 hour (±15 min) after vaccine/placebo injection.
- Follow-up and long-term follow-up visits (V3; V5; V6; V7; V8)

* Vital signs can be measured in sitting or supine position as well as long as within 1 patient the measurements are always done in the same position.

During these visits, the investigator may order one re-test if they need to evaluate the evolution of one or several vital signs parameter(s) or to confirm the value observed. The reason and results of this re-test will be documented in the participant’s source data and in the eCRF.

Significant changes from baseline measurements performed at Screening visit, will be assessed, documented in the participant’s source data and recorded as AEs in the eCRF.

The severity of out of range vital signs will be graded according to the “Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials” (Appendix 2).

8.1.4. Physical examination

A **complete** physical examination will be performed by a study physician at:

- Screening visit (VS) and long-term follow-up visits (V8)

A **directed** physical examination will be performed, in case of suspected symptoms, at:

- 1st injection visit (V1): before injection.
- Day 7 (V2) for “Sentinel Groups”
- Follow-up visit (V3)
- 2nd injection visit (V4): before injection.
- Follow-up visit (V6)

Significant changes from baseline examination performed at screening visit, will be assessed documented in the participant’s source data and recorded as AEs in the eCRF.

The severity of clinical abnormality will be graded according to the modified “Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials” (Appendix 2).

8.1.5. Assessment of local Reaction of Injection Site

Assessment of local reaction will be made at the following time points:

- 1st injection visit (V1)
    - For “Sentinel Groups”: 1 hour (±15 min) after vaccine injection

- For “Main Cohorts”: 1 hour (±15 min) after vaccine/placebo injection.

- Day 7 (V2) for “Sentinel Groups”
- 2nd injection visit (V4): 1 hour (±15 min) after vaccine/placebo injection.
- Follow-up and long-term follow-up visits (V3; V5; V6)

Any local reaction will be assessed, documented in the participant’s source data and recorded in the eCRF.

The severity of local reaction will be graded according to the “Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials” (Appendix 2).

8.1.6. 12-Lead ECG

A 12-lead ECG will be performed at Screening visit (VS)

During this visit, the investigator may order one re-test if they need to evaluate the evolution or to confirm the value observed during the first 12-lead ECG. The reason and results of this re-test will be documented in the participant’s source data and in the eCRF.

Any ECG abnormality determined by the study physician to be clinically significant will be assessed, documented in the participant’s source data and noted as an AE in the eCRF. Such abnormalities will be closely monitored until stabilized or resolved.

8.1.7. Safety Laboratory tests

Safety laboratory evaluations will be performed by laboratories of the study site at the following time points.

- Screening visit (VS)
- Day 7 (V2) for “Sentinel Groups”
- 2nd injection visit (V4): before injection
- Follow-up and long-term follow-up visits (V3; V6; V8)

The laboratory assessment variables are detailed in Appendix 1

During these visits, the investigator may order one re-test if they need to evaluate the evolution of one or several laboratory parameter(s) or to confirm the value observed. The reason and results of this re-test will be documented in the participant’s source data and in the eCRF.

Laboratory tests which are outside the normal range from the normal ranges defined by site laboratories will be assessed by the study physician. All abnormal laboratory test results that are considered to be clinically significant by the study physician will be documented in the participant’s source data and reported as an AE in the eCRF.

The severity of laboratories abnormalities will be graded according to the “Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials” (Appendix 2).

8.1.8. Pregnancy Tests

Serum β-HCG will be tested in female subjects at Screening visit (VS). Urine pregnancy test will be performed at:

- 1st injection visit (V1) and at 2nd injection visit (V4) before injection
- Follow-up visit V6 (D56±3), V7 (D91±7) and V8 (D210±14)

During these visits, the investigator may order one re-test if they need to confirm the value observed. The reason and result of this re-test will be documented in the participant's source data and in the eCRF.

8.2. Participant Diary

The participant will receive a diary on each vaccination day (visit 1 and 4) for 14±1 days completion. They will be requested to record any local or systemic reaction (vaccination day included) and body temperature. In this frame, participants will receive a ruler to measure the size of local reaction if occurs and a thermometer to measure oral body temperature.

Solicited local and solicited systemic reactions will be assessed by the participants themselves by checking for presence of the listed symptoms and measuring the size of the affected area where appropriate (a template will be provided for local reaction grading, as shown in Appendix 3). The diary will also provide space for recording unsolicited AEs and concomitant medication.

Recording should be done approximately at the same time each day, starting on the day of vaccination.

The participants´ diaries will be collected and verified for completeness by the investigator. Any symptoms recorded in the participant diaries will be documented in the source data by the investigator or authorized delegates. The investigator will re-evaluate the severity of the reported local and systemic reactions according to the "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" (Appendix 2). After assessment of the Investigator, clinically significant symptoms (i.e. moderate/severe) and mild symptoms for which a treatment is required will be reported as Adverse Events in the eCRF.

The diary includes the following:

- **Solicited systemic AEs**: Myalgia (osteomuscular pain), rash, nausea, vomiting, fever (body temperature ≥ 38°), headache and fatigue.
- **Solicited local reaction to injection**: Pain, itching, erythema (redness), swelling, induration.

these should also be documented in the participant' source data and in the eCRF.

In addition, body temperature will be checked during 14±1 days following each injection and fever will be graded by the investigator according to "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" (Appendix 2).

8.3. Measles virus shedding assessment

Nasal swab, saliva, blood and urine sample will be collected in the 6 participants of the "Sentinel Groups" for performing a measles virus shedding assessment at the following time points:

- 1st injection visit (V1)
- Day 7 (V2)

- Follow-up visit (V3)
- 2nd injection visit (V4)
- Follow-up visit (V5)

Central laboratory will be used for analysis of all specimens collected.

The procedures of sample collection, preparation, storage, shipping and analysis will be described in detail in a study specific Lab-Manual.

8.4. Immunological sample handling

Blood samples will be drawn for immunological assessments at the following time points:

- 1st injection visit (V1): before injection
- 2nd injection visit (V4): before injection.
- Follow-up and long-term follow-up visits (V3; V5; V6; V7)

Central laboratories will be used for analysis of all specimens collected.

The procedures of sample collection, preparation, storage, shipping and analysis will be described in detail in a study specific Lab-Manual.

8.5. Measles virus shedding analysis

The shedding of infectious measles virus particles will be determined from the “sentinel Groups”, i.e. six immunized participants treated in an unblinded and non-randomized manner in cohort A and B. The samples will be analyzed by quantitative real-time Polymerase Chain Reaction (qPCR) to detect measles virus RNA. Any PCR positive sample will be further tested in an in vitro infectivity assay for the presence of infectious virus. The Measles virus shedding analysis will be performed at Texcell, Evry, France.

8.6. Calendar of study

- Provisional start recruitment date: Q2 2020
- Provision start enrollment date : Q3 2020
- Provisional inclusion duration: approximately 6 weeks
- Patient’s participation duration: approximately 7 months
- Projected study duration: approximately 15 months
- Data archiving duration: 25 years after the completion of the study
- Biobanks duration: 15 years

9. SAFETY AND PHARMACOVIGILANCE

9.1. DEFINITION

9.1.1. Adverse Event (AE)

An Adverse Event is defined as unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the investigational medicinal product.

AEs do not include the following:

- Stable or intermittent chronic conditions (such as myopia requiring eyeglasses) that are present prior to study entry and do not worsen during the study
- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion). The condition that leads to the procedure is an AE if not present at baseline
- Hospitalization for elective surgery planned prior to study (situation where an untoward medical occurrence has not occurred)

AE will be graded according to the “Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials” (Appendix 2).

9.1.2. Adverse Reaction (AR)

An adverse reaction (AR) is any untoward or unintended response in a participant to an IMP. This means that a causal relationship between the IMP and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out. All cases judged by the reporting Investigator as having a reasonable suspected causal relationship to an IMP (i.e. possibly, probably or definitely related to an IMP) will qualify as AR.

9.1.3. Serious Adverse Events (SAEs)

An SAE is any AE occurring at any dose that suggest a significant hazard or side effect, regardless of the Investigator or Sponsor's opinion on the relationship to the investigational product and that results in, but may not be limited to, any of the following outcomes:

- death (regardless of the cause)
- a life-threatening adverse event or suspected adverse reaction
- a persistent or significant disability/incapacity or a substantial disruption of the ability to conduct normal life functions
- An inpatient hospitalization or prolongation of existing hospitalization
- An important medical event (that may not result in death, be life-threatening, or require hospitalization) that may be serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.
- a congenital anomaly or birth defect

9.1.4. Serious adverse drug reaction (SADR)

An event (expected or unexpected) that is both serious and, in the opinion of the reporting investigator or Sponsors, believed to be possibly, probably or definitely due to an IMP, based on the information provided.

9.1.5. Suspected unexpected serious adverse reaction (SUSAR)

A SUSAR is a SAE that is unexpected and thought to be possibly, probably or definitely related to an IMP.

9.1.6. Relevant medical event/ Emerging safety issue “fait nouveau”

Any new safety information which could significantly modify the evaluation of the benefit/risk ratio of the investigational medicinal product or the clinical trial, likely to affect the safety of participants or that could modify the investigational medicinal product administration, the trial documentation or the conduct of the trial (eg: a significant hazard to the subject population such as unexpected occurrence of an unwanted reaction, serious adverse event related to study procedure, lack of efficacy of an investigational medicinal product used for the treatment of a life-threatening disease).

For all safety issues qualifying the definition of New Event or Urgent Safety Measure and therefore, requiring immediate notification, sponsor will contact the CA, IRB, EC and ARS (France) without delay in order to share any relevant information for the evaluation of the event and communicate any urgent safety measures implemented if necessary.

Expedited reporting to CAs, ECs and investigators of each site will be managed by SGS Medical Affairs according to the SOP “Processing and Reporting of Individual Serious Adverse Events of Interventional Clinical Trials”, the ICH guideline E2A “Note for Clinical Safety Data Management” and the Safety Management Plan. CRAs will be in charge to inform investigator of each site of any relevant medical event/emerging safety issue occurring during the study. An Acknowledgment of Receipt will be completed and signed by the investigator and then retrieved by the CRA.

9.1.7. Definitions of Adverse Event Severity

AEs must be graded by a medically qualified person as being mild, moderate, severe or life-threatening and their approximate duration given. Definitions of severity are as follows:

• Mild: An AE that requires minimal or no treatment and does not interfere with daily activities

• Moderate: An AE that is sufficiently discomforting to interfere with normal activities

• Severe: An AE that is incapacitating or prevents normal activities and may require systemic drug therapy or other treatment

• Potentially Life-Threatening: An AE that requires immediate intervention to prevent death

"Life-threatening" refers to an AE in which the participant was at risk of death at the time of the event, it does not refer to an AE which hypothetically might have caused death if it were more severe.

The investigator will assess the severity of an AE according to the "Guidance for Industry: “Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials” (Appendix 2).

9.1.8. Definitions of Adverse Event Causality

The Investigator will document in his/her opinion the relationship of the AE to the study drug according to the following definitions:

- Definitely: Temporal relationship to the administration of the study drug and course following a known reaction pattern
- Probably: Good reasons and sufficient documentation to assume a causal relationship
- Possibly: A causal relationship is conceivable and cannot be dismissed
- Unlikely: The event is most likely related to an etiology other than the trial treatment
- Not Related: No temporal relationship to the administration of the drug or other factors have caused the event.

9.1.9. Expectedness

Expectedness will be determined considering the current IB.

- Expected: A SAR that is listed in the current IB
- Unexpected: An AE that is not listed in the current IB or that differs due to greater severity or greater specificity
- All SAEs assessed as unexpected and suspected to be (at least possibly) related to the IMP qualify for a SUSAR and require expedited reporting.

9.1.10. Outcome

- Recovered/Resolved: A participant has recovered from an AE, when all signs or symptoms returned to normal
- Recovered / Resolved with sequelae: An AE is stabilized when, according to the investigator, the participant is in a clinically stable condition. This term should only be used for chronic conditions and for a given participant only when he/she has completed the study
- Recovered with sequelae: As a result of the SAE, the subject is suffering from persistent or significant disability/incapacity (e.g. became blind, deaf, paralyzed). Any AE recovered with sequelae should be rated as an SAE since an SAE criterion is fulfilled
- Not Recovered/Not Resolved: An AE currently ongoing
- Recovering / Resolving: An AE ongoing at the participant´s last visit
- Fatal: An AE that caused death
- Unknown: AE outcome is unknown by the investigator at the participant´s last visit

9.1.11. Fever and respiratory tract disease

In case of fever (body temperature ≥ 38°C), respiratory tract disease (persistent dry (non-productive) cough, tachypnea or dyspnea) or unexplained, severe symptoms triggering the nasal swab are reported as AE a root cause clarification has to be induced to explore if the AE may be due to a wild type COVID-19 infection.

Participants should be trained during each visit to contact the site via phone in case of above-mentioned AEs to scheduled proper on-site visits to performed further actions.

Therefore, the investigator should make every effort to diagnose the etiology, considering typical symptoms as outlined in the COVID-19 Clinical Working Group, dated 21-Apr-2020 " Criteria for clinical diagnosis of incident COVID-19 disease in adults in interventional trials" .

In case of contact with a confirmed case or in case of suspected SARS-CoV-2 infection given by the presence of any symptoms listed below, the participant will be invited, according to the local procedure to attend an unscheduled visit or to contact his/her GP (see section 7.2.14). During this visit, vital signs including SpO_2, Respiratory Rate, Heart Rate, Body Temperature will be measured and a collection of upper respiratory tract specimens (nasal swab) for testing by reverse transcription polymerase chain reaction (RT-PCR) will be performed for the diagnosis of a recent infection.

Symptoms triggering the nasal swab are:

- Fever,
- cough with or without production (sputum or blood),
- Sore throat,
- Rhinorrhea,
- Dizziness,
- Wheezing,
- Chest pain,
- Myalgia,
- Arthralgia,
- Fatigue,
- Dyspnea,
- Headache,
- Altered consciousness / confusion,
- Abdominal pain,
- Vomiting / Nausea,
- Diarrhea,
- Conjunctivitis,
- Skin rash,
- Ageusia,
- Anosmia

Data related to date of symptoms onset, source of possible exposure (e.g. contact with a confirmed case within 14 days prior to symptoms onset), physical examination, vital signs measurement, results of laboratory tests will be documented in the participant' source data. The result of the SARS-CoV-2 PCR will be documented in the participant' source data and in the eCRF. In case of confirmed SARS-CoV-2 infection and according to the severity of the disease, the participant will be referred to a specialist and will be followed according to the national guidelines.

Virologically-confirmed COVID-19 clinical disease is defined as:

- An acute respiratory illness that is clinically consistent with COVID-19 based on presence of at least two of the following:
- Fever or history of new-onset fever (defined as body temperature of >38.0°C irrespective of method)

- New onset *lower* respiratory tract disease (LRTI) (any):
  - Persistent dry (non-productive) cough
  - Tachypnea or dyspnea
  - Low peripheral oxygen saturation (< 95%)
  - Radiographic findings consistent with LRTI
- New onset systemic symptoms consistent with viral illness (any):
  - Sore throat
  - Myalgia
  - Chills
  - Loss of smell or taste
  - Headache
  - fatigue
  - Congestion or runny nose
  - Nausea or vomiting
  - Diarrhea

AND

- Positive SARS-CoV-2 specific reverse transcriptase polymerase chain reaction (RT-PCR)

Severe COVID-19 clinical disease is defined as

- Virologically-confirmed COVID-19 clinical disease

AND

- A NEWS-2 score of >6

COVID-19-naive: Person testing negative for anti-SARS-CoV-2 antibodies at baseline [using an antibody test with high sensitivity]

Furthermore, the place of subject's residence, travel history and exposures to areas with known virus transmission within 15 days prior to the onset of symptoms have to be regarded when investigating a possible infection.

In case, the investigator cannot rule out a COVID-19 wild type infection, SARS CoV 2 PCR and serology will be performed.

If a subject is suspected/diagnosed with an actual COVID-19 infection he/she should not receive any subsequent study vaccination but should perform all visits for safety follow up reasons.

9.1.12. Reporting and follow-up of Adverse Events

9.1.12.1. Recording of AEs

All AEs, whether observed by the Investigator or designee or volunteered by or elicited from the subject, occurring after consent signature should be recorded individually in the CRF with the following information: the specific event or condition, the dates and times (using the 24 hour clock, where midnight is 00:00 and noon is 12:00) of occurrence, duration, severity, relationship to study medication, specific countermeasures, outcome, and whether considered non-serious or serious, drug-related or not. AEs will

be recorded from the time a subject has signed the ICF and throughout the study, including the follow up period. The solicited AEs should be reported by the investigator from the day of injection up to 14 days after each injection. The investigator should record all AEs for the whole period of the study.

An SAE must fulfill the requirements listed in the Section 9.1.3.

Outcome to Date of an AE are classified according to definitions described in section 9.1.9.

AEs will be coded by Data Management using the Medical Dictionary for Regulatory Activities (MedDRA) AE dictionary.

9.1.12.2. Recording of Adverse Events of special Interest (AESI)

A noteworthy event for the particular product or class of products that a sponsor may wish to monitor carefully. It could be serious or non-serious, and could include events that might be potential precursors or prodromes for more serious medical conditions in susceptible individuals.

In this study, the AESI for COVID-19 vaccine will be defined as:

- Acute respiratory distress syndrome (ARDS)
- Pneumonitis
- Acute cardiac injury
- Arrhythmia
- Septic shock-like syndrome
- Acute kidney injury
- Vascularitis
- Autoimmune disease (AID)
- Meningitis
- Atypical measles
- Anosmia
- Dysgeusia

The investigator should report all AESIs for the whole period of the study.

9.1.12.3. Reporting of Serious (Expected or Unexpected) AEs

If the Investigator identifies a SAE or a SUSAR, it should be reported by the Principal Investigator to the sponsor without delay. The investigator should report all SAEs for the whole period of the study.

To proceed with notifying the sponsor of a serious adverse event, the investigator completes an initial notification form and immediately faxed or emailed it to SGS Medical Affairs.

[redacted]

Any fatal or life-threatening event should be reported immediately by phone or fax to the Sponsor. These preliminary reports will be followed within 24 hours by more detailed descriptions that will include a completed SAE form, as described below.

If the investigator is not capable of declaring the serious adverse events by the means listed above, they contact Institut Pasteur exclusively on the following number or email inbox:

For regulatory purposes, initial SAE reports should be submitted to the Sponsor immediately and should include:

- a suspected investigational medicinal product
- an identifiable subject (e.g., study subject code number)
- an adverse event with a seriousness and the Investigator's assessment of the relationship to study drug
- an identifiable reporting source (investigator contact details)

Once faxed or emailed, the printed SAE form and accompanying documentation should be placed in the SAE section of the Investigator's site file.

The sponsor responsibility is to assess the relationship with the study vaccine and the expectedness of the reported serious adverse event.

Since healthy volunteers are considered in this study, the sponsor should report immediately:

- Any deaths, life threatening event,
- SAE and SUSARs including event of medical importance
- Serious safety-related protocol deviations

to Competent Authorities, Ethics committees, Eudravigilance registry, and inform the investigators of all study site.

The clock starts at the time a sponsor representative is formally informed and confirmed the receipt of the report. The report to Competent Authorities, Ethics committees Eudravigilance registry (EVCTM) should be done, without delay, as soon as the following data have been ascertained:

- a suspected relationship with the investigational medicinal product
- an identifiable subject (e.g., study subject code number)
- an adverse event with a seriousness and the Investigator's assessment of the relationship to study vaccine
- an identifiable reporting source (investigator contact details).

In all cases, all SUSAR, relevant complementary information should be collected and notified within 8 extra-days:

- From the first report for deaths and life-threatening event,
- From the end of the allowed delay set for other SUSAR and event of medical importance.

Expedited reporting to CAs, ECs and investigators of each site will be managed by SGS Medical Affairs according to the SOP “Processing and Reporting of Individual Serious Adverse Events of Interventional Clinical Trials”, the ICH guideline E2A “Note for Clinical Safety Data Management” and the Safety Management Plan. CRAs will be in charge to inform investigator of each site. Acknowledgment of Receipt will be completed and signed by the investigator and then retrieved by the CRA.

In addition to this expedite reporting to Competent Authorities and Ethics committees, the overall SAE/SUSAR notified by investigator will be reported to Competent Authorities and Ethics Committees via the Annual report of Safety (see section 9.1.12.7).

If a SUSAR or IMP are likely to endanger the immediate safety of the study participant, the sponsor and the investigator should put in place urgent safety measures to protect the participants.

If urgent safety measures are put in place, Competent Authorities and Ethics Committees should be immediately informed and a protocol amendment should be submitted to the CA/EC within 15 days.

Participant will be informed about the new safety measures by the investigators as soon as possible (e.g. prior next dosing as appropriate) and through an updated informed consent.

9.1.12.4. Follow-up of AEs

Subjects who have had an AE during the treatment period must be followed clinically until all parameters (including laboratory) have either returned to normal or have stabilized or are otherwise explained.

Any newly emergent SAE after treatment is discontinued or the subject has completed the study and is considered to be related to the study drug or study participation should be recorded and reported immediately. The post-study period for the purpose of SAE reporting is up to 30 days following last visit of the study or until the SAE is resolved or stabilized.

9.1.12.5. Reporting of SUSARs

Reports of SUSARs will be reported in an expedited manner to the EC and CAs as required per French and Belgium regulations within the required time frame.

9.1.12.6. In Case of Pregnancy

If a study subject becomes or is found to be pregnant during the subject’s treatment, the Investigator must submit this information to the Sponsor. The information submitted should include the anticipated date of delivery.

Follow-up is conducted to obtain general information on the pregnancy and its outcome. The Investigator will follow the pregnancy until completion (or until pregnancy termination) and notify the Sponsor of the outcome.

If the outcome of the pregnancy meets the criteria for an SAE (i.e. ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly, the Investigator should follow the procedures for reporting SAEs.

Male subjects whose female partner has become pregnant during the study will be requested to report to the Principal investigator on the follow-up and outcome of the pregnancy, if his partner consents to provide this information.

9.1.12.7. Development Safety Update Reports

A DSUR will be submitted once a year throughout the clinical trial to the national CA and the EC according to applicable regulations and requirements.

10. QUALITY CONTROL AND QUALITY ASSURANCE

The study will be conducted according to GCP as outlined by ICH Topic E6 step 5 guidelines. The Sponsor maintains a quality assurance system with written SOPs to ensure that clinical trials are conducted and data are generated, documented and reported in compliance with the protocol, GCP and applicable regulatory requirements.

10.1. Audits and Inspections

The study may be audited according to the Sponsor and vaccine developer's QA inspection programs. The purpose of the audit is to determine whether or not the study is being conducted and monitored in compliance with study protocol and ICH GCP guideline. Audit visit(s) will be arranged in advance with site personnel at a mutually acceptable time.

The Investigator should understand that source documents for this trial should be made available to appropriately qualified personnel from the Sponsor quality assurance or its designees or to regulatory authority inspectors after appropriate notification. The verification of the CRF data must be by direct inspection of source documents. These audits or inspections may take place at any time, during or after the study, and are based on the national regulations, as well as ICH guidelines.

Please note that IMP handling may be potentially audited by the vaccine developer.

Furthermore, CEPI, as funder of the start-up activities, reserves the right to perform, pre-, during or post-study audits by professionally trained auditors.

10.2. Study Monitoring

Monitoring of the study is the responsibility of the Sponsor and may be delegated to a CRO. Study monitors (one in charge of data audit and one in charge of IMPs accountability) will advise the Investigator and the pharmacist regarding the practical conduct of the study and maintaining compliance with the protocol, GCP and all applicable regulatory requirements.

Before study initiation, at a site initiation visit or at an Investigator's meeting, a CRO representative will review the protocol and CRFs with the Investigator and his staff.

Throughout the course of the study, the study monitor in charge of data audit will remain blinded. He/She will oversee the conduct and the progress of the study by frequent contacts with the Investigator. This will include telephone calls and on-site visits. During the on-site visits, the eCRF will be reviewed for completeness with corresponding source documents and may periodically request review of the Investigator study file to ensure completeness of documentation in all respects of clinical study conduct. As

part of the data audit, source documents will be made available for review by the study monitor. the unblinded study monitor will perform IMPs accountability checks at pharmacy.

Periodically, some or all of the facilities used in the study (e.g., local laboratory, pharmacy) may be reviewed. Monitoring visits will be arranged in advance with site personnel at a mutually acceptable time. Sufficient time must be allowed by the site personnel for the monitor to review CRFs and relevant source documents. The Investigator should be available to answer questions or resolve data clarifications. The Investigator or appointed delegate will receive the study monitor during these on-site visits, cooperate in providing the documents for inspection, and respond to inquiries.

The Investigator will ensure that the study participants are aware of and consent that personal information may be scrutinized during the data verification process as part of study-related monitoring and auditing by properly authorized persons associated with The Sponsor or inspection by domestic and/or foreign regulatory authorities. However, participation and personal information should be treated as strictly confidential to the extent that the applicable law permits and not be publicly available.
Upon completion of the study, the study monitor will arrange for a final review of the study files after which the files should be secured for the appropriate time period.

10.3. Quality Laboratory Standards

Laboratory tests or evaluations described in this protocol will be conducted in accordance with quality laboratory standards as described in the SOPs of the local institution laboratory and central laboratories.

Before the study begins, the laboratories to be used in the study will provide a list of the reference ranges for all laboratory tests to be undertaken and details of the method used for quality control. These will be held in the Investigator file and the trial master file. The methods employed for each assay should be available on request. Any change in the laboratory, its procedures, references, values, etc. during the study must be notified promptly to the Sponsor.

10.4. Study Documentation

Study documents will include the following:

- Signed ICFs
- Source documents (e.g., subject files, medical notes, study worksheets)
- Investigator copies of the CRFs and SAE reports
- Investigator site file + contents
- Laboratory manual
- Pharmacy manual

Upon completion of the study, the study monitor will arrange for a final review of the study files after which the files should be secured for the appropriate time period.

10.5. Source Document

The Investigator will permit study-related monitoring, audits by or on behalf of the Sponsor, regulatory inspections providing direct access to source data documents. Source documents are original records in

which raw data are first recorded. These may be office/clinic/hospital records, charts, diaries, ultrasound images, and laboratory results, ECG printouts, pharmacy records, care records, completed scales for each study participant and/or worksheets provided by the Sponsor. Source documents should be kept in a secure and limited access area. All source documents must be accurate, clear, unambiguous, permanent and capable of being audited. They should be made using a permanent form of recording (ink, typing, printing, optical disc, etc.). They should not be obscured by correcting fluid or have temporary attachments (such as removable self-stick notes). Source documents that are computer generated and stored electronically.

Source data for subjects registered to the study should indicate date ICF was signed, participation in clinical protocol number and title, treatment number, evidence that inclusion/exclusion criteria have been met.

10.6. Recording of Data on Case Report Form (CRF)

No data will be directly entered into the CRF without source documentation.

Completed, reviewed and signed CRFs must be available for monitoring and collection by the monitor at the end of the study.

All corrections on a CRF and on source data/documents must be made in a way which does not obscure the original entry. The correct data must be inserted, dated and initialled by relevant, authorized study site personnel. For eSource Data any changes or correction should be available via the audit trial. If the reason for the correction is not obvious, an explanation should be provided.

10.7. Investigator Site File

All documents required for the conduct of the study as specified in the ICH-GCP guidelines will be maintained by the Investigator in an orderly manner and made available for monitoring and/or auditing by the Sponsor, the vaccine developer and regulatory agencies.

10.8. Retention of Study Data

It is the responsibility of the Principal Investigator to maintain a comprehensive and centralized filing system of all relevant documentation. Investigators will be instructed to retain all study records required by the Sponsor as well as the regulatory documents in a secure and safe facility with limited access for at least 25 years after the completion of the study. Further retention, if required, will be negotiated at the end of this 25-year period. In that case the Sponsor will notify, in writing, the Principal Investigator when the clinical study data may be discarded. The Principal Investigator will take measures to prevent accidental or premature destruction of these documents.

11. DATA COLLECTION AND MANAGEMENT

11.1. Data collection

During each study visit, the investigator will collect and maintain notes in the participant´s study records to document all procedures, significant observations and assessments, which are regarded as source data. Additionally, diaries and laboratory result reports signed and dated by the investigator, have to be kept within the participant´s records. Changes to information in the study record and other source documents will

be initiated and dated on the day the change is made or available via audit trial in case of eSource data. All documents will be stored safely under confidential conditions

11.2. Data Management

An electronic CRF (eCRF) will be filled-in by the Investigator and/or his/her designee.

Front-end edit checks will run at the time of data collection and back-end edit checks will be used by the Data Manager to check for discrepancies and to ensure consistency and completeness of the data.

Safety assessments will be processed locally and the results will be entered in the eCRF by the Investigator and/or his/her designee.

Medical history, adverse events and concomitant procedures will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary; medications will be coded using the WHO Drug Dictionary and Anatomical Therapeutic Chemical classification (ATC).

Access to electronic systems used for data collection will be granted to the study personnel only after appropriate training.

Once the database has been declared to be complete and accurate, it will be locked, the randomization codes will be opened and the planned statistical analysis will be performed.

If the database is unlocked after the initial lock, the process must be carefully controlled and documented; updates to the study data must be authorized by sponsor.

12. DATA ANALYSIS AND STATISTICAL PROCEDURES

This section outlines the data analysis strategy and statistical procedures to be employed when addressing the primary, secondary and exploratory endpoints of the study. A Statistical Analysis Plan will be further prepared to complement this section of the protocol.

Intermediate reports including safety and immunogenicity data will be provided:

1. Intermediate Report 1 (IR1): After all six sentinel subjects completed visit 4 (day 28)
2. Intermediate Report 2 (IR2): After all six sentinel subjects completed visit 5 (day 42)
3. Intermediate Report 3 (IR3): After all (or at least 50% depending on the enrolment rate) subjects completed visit 4 (day 28).
4. Interim analysis for interim CSR after all subjects completed visit 7 (day 91) or the Early Termination visit (ET)

The purpose of these intermediate analyses is to provide safety and some immunogenicity data for further SARS-CoV-2 vaccine development. Intermediate analyses will also be presented to an independent data review monitoring board (DSMB).
An interim analysis for the preparation of an interim CSR will be generated. Upon request, the DSMB members will have access to interim CSR.

The final analysis (final CSR) will be conducted once the last participant has completed the study.

12.1. Per-protocol and intention to treat analyses

The following populations will be defined and analyzed:

- In the Modified Intention To Treat (Modified ITT) population, all randomized/assigned subjects who received at least one injection are included in the analysis in the group in which they were initially randomized.

- The Per Protocol (PP) population is defined as all randomized/assigned subjects who received two injections according to protocol and completed the study without major protocol deviations. The PP analysis will be conducted based on the group in which the subjects were initially randomized/assigned.

- The modified ITT population will be used for the safety analyses, and will include sentinel subjects. The immunogenicity analyses will be performed in participants having received at least one injection (modified ITT population) as well as in participants having received two injections (PP population). For immunogenicity analyses, sentinel subjects will be included.

12.2. Descriptive Statistics

– Quantitative variables

Quantitative variables will be described in terms of absolute frequency, mean, standard deviation, standard error, median, interquartile range, minimum, and maximum. Intra-group comparisons will be made using paired Student t-test or Wilcoxon paired signed-ranks test according to the distribution of variable of interest (vital signs) for analyzing change from pre to post-vaccination within a given group.

– Qualitative variables:

Qualitative variables will be described in terms of number, proportion and exact binomial confidence interval of proportion.

Titers: Geometric means and their confidence interval will be performed for titers.

12.3. Analysis of Safety objectives

All treated subjects will be included in the safety analysis. All adverse events will be coded according to coding dictionaries (MedDRA version 23.0 or higher) for System Organ Class (SOC) and Preferred Term (PT).
The adverse events will then be grouped by MedDRA preferred term into frequency tables according to SOC. These summaries will be presented by vaccination group and by interval of study observation. The overall frequencies per vaccine group as well as frequencies according to severity will be calculated for solicited (local and general) AEs, unsolicited AEs, serious AEs (SAEs), adverse events of special interest (AESI) and clinically significant abnormal laboratory values (grade 3 or 4). Solicited (local and systemic) and unsolicited AEs will be compared between treatment groups using Fisher-Freeman-Halton tests.

12.4. Analysis of Immunogenicity and exploratory objectives

The secondary immunogenicity endpoints are:

- Onset: SARS-CoV-2 specific antibodies up to study day 56 as measured by spike protein-specific ELISA and serum neutralization assay.

- Durability: SARS-CoV-2 specific antibodies on day 91 for each cohort (treatment groups) as measured by spike protein-specific ELISA and serum neutralization assay.
  SARS-CoV-2 spike protein-specific T cell-mediated immune response up to study day 91 induced by one or two doses as measured by intracellular staining and flow cytometry.

ELISA for SARS-CoV-2 S-specific serum antibodies:
An in-house ELISA for immunoglobulin G (IgG) will be used as classical test to quantify the serum antibody responses against the S protein. The ELISA will use as target antigen a recombinant, purified, trimerized Spike protein ectodomain stabilized in the pre-fusion configuration (COVID-19 Pre-Spike IgG ELISA). The ELISA analyses will be performed at Nexelis Laval, Canada.

Serum neutralization assay:
The presence of serum neutralizing antibodies will be assessed using a pseudotyped virus neutralization assay on Vero E6 cell monolayers. Pseudotyped viral particles are made from a Vesicular Stomatitis Virus (VSVΔG) backbone and bear the full-length Spike glycoprotein of the SARS-CoV-2 coronavirus. The pseudotyped virus contains a Luciferase reporter gene which allows the quantification of pseudoparticles entering the Vero cells in relative luminescence units (RLU). Neutralization of the pseudotyped virus results in reduction of RLU. The neutralization assay will be performed at the Nexelis, Laval, Canada.

T cell-mediated immune response:
T cell responses to vaccination will be assessed by intracellular staining and flow cytometry. PBMC will be stimulated for 6 h with 2 separate peptide pools spanning the whole S1 and S2 domains of the S protein, containing 15 amino acid peptides with 10 amino acids overlap. Secretion of cytokines will be blocked by Brefeldin A. The staining panel will include but are not limited to antibodies against: CD3, CD4, CD8 to differentiate the T cells, INF-γ and TNF-α to detect Th1-type responses, and IL-5 and IL-13 to detect Th2-type responses. Simultaneous expression of INF-γ and TNF-α or IL-5 and IL-13, respectively, will be used as indication of a functionally significant subset. The T cell analyses will be performed at BioAster, Lyon, France. For assay harmonization in the field and comparability assessment to results from other vaccine trials, T cell analyses of selected time points are also performed at Caprion, Montreal, Canada

The immunogenicity analysis will compare the SARS-CoV-2 specific ELISA and neutralizing antibody geometric mean titer (GMT) in the Per Protocol (PP) analysis population between the four groups (three treatment groups and the pooled group of placebo recipients) by applying an analysis of variance. GMTs and GMT ratios will be estimated using log10 transformed data and taking the anti-log of the resulting point estimates for the least squares means, least squares means differences and the corresponding two-sided 95% CIs.

In post-hoc tests after analysis of variance, pair-wise comparisons of GMTs between the treatment groups and the pooled placebo group and between the three treatment groups will be performed adjusted for multiple comparisons. Seroconversion rates will be compared between the treatment groups by using Fisher-Freeman-Halton tests and groups will be compared pair-wise with Fisher's exact test.

The exploratory endpoints are:

- Measles virus antibody levels as assessed by standard ELISA assays on day 0, 28, and 56.
- SARS-CoV-2 N protein-specific antibody up to study day 91 as assessed by immunoassay.

- Occurrence of COVID-19 cases in study participants all along the duration of the study

The results will be summarized by treatment groups.

Immunoassay for SARS-CoV-2 N serum antibodies:
Serum antibody responses (IgG and IgM) to the SARS-CoV-2 nucleoprotein (N) will be measured using the Roche-Elecsys® Anti-SARS-CoV-2 immunoassay. The assay is a double-antigen sandwich assay using electro-chemiluminescence for detection (electro-chemiluminescence immunoassay, ECLIA). The analyses will be performed at PPD Central Labs.

As the N protein is not included in the COVID-19 vaccine candidate, assessment of antibody responses to the N protein differentiates immune responses to vaccination from immune responses to SARS-CoV-2. Positive anti-N results will indicate that the subjects have been exposed to the SARS-CoV-2 virus. As not all subjects might experience COVID-19 disease, this analysis will detect asymptomatic cases.

ELISA for measles serum antibodies:
IgG to measles will be assessed using the commercially available ELISA kit. The ELISA analyses will be performed at BioAster, Lyon, France.

Assessment of the baseline of anti-measles antibodies of the subjects at baseline (day 0) is important to assess any potential impact of pre-existing immunity on the take of the vaccine. In addition, IgG levels to measles are assessed after the first and second immunization. This provides a control to assess if the vaccine backbone elicited an immune response in a given subject in case no response to the S protein was detected.

12.5. Subject Demographics and concomitant treatments

All baseline data collected at screening visit and before 1st injection, as subject demographics, medical history, and concomitant medications, will be tabulated by treatment group and as a total. Concomitant Medications will be coded using the World Health Organization (WHO) Drug Dictionary and summarized by Anatomical Therapeutic Chemical (ATC) classification.

12.6. Sample size consideration

A formal sample size calculation was not conducted. The sample size of 90 participants has been determined based on prior experience in evaluating the safety and immunogenicity of vaccines and is typical for early phase clinical studies. Sample size for this study was determined on grounds of feasibility and common practice in similar trials. The sample size of 24 subjects per vaccine treatment will give an indication in case of big differences between the groups but has not been designed for a detailed comparison.

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. Regulatory framework of study

This study will be conducted in accordance with the protocol, the Sponsor's standards operating procedures and the following regulatory framework:

For French side

- The French regulations including provisions related to interventional research in the Public Health Code, Article L. 1121-1 and following,
- The French regulation related to registration of French participants in the national registry of "persons who have no medical condition and who voluntarily participate in such research, as well as of sick persons when the object of the research is unrelated to their medical condition" in the Public Health Code, Article L. 1121-16,
- The French laws of Bioethics,
- The French law relating to the data protection (law of January 6th, 1978) and particularly its Chapter relating to the processing of personal data in human health-related research,

For Belgium Side

- The Belgium regulations including the law of May 7th, 2004 related to experiments on humans and the applicable royal decrees and the law of December 19th, 2008 on the acquisition and use of human body material with a view to medical application to humans or scientific research, and the applicable royal decrees.
- The Belgium law relating to the data protection (law of July 30th, 2018 on the protection of natural persons with regard to the processing of personal data).

For both countries

- The European Directive 2001/20/CE on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use (and when it will come into force the subsequent European Regulation 536/2014 clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC)
- The European Regulation 2016/679 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation)
- The Declaration of Helsinki,
- The ICH Good Clinical Practices (ICH-E6(R2)).

The final version of the study protocol will be submitted, approved and signed by all principal investigators (PI) involved in this research and by the sponsor.

The sponsor obtains approval for the study protocol and its eventual subsequent amendment for:

The French side

- From Institutional Review Board (IRB) of Institut Pasteur (IRB00006966 Institut Pasteur IRB #1)
- From a Comité de Protection des Personnes (CPP, the French Ethics Committee) and the authorization of the ANSM (the French competent Health authority) prior to the initiation of the study. All necessary documents (protocol, ICF, as well as any other relevant document) will be provided to CPP and ANSM.

For the Belgium side from

- From the Belgian competent health authorities (FAMHP) and an independent Belgian Ethics Committee. All necessary documents (protocol, ICF, as well as any other relevant document) will be provided FAMHP and to independent Belgian Ethics Committee.

Changes to the protocol may be made only after an approval from the Sponsor.

Any substantial modification in the protocol must also be sent by the sponsor (or designee) to IRB-Institut Pasteur, CPP, ANSM, FAMHP, and independent Belgian Ethics Committee either as an amendment or a notification according to the type of modifications in accordance with local procedures and regulatory requirements. The information sheet and the consent form can be revised if necessary.

In accordance with Article L1243-3 of the Public Health Code, sample collection will be declared to the French Ministry of Health (Ministère de la recherche) by the end of the study.

13.2. Deviations from the Protocol

A protocol deviation is any noncompliance with the clinical trial protocol, ICH GCP, manuals or local requirements. The noncompliance may be either on the part of the participant, the Investigator, or the study site staff. Consequently, corrective actions are to be developed and implemented promptly.

Important protocol deviations are deviations that might significantly affect the completeness, accuracy and/or reliability of the study data or that might significantly affect a participant´s rights, safety or well-being.

All protocol deviations will be listed in the study report and assessed as to their influence on the quality of the study analysis. No deviations from the protocol of any type will be made without complying with all the EC´s or CA´s established procedures in accordance with applicable regulations.

13.3. Subject information, consent

Before any trial specific procedures are performed participants will be informed about the exact nature of the trial, what it will involve for the participant, all procedures as determined by the clinical protocol, the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the trial at any time for any reason without prejudice to future care, without affecting their legal rights and with no obligation to give the reason for withdrawal.

The participant will be allowed as much time as needed to consider the information, and the opportunity to question the investigator or other independent parties to decide whether they will participate in the trial.

Written informed consent will then be obtained by means of participant's dated signature and dated signature of the qualified and experienced person (according to local regulations) who presented and obtained the informed consent. A copy or the second original (according to local process) of the fully signed and dated informed consent will be provided to the participant and one original fully signed and dated form must be retained at the site.

13.4. Data protection

Personal data processing for this study should comply with the European General Data Protection Regulation, the French Data protection act (law n° 78-17 of 6 January 1978 relating to the data protection "Loi Informatique et Libertés") and particularly its Chapter IX relating to the processing of personal data in human health-related research and the Belgian Law of 30 July 2018 on the protection of natural persons with regard to the processing of personal data

As a result, the Institut Pasteur is the controller of the data processing.

Accordingly, information on the data-protection rights of persons participating in this research are included in the information notice.

The current research is covered by article L1121-1 of the French Public Health Code and included in the scope of the MR-001 “Reference Methodology” for automated management of personal data in health related research in which an informed consent is given. The Institut Pasteur, sponsor of the research, has already signed a commitment with the CNIL to comply with this Reference Methodology.

Following its internal review of the compliance with the last MR001 version and an impact analysis, the study processings have been included in the Institut Pasteur records of processing activities.

If the processing of personal data for this research study does not comply with the MR 001 reference methodology, the sponsor will obtain authorization from the CNIL.

If the subject agrees, data collected for research and generated data may be used for subsequent analyses not planned in the protocol. The review of the compliance with the regulatory requirements will be renewed as much as necessary for this purpose. Dispositions will then be defined between the Institut Pasteur and the data recipients to ensure the data protection and the rights of the concerned participants in those study.

13.5. Identity coding rule

The sponsor complies with the principle of subject’s right to protection against personal data breach. Throughout this study, the data and samples will be collected under pseudonymised conditions: the identity of the participant is coded in a way that does not allow third-party persons to detect the identity of the person. The identification code will be assigned for each enrolled participant as follow:

- at screening a « screening number » (S001…),
- before dosing a « lead in » number (L001…),
- after dosing, the participant will receive the assigned subject number

13.6. Data-base property and sharing

As part of the development program for this vaccine candidate, unblinded coded data (treatment assignment, unblinded immunogenicity data, and unblinded reports for the DSMB) collected from this clinical trial will be shared between unblinded teams of the sponsor and the vaccine developer (see section 3.3), which will carry out the registration process of this vaccine candidate with the health authorities.

In May 2017, the Institut Pasteur committed to comply with the WHO joint statement on public disclosure of results from clinical trials it sponsors. Therefore, the Institut Pasteur will ensure according to its internal procedures:

- Registration of this clinical trial in a public registry that complies with the WHO requirements,
- Reporting the results whatever they will be positive or negative to the competent authorities or committees, scientific and medical community and the public,
- Sharing of individual data in compliance with information given to participant, ethical approval and regulatory requirements.

In addition, the International Committee of Medical Journal Editors (ICMJE) member journals have adopted a trials-registration policy as a condition for publication. This policy requires that all clinical trials be registered in a public, clinical trials registry. Thus, it is the responsibility of the Sponsor to register the trial in appropriate registries.

13.7. Conservation, secondary use and transfer of the collection

If the participant do not have any objection, it is intended to collect samples during the study for additional future analyses. Such analyses might comprise additional immunological analyses, including but not limited to antibody responses to other human coronaviruses, particularly at study start, antibody isotypes and sub-classes, antibody affinity and avidity, B cell memory responses, detailed CD4 T cell repertoire characterization, CD8 T cell functional assays. The samples might also be used to develop, assess, improve, or implement high throughput assays that will facilitate immunological testing in larger future clinical trials, e.g. pseudotype neutralization assays that can be done faster and at lower security levels than PRNT assays.

Biological samples will be stored at the clinical sites during the course of the clinical trial. Samples will then be shipped at regular time points to central labs for immunological analysis. The Institut Pasteur, as Sponsor, will also receive some of the biological samples for long-term storage and immunological analysis. The samples will be kept for up to 15 years.

Participants may choose at any time to have their specimens destroyed and must inform the Investigator about their decision in a written request. Moreover, if a participant chooses to withdraw from the study any of the previously collected remaining samples and data will be discarded except if he/she tells us that we can keep them for the purpose of this specific research. However, some biological samples and data previously collected may not be deleted if their deletion is likely to make it impossible or to seriously compromise the achievement of the objective of the study. This is described in the consent form.

13.8. Archiving

To meet a regulatory requirement, all the study documents should be archived for a minimum of 25 years after its completion. Those documents include but are not limited to:

- Signed study protocol,
- Signed informed consent,
- Filled case report form,
- Laboratory records,
- Study final report

14. FINANCING AND INSURANCE

14.1. Financing

This study is funded by CEPI and Themis Bioscience GmbH, a subsidiary of Merck & Co., Inc., Kenilworth, New Jersey, USA.

14.2. Contractual details with investigation site

The investigator and the sponsor will sign a clinical study agreement prior to the start of the study outlining overall sponsor and investigator responsibilities in relation to the study. The contract will describe costs for pharmacy, laboratory and other protocol-required services.

14.3. Insurance

As sponsor, the Institut Pasteur has taken out an insurance policy for its civil responsibility for the duration of the study with:

- Zurich Insurance Public Limited Company domiciled in France at 112 avenue de Wagram, 75808 Paris cedex 17 under the policy number N° 07401372 ,
- Zurich Insurance Public Limited Company, Belgium Branch domiciled in Belgium at Da Vincilaan 5, Building Caprese, 1930 Zaventem, under the policy number N° 5030139

in compliance with French regulatory requirements for biomedical research.

All compensation claims issued by a subject participating in the study described in this protocol must be sent without delay to the sponsor's representative by the investigator as soon as they have knowledge of it.

14.4. Subjects compensation

Participants are compensated or the time spent in the clinical trial and associated travel costs according to the number and duration of visits in the study investigational site. Each day is compensated according to France and Belgium rules. By Ministerial decree of the French Ministry of Health, the total amount of compensation received by a participant must not exceed an amount of 4,500 euros for a period of 12 months.

15. PUBLICATION POLICY

Study results will be published in scientific journals with pair-review committee or presented in scientific or medical congress.

Authors list will be determined according people's involvement in the study preparation, setting up, regulatory follow-up or samples and data analyses.

The authors list could also be completed by contract between collaborating institutes participating in the research.

Any article of the study results or the collected samples or data should mention the Institut Pasteur as the legal responsible of the study. The support of the CRT-CC (Clinical Research Department) should be included in those articles, whenever possible as a contributing author (e.g. for the ethical and regulatory statements), or at least in the acknowledgment section for the study document preparation and the ethical and regulatory support.

16. REFERENCES

- Centre for Evidence Based Medicine (CEBM) - COVID-19: What proportion are asymptomatic? (https://www.cebm.net/covid-19/covid-19-what-proportion-are-asymptomatic/). Accessed on 9 April 2020.
- Combredet C, Labrousse V, Mollet L, Lorin C, Delebecque F, et al. A Molecularly Cloned Schwarz Strain of Measles Virus Vaccine Induces Strong Immune Responses in Macaques and Transgenic Mice. J Virol. 2003; 77(21):11546-54.
- Du L, He Y, Zhou Y, Liu S, Zheng BJ, Jiang S. The Spike Protein of SARS-CoV—a Target for Vaccine and Therapeutic Development. Nat Rev Microbiol. 2009:7(3), 226-36.
- Duan K, Liu B, Li C, Zhang H, Yu T, et al. Effectiveness of convalescent plasma therapy in severe COVID-19 patients. Proc Natl Acad Sci U S A. 2020. 117:9490-9496
- Escriou N, Callendret B, Lorin V, Combredet C, Marianneau P, Février M, Tangy F. Protection From SARS Coronavirus Conferred by Live Measles Vaccine Expressing the Spike Glycoprotein. Virology. 2014; 452-453, 32-41.
- European Centre for Disease Prevention and Control (ECDC) – Coronavirus disease 2019 (COVID-19) in the EU/EEA and the UK – eight update. (https://www.ecdc.europa.eu/sites/default/files/documents/covid-19-rapid-risk-assessment-coronavirus-disease-2019-eighth-update-8-april-2020.pdf). Accessed on 9 April 2020.
- Gao Q, Bao L, Mao H, Wang L, Xu K, et al. Rapid development of an inactivated vaccine for SARS-CoV-2. bioRxiv preprint. 2020. doi: https://doi.org/10.1101/2020.04.17.046375.
- Guerbois M, Moris A, Combredet C, Najburg V, Ruffié C, et al. Live attenuated measles vaccine expressing HIV-1 Gag virus like particles covered with gp160ΔV1V2 is strongly immunogenic. Virology. 2009. 388:191–203
- Li CK, Wu H, Yan H, Ma S, Wang L, et al. T cell responses to whole SARS coronavirus in humans. J Immunol. 2008. 181:5490-5500.
- Malczyk AH, Kupke A, Prüfer S, Scheuplein VA, Hutzler S, et al. A Highly Immunogenic and Protective Middle East Respiratory Syndrome Coronavirus Vaccine Based on a Recombinant Measles Virus Vaccine Platform. J Virol. 2015; 89(22):11654-67.
- Mateo M, Reynard S, Carnec X, Journeaux A, Baillet N, et al. Vaccines Inducing Immunity to Lassa Virus Glycoprotein and Nucleoprotein Protect Macaques After a Single Shot. Sci Transl Med. 2019; 11(152).
- Mura M, Ruffié C, Billon-Denis E, Combredet C, Tournier JN, Tangy F. hCD46 Receptor Is Not Required for Measles Vaccine Schwarz Strain Replication in Vivo: Type-I IFN is the Species Barrier in Mice. Virology. 2018. 524:151-159.
- Ramsauer K, Schwameis M, Firbas C, Müllner M, Putnak RJ, et al. Immunogenicity, safety, and tolerability of a recombinant measles-virus-based chikungunya vaccine: a randomised, double-blind, placebo-controlled, active-comparator, first-in-man trial. Lancet Infect Dis. 2015; 15:519-27.
- Reisinger EC, Tschismarov R, Beubler E, Wiedermann U, Firbas C, et al. Immunogenicity, safety, and tolerability of the recombinant measles-vectored chikungunya virus vaccine MV-CHIK: a double-blind, randomised, placebo-controlled and active-controlled phase 2 trial. Lancet. 2018; 392:2718-27.
- Sciensano. Fact Sheet COVID-19 disease (SARS-CoV-2 virus). 1 April 2020, version 1 (https://epidemio.wiv-isp.be/ID/Documents/Covid19/COVID-19_fact_sheet_ENG.pdf), accessed on 7 April 2020.

- Shen C, Wang Z, Zhao F, Yang Y, Li J, et al. Treatment of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma. JAMA [published online ahead of print, 2020 Mar 27].
- Team Novel Coronavirus Pneumonia Emergency Response Epidemiology (Team NCPERE). The Epidemiological Characteristics of an Outbreak of 2019 Novel Coronavirus Diseases (COVID-19) in China. Zhonghua Liu Xing Bing Xue Za Zhi. 2020;41 (2), 145-151 (article in Chinese)
- Verity R, Okell LC, Dorigatti I, Winskill P, Whittaker C, et al. Estimates of the severity of COVID-19 disease. medRxiv 2020.03.09.20033357; doi: https://doi.org/10.1101/2020.03.09.20033357
- Walls AC, Park YJ, Tortorici MA, Wall A, McGuire AT, Veesler D. Structure, Function, and Antigenicity of the SARS-CoV-2 Spike Glycoprotein. Cell [published online ahead of print, 2020 Mar 6].
- World Health Organization (WHO). Coronavirus disease 2019 (COVID-19) situation reports. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports. Accessed on 13 April 2020.
- World Health Organization (WHO). Coronavirus Symptoms. https://www.who.int/health-topics/coronavirus#tab=tab_3. Accessed on 13 May 2020.
- World Health Organization (WHO). Draft landscape of COVID-19 candidate vaccines https://www.who.int/who-documents-detail/draft-landscape-of-covid-19-candidate-vaccines. Accessed on 13 May 2020.
- World Health Organization (WHO). “Immunity passports” in the context of COVID-19. https://www.who.int/publications-detail/immunity-passports-in-the-context-of-covid-19. Accessed on 13 May 2020
- World Health Organization (WHO). Measles Immunization Coverage. https://www.who.int/gho/mdg/child_mortality/situation_trends_measles_immunization/en/. Accessed on 13 May 2020
- World Health Organization (WHO). “Solidarity” clinical trial for COVID-19 treatments. (https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments). Accessed on 8 April 2020.
- Wu F, Wang A, Liu M, Wang Q, Chen J, et al. Neutralizing antibody responses to SARS-CoV-2 in a COVID-19 recovered patient cohort and their implications. medRxiv doi: https://doi.org/10.1101/2020.03.30.20047365
- Zhao J, Yuan Q, Wang H, Liu W, Liao X, et al. Antibody responses to SARS-CoV-2 in patients of novel coronavirus disease 2019. Clin Infect Dis. 2020. doi: 10.1093/cid/ciaa344. [Epub ahead of print]
- Zhou F, Yu T, Du R, Fan G, Liu Y, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study [published correction appears in Lancet. 2020 Mar 28;395(10229):1038] Lancet. 2020;395(10229):1054–1062.

APPENDIX

Appendix 1: Safety Laboratory Parameters

SERUM BIOCHEMISTRY

- Total Protein
- Albumin
- Total bilirubin
- ALT
- AST
- GGT
- LDH
- CPK
- Alkaline phosphatase
- Glucose
- Sodium, Potassium
- BUN
- Creatinine
- Serum Ferritin

HEMATOLOGY

- Red Blood Cell Count
- Hemoglobin (HGB)
- Hematocrit (HCT)
- Mean Cell Hemoglobin (MCH)
- Mean Cell Hemoglobin Concentration (MCHC)
- Mean Corpuscular Volume (MCV)
- White Blood Cell (WBC) Count and Differential
- Platelet Count
- PT/INR

URINALYSIS

- Protein (*qualitative and/or quantitative*)
- Nitrates
- Glucose (*qualitative and/or quantitative*)
- Specific Gravity
- Ketones
- Urobilinogen
- Bilirubin
- pH
- Blood (Hemoglobin) (*qualitative and/or quantitative*)
- Leukocytes (*qualitative and/or quantitative*)

SEROLOGY

- HIV Ab
- HBSAg
- HCV Ab

DRUGS IN URINE

- Cannabinoids
- Amphetamines/metamphetamines
- Benzodiazepines
- Opiates
- Ecstasy

FEMALE SUBJECTS

Serum β-human chorionic gonadotropin (β-HCG)

Appendix 2: Toxicity grading scale tables adapted from FDA "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials"

Tables for Clinical Abnormalities

Local Reaction to Injectable Product	Mild (Grade 1)	Moderate(Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room (ER) visit or hospitalization
Erythema/Redness *	2.5 – 5 cm	5.1 – 10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling **	2.5 – 5 cm and does not interfere with activity	5.1 – 10 cm or interferes with activity	> 10 cm or prevents daily activity	Necrosis
Itching	Does not interfere with activity	Interferes with activity or repeated use of non-narcotic pain reliever	Prevents daily activity or repeated use of anti-inflammation and pain-relieving ointment	ER visit or hospitalization

* In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.

** Induration/Swelling should be evaluated and graded using the functional scale as well as the actual measurement

Vital Signs *	Mild (Grade 1)	Moderate(Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Fever (°C) ** (°F) **	38.0 – 38.4 100.4 – 101.1	38.5 – 38.9 101.2 – 102.0	39.0 – 40 102.1 – 104	> 40 > 104
Tachycardia - beats per minute	101 – 115	116 – 130	> 130	ER visit or hospitalization for arrhythmia
Bradycardia - beats per minute***	50 – 54	45 – 49	< 45	ER visit or hospitalization for arrhythmia
Hypertension (systolic) - mm Hg	141 – 150	151 – 155	> 155	ER visit or hospitalization for malignant hypertension
Hypertension (diastolic) - mm Hg	91 – 95	96 – 100	> 100	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) – mm Hg	85 – 89	80 – 84	< 80	ER visit or hospitalization for hypotensive shock
Respiratory Rate – breaths per minute	17 – 20	21 – 25	> 25	Intubation

* Subject should be at rest for all vital sign measurements.

** Oral temperature; no recent hot or cold beverages or smoking.

*** When resting heart rate is between 60 – 100 beats per minute. Use clinical judgement when characterizing bradycardia among some healthy subject populations, for example, conditioned athletes.

Systemic (General)	Mild (Grade 1)	Moderate(Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Nausea/vomiting	No interference with activity or 1 – 2 episodes/24 hours	Some interference with activity or > 2 episodes/24 hours	Prevents daily activity, requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Headache	No interference with activity	Repeated use of non-narcotic pain reliever > 24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Osteomuscular pain (Myalgia)	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Rash	No interference with activity	Some interference with activity	Significant; prevents daily activity or repeated use of pain-relieving ointment	ER visit or hospitalization

Systemic Illness	Mild (Grade 1)	Moderate(Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Illness or clinical adverse event (as defined according to applicable regulations)	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	ER visit or hospitalization

Tables for Laboratory Abnormalities

The laboratory values provided in the tables below serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate

Serum *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)****
Sodium – Hyponatremia mEq/L	132 – 134	130 – 131	125 – 129	< 125
Sodium – Hypernatremia mEq/L	144 – 145	146 – 147	148 – 150	> 150
Potassium – Hyperkalemia mEq/L	5.1 – 5.2	5.3 – 5.4	5.5 – 5.6	> 5.6
Potassium – Hypokalemia mEq/L	3.5 – 3.6	3.3 – 3.4	3.1 – 3.2	< 3.1
Glucose – Hypoglycemia mg/dL	65 – 69	55 – 64	45 – 54	< 45
Glucose – Hyperglycemia Fasting – mg/dL Random – mg/dL	 100 – 110 110 – 125	 111 – 125 126 – 200	 >125 >200	Insulin requirements or hyperosmolar coma
Blood Urea Nitrogen BUN mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Calcium – hypocalcemia mg/dL	8.0 – 8.4	7.5 – 7.9	7.0 – 7.4	< 7.0
Calcium – hypercalcemia mg/dL	10.5 – 11.0	11.1 – 11.5	11.6 – 12.0	> 12.0
Magnesium – hypomagnesemia mg/dL	1.3 – 1.5	1.1 – 1.2	0.9 – 1.0	< 0.9
Phosphorous – hypophosphatemia mg/dL	2.3 – 2.5	2.0 – 2.2	1.6 – 1.9	< 1.6
CPK – mg/dL	1.25 – 1.5 x ULN***	1.6 – 3.0 x ULN	3.1 –10 x ULN	> 10 x ULN
Albumin – Hypoalbuminemia g/dL	2.8 – 3.1	2.5 – 2.7	< 2.5	--
Total Protein – Hypoproteinemia g/dL	5.5 – 6.0	5.0 – 5.4	< 5.0	--
Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	> 10 x ULN
Liver Function Tests –ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	> 10 x ULN
Bilirubin – when accompanied by any increase in Liver Function Test increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	> 1.75 x ULN
Bilirubin – when Liver Function Test is normal; increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
Cholesterol	201 – 210	211 – 225	> 226	---
Pancreatic enzymes – amylase, lipase	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	> 5.0 x ULN

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

** The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as Potentially Life Threatening (Grade 4). For example. a low sodium value that falls within a grade 3 parameter (125-129 mE/L) should be recorded as a grade 4 hyponatremia event if the subject had a new seizure associated with the low sodium value.

***ULN" is the upper limit of the normal range.

Hematology *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Hemoglobin (Female) - gm/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	< 8.0
Hemoglobin (Female) change from baseline value - gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
Hemoglobin (Male) - gm/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	< 8.5
Hemoglobin (Male) change from baseline value – gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
WBC Increase - cell/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	> 25,000
WBC Decrease - cell/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	< 1,000
Lymphocytes Decrease - cell/mm^3	750 – 1,000	500 – 749	250 – 499	< 250
Neutrophils Decrease - cell/mm^3	1,500 – 2,000	1,000 – 1,499	500 – 999	< 500
Eosinophils - cell/mm^3	650 – 1500	1501 - 5000	> 5000	Hypereosinophilic
Platelets Decreased - cell/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	< 25,000
PT – increase by factor (prothrombin time)	1.0 – 1.10 x ULN**	1.11 – 1.20 x ULN	1.21 – 1.25 x ULN	> 1.25 ULN
PTT – increase by factor (partial thromboplastin time)	1.0 – 1.2 x ULN	1.21 – 1.4 x ULN	1.41 – 1.5 x ULN	> 1.5 x ULN
Fibrinogen increase - mg/dL	400 – 500	501 – 600	> 600	--
Fibrinogen decrease - mg/dL	150 – 200	125 – 149	100 – 124	< 100 or associated with gross bleeding or disseminated intravascular coagulation (DIC)

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

** "ULN" is the upper limit of the normal range.

Urine *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Protein	Trace	1+	2+	Hospitalization or dialysis
Glucose	Trace	1+	2+	Hospitalization for hyperglycemia
Blood (microscopic) – red blood cells per high power field (rbc/hpf)	1 - 10	11 – 50	> 50 and/or gross blood	Hospitalization or packed red blood cells (PRBC) transfusion

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

Appendix 3: Template provide to participants for assessing local reaction