Assessment of the immunogenicity and safety of marketed vaccines for COVID-19 after regular schedule and adapted vaccine schedules and routes: BNT162b2 (Comirnaty®; Pfizer-BioNTech), mRNA-1273 Vaccine (®; Moderna) and COVID-19 Vaccine (ChAdOx1-S [recombinant]) (Vaxzevria®, AstraZeneca)

SHORT STUDY TITLE: Immunogenicity after COVID-19 vaccines in Adapted Schedules “IMCOVAS”

PROTOCOL VERSION NUMBER AND DATE: protocol COVID-KCE-final version 2 (Amendment 2)

RESEARCH REFERENCE NUMBERS

EudraCT Number: 2021-001993-52
Clinical trials.gov Number / Other registry Number: NA
SPONSOR Number: NA
KCE Trials Number: COV20-1288
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SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the requirements for the conduct of clinical trials in the EU as provided for in "Directive 2001/20/EC", and any subsequent amendments, GCP guidelines, the Belgian law of May 7th 2004 regarding experiments on the human person, the Sponsor’s SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the study publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

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**KEY TRIAL CONTACTS**

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<tr>
<td><strong>Chief Investigator</strong></td>
<td>Dr Katie Steenackers</td>
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<td>+32 3 265 92 83</td>
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Clinical Trial Scientist CTU ITM (Natacha Herssens; nherssens@iltg.be and Carolien Hoof; choof@iltg.be) |

**TRIAL SUMMARY**

| **Trial Title** | **Assessment of the immunogenicity and safety of marketed vaccines for COVID-19 after regular schedule and adapted vaccine schedules and routes: BNT162b2 (Comirnaty®; Pfizer-BioNTech), mRNA-1273 Vaccine (COVID-19 Vaccine Moderna®; Moderna) and COVID-19 Vaccine (ChAdOx1-S [recombinant]) (Vaxzevria®, AstraZeneca)** |
| **Short title** | Immunogenicity after COVID-19 vaccines in Adapted Schedules |
| **Internal reference** | “IMCOVAS” |
| **Trial Design** | A prospective, post marketing, randomized, partially single blind, multicenter, interventional study |
| **Trial Subject and setting** | 560 healthy adults 18-55y  
Most important exclusion criteria:  
- Confirmed previous covid-19-infection  
- Previous covid-19 vaccination  
Study will be carried out in 4 study centres, specialised in vaccination trials, in Belgium. The exact number of recruited participants will be predefined per study centre as well as the exact number of participants included in the immunogenicity subset. |
| **Intervention(s)** | Vaccines:  
- BNT162b2 (Comirnaty®; Pfizer-BioNTech): 30 mcg (IM), 20 mcg (IM) and 6mcg (ID)  
- mRNA-1273 Vaccine (Spikevax®; Moderna): 100mcg (IM) and 50mc (IM)  
- COVID-19 Vaccine (ChAdOx1-S [recombinant]) (Vaxzevria®, AstraZeneca): 0.5mL (IM) |
• Doses:
  • 2 vaccine doses: first dose and second dose COVID-19 vaccine.
  • Low dose (LD) is defined as “a half standard dose” for mRNA-1273 Vaccine and as “2/3rd of the standard dose” for BNT162b2 vaccine.
  • Intradermal (ID) dose is defined as 1/5th of the Standard dose (SD) of BNT162b2 (Comirnaty®; Pfizer-BioNTech)

Routes of administration:
• Intramuscular (IM)
• Intradermal (ID)

Groups for the first and second COVID-19 vaccine dose:
• 4 groups of 70 subjects have received either Standard dose (SD) or low dose (LD) of an approved COVID-19 vaccine on the Belgian market. The vaccine is administered intramuscularly, as a series of two doses, depending on the regimen as authorized by the EMA.
• 1 group of 70 subjects have received a Standard dose (SD) of an approved COVID-19 vaccine on the Belgian market with a long interval between both doses.
• 2 groups of 70 subjects have received Standard dose (SD) of an approved COVID-19 vaccine on the Belgian market, and have received a Standard dose of different brand of an approved COVID-19 vaccine on the Belgian market for the boost dose.
• 1 group of 70 subjects has received 1/5th of the Standard dose (SD) of BNT162b2 (Comirnaty®; Pfizer-BioNTech) via intradermal (ID) route.

In the group that receives Vaxzevria® as second vaccine dose, the age range is limited to 41-55 YOA.

All the vaccines used in this trial have been authorized by the European Medicines Agency.

Third COVID-19 vaccine dose will be offered by the Belgian government as a part of the accelerated vaccination campaign for the third vaccine dose.

Control
Approved routine schedule of marketed covid-19-vaccines in Belgium

Primary Endpoint
GMT of antibodies binding to the RBD of SARS-CoV-2 S protein 28days post second vaccine dose: Non-inferiority of the humoral immune response against SARS-CoV-2 infection of different vaccines and the immunogenic response of adapted vaccine schedules in comparison with the reference schedule.

Secondary Endpoints
- Safety:
- Solicited adverse events within 5 days after each vaccination
- Unsolicited adverse events within 14 days after each vaccination
- MAAEs, AESIs and SAEs continuously throughout the study

- Health economics
  - 2 questions about absenteeism daily within 5 days after each vaccination

- Immunogenicity:
  - GMT of antibodies binding to the RBD of SARS-CoV-2 S protein 28 days post third vaccine dose: Non-inferiority of the humoral immune response against SARS-CoV-2 infection of different vaccines and the immunogenic response of adapted vaccine schedules in comparison with the reference schedule, after all participants received a third vaccine dose outside of the trial.
  - GMT of antibodies binding to the RBD of SARS-CoV-2 S protein of Ancestral D614 SARS-CoV-2 virus strain at all available time points
  - GMT of antibodies of Variants of concern (VOCs) binding to the RBD of SARS-CoV-2 S protein at 28d post 2nd and 3rd COVID-19 vaccine dose
  - GMT of Neutralizing antibodies to Ancestral D614 SARS-CoV-2 virus strain and VOCs at 28d post second and third COVID-19 vaccine dose
  - T cell response to relevant peptide pools of SARS-CoV-2 virus strain at day 0, 28 days post 2nd vaccine dose, day 182 and 28 days following 3rd vaccination
  - Memory B cell responses to S protein of Ancestral D614 SARS-CoV-2 virus strain and VOCs SARS-CoV-2 spike (S) protein specific serum IgG glycosylation (affinity) (Time points based on results from the primary and secondary endpoints)

Exploratory endpoints

- Immunogenicity:
  - GMT of antibodies binding to the RBD of SARS-CoV-2 S protein at all available time points, comparing 2 reference vaccine schedules
  - Analysis biophysical characteristics (subclasses and glycosylation) and non-neutralizing functions of Ab of all vaccine schedules
  - GMT of Neutralizing antibodies to Ancestral D614 SARS-CoV-2 virus strain and VOCs (Time points based on results from the primary and secondary endpoints)
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<td>From 4 weeks after 2nd vaccination until end of study</td>
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<td>Duration of the trial (FPI-CSR)</td>
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- **Efficacy**
  - T-cell response to relevant peptide pools of SARS-CoV-2 virus strain at time points based on results from the primary and secondary endpoints
  - Memory B cell responses to S protein of Ancestral D614 SARS-CoV-2 virus strain and variants (Time points selection based on results from the primary and secondary endpoints)
  - Protection against PCR-confirmed COVID-19 infections
**Trial Steering Committee (TSC)**

The role of the Trial Steering Committee (TSC) is to provide the overall supervision of the trial. Ideally, the TSC should include members who are independent of the investigators, their employing organisations, funders and sponsors. The TSC should monitor trial progress, conduct and advise on scientific credibility. The TSC will consider and act, as appropriate, and ultimately carries the responsibility for deciding whether a trial needs to be stopped on grounds of safety or efficacy.

The TSC will meet on average 3 times per year the first year and twice a year after that. The TSC is composed of the CI, the trial statistician, the trial PM, an independent expert, a representative of other participating centres or groups, up to 2 subjects or members of the public, 1 representative of the sponsor, 1 representative of the funder.

The day-to-day management of the study will be performed by the Trial Management Group (TMG) which is distinct from the TSC.
### LIST OF ABBREVIATIONS

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<tr>
<td>CMI</td>
<td>Cell Mediated immunity</td>
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<td>CRF</td>
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<td>CTU</td>
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<tr>
<td>CTIMP</td>
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</tr>
<tr>
<td>DSUR</td>
<td>Development Safety Update Report</td>
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<td>EC</td>
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<td>European database for Pharmacovigilance</td>
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<td>ICH</td>
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<td>Immunglobuline G</td>
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<td><strong>Description</strong></td>
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<td>ISF</td>
<td>Investigator Site File</td>
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<td>ISRCTN</td>
<td>International Standard Randomised Controlled Trials</td>
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<td>KCE</td>
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<tr>
<td>LD</td>
<td>Low Dose (= half standard dose)</td>
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<td>LMIC</td>
<td>Low- and Middle Income Countries</td>
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<td>Marketing Authorisation</td>
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<td>Medically Attended Adverse Events</td>
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<td>nAB</td>
<td>Neutralising Antibodies</td>
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<td>Non-Investigational Medicinal Product</td>
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<td>RCT</td>
<td>Randomised Control Trial</td>
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<td>Serious Adverse Event</td>
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<td>SAR</td>
<td>Serious Adverse Reaction</td>
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<td>Standard Dose</td>
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<td>Standard Operating Procedure</td>
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<td>Trial Master File</td>
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<td>Full Form</td>
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<td>TTS</td>
<td>Thrombosis with Thrombocytopenia Syndrome</td>
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<tr>
<td>VITT</td>
<td>Vaccine-induced Immune Thrombotic Thrombocytopenia</td>
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<td>VOC</td>
<td>Variant of concern</td>
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<td>WHO</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>WOCBP</td>
<td>Women of child bearing potential</td>
</tr>
<tr>
<td>YOA</td>
<td>Years of Age</td>
</tr>
</tbody>
</table>
**TRIAL FLOW CHART**

1. Visit 1 (D0)
   - Screening
   - Humoral Immunity
   - Cellular Immunity
   - 1st vaccination

2. Visit 2 (D28)
   - Short interval (28d)*
   - Humoral Immunity
   - Cellular Immunity
   - 2nd vaccination

3. Visit 3a (D56)
   - Analysis prim. Endpoint
   - Humoral Immunity
   - Cellular Immunity

4. Visit 3b (D84)
   - Long interval (84d)**
   - Humoral Immunity
   - Cellular Immunity

5. Visit 4 (D112)
   - Humoral Immunity
   - Cellular Immunity

6. Visit 5 (D182)
   - Humoral Immunity
   - Cellular Immunity

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*Group 1a, 1b, 1c, 1d, 1f, 2a, 2b (n=490)

**Group 1e (n=70)

1 Subset only

**Figure 1: trial flow chart**
Subset only

Figure 2: trial flow chart Ad hoc post 3rd dose visit

1 Subset only
STUDY PROTOCOL

1. BACKGROUND

COVID-19 is a disease caused by an infectious outbreak of the SARS-CoV-2 virus. It was first reported in the city of Wuhan, Hubei province, People’s Republic of China on 31 December 2019\(^1\),\(^2\). Unfortunately today, the virus is widely spread throughout the world and declared by the World Health Organization (WHO) as a pandemic\(^3\). During the last year, the pandemic caused by SARS-CoV-2 has been dominating human life on the planet.

Coronaviruses are spherical, enveloped, large positive-sense single-stranded RNA genomes. One fourth of their genome is responsible for coding structural proteins, such as the spike (S) glycoprotein, envelope (E), membrane (M) and nucleocapsid (N) proteins. E, M, and N are mainly responsible for virion assembly whilst the S protein is involved in receptor binding, mediating virus entry into host cells during COVID-19 infection via different receptors\(^4\).

There is a broad range of clinical presentations of a SARS-CoV-2 viral infection varying from asymptomatic, sensation of a mild cold or flu to severe bilateral pneumonia and death. The mortality is the highest in the elderly and in people with a pre-existing condition\(^5\).

To protect the population from the spreading virus, governments had to take harsh measures interfering with normal human life, and having a big influence in various areas, including economics of the country and mental health of the population\(^6\).

The availability of vaccines against COVID-19 gives new perspectives to protect persons who are at high risk for complications and thus to resume a normal way of living for the whole population.\(^7\) Several vaccines have successfully demonstrated high protection against COVID-19 through placebo controlled clinical trials. This has paved the way for approval / emergency use authorization in several countries starting in Q4/2020. Yet, in many LMICs, vaccination coverage is still less than 5%.

Many countries which implemented COVID-19 vaccination programs early and have achieved high vaccine coverage are now considering additional vaccine doses (a third dose in the case of a two-dose primary series), particularly in populations at risk of severe disease. This is to improve, broaden, and maintain the immune response over time to protect against COVID-19 disease as well as possibly reducing SARS-CoV-2 transmission and infection rates, especially with the raise of new variants of concern.

2. RATIONALE

Two different mRNA vaccines (BNT162b2 (Comirnaty\(^8\); Pfizer-BioNTech), mRNA-1273 Vaccine (Spikevax\(^8\); Moderna)) and two different DNA vaccine (COVID-19 Vaccine (ChAdOx1-S [recombinant]) (Vaxzevria\(^8\), AstraZeneca) and Ad26.COV2.S (Janssen COVID-19 vaccine\(^8\), Janssen)) have now shown remarkable effectiveness in preventing and minimizing impact of COVID-19 disease in adults\(^8,9,10,11\) and have been recommended by the EMA for authorization in the EU\(^12,13\). An efficient vaccination program is especially paramount as hospital wards fill up, particularly now knowing that SARS-CoV-2 is able to mutate.
Supply of vaccines is a delicate process, depending on a lot of factors like availability of raw materials, production capacity, storage capacity, packaging and transportation. Unforeseen issues in the supply of a certain brand can cause a significant delay in the national vaccination program. Also, in case of unexpected limited availability of vaccines, administration of the second vaccine dose may not be possible in the prescribed timeframe. Given the anticipated challenges we are facing with immunizing a large part of the population, a more flexible immunization program would have many advantages.

The number of vaccines that can be made available for and administered to the people who need them can be doubled if half a dose is used for the recommended first and second vaccination. The acceleration could even be higher using the intradermal route with one fifth of the recommended dose. If such approach is found safe and the immune response is non-inferior to the schedules that have proven their efficacy, the vaccination campaign could progress at a much higher speed than anticipated, and possibly with somewhat lower local and systemic reactogenicity (side-effects), improving acceptability.

Therefore, we urgently need insights in the effect on the immune response after delaying the second vaccine dose, after switching to another brand for the second dose and after using only a part of the recommended vaccine dose for the first and second dose.

For the Pfizer vaccine the recommended dose is 30µg. Higher doses were not further tested because of side effects seen after the BNT162b1 second dose 50 µg\textsuperscript{14}. For subjects 18-55 years old in the dose finding study the levels of anti-S IgG (spike protein antibodies) and the 50% neutralisation titre after two doses of 10, 20 or 30 µg were largely overlapping. The numerically highest response for the 50% virus neutralisation titre was actually seen for the 20µg dose for the 50% virus neutralisation titre\textsuperscript{15}. One study suggest equal immunogenicity when using a dose as low as 10µg compared to 30µg BNT162b1\textsuperscript{16}. Building on these promising results we will evaluate in this study the immune response of a 20µg dose.

For the Moderna vaccine mRNA-1273 evidence for suggesting a half dose regime could work, is available\textsuperscript{17} and also the FDA briefing book contains the following\textsuperscript{18}:

“Study mRNA-1273-P201 is an ongoing phase 2a, randomized, observer-blind, placebo-controlled, dose-confirmation study to evaluate the safety, reactogenicity, and immunogenicity of mRNA-1273 in healthy adults 18 years and older. The study enrolled 600 participants, consisting of 300 participants 18 to <55 years old and 300 participants 55 years and older, who were randomized equally to receive either 2 doses of 50ug of mRNA-1273, 100ug of mRNA-1273, or saline placebo given 28 days apart. Participants will be followed for safety and immunogenicity for 12 months post last vaccination.”

“The immune response as assessed by bAb (binding antibody) and nAb (neutralizing antibody titer) after 2 doses were comparable in the 50-µg and 100-µg dose groups, with an overall geometric mean fold rise (GMFR)>20-fold in bAB as measured by ELISA and >50-fold in nAb as measured by microneutralization assay at 28 days post-dose 2.”

Also, half doses of the adenovirus vector COVID-19 vaccines of Vaxzevria® (AstraZeneca) would be interesting to investigated as until this date no data for the schemes used in this study are published. However Vaxzevria® is in Belgium only allowed for people over the age of 41, and therefore it is difficult to recruit enough subjects who are not yet vaccinated. With only limited recruitment possibilities for this age category, it was chosen to only focus on interchangeability between mRNA-DNA-vaccine.
In this study the Janssen vaccine will not be studied given the similarity between AstraZeneca (COVID-19 Vaccine (ChAdOx1-S [recombinant])) and Ad26.COV2.S (Janssen COVID-19 vaccine®), as they are both adenoviral vector vaccines. Since Ad26.COV2.S can be administered in a single dose, no issues with unavailability of the second dose will have to be overcome, therefore we will focus on the 2-dose adenovirus vector vaccine Vaxzevria® in this study when studying interchangeability with mRNA-vaccines.

Moderna vaccine will be investigated in halve dose and will be used as a second dose after first dose of the Pfizer vaccine to investigate interchangeability between the 2 currently available mRNA vaccines. Additionally, interchangeability for prime and boost between the Pfizer vaccine and the AstraZeneca vaccine will be explored. Given the similarities between the two mRNA vaccines (Comirnaty® and Spikevax®) the interchangeability between Spikevax® and Vaxzevria® will not be explored in this study.

Non-inferiority of one or more of the experimental schemes would give more flexibility to the national vaccination campaign, making it less dependent on the availability of sufficient doses of one specific brand.

This knowledge can help optimize immunization programs, increase feasibility of vaccination programs, and possibly accelerate them.

Beginning with the sixth decade of life, the human immune system undergoes dramatic aging-related changes, which continuously progress to a state of immunosenescence. In the aging immune system the ability to protect against infections diminishes and vaccine responses are typically impaired in older individuals. Therefore, a trial to study partial doses is more interesting to perform in adults under the age of 55 years.

Although some concerns are currently raised about very rare cases of blood clots with low blood platelets, occurred following vaccination (thrombosis with thrombocytopenia syndrome (TTS), also called vaccine-induced immune thrombotic thrombocytopenia (VITT)) after adenovirus vector vaccines, especially after administration of Vaxzevria®, and Vaxzevria® is currently under investigation by the EMA, it is still very valuable to study the possibilities of interchangeability between mRNA-vaccines and this type of vaccines. The information about immune responses against COVID-19-vaccines that will be collected through this study, will be of huge scientific value as this study has the unique possibility to investigate a large group of COVID-19-vaccine-naïve subjects. Furthermore, the EMA made following statement: “The benefits of the vaccine continue to outweigh the risks for people who receive it. The vaccine is effective at preventing COVID-19 and reducing hospitalisations and deaths.” Extra attention should be paid to signs that can be related to this kind of clotting disorder and to minimize the risk of TTS, the age-limit of 41 YOA and older for Vaxzevria®, recently recommended by the Belgian authorities, will also be implemented in this trial.

In addition, intradermal (ID) delivery may have several advantages over IM delivery. The skin is one of the largest organs of the body providing the first line of defense against invading pathogens and one of the most obvious sites for achieving immune responses due to the presence of a high number of T cells and specialized cells including dendritic cells and macrophages in the epidermis and dermis. Studies have shown that for several vaccines ID administration can induce a higher or equal immunogenicity compared to IM, especially in people with lower immunogenicity, such as elderly. Studies have shown that 1/5 of the amount of antigen required for IM vaccination elicited similar
immunogenic responses with ID administration; such dose-saving potential could be an important economic argument when facing expensive antigens or limited antigen production capacity. When production of vaccine antigen is under time-pressure or in case of production capacity problems the dose saving potential could also lead to improved mass vaccination in high-risk populations or in pandemic situations. One publication is currently available about intradermal delivery of the COVID-19 vaccines used in this trial and shows promising results for the use of intradermal administration of COVID-19 vaccine Spikevax. Preliminary data from this trial are supporting the use of Comirnaty via the intradermal route. Data from other types of COVID-19-vaccines, delivered ID in mice, is available and promising. Data from intradermally delivered DNA-vaccines to rhesus macaques supports the need for only 1/5th of the IM-dose. ID-administration of other mRNA-vaccines has been tested and proven to work and also for cancer treatments with RNA-vaccines, the ID-route has been successfully investigated. Given the similarities between the two mRNA vaccines (Comirnaty and Spikevax), the intradermal administration route for mRNA-vaccines will only be explored for Comirnaty in this study.

In conclusion, we will investigate in this study non-inferiority of the immune response of marketed COVID-19 vaccines after IM vaccination with half dose first/second vaccine, changing brand of second vaccine or prolongation of the interval between first and second vaccine and after intradermal injection of only 1/5th of the prescribed dose for first and second vaccine. Immunogenicity and safety results can give guidance for future national and international immunization practice and recommendations.

Published data from the United Kingdom are supporting the possibility of heterologous schedules for first and second vaccine dose. “Participants boosted with ChAd following BNT prime (BNT/ChAd) had significantly higher SARS-CoV-2 anti-spike IgG (p < 0.0001) and PNA NT50 (p < 0.0001) than those primed with ChAd (ChAd/ChAd).” “All the schedules studied induced concentrations of SARS-CoV-2 anti-spike IgG concentrations at least as high as those induced after a licensed ChAd/ChAd schedule, which is effective in preventing symptomatic COVID-19 when administered at a 4-12 week prime-boost interval.”

The first preliminary results of the IMCOVAS data are showing that all used adapted schedules elicit a seroconversion in antibodies binding to the RBD of SARS-CoV-2 S protein of the ancestral D614 SARS-CoV-2 virus strain (Wuhan).

When comparing the anti-RBD-data 28days post second COVID-19 vaccine, with the recently published data from the ComCov-trial, both trials come to the same conclusion about the mixed group (1c) BNT16b2/ COVID-19 Vaccine (ChAdOx1-S [recombinant]), when comparing it to two standard doses BNT162b2 (group 1a). In the ComCov-trial, also data from two standard doses COVID-19 Vaccine (ChAdOx1-S [recombinant]) could be taken into consideration. All vaccines are administered 28days apart. In the ComCov-trial, the following conclusion stands: “Despite the BNT/ChAd regimen not meeting non-inferiority criteria, the SARS-CoV-2 anti-spike IgG concentrations of both heterologous schedules were higher than that of a licensed vaccine schedule (ChAd/ChAd) with proven efficacy against COVID-19 disease and hospitalisation.”
All used schedules for the first and second vaccination of the IMCOVAS trial elicit an antibody level that is non-inferior to the mixed schedule with 30 µg BNT162b1 followed by 0,5 ml COVID-19 Vaccine (ChAdOx1-S [recombinant] (BTN/ChAd).

After the first 2 vaccine doses in the IMCOVAS trial, all study groups reached a level of anti-RBD-IgG’s that is at least as high or higher than group 1c, the group that received SD BNT162b2 followed by SD COVID-19 Vaccine (ChAdOx1-S [recombinant]) administered intramuscularly 28 days apart. Therefore at this point in time, no ‘early exit schedule’ (additional vaccine doses) are yet administered.

However, in view of the rapid spread of B.1.1.529 (omicron), we now observe in the general population that an additional (third dose in case of two-dose regime) COVID-19 vaccination will be of important added value for all the different IMCOVAS groups, also the reference schedules. During the 4th COVID-19-wave in Belgium (fall 2021), COVID-19 infections are observed in all different vaccine schedules, as well as in the general population, vaccinated following the reference schedules. Therefore offering a third vaccine dose to all study participants, and not only to those who are not meeting the primary endpoint after the second vaccination of this trial, will be necessary. By closely monitoring the immune response after a third dose, the effect of an additional vaccination can be better estimated.

People in the general population will all have slightly different immunisation levels and backgrounds (due to adapted schedules, immunocompromised people, healthy people with a low immune response, people with a history of COVID-19 infection, ...).

It is therefore of great importance and scientific value to be able to evaluate the impact of the level previous immunisation on the effect of a third COVID-19 vaccine dose, when administered in the officially recommended dose to previously immunized persons.

3. ASSESSMENT AND MANAGEMENT OF RISK

This trial is categorised as: Low intervention clinical trial and provide justification in Appendix 1.

3.1 Risks associated to possible lower immune response

Subjects in this trial will all be vaccinated with COVID-19 vaccines that are approved by the EMA and the Belgian authorities and used for the national vaccination campaign. Age restrictions given by the Belgian authorities will be respected. However, the way of administration route (intramuscular versus intradermal), the antigen dose of the first injection, and the antigen dose, interval and brand of the boost can differ from the prescribed schedule. Immunogenicity results will be studied throughout the study and if it would turn out that a group or an individual does not respond well to the third vaccine dose, the study team will look into this and will propose an individual approach on how to proceed.

If a correlate of protection would become available during the execution of this trial, protection against SARS-CoV-2 and thus need for extra vaccination, will be evaluated on individual level based on this

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a Results of the long interval group (1e) are not yet known at this time
correlate of protection. At this moment, this is not available, therefore the non-inferiority hypothesis is a good alternative to protect the safety of the participants.

3.1 Risks associated with blood draw

Blood draw may cause local pain, tenderness or bruising. Also, general reactions can occur such as dizziness, vasovagal reaction or syncope. These risks are considered low as blood draw will be done by trained medical personnel and subjects will remain under medical observation during at least 30 minutes after vaccination.

3.2 Risks associated with vaccination

For specific details we refer to the respective SmPC of each vaccine.

Diary card with questions about solicited and unsolicited adverse events will be completed in the days after vaccination. The investigator can closely monitor the safety after vaccination. Holding rules will be defined so safety concerns can be picked up and investigated in a timely manner.

Intramuscular vaccination can cause a local reaction at the injection site which can include pain, erythema, swelling and/or induration and rash. General symptoms such as fatigue, headache, fever, chills, myalgia, arthralgia, lymphadenopathy and gastro-intestinal symptoms can occur. Most reactions are transient and of short duration.

Higher incidence of some adverse events is seen in younger age groups. Overall incidence of AEs is lower and milder in older age groups. For mRNA vaccines reactions occur more frequent after dose2 than after dose1 while adverse events after administration of adenovector based vaccines are often milder after 2nd dose.

Vaccination should be postponed in individuals suffering from an acute severe febrile illness or acute infection. However, the presence of a minor infection and/or low-grade fever should not delay vaccination.

As with other intramuscular injections, the vaccine should be given with caution in individuals receiving anticoagulant therapy or those with thrombocytopenia or any coagulation disorder because bleeding or bruising may occur following an intramuscular administration in these individuals.

The efficacy, safety and immunogenicity of the vaccines have not been assessed in immunocompromised individuals, including those receiving immunosuppressant therapy. The efficacy of these COVID-19 vaccines may be lower in immunosuppressed individuals.

3.3 Allergy

Events of anaphylaxis have been reported. To mitigate this risk subjects with severe allergic reaction to vaccine components (and particular allergy to polyethylene glycol or polysorbate) or anaphylaxis in the past will be excluded. Appropriate medical treatment and supervision should always be readily available in case of an anaphylactic reaction following the administration of the vaccine. In this study subjects will remain at the site for at least 30 minutes after vaccination for close observation.
3.4 Risks associated with intradermal vaccination

Similar to intramuscular vaccination local reactions can occur as pain, erythema, rash, swelling and induration. Some temporary local hyperpigmentation have been observed during the IMCOVAS trial, however rather limited in level of discoloration as well as limited in time (based on preliminary data until visit 4 of this current trial).

No serious adverse events related to the intradermal route have been observed during the IMCOVAS trial up until now. None of the pausing rules defined in the IMCOVAS protocol have been met during the vaccination phase of the IMCOVAS trial.

Since only limited data of intradermal route are available for these vaccines it is possible that unforeseen risks occur during the study. The same general reactions as to intramuscular administration can be expected however to what extend will be identified in this study.

Holding rules are defined so safety concerns can be picked up and investigated in a timely manner.

4. OBJECTIVES AND ENDPOINTS / OUTCOME MEASURES

4.1 Primary objective and outcome measure

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<th>Objective</th>
<th>Timepoint</th>
<th>Assay</th>
<th>Outcome measure</th>
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<tbody>
<tr>
<td>Non-inferiority of the humoral immune response against SARS-CoV-2 infection of different vaccines and adapted vaccine schedules in comparison with the reference schedule, after 2 vaccine doses (‘group a’* of each brand)</td>
<td>28d post second study vaccine</td>
<td>SARS-CoV-2 binding antibodies (ELISA)</td>
<td>GMT of antibodies binding to the RBD of SARS-CoV-2 S protein of the ancestral D614 SARS-CoV-2 virus strain</td>
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*Groups are described in section 5: Trial design

4.2 Secondary objectives and outcome measures

Safety:

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<th>Outcome measure</th>
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<td>Evaluate safety and reactogenicity of all different vaccination schedules</td>
<td>within 5d after 1st and 2nd vaccination</td>
<td>solicited AEs (local + systemic)</td>
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<tr>
<td></td>
<td>within 14 days after 1st and 2nd vaccination</td>
<td>unsolicited AEs</td>
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<tr>
<td></td>
<td>Continuously throughout the study</td>
<td>MAAEs, AESIs and SAEs</td>
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Health economics:

<table>
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<th>Timepoint</th>
<th>Outcome measure</th>
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**Assess the impact of all different vaccination schedules on productivity within 5d after 1st and 2nd vaccination**

2 questions about absenteeism

### Immunogenicity:

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<th>Assay</th>
<th>Outcome measure</th>
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<td>Non-inferiority of the humoral immune response against SARS-CoV-2 infection of different vaccine schedules in comparison with the reference schedule, after 3rd vaccine dose</td>
<td>28d post third COVID-19 vaccine</td>
<td>SARS-CoV-2 binding antibodies (ELISA)</td>
<td>GMT of antibodies binding to the RBD of SARS-CoV-2 S protein of the ancestral D614 SARS-CoV-2 virus strain</td>
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<tr>
<td>Analysis of the humoral immune response against SARS-CoV-2 infection on 3rd vaccine dose</td>
<td>D182 and 28days post 3 COVID-19 vaccine</td>
<td>SARS-CoV-2 binding antibodies (ELISA)</td>
<td>GMT of antibodies binding to the RBD of SARS-CoV-2 S protein of the ancestral D614 SARS-CoV-2 virus strain</td>
</tr>
<tr>
<td>Non-inferiority of the humoral immune response against SARS-CoV-2 infection of different vaccines and adapted vaccine schedules in comparison with the reference schedule, after 2nd and 3rd vaccine dose</td>
<td>all available time points</td>
<td>SARS-CoV-2 binding antibodies (ELISA)</td>
<td>GMT of antibodies binding to the RBD of SARS-CoV-2 S protein of the ancestral D614 SARS-CoV-2 virus strain</td>
</tr>
<tr>
<td></td>
<td>28d post 2nd study vaccine and post 3rd COVID-19 vaccine</td>
<td>SARS-CoV-2 binding antibodies (Fluorescence bead array)*</td>
<td>GMT of neutralizing antibodies to Ancestral D614 SARS-CoV-2 virus strain and VOCs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SARS-CoV-2 neutralization*</td>
<td></td>
</tr>
<tr>
<td>Analysis of specific T cell immunogenicity for all vaccine schedules after 2 and 3 vaccine doses **</td>
<td>D0 (pre 1st vaccine) and 28d post 2nd study vaccine, D182 and 28days post 3 COVID-19 vaccine</td>
<td>Flow cytometric intracellular cytokine staining</td>
<td>T cell response to relevant peptide pools of SARS-CoV-2 virus strain</td>
</tr>
<tr>
<td>Analysis of specific B cell immunogenicity of all vaccine schedules after 2 vaccine doses ***</td>
<td>28d post 2nd study vaccine, D182 and 28days post 3 COVID-19 vaccine</td>
<td>B cell Elispot</td>
<td>Memory B cell responses to S protein of Ancestral D614 SARS-CoV-2 virus strain and VOCs</td>
</tr>
<tr>
<td>Analysis biophysical characteristics (subclasses and glycosylation) of all vaccine schedules</td>
<td>Time points based on results from the primary and secondary endpoints</td>
<td>Affinity purification and capillary electrophoresis</td>
<td>Ancestral D614 SARS-CoV-2 virus and VOCs spike (S) protein specific serum IgG glycosylation</td>
</tr>
</tbody>
</table>

*Subset (30 per group), selection based on the results of the primary endpoint*
**Only in immunogenicity-subset (n = 30 per group – 240 subj in total)

***Only in immunogenicity-B-cell-subset (n = 15 per group – 120 subj in total)

### 4.3 Exploratory objectives and outcome measures

#### Immunogenicity:

<table>
<thead>
<tr>
<th><strong>Objective</strong></th>
<th><strong>Timepoint</strong></th>
<th><strong>Assay</strong></th>
<th><strong>Outcome measure</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Comparison between 2 reference vaccine schedules (group a of each brand), who are all proven to be effective in protecting against COVID-19</td>
<td>all available timepoints</td>
<td>SARS-CoV-2 binding antibodies (ELISA)</td>
<td>GMT of antibodies binding to the RBD of SARS-CoV-2 S protein</td>
</tr>
<tr>
<td>Analysis biophysical characteristics (subclasses and glycosylation) and non-neutralizing functions of Ab of all vaccine schedules</td>
<td>Time points based on results from the primary and secondary endpoints</td>
<td>Fluorescence bead arrays</td>
<td>Ancestral D614 SARS-CoV-2 virus and VOCs SARS-CoV-2 spike (S) protein specific serum antibody subclasses and binding to complement and Fc receptors</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fluorescence bead array and flow cytometry</td>
<td>Ancestral D614 SARS-CoV-2 virus and VOCs SARS-CoV-2 spike (S) protein specific non-neutralizing effector functions (phagocytosis, complement and NK cell activation)</td>
</tr>
<tr>
<td>Non-inferiority of adapted vaccine schedule in comparison with the reference schedule (group a of each brand)*</td>
<td>Time points based on results from the primary and secondary endpoints</td>
<td>SARS-CoV-2 neutralization</td>
<td>GMT of Neutralizing antibodies to Ancestral D614 SARS-CoV-2 virus strain and VOCs</td>
</tr>
<tr>
<td>Analysis of immunogenicity (T cell response) of all vaccine schedules**</td>
<td>Time points based on results from the primary and secondary endpoints</td>
<td>Flow cytometric intracellular cytokine staining</td>
<td>T-cell response to relevant peptide pools of SARS-CoV-2 virus strain</td>
</tr>
<tr>
<td>Analysis of immunogenicity (B cell response) of all vaccine schedules***</td>
<td>Time points based on results from the primary and secondary endpoints</td>
<td>B cell Elispot</td>
<td>Memory B cell responses to S protein of ancestral D614 SARS-CoV-2 virus strain and VOCs</td>
</tr>
</tbody>
</table>

*groups selected on the results of the binding and neutralizing antibody data of 28d post second study vaccine

**Only in immunogenicity-subset (n = 30 per group – 240 subj in total)

***Only in immunogenicity-B-cell-subset (n = 15 per group – 120 subj in total)

Efficacy:
<table>
<thead>
<tr>
<th>Objective</th>
<th>Timepoint</th>
<th>Outcome measure</th>
</tr>
</thead>
</table>
| Protection against Covid-19: | Continuously throughout the study | - PCR-confirmed SARS-CoV-2 infection (any variant) with COVID-19 symptoms (any severity)  
- PCR-confirmed SARS-CoV-2 infection (any variant) with severe COVID-19 (hospitalisation, death) |
| - Asymptomatic  
- Symptomatic  
- Severe COVID-19 (hospitalisation, death) | |

## 5. TRIAL DESIGN

This study is a prospective, post marketing, randomized, partially single blind, multicenter, interventional study in about 560 healthy adults (age range 18-55 years) to determine immunogenicity and reactogenicity of adapted vaccine regimes. The study will be conducted at 4 sites in Belgium.

- 4 groups of 70 subjects have received either two Standard dose (SD) or two low dose (LD) of an approved COVID-19-vaccine on the Belgian market. Low dose is defined as “a half standard dose” for mRNA-1273 Vaccine and as “2/3 of the standard dose” for BNT162b2. The vaccine is administered intramuscularly, as a series of two doses, depending on the regimen as authorized by the EMA.
- 1 group of 70 subjects have received a Standard dose (SD) of an approved COVID-19-vaccin on the Belgian market with a long interval between both doses.
- 2 groups of 70 subjects have received Standard dose (SD) of BNT162b2 as prime dose, but have received a different brand of an approved COVID-19-vaccin on the Belgian market for the boost dose.
- 1 groups of 70 subjects have received 1/5e of the Standard dose (SD) of BNT162b2 via intradermal (ID) route.

For the group that will receive Vaxzevria® as a boost dose, the age range will be limited to 41-55 YOA. All the vaccines used in this trial have been authorized by the EMA.

There are 3 vaccine brands used in the study with 8 groups in total. Table 1 summarizes the study groups and treatment schedules foreseen to be administered within the study (first and second COVID-19 vaccine dose).

### Pfizer groups: reference group = Pfizer regular scheme

- **Group 1a** - 70 subjects received SD BNT162b2 followed by SD BNT162b2 administered intramuscularly 28 days apart.
- **Group 1b** - 70 subjects received SD BNT162b2 followed by SD mRNA-1273 Vaccine administered intramuscularly 28 days apart.
- **Group 1c** - 70 subjects received SD BNT162b2 followed by SD COVID-19 Vaccine (ChAdOx1-S [recombinant]) administered intramuscularly 28 days apart.
• Group 1d - 70 subjects received LD BNT162b2 followed by LD BNT162b2 administered intramuscularly 28 days apart.
• Group 1e – 70 subjects received SD BNT162b2 followed by SD BNT162b2 administered intramuscularly 12 weeks apart.
• Group 1f - 70 subjects received BNT162b2 followed by BNT162b2 administered intradermal 28 days apart

Moderna groups: reference group = Moderna regular scheme
• Group 2a - 70 subjects received SD mRNA-1273, followed by SD mRNA-1273 Vaccine administered intramuscularly 28 days apart.
• Group 2b - 70 subjects receiving LD mRNA-1273, followed by LD mRNA-1273 Vaccine administered intramuscularly 28 days apart.
Table 1: study groups and treatment schedules foreseen in the study

Pfizer groups: reference group = Pfizer regular scheme

<table>
<thead>
<tr>
<th>Group</th>
<th>Day 0</th>
<th>Day 28</th>
<th>Day84</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>SD BNT162b2 1</td>
<td>SD BNT162b2</td>
<td></td>
</tr>
<tr>
<td>1b</td>
<td>SD BNT162b2</td>
<td>SD mRNA-1273 vaccine 3</td>
<td></td>
</tr>
<tr>
<td>1c</td>
<td>SD BNT162b2</td>
<td>SD COVID-19 Vaccine (ChAdOx1-S [recombinant]) 5</td>
<td></td>
</tr>
<tr>
<td>1d</td>
<td>LD BNT162b2 2</td>
<td>LD BNT162b2</td>
<td></td>
</tr>
<tr>
<td>1e</td>
<td>SD BNT162b2</td>
<td>SD BNT162b2</td>
<td></td>
</tr>
<tr>
<td>1f</td>
<td>Intradermal BNT162b2 3</td>
<td>Intradermal BNT162b2</td>
<td></td>
</tr>
</tbody>
</table>

Moderna groups: reference group = Moderna regular scheme

<table>
<thead>
<tr>
<th>Group</th>
<th>Day 0</th>
<th>Day 28</th>
<th>Day84</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td>SD mRNA-1273 vaccine</td>
<td>SD mRNA-1273 vaccine</td>
<td></td>
</tr>
<tr>
<td>2b</td>
<td>LD mRNA-1273 vaccine 6</td>
<td>LD mRNA-1273 vaccine</td>
<td></td>
</tr>
</tbody>
</table>

1 SD BNT162b2 = 0.3mL Comirnaty® (30 micrograms of COVID-19 mRNA Vaccine)
2 LD BNT162b2 = 0.2mL Comirnaty® (20 micrograms of COVID-19 mRNA Vaccine)
3 Intradermal BNT162b2 = 0.06mL Comirnaty® (6 micrograms of COVID-19 mRNA Vaccine)
4 SD mRNA-1273 vaccine = 0.5mL Spikevax® (100 microgram mRNA)
5 SD COVID-19 Vaccine (ChAdOx1-S [recombinant]) = 0.5mL COVID-19 Vaccine AstraZeneca® (not less than 2.5 × 108 infectious units (Inf.U) Chimpanzee Adenovirus encoding the SARS-CoV-2 Spike glycoprotein (ChAdOx1-S))
6 LD mRNA-1273 vaccine = 0.25mL Spikevax® (50 microgram mRNA)

6. STUDY SETTING

Study will be carried out in 4 study centres, specialised in vaccination trials, in Belgium. The exact number of recruited participants will be predefined per study centre as well as the exact number of participants included in the immunogenicity subset.

7. ELIGIBILITY CRITERIA

7.1 Inclusion criteria

Eligible participants must meet all of the below criteria at the time of enrollment:
1. Male, female, or X (non-binary gender) subjects, 18-55y inclusive on the day of signing of the ICF
2. Provision of signed and dated informed consent form
3. Available at all provided timepoints of the study and is not planning to move abroad for the whole duration of the study, when this move would prohibit participating in the trial until study end.
4. In good general health as evidenced by medical history and/or physical examination or adults with pre-existing medical conditions who are in stable condition. A stable medical condition is defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 3 months before enrollment.
5. Willing and able to comply with all study procedures
6. Participants born female must be either:
   - of childbearing potential and using acceptable contraception for at least 1 month prior to first vaccination and agree to use such a method during study participation until 1 months following the last study dose administration.
   - of non-childbearing potential.

See Appendix 5, *Contraceptive Guidance and Collection of Pregnancy Information*

**7.2. Exclusion criteria**

Participants meeting any of the below criteria at the time of enrolment will be ineligible to participate in the trial:

1. Previous clinical or microbiological confirmed diagnosis of COVID-19, based on individual interview or medical file (if available) during first visit.
2. Febrile illness or acute infection within 72 hours before first vaccination (this is a temporary exclusion criterion). People with a minor infection and/or low-grade fever can participate based on the opinion of the investigator.
3. Unstable, severe, progressive disease in the past 3 months.
4. History of malignancy (exceptions are squamous and basal cell carcinomas of the skin and carcinoma in situ of the cervix, or a malignancy which have been successfully treated with appropriate follow up and therefore, in the opinion of the investigator, can be considered ‘cured with minimal risk of recurrence’).
5. History of severe adverse reaction associated with a vaccine and/or anaphylaxis.
6. Known allergic reactions of any severity to polyethylene glycol [PEG] or to polysorbate (due to potential cross-reactive hypersensitivity with the vaccine ingredient PEG).
7. Primary or secondary immunodeficiency disorders (e.g. immunosuppressive disease or therapy, human immunodeficiency virus (HIV) infection...).
8. Chronic administration (defined as more than 14 days in total) of immunosuppressant or other immune-modifying drugs during the period starting 6 months prior to the first vaccine dose. For corticosteroids, this will mean prednisone 20 mg/day, or equivalent. Inhaled, nasal, ophthalmic and topical steroids are allowed. (See also appendix 8)
9. Known bleeding disorder that would, in the opinion of the investigator, contraindicate intramuscular injection.
10. Pregnancy or lactation.
11. History of drug or alcohol abuse, that in the opinion of the investigator could have an influence on the conduct of the study.

12. Anything in the opinion of the investigator that would prevent volunteers from completing the study or put the volunteer at risk, including relevant psychiatric diagnosis.

13. Criterion modified per Amendment 3:

13.1 Previous vaccination or planned to accept other vaccination during this study with any coronavirus vaccine outside this study, with the exception of a third COVID-19 vaccine during fall/winter ’21-’22.

14. Vaccination with any licensed vaccine, 14 days before or planned within 14 days after each study vaccination (28 days for live attenuated vaccines).

15. Receipt of blood/plasma products or immunoglobulin, from 60 days before study intervention administration or planned receipt throughout the study.

16. Participation in another clinical trial with an IMP or a new medical device within 28 days prior to study entry or within 5 terminal elimination half-lives, whichever is longer and/or during study participation.

17. Participant is an employee of the investigator or study site, with direct involvement in the proposed study or other studies under the direction of that investigator or study site, as well as first degree family members and household members of the employees or the investigator, or an employee of the sponsor, with direct involvement in the proposed study.

8. TRIAL PROCEDURES

8.1 Recruitment and enrolment

The aim is to enroll up to 560 participants into the trial.

Recruitment is carried out using approved recruitment methods. E.g. email to the database, website, posters, social media. Prescreening web questionnaire will be used to prevent high screening failure rates. These material have to be approved by the Independent Ethics Committee (IEC).

The recruitment and randomization process will aim to have a balanced representation of age and gender distribution across the study groups. Participants will be randomly enrolled over all the different study groups that apply for their age-category. For groups 1a, 1b, 1d, 1e, 1f, 2a and 2b, participants will be enrolled in 2 age categories with as much as possible a balance between males and females and randomized over all 7 groups.

Participants aged 41 years to 55 YOA, will be randomized over all groups, but with a higher chance to be enrolled into group 1c, since this is necessary to guarantee that the number of participants be allocated to this group will be sufficient to carry out the planned statistical analysis.

Study sites are encouraged to enroll males and females in a balanced way, and are encouraged to enroll subjects of all the different ages allowed in this trial.

Given the situation during recruitment and enrolment, where already a big part of the population 41 YOA and older are invited to be vaccinated via the national vaccination campaign, a stratification for age is no longer preferred since this would endanger the recruitment of the trial and therefore would endanger the value of the results, obtained in this trial. The balance between males and females is not
a problem since, based on the enrollment of the first 311 participants, about an equal number of males and females are willing to participate (152 females versus 159 males).

8.2 Consent: Informed consent process

Each subject must give written consent according to local requirements after the nature of the study has been fully explained. The ICF must be signed before any study-related activity. The ICF that is used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the subject can read and understand.

The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

The Principal Investigator (PI) may delegate the task of administering and obtaining informed consent to a qualified individual; however, he or she is ultimately responsible for ensuring the process is conducted properly.

Before enrolment in the study, the PI/delegate must explain to potential subject the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail.

The PI gives the potential subject ample time and opportunity to ask questions about the trial and discuss it with relatives and family members.

If the potential subject decides to get involved in the trial, he or she provides voluntary consent by signing and dating the written-informed consent document of which he or she also receives a copy. The subject has the right to withdraw consent at any time without penalty, repercussions, or reason.

The consent process should be documented in the subject’s source documents. This is done by the person obtaining the consent. Details to be documented are as follows:

- The subject’s level of comprehension, that is, did the subject understand the main purpose of the study, procedures to be done, risks involved in participating and frequency and duration of visits?
- Time of consent process.
- Possibility for the subject to ask questions before signing the ICF-document.

An updated version of the ICF will be discussed with the study participant and signed before administration of the third vaccine dose.

8.3 Trial randomisation

Subject randomization is be conducted using a randomization system implemented in the eCRF-system (RedCap). The system will ensure proper distribution of subjects across study arms.

Subjects aged 18-40 YOA were randomly allocated to one of the 7 groups without Vaxzevria® (groups 1a, 1b, 1d, 1e, 1f, 2a and 2b). Subjects aged 41-55YOA were randomly allocated to one of 8 groups as shown in table 1, but with a higher chance to end up in group 1c, to ensure the number of participants be allocated to this group will be sufficient to carry out the planned statistical analysis.
The recruitment and randomization process will aim to have a balanced representation of age and gender distribution across the study arms but this will not be made a mandatory condition.

Allocation of participants to the immunogenicity subset:
Participants contributing to the immunogenicity subset will be recruited from a selected number of sites and will be allocated by the randomization system. 30 subjects per group will be allocated to the immunogenicity subset. 15 of these allocated subjects will also be allocated more specifically to the Immunogenicity-B-cell-subset. These 15 Immunogenicity-B-cell-subset-subject will only be allocated specified after recruitment is finished, so the balance between age and gender as well as a balance in the results for the anti-RBD-IgG can be taken into account as much as possible for this allocation.

**8.4 Blinding/unblinding**

The study will be a partially single blind study. Subjects will not be informed about the brand or dose of the first and second study vaccination, until 14 days after the second vaccination, when the reporting period of solicited and unsolicited adverse events is finished. Because of the nature of the study, subjects who are randomized into the groups with ID administration of the vaccine, these subjects will know the brand of the vaccine they have received. Subjects who are randomized into the long-interval group will also know which brand of vaccine they have received. Since these subjects are not blinded, the administered vaccine can be officially registered already after the first dose. Subjects who are randomized into the other groups with IM administration, will be asked to look away when the vaccine will be administered. Although no attempt will be made to keep the study personnel, not involved in the vaccine administration, blinded for the brand or dose of the vaccination, this study personnel will not actively be informed about the brand or dose of the vaccine the subject received, and it will only be made available starting from 2 weeks after the last vaccination dose, when the collection of adverse events via the diary will be finished. The unblinding information can also be made available in case of emergency. Subjects will receive a participation card which includes a phone number on which the study site can always be reached in case of emergency to obtain emergency unblinding information.

**8.5 Baseline data**

Age, gender, race, and other baseline characteristics (vital signs, relevant medical history, concomitant medication, and physical examination) will be summarized descriptively by study arm for all randomized subjects. Check 8.6 Trial assessments and 8.8 Safety data for more details about this data.

**8.6 Trial assessments**

The total study duration will be 364 days during which each subject will be vaccinated within the trial two times with an authorized vaccine, either following the authorized schedule in terms of dose, interval and brand of second vaccination, either following an adapted schedule. Different intervals for administering the second dose will be evaluated. It will depends on the group a subject is allocated to, whether a second study vaccine dose will be administered on day 28 or on day 84. All subjects will visit the study center on 6 different time points for blood sampling in the context of the evaluation of immunogenicity and the final visit is planned on day 364 for all groups.
Subjects will be invited via the official governmental way to receive a third COVID-19 vaccine dose. Subjects are encouraged to accept this invitation and receive this third COVID-19 vaccine dose outside of the trial. Subjects will be invited to make an appointment for an extra visit (‘ad hoc post 3rd dose visit’) approximately 28 days after their third COVID-19 vaccine dose, for an additional blood draw. This additional visit is only applicable for participants who received both COVID-19 vaccinations within the IMCOVAS study, and NO additional COVID-19 vaccinations outside the study between May2021 and September 2021.

An oversight of all visits and accompanying study procedures can be found in table 2,3 and 4: Schedule of activities (SoA)

**During Visit 1/day 0 following procedures are carried out:**

- written informed consent (approved by the IEC) will be obtained according to local requirements before any study-related assessment will be carried out. Potential study participants will receive the ICF at least 24 hours in advance of D0 via electronic way and will have the possibility to ask questions or demand further clarification of certain aspects of the study.
- check inclusion / exclusion criteria
- collect demographic data – year of birth, gender, race
- collect relevant medical history and medication history
- record height and weight
- WOCPB are supposed to have a urine pregnancy test prior to vaccination
- Assess pre vaccination vital signs - oral temperature in Celsius, blood pressure and heart rate
- full physical examination
- pre vaccination blood sampling for immunogenicity assessments

Subjects will receive the first dose of study vaccine on day 0. The subjects will be kept under medical supervision for at least 30 minutes after vaccination.

Thermometers, a tape measure and a diary will be distributed to subjects and the use of the diary will be explained.

**Subsequent visits:**

Follow up visits will take place as per the SoA table 2 and table 3. Adverse events (AE’s) and the intake of concomitant medications will be monitored continuously from the time of signing informed consent until the last study-related activity. The subjects can record solicited AE’s up to 5 days after each vaccination and unsolicited AE’s up to 14 days after each vaccination on their diary card. From 14 days after each vaccination only serious adverse events, adverse events of special interest (AESI) (including COVID-19 infections and pIMD’s (potential immune mediated diseases), full list of AESIs can be found in appendix 7), medically attended adverse events (MAAE) and concomitant therapy related to these adverse events will be collected. Concomitant vaccination will be collected throughout the study. Blood will be taken for immunogenicity assessments. Observations and physical exam will be performed at the discretion of the investigator.
At the visit of second study vaccination, following procedures are carried out:

- Check AEs, SAEs, AESIs, MAAE and concomitant therapy
- WOCBP are supposed to have a urine pregnancy test prior to vaccination
- Assess pre vaccination vital signs - oral temperature in Celsius, blood pressure (supine) and heart rate
- Symptom directed physical examination
- Pre vaccination blood sampling for immunogenicity assessments

Subjects will receive the second dose of study vaccine on day 28 or day 84, depending on the interval of the group they are randomized into. The subjects will be kept under medical supervision for at least 30 minutes after vaccination. Thermometers, a tape measure and a diary will be distributed to subjects and the use of the diary will be explained.

At the ‘ad hoc post 3rd dose visit’, following procedures are carried out:

- Written informed consent (approved by the IEC) of the updated ICF will be obtained according to local requirements before any study-related assessment will be carried out. Potential study participants will receive the ICF at least 24 hours in advance of D0 via electronic way and will have the possibility to ask questions or demand further clarification of certain aspects of the study.
- Check if participant is eligible for this visit (received both COVID-19 vaccinations within the IMCOVAS study, and NO additional COVID-19 vaccinations outside the study between May 2021 and September 2021)
- Register date and brand of third COVID-19 vaccine dose, administered outside of the trial
- Check SAEs, AESIs, MAAE and concomitant therapy related to those AEs
- Check for concomitant vaccination
- Symptom directed physical examination
- Blood sampling for immunogenicity assessments

Blood sampling:

For all subjects, blood samples for assessment of humoral immunity (10mL) will be collected at baseline (Day 0 pre-dose), and at all visits as specified in SoA table 2 and table 3.

A volume of 36mL whole blood (heparinized tubes) will be drawn for PBMC assay from the immunogenicity subset of subjects at pre-defined time point as shown SoA table 2 and table 3 (45mL during the ‘ad hoc post 3rd dose visit’).

8.7 Laboratory data

To answer the objectives of the study, both serological and CMI (cell mediated immunity) data will be obtained and analyzed.
8.7.1 Humoral immunity
Serological assays will be performed at the Laboratories of the BelCoVac Consortium (Sciensano, ITM, UAntwerp, ULB). Components that may be tested are as follows:

- Antibodies binding to S protein and RBD domain of SARS-CoV-2 Ancestral D614 SARS-CoV-2 virus strain
- Antibodies binding to RBD domain of SARS-CoV-2 VOCs
- nAb to SARS-CoV-2 Ancestral D614 SARS-CoV-2 virus strain
- nAb to SARS-CoV-2 VOCs
- Ancestral D614 SARS-CoV-2 virus SARS-CoV-2 spike (S) protein specific antibody subclasses
- VOC SARS-CoV-2 spike (S) protein specific antibody subclasses
- Ancestral D614 SARS-CoV-2 virus SARS-CoV-2 spike (S) protein specific serum IgG glycosylation
- VOC SARS-CoV-2 spike (S) protein specific serum IgG glycosylation
- Ancestral D614 SARS-CoV-2 virus SARS-CoV-2 spike (S) protein specific non-neutralizing antibody effector functions (including but not limited to phagocytosis, complement activation and NK cell activation)
- VOC SARS-CoV-2 spike (S) protein specific non-neutralizing antibody effector functions (including but not limited to phagocytosis, complement activation and NK cell activation)

8.7.2 Cell mediated immunity
T and B cell response assays will be performed at the Laboratories of the BelCoVac Consortium (Sciensano, ITM, UAntwerp, ULB). Components that may be tested are as follows:

- CD4 and CD8 T cell responses to relevant peptide pools of SARS-CoV-2 virus strain
- B cell memory response to Ancestral D614 SARS-CoV-2 virus strain
- B cell memory response to VOCs

8.7.3 Additional exploratory analyses
Serum and PBMC samples may be further analyzed for additional exploratory endpoints to investigate the molecular and cellular characteristics of SARS-CoV-2 immunity as well as non-SARS-CoV-2 coronaviruses and other common pathogen and vaccine antigens. In addition, non-pathogen-specific immunity may also be explored to assess immune phenotypes prior to and after vaccination. Such analyses may focus on candidate immune pathways or involve Omics approaches, including transcriptomics, proteomics and metabolomics. Together, these additional exploratory endpoints should further increase understanding of vaccine-induced immunity and could help identify predictors of vaccine responses.

8.8 Safety data
The study will include the evaluations of safety and reactogenicity according to the time points provided in the Table 2, 3 and table 4 SoA.
In absence of a diagnosis, abnormal assessments (e.g. physical examination signs or symptoms) that are judged by the investigator to be clinically significant will be recorded as AE or SAE if they meet the respective definition and occur in the defined time.

8.8.1 Physical Examinations
A full physical examination, including height and body weight, will be carried out at screening. At all other visits, an abbreviated, symptom-directed examination might be performed by the investigator based on any clinically relevant issues or symptoms, and medical history. Symptom-directed physical examination may be repeated if deemed necessary by the investigator.

Any clinically relevant abnormalities or changes in severity observed during the review of body systems should be documented in the source documents.

8.8.2 Vital Signs
Body temperature (oral route preferred), heart rate, and resting systolic and diastolic blood pressure (SBP and DBP, respectively) will be assessed prior to each vaccination and symptom-directed on the other visits or to the opinion of the investigator.

Subject will utilize a diary to record body temperature measurements post-vaccination for 5 days.

Blood pressure and heart rate measurements will be assessed supine with a completely automated device. Manual techniques will be used only if an automated device is not available.

Fever is defined as endogenous elevation of body temperature ≥38.0°C.

8.8.3 Pregnancy Testing
A urine pregnancy test for women of childbearing potential will be performed on each vaccination visit, before the vaccination. Additional pregnancy tests may be performed, as determined necessary by the investigator, to establish the absence of pregnancy at any time during the participation in the study.

8.9 Health economics
2 questions about absenteeism will be asked within 5d after each vaccination though a questionnaire, included in the diary of the participants. This to assess the impact of all different vaccination schedules on productivity.

8.10 Schedule of activities

8.10.1 SoA per vaccine interval
Table 2: SoA short interval groups (group 1a, 1b, 1c, 1d, 1f, 2a, 2b)

<table>
<thead>
<tr>
<th>VISIT</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time of Visit (days)</td>
<td>D0 (1st vaccination)</td>
<td>D28 (2nd vaccination)</td>
<td>D56 (2nd vaccination +28D)</td>
<td>D112 (1st vaccination +112D)</td>
<td>D182 (1st vaccination +182D)</td>
<td>D364 (1st vaccination +364D)</td>
</tr>
<tr>
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<td>+/-1D</td>
<td>+/-2D</td>
<td>+/-14D</td>
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<td>+/-14D</td>
</tr>
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<td>x</td>
<td>x</td>
<td>x</td>
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</tr>
<tr>
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<tr>
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</tr>
<tr>
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<td>x</td>
<td>x</td>
<td>x</td>
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</tr>
<tr>
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<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Physical examination¹</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Vital signs²</td>
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<td>x</td>
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<td>Pregnancy test³</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Humoral immunity (serum), mL⁴</td>
<td>X 10 mL</td>
<td>X 10 mL</td>
<td>X 10mL</td>
<td>X 10mL</td>
<td>X 10mL</td>
<td>X 10mL</td>
</tr>
<tr>
<td>Cellular immunity (PBMC), mL⁴,⁵</td>
<td>X 36 mL</td>
<td>X 36 mL</td>
<td>X 36 mL</td>
<td>X 36 mL</td>
<td>X 36 mL</td>
<td>X 36 mL</td>
</tr>
<tr>
<td>Stratified randomization</td>
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<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Administration of vaccine</td>
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<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
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<td>30min post vaccine observation</td>
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<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Concomitant therapies⁶</td>
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<td>x</td>
<td>x</td>
<td>x</td>
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<td>Adverse events⁶</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
</tbody>
</table>

¹. Includes weight and height at Day 0. After Day 0, only symptom-directed physical examination
2. Blood pressure and heart rate (supine) and oral body temperature. On the day of vaccination, vital signs will be assessed prior to vaccination. To be assessed prior to each vaccination and symptom-directed on the other visits or to the opinion of the investigator.
3. Prior vaccination
4. If blood sampling is on the day of vaccination, blood draw should happen prior to vaccination
5. Immunogenicity subset only (n = 30 per group)
6. Adverse events and intake of concomitant medication(s) will be monitored continuously from informed consent until the last study-related activity. The subjects can record solicited and unsolicited AEs on their diary card until 5 respectively 14 days after each vaccination. Only serious adverse events, adverse events of special interest (including COVID-19 infections and pIMD’s (potential immune mediated diseases) full list see appendix 7), medically attended adverse events (MMAE) and concomitant medications related to these adverse events will be collected until the end of the study. Concomitant vaccinations will be collected throughout the study.
### Table 3: SoA long interval groups (group 1e)

<table>
<thead>
<tr>
<th>VISIT</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time of Visit (days)</td>
<td>D0 (1st vaccination)</td>
<td>D28</td>
<td>D84 (2nd vaccination)</td>
<td>D112 (2nd vaccination +28D)</td>
<td>D182 (1st vaccination +182D)</td>
<td>D364 (1st vaccination +364D)</td>
</tr>
<tr>
<td>Visit window</td>
<td>+/-1D</td>
<td>+/-1D</td>
<td>+/-2D</td>
<td>+/-14D</td>
<td>+/-14D</td>
<td></td>
</tr>
<tr>
<td>Informed consent</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-/exclusion criteria</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical history/concomitant diseases</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-study Medication</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Demographic data</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical examination(^1)</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Vital signs(^2)</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Pregnancy test(^3)</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Humoral immunity (serum), mL(^4)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Cellular immunity (PBMC), mL(^5, 6)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Stratified randomization</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Administration of vaccine</td>
<td>x</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>30min post vaccine observation</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concomitant therapies(^6)</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Adverse events(^6)</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
</tbody>
</table>

1. Includes weight and height at Day 0. After Day 0, only symptom-directed physical examination
2. Blood pressure and heart rate (supine) and oral body temperature. On the day of vaccination, vital signs will be assessed prior to vaccination. To be assessed prior to each vaccination and symptom-directed on the other visits or to the opinion of the investigator.
3. Prior vaccination
4. If blood sampling is on the day of vaccination, blood draw should happen prior to vaccination
5. Immunogenicity subset only (n = 30 per group)
6. Adverse events and intake of concomitant medication(s) will be monitored continuously from informed consent until the last study-related activity. The subjects can record solicited and unsolicited AEs on their diary card until 5 respectively 14 days after each vaccination. Only serious adverse events, adverse events of special interest (including COVID-19 infections and pIMD’s (potential immune mediated diseases) full list see appendix 7), medically attended adverse events (MAAE) and concomitant medications related to these adverse events will be collected until the end of the study. Concomitant vaccinations will be collected throughout the study.
8.10.2 Early exit schedule

The first preliminary results of the IMCOVAS data are showing that all used adapted schedules elicit a seroconversion in antibodies binding to the RBD of SARS-CoV-2 S protein of the ancestral D614 SARS-CoV-2 virus strain (Wuhan).

Published data from the United Kingdom are supporting the possibility of heterologous schedules for first and second vaccine dose. “Participants boosted with ChAd following BNT prime (BNT/ChAd) had significantly higher SARS-CoV-2 anti-spike IgG (p<0.0001) and PNA NT50 (p<0.0001) than those primed with ChAd (ChAd/ChAd).” “All the schedules studied induced concentrations of SARS-CoV-2 anti-spike IgG concentrations at least as high as those induced after a licensed ChAd/ChAd schedule, which is effective in preventing symptomatic COVID-19 when administered at a 4-12 week prime-boost interval.”

When comparing the anti-RBD-data 28days post second COVID-19 vaccine, with the recently published data from the ComCov-trial, both trials come to the same conclusion about the mixed group (1c) BNT16b2/ COVID-19 Vaccine (ChAdOx1-S [recombinant]), when comparing it to two standard doses BNT162b2 (group 1a). In the ComCov-trial17, also data from two standard doses COVID-19 Vaccine (ChAdOx1-S [recombinant]) could be taken into consideration. All vaccines are administered 28days apart. In the ComCov-trial18, the following conclusion stands: “Despite the BNT/ChAd regimen not meeting non-inferiority criteria, the SARS-CoV-2 anti-spike IgG concentrations of both heterologous schedules were higher than that of a licensed vaccine schedule (ChAd/ChAd) with proven efficacy against COVID-19 disease and hospitalisation.”

All used schedules in the the IMCOVAS trial elicit an antibody level that is non-inferior to the mixed schedule with 30 µg BNT162b1 followed by 0,5 ml COVID-19 Vaccine (ChAdOx1-S [recombinant] (BTN/ChAd).

After the first 2 vaccine doses in the IMCOVAS trial, all study groups reached a level of anti-RBD-IgG’s that is at least as high or higher than group 1c, the group that received SD BNT162b2 followed by SD COVID-19 Vaccine (ChAdOx1-S [recombinant]) administered intramuscularly 28 days apart. Therefore at this point in time, no ‘early exit schedule’ (additional vaccine doses) are yet administered.

8.10.3 Ad hoc post 3rd dose visit

In view of the rapid spread of B.1.1.529 (omicron), we now observe in the general population that a third COVID-19 vaccination will be of important added value for all the different IMCOVAS groups, also the reference schedules. During the 4th COVID-19-wave in Belgium, break-through infections are observed in all different vaccine schedules, as well as in the general population, vaccinated following the reference schedules. Therefore offering a third vaccine dose to all study participants, and not only to those who are not meeting the primary endpoint after the second vaccination of this trial, will be necessary. The immune response after a third dose should be closely monitored.

Subjects will be invited via the official governmental way to receive a third COVID-19 vaccine dose. Subjects are encouraged to accept this invitation and receive this third COVID-19 vaccine dose outside of the trial. Subjects will be invited to make an appointment for an extra visit (‘ad hoc post 3rd dose visit’) approximately 28days after their third COVID-19 vaccine dose, for an additional blood draw. This

Results group 1e (long interval group) are not yet known at this time
additional visit is only applicable for participants who received both COVID-19 vaccinations within the IMCOVAS study, and NO additional COVID-19 vaccinations outside the study between May 2021 and September 2021.

Table 4: SoA ‘ad hoc post 3rd dose visit’

<table>
<thead>
<tr>
<th>Time of Visit (days)</th>
<th>3rd COVID-19 vaccination outside of trial</th>
<th>Ad hoc post 3rd dose VISIT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>D0</td>
<td>3rd vaccination + 28D</td>
</tr>
<tr>
<td>Visit window</td>
<td></td>
<td>+/- 5D</td>
</tr>
<tr>
<td>Informed consent</td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Check eligibility</td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Concomitant therapies¹</td>
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<td>x</td>
</tr>
<tr>
<td>Adverse events³</td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Physical examination²</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Vital signs³</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Humoral immunity (serum), mL</td>
<td>X, 10 mL</td>
<td>X</td>
</tr>
<tr>
<td>Cellular immunity (PBMC), mL⁴</td>
<td>X, 45 mL</td>
<td>X</td>
</tr>
</tbody>
</table>

1. Only serious adverse events, adverse events of special interest (including COVID-19 infections and pIMD’s (potential immune mediated diseases) full list see appendix 7), medically attended adverse events (MAAE) and concomitant medications related to these adverse events will be collected. Concomitant vaccinations will be collected throughout the study.
2. Only symptom-directed
3. Blood pressure and heart rate (supine) and oral body temperature.
4. Immunogenicity subset only (n = 30 per group)

8.11 Withdrawal criteria

Subjects who discontinue prior to administration of the prime vaccine will be replaced, whereas those withdrawn after administration of the prime vaccine will not be replaced.

The reason for and date of subject discontinuation will be documented in the source documents and relevant electronic Case Report Form (eCRF).
8.11.1 Discontinuation of study vaccine

If the study vaccine is stopped early, the reason should be recorded in the subject’s medical records and be reported on the appropriate CRF whether it is due to either the subject’s, legal guardian’s or clinician’s decision. Reasons for stopping protocol treatment may include, but are not limited to:

- The subject and/or subject’s guardian does not wish to continue with further trial intervention
- Safety reasons
  - Any related AE, worsening of health status or intercurrent illnesses that, in the opinion of the investigator, requires discontinuation from study vaccine
  - Anaphylactic reaction following vaccination, not attributable to causes other than vaccination
  - SAE or other potentially life-threatening (Grade 4) event that is determined to be related to study vaccine
  - Other safety reasons: The details of discontinuation of study vaccine should be clearly documented in the subject’s records and in the eCRF
- Pregnancy prior to boost vaccination
- Subject received other covid-19 vaccine outside of the study
- Other reason: The details of discontinuation of study vaccine should be clearly documented in the subject’s records and in the eCRF

The trial will be analysed on a per-protocol analysis (PP) and all subjects who stop randomised trial intervention will remain in the trial for follow-up unless the subject and/or legal guardian explicitly withdraws consent for data collection.

8.11.2 Discontinuation of trial participation

8.11.2.1 Withdrawal of consent

Participation in the study is strictly voluntary. The subject and/or legal guardian may withdraw consent at any time during the study. For the purposes of this trial, withdrawal is defined as:

The subject would like to withdraw consent from study and is not willing to be followed up for the purposes of the trial at any further visits (i.e. only data collected prior to the withdrawal of consent can be used in the trial analysis, no data can be collected anymore from this time point).

A subject that is not willing to sign an updated and approved ICF, will also be registered as a consent withdrawal.

The details of withdrawal should be clearly documented in the subject’s medical records and in the eCRF.

8.11.2.2 Loss to follow-up

If a subject is lost to follow-up, study staff are to make at least three attempts at different days and times to contact the subject and/or legal guardian. These attempts should be documented in the source documents of the subject.

For subjects considered lost to follow-up, the discontinuation date for the subject to be captured on the discontinuation eCRF page is the date of the subject’s last completed study visit.
8.11.2.3 Death
In case of death, the trial is discontinued for this study participant. Data collected prior to the death can be used in the trial analysis. The discontinuation date for the subject to be captured on the discontinuation eCRF page is the date of the subject’s deceased.

8.11.2.4 Decision of the investigator
In case a participant repeatedly fails to comply with protocol requirements, the trial can be discontinued for this study participant. Data collected prior to discontinuation can be used in the trial analysis. The discontinuation date for the subject to be captured on the discontinuation eCRF page is the date of the subject’s deceased.
In case the group of a participant does not meet the primary end point, and the participant chooses not to follow the early exit schedule, the trial will be discontinued for this study participant.

8.12 End of trial
The end of trial is the date of the last visit of the last subject in the trial. A subject will be considered to have completed the study if he or she has completed all study visits or after having completed the early exit schedule in case the group of that subject does not meet the primary endpoint. The study duration for each subject is approximately 1 year after study start or until 28 day after full reference schedule in case of early exit schedule. The sponsor must notify the FAMHP and main EC of the end of a clinical trial within 90 days of its completion.

9. TRIAL INTERVENTION

9.1 Name and description of intervention(s)
SD = Standard Dose, this is the dose authorized by the EMA
LD = Low Dose (=half of a standard dose for mRNA-1273 Vaccine and COVID-19 Vaccine (ChAdOx1-S [recombinant]) and 2/3 of a standard dose for Comirnaty)
ID = Intradermal Dose, this is 1/5th dose of a Standard Dose

Vaccines used in the study:
BNT162b2 (Comirnaty®; Pfizer-BioNTech)
SD BNT162b2 = 0.3mL Comirnaty® (30 micrograms of COVID-19 mRNA Vaccine)
LD BNT162b2 = 0.2mL Comirnaty® (20 micrograms of COVID-19 mRNA Vaccine)
ID BNT162b2 = 0.06mL Comirnaty® (6 micrograms of COVID-19 mRNA Vaccine)

mRNA-1273 Vaccine (Spikevax®; Moderna)
SD mRNA-1273 vaccine = 0.5mL Spikevax® (100 microgram mRNA)
LD mRNA-1273 vaccine = 0.25mL Spikevax® (50 microgram mRNA)

COVID-19 Vaccine (ChAdOx1-S [recombinant]) (Vaxzevria®, AstraZeneca)
SD COVID-19 Vaccine (ChAdOx1-S [recombinant]) = 0.5mL Vaxzevria® (not less than 2.5 × 108 infectious units (Inf.U) Chimpanzee Adenovirus encoding the SARS-CoV-2 Spike glycoprotein (ChAdOx1-S))
9.2 Legal status of the intervention
All vaccines used during this trial have been granted a conditional marketing authorization by the European Union.
The needles and syringes used in the trial are commercially available CE-marked medical materials.

9.3 Summary of Product Characteristics (SmPC), storage and preparation
See IMP-manual for more details.

9.4 Intradermal vaccination
The standard method for intradermal injection is the Mantoux technique using a hypodermic needle and syringe. The needle for intradermal delivery is typically finer in gauge and shorter in length than needles for other types of injections, e.g., ½ in. 29 gauge needles for intradermal. For the Mantoux technique, the needle is inserted at a grazing angle to skin, i.e., 10–15° compared to 45° for subcutaneous and perpendicular for intramuscular injections. This method is reliable in the hands of a skilled administrator and requires no tools beyond a needle and syringe. Therefore the personnel who will administer the intradermal vaccination, will receive proper training on executing the Mantoux technique.

9.5 Dosage schedules or Intervention schedule
All vaccines to be given via intramuscular route will be given in the deltoid muscle of the non-dominant arm following the schedule and dose indicated in table 1.
All vaccines to be given via intradermal route will be given in the dorsal skin of the forearm of the non-dominant arm following the schedule and dose indicated in table 1.
The short interval schedule has a first vaccination on day 0 and a second vaccination on day 28. Group 1a, 1b, 1c, 1d, 1f, 2a and 2b will follow this schedule.
The long interval schedule has a first vaccination on day 0 and a second vaccination on day 84. Group 1e will follow this schedule.
Third COVID-19 vaccination will be administered outside of the trial and is therefore no trial intervention.

9.6 Study vaccination pausing rules
Since the vaccines are all marketed vaccines, authorized by EMA to use, there is only one pausing rule in place for the groups that receive intramuscular vaccination: a vaccination pause is triggered for vaccination with a certain brand if the EMA or the Belgian authorities (IMC) would announce this.
For the groups who receive their study vaccine via intradermal route, extra pausing rules are in place:

1. Death of a participant, considered related to the intradermal administered study vaccine or if the causal relationship to the intradermal administration of the study vaccine cannot be excluded; OR
   
   Note: All cases of death will be sent to CTU for review by the pharmacovigilance team and the Chief Investigator. CI may then decide whether a study pause is required.

2. One or more participants experience an SAE or a Grade 4 (solicited or unsolicited) AE that is determined to be related to the intradermal administration of the study vaccine; OR

3. Three or more participants experience a Grade 3 unsolicited AE of the same type (as per medical judgment of the sponsor), that is determined to be related to the intradermal administration of the study vaccine; OR

4. Three or more participants experience a Grade 3 solicited AE of the same type, determined to be related to intradermal administration of the study vaccine, and persisting as Grade 3 for longer than 3 consecutive days.

10. SAFETY RECORDING AND REPORTING

10.1 Definitions

10.1.1 Definitions (IMPs)

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse Event (AE)</strong></td>
<td>An AE is any untoward medical occurrence in a clinical study subject administered a pharmaceutical (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the vaccine. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per ICH). This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities. Adverse events also include adverse events of special interest (AESI) (including COVID-19 infections and pIMDs (potential immune mediated diseases) full list in appendix 7), and medically attended adverse events (MAAE).</td>
</tr>
<tr>
<td><strong>Adverse Reaction (AR)</strong></td>
<td>An untoward and unintended response in a subject to an investigational medicinal product which is related to any dose administered to that subject. The phrase &quot;response to an investigational medicinal product&quot; means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions.</td>
</tr>
</tbody>
</table>
### Serious Adverse Event (SAE)

A serious adverse event is any untoward medical occurrence that:

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- consists of a congenital anomaly or birth defect

Other ‘important medical events’ may also be considered serious if they jeopardise the subject or require an intervention to prevent one of the above consequences.

**NOTE:** The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

### Serious Adverse Reaction (SAR)

An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.

### Suspected Unexpected Serious Adverse Reaction (SUSAR)

A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out:

- in the case of a product with a marketing authorisation, in the summary of product characteristics (SmPC) for that product
- in the case of any other investigational medicinal product, in the investigator’s brochure (IB) relating to the trial in question

**NB:** to avoid confusion or misunderstanding of the difference between the terms “serious” and “severe”, the following note of clarification is provided: “Severe” is often used to describe intensity of a specific event, which may be of relatively minor medical significance. “Seriousness” is the regulatory definition supplied above.

### 10.2 Recording of safety findings in function of the available evidence

Timely, accurate, and complete reporting and analysis of safety information, including AEs, SAEs, AESIs and MAAEs from clinical studies are crucial for the protection of subject, investigators, and the sponsor, and are mandated by regulatory agencies worldwide.

### 10.2.1. General considerations for the recording of safety findings

AEs and special reporting situations, whether serious or non-serious, that are related to study procedures will be reported for all subjects from the time a signed and dated ICF is obtained until the end of the study/early withdrawal.
Solicited AEs, collected through a diary, will be recorded for first and second study vaccination from the time of vaccination until 5 days post-study vaccination.

All other unsolicited AEs will be reported for each vaccination for first and second study vaccination from the time of study-vaccination until 14 days post-vaccination, using a diary.

Unsolicited AEs with the onset date outside the timeframe defined above, should be recorded only in case of serious adverse events (SAE), adverse events of special interest (AESI) (including COVID-19 infections and pIMD (potential immune mediated diseases) full list of AESI in appendix 7, and medically attended events (MAAE).

All AEs will be followed until resolution or until clinically stable.

10.2.2. Solicited Injection Site (Local) Adverse Events

Subject will be asked to note in the diary occurrences of injection site events daily for 5 days post-study vaccination (day of vaccination and the subsequent 5 days). The extent (largest diameter) of any erythema and swelling should be measured and recorded daily.

Event that will be asked for:

- Pain/tenderness at injection site
- Erythema at injection site
- Swelling at injection site
- Induration at injection site

10.2.3. Solicited Systemic Adverse Events

Subject will be instructed on how to record daily temperature using a thermometer provided for home use. Subject should record the temperature in the diary in the evening of the day of study vaccination, and then daily for the next 4 days approximately at the same time each day. If more than one measurement is made on any given day, the highest temperature of that day will be noted. Fever is defined as endogenous elevation of body temperature ≥38°C.

Subject will also be instructed on how to note signs and symptoms in the diary daily for 5 days post-study vaccination (day of vaccination and the subsequent 4 days), for the following events:

- temperature
- fatigue
- headache
- nausea
- vomiting
- shivering
- arthralgia
- myalgia
- malaise
- shortness of breath
- chest pain
- leg swelling
- persistent abdominal pain
- neurological symptoms, such as severe and persistent headaches or blurred vision
- tiny blood spots under the skin beyond the site of the injection.

10.2.4. Unsolicited Adverse Events

Unsolicited AEs are all AEs for which the subject is not specifically questioned. Those include also adverse events of special interest (AESI) (including COVID-19 infections and piMD (potential immune mediated diseases) full list of AESI in appendix 7), serious adverse events (SAE) and medically attended adverse events (MAAE). For AEs related to an SAE, report the start and end date of the AE, independent of de dates when meeting the serious criteria.

10.2.5. COVID-19 infections

COVID-19 infections are AESIs and should be reported until the end of the study. Study participants should be encouraged to contact their treating physician (GP or other) if they have COVID-19-like signs and symptoms, and get tested for COVID-19 via the official local testing procedures (eg. local test centers, ...). The most recent case definition can be found in the protocols created by Sciensano40, which is in line with the case definition proposed by the WHO41.

A confirmed COVID-19 infection is defined as40:
- a clinically suggestive presentation in combination with a compatible CT thorax
- OR a positive PCR test for COVID-19
- OR a positive antigen test for COVID-19 (rapid antigen test or laboratory antigen test)

All confirmed COVID-19 infections should be reported in the eCRF, regardless of the participant is symptomatic or asymptomatic.

The investigator should make any possible attempt to receive the official test result from the COVID-19 positive study participant. This document should be added to the participants source documentations.

10.2.6. Attribution Definitions

Assessment of Causality

The causal relationship to study vaccine is determined by the investigator. The following selection should be used to assess all AEs.

<table>
<thead>
<tr>
<th>Related</th>
<th>There is a reasonable causal relationship between study vaccine administration and the AE. (probable or possible related)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not Related</td>
<td>There is not a reasonable causal relationship between study vaccine administration and the AE.</td>
</tr>
</tbody>
</table>

The term “reasonable causal relationship” means there is evidence to support a causal relationship.

By definition, all solicited AEs at the injection site (local) will be considered related to the study vaccine administration.
Severity Criteria

All AEs and laboratory data will be coded for severity using a modified version of the FDA grading table, based on version of September 2007,42 included as Appendix 6, Toxicity Grading Scale.

For AEs not identified in the grading table, the following guidelines will be applied:

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Mild</th>
<th>Events require minimal or no treatment and do not interfere with the subject’s daily activities.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 2</td>
<td>Moderate</td>
<td>Events introduce a low level of inconvenience or concern to the participant and may interfere with daily activities, but are usually improved by simple therapeutic measures; moderate experiences may cause some interference with functioning.</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Severe</td>
<td>Events interrupt a subject’s usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Potentially life-threatening</td>
<td>Subject at risk for death at the time of the event</td>
</tr>
</tbody>
</table>

The severity of solicited signs and symptoms will be graded in the diary by the subject based on the severity assessment provided in the diary and then verified by the investigator using the toxicity grading scale in Appendix 3.

10.3 Expedited reporting of SAEs, SUSARs SADEs, USADEs

All SAEs / SUSARs occurring from the time of written informed consent until end of study/early withdrawal must be recorded on the SAE Form and send to the CTU within 24 hours of the research staff becoming aware of the event.

Expectedness of SAR will be defined based on the SmPC section 4.8 of each vaccine.

Once all resulting queries have been resolved, the Sponsor will request the original form should also be posted to the Sponsor and a copy to be retained on site.

For each SAEs/ SUSARs the following information will be collected:

- full details in medical terms and case description
- event duration (start date (date on which event became serious) and end date (date when it no longer meets the ‘Serious’ criteria), if applicable)
- action taken
- outcome
- seriousness criteria
- causality (i.e. relatedness to trial drug/device), in the opinion of the investigator
- whether the event would be considered expected or unexpected.
Any change of condition or other follow-up information should be faxed to the CTU as soon as it is available or at least within 24 hours of the information becoming available. Events will be followed up until the event has resolved or a final outcome has been reached.

All SAEs assigned by the PI or delegate (or following central review) as both suspected to be related to IMP-treatment (or medical device) and unexpected will be classified as SUSARs and will be subject to expedited reporting to the Federal agency for medicines and health products (FAMHP). The Sponsor will inform the FAMHP, the EC and the Marketing Authorisation Holder of SUSARs within the required expedited reporting timescales.

**Reporting of adverse events and reactions and timelines**

All SAE’s whether or not deemed drug related or expected must be reported immediately or within 24 hours (one working day) using the SAE Notification Form by email to:

Clinical Trials Unit  
Institute of Tropical Medicine  
Nationalestraat 155  
B-2000 Antwerp – Belgium  
Email: pharmacovigilance@itg.be

Line listings of all reported SAE’s will be sent to the independent EC, on a yearly basis. An annual safety and status report will be sent to the Belgian Competent Authorities.

Suspected and unexpected SAE’s (SUSARs) must also be reported by the sponsor to the Belgian Competent Authority (for death and life-threatening, within 7 days, for all other SUSARs within 15 days).

**10.4 Responsibilities**

**Principal Investigator (PI):**

Checking for AEs and ARs when subject attend for treatment / follow-up.

1. Using medical judgement in assigning seriousness and causality using the Reference Safety Information approved for the trial.

2. Ensuring that all SAEs and SARs (including SUSARs) are recorded and reported to the Sponsor within 24 hours of becoming aware of the event and provide further follow-up information as soon as available. Ensuring that SAEs and SARs (including SUSARs) are chased with Sponsor if a record of receipt is not received within 2 working days of initial reporting.

3. Ensuring that AEs and ARs are recorded and reported to the Sponsor in line with the requirements of the protocol.

**Chief Investigator (CI) / delegate or independent clinical reviewer:**

1. Clinical oversight of the safety of subjects participating in the trial, including an ongoing review of the risk / benefit.
2. Using medical judgement in assigning seriousness, causality and expectedness of SAEs where it has not been possible to obtain local medical assessment.

3. Immediate review of all SUSARs.

4. Review of specific SAEs and SARs in accordance with the trial risk assessment and protocol as detailed in the Trial Monitoring Plan.

5. Assigning Medical Dictionary for Regulatory Activities (MedDRA) or Body System coding to all SAEs and SARs.


Sponsor:

1. Central data collection and verification of AEs, ARs, SAEs, SARs and SUSARs according to the trial protocol onto a safety database.

2. Reporting safety information to the CI, delegate or independent clinical reviewer for the ongoing assessment of the risk / benefit according to the Trial Monitoring Plan.

3. Reporting safety information to the independent oversight committees identified for the trial (Independent Safety Monitoring (ISM) and / or Trial Steering Committee (TSC)) according to the Trial Monitoring Plan.

4. Expedited reporting of SUSARs to the Competent Authority (FAMHP IN be) and EC within required timelines.

5. Notifying Investigators of SUSARs that occur within the trial.

6. Checking for (annually) and notifying PIs of updates to the Reference Safety Information for the trial.

7. Preparing standard tables and other relevant information for the DSUR in collaboration with the CI and ensuring timely submission to the FAMHP and REC.

Trial Steering Committee (TSC):

In accordance with the Trial Terms of Reference for the TSC, periodically reviewing safety data and liaising with the DMC regarding safety issues.

CTU Pharmacovigilance:

The person in charge at the CTU (Clinical Trial Scientists) receives notifications about SAEs (both for the initial report and for the follow-up report), pregnancy of a participant and/or the pregnancy outcome, reported by the investigator. The person in charge at the CTU (Clinical Trial Scientists) immediately verifies the information received from the site and, if needed, asks the site reporting Investigator to provide immediately any missing details and/or to give reasons for any reporting delays and/or to clarify any inconsistencies. If the minimal requirements are fulfilled, the person in charge at the CTU acknowledges receipt of the SAE report, pregnancy notification and/or pregnancy outcome report, by sending an e-mail from the “pharmacovigilance” address to:

- The site reporting Investigator
- The principal investigator (PI)

The person in charge at the CTU notifies the SAE (both for the initial and follow-up report), pregnancy and/or pregnancy outcome to the members of the TMG within 24 working hours after the CTU was notified of the SAE by the site reporting investigator and ask for comments on an event-by-event basis.

The person in charge at the CTU verifies that the TMG members provide their reply (even if there are no comments) within 2 working days, and forwards the comments to the site reporting investigator and PI. The PI has the final responsibility for correct reporting of the SAE.
The person in charge at the CTU will seek additional verification from the clinician appointed by the sponsor: Katie Steenackers, Ilse De Coster and Pierre Van Damme, concerning the relatedness and expectedness of the SAE. In case the SAE is considered possibly, probably or definitely related to the IMP, either by the site reporting investigator or by the sponsor clinician or both, and is not to be expected according to Reference Safety Information, it should be considered a SUSAR.

The person in charge at the CTU includes the information of the SAE (both for the initial report and for the follow-up report) in the aggregate data summary of the trial’s SAE, which must be sent on a yearly basis to the Ethical Committee as SAE line listings. SUSARs will be sent immediately. These reports will be submitted to the EC by the sponsor (UAntwerp).

Aggregated safety data information will be sent to the Belgian CA on a yearly basis, using a Development Safety Update Report (DSUR). This report should be sent via the CESP platform (including a cover letter) and this will be done by the sponsor (UAntwerp).

Independent Safety Monitor
The person in charge at the CTU notifies the SAE (both for the initial and follow-up report) to the study Independent Safety Monitors (ISM) at following email addresses as soon as possible after the CTU was informed about the SAESUSARs will be sent immediately.

The person in charge at the CTU verifies that the ISM provides reply (even if there are no comments) within 2 working days and forwards those comments to the site reporting investigator and PI.

10.5 Notification of deaths
Only deaths that are assessed to be caused by the IMP/intervention will be reported to the sponsor. This report will be immediate.

10.6 Reporting urgent safety measures
If any urgent safety measures are taken the CI/Sponsor shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the FAMHP and the relevant EC of the measures taken and the circumstances giving rise to those measures.

Please refer to the following website for details on clinical trials safety reporting:

11. STATISTICS AND DATA ANALYSIS

11.1. Sample size calculation
Within each brand for prime dose, the primary analysis is a non-inferiority comparison at 28 days after the second vaccination, for the GMT of antibodies binding to the RBD of the SARS-COV-2 S protein, comparing the reference schedule (group a) with each of the adapted vaccine strategies (groups b and following).

Currently available data from published and ongoing COVID-19 trails suggest that:

- Antibodies binding to the RBD of the SARS-COV-2 S protein
  - at 7 days after a second vaccine of BNT162b2 equals 1480 (GMT), standard deviation on the log scale (base 10) is 0.37 (PICOVAC-trial (Sciensano)).
  - at 28 days after a second vaccine of BNT162b2 equals 2125 (GMT), standard deviation on the log scale (base 10) is 0.27 (PICOVAC-trial (Sciensano)).
The following assumptions are made in the sample size calculations:

- The non-inferiority margin is -0.2 absolute difference of GMT on log scale base 10, between an adapted vaccine schedule and the reference schedule.
- The standard deviation of GMT on the log_{10} scale is 0.27, based on the currently available data.
- The true difference of GMT on log_{10} scale is 0.
- A one-sided 2.5% FWER (at the level of the prime dose groups). A Bonferroni correction for multiple testing, based on the number of comparisons made for the groups with as prime dose BNT162b2 was used: 2.5%/5 = 0.5% significance level.

In this study a non-inferiority margin is -0.2 has been chosen, based upon what has been implemented in comparable trials and to assure that subjects are not exposed to being vulnerable for COVID-19 disease\textsuperscript{43,44}.

Based on these assumptions, the comparison will need 56 participants per group, who are seronegative for SARS-CoV-2 at baseline to achieve 90% of power. For the groups with prime dose mRNA-1273, less than 5 adapted vaccine strategies are used and the power for a non-inferiority margin of -0.20 is higher, i.e. 99%.

But we opt for an equal number of participants for all study groups, this will result in equal accuracy for the 8 study groups.

We assume that 20% of the participants will be excluded from the primary analysis due a seropositive RBD-antibody-test in the blood draw at baseline or due to loss of follow-up during the study, therefor the sample size will be increased to 70 per group.

At this moment, a correlate of protection against SARS-CoV-2 infection is not available. If we make assumptions for the proportion of participants protected after the reference vaccine strategy; we can calculate the power to demonstrate non-inferiority of an adapted vaccine strategy. The table below shows the power for ranges of the proportion protected under the reference vaccine strategy, a non-inferiority margin of 10% or 15% and using a one-sided significance level of 5%.

<table>
<thead>
<tr>
<th>Proportion of participants protected in the reference vaccine strategy</th>
<th>Non-inferiority margin</th>
<th>Power when including 56 participants per group</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.80</td>
<td>-0.1</td>
<td>37%</td>
</tr>
<tr>
<td>0.85</td>
<td>-0.1</td>
<td>42%</td>
</tr>
<tr>
<td>0.90</td>
<td>-0.1</td>
<td>51%</td>
</tr>
<tr>
<td>0.95</td>
<td>-0.1</td>
<td>66%</td>
</tr>
<tr>
<td>0.80</td>
<td>-0.15</td>
<td>62%</td>
</tr>
<tr>
<td>0.85</td>
<td>-0.15</td>
<td>69%</td>
</tr>
<tr>
<td>0.90</td>
<td>-0.15</td>
<td>79%</td>
</tr>
<tr>
<td>0.95</td>
<td>-0.15</td>
<td>92%</td>
</tr>
</tbody>
</table>
11.2. Planned recruitment rate

Recruitment will be planned over a time period maximal 8 weeks between first patient first visit and last patient first visit.

Groups will be filled up brand by brand per study center. Randomization will take place between all the groups of 1 brand. It will be randomly allocated which study center will start with which vaccine brand. Only after all the spots for this center for this brand are filled up, the center can switch to the second vaccine brand to randomize subjects into. This strategy is chosen from an ethical point of view, to minimize the amount of doses, remaining in the multi-dose vial at the end of each vaccination day. Also a strategy to deliver these remaining doses to the general population, needs to be in place for each participating study center.

11.3. Statistical analysis plan

A detailed statistical analysis plan will be prepared prior to any data analyses.

11.3.1. Summary of baseline data of subjects

Descriptive summary statistics will be presented, to assess baseline differences between the standard schedules and the adapted schedules. Continuous variables will summarized by means and standard deviations for normally distributed variables and medians and inter-quartile ranges otherwise. Categorical variables will be presented as frequencies and percentages.

11.3.2. Primary outcome analysis

For the primary endpoint analysis, the geometric mean titres (GMT) of antibodies binding to the RBD of the SARS-CoV-2 S protein, 28 days post second study vaccine, will be compared between the reference group and the adapted schedules. Specially, the following groups will be compared:

- Pfizer groups
  - group 1a versus group 1b, at day 56
  - group 1a versus group 1c, at day 56
  - group 1a versus group 1d, at day 56
  - group 1a versus group 1e, at day 112
  - group 1a versus group 1f, at day 56

- Moderna groups
  - group 2a versus group 2b, at day 56

A logarithmic transformation (base 10) will be applied to the antibodies, to render an approximately normal distribution. For each prime dose group separately, a linear mixed model will be fitted to the data. The data at 28 days post second study vaccine will be used. This model will include age, gender and study group as fixed factors, and study site as a random factor. By incorporating age and gender as an explanatory variable in the model, age/gender imbalances between groups are corrected for. Based on this model, the mean difference (adapted schedule – standard schedule) of log10GMT for each comparison will be presented with a 95% (FWER) confidence interval. A Bonferroni correction (at level of the prime dose) will be used to control the Type I error. This implies that 99.5% CI intervals will be presented for the Pfizer prime dose comparisons, and 97.5% CI intervals for the Moderna comparison.

Non-inferiority of the adapted schedule compared to the standard schedule will be claimed if the lower limit of the confidence interval lies above -0.20.
An interim database lock is foreseen when the primary endpoint 28 days after second vaccination is available (i.e. day 112 for group 1e; day 56 for groups 1a, 1b, 1c, 1d, 1f, 2a and 2b). The primary endpoint analysis will be carried out then.

The primary analysis will be a modified intention-to-treat analysis. Only participants who were seronegative at baseline and who received two vaccines \textit{and} whose primary endpoint 28 days after second vaccination is available will be included in the primary analysis.

As a sensitivity analysis, the groups will also be compared using a mixed model for repeated measurements, including all available repeated measures of the primary endpoint up until 28 days after vaccination. This analysis will thus also include participants with missing antibodies 28 days after vaccination. Only participants who were seronegative at baseline and who received two vaccines, will be included.

11.3.3. Secondary outcome analysis

\textbf{a. Safety endpoints}

The study groups will be compared for the number of solicited and unsolicited AEs. Tables will present the AEs reported within 5 days after each vaccination and until 14 days after each study vaccination. The study groups will be compared for the proportion of participants reporting a specific solicited AE (within 5 days) by means of generalized linear mixed models (logistic models), including a fixed study group, age and gender effect, and a random study site effect. In addition, a tabular overview of the proportion of participants reporting MAAEs, AEIs and SAEs throughout the study will be given, and these proportions will be compared by means of generalized linear mixed models.

\textbf{b. Health economics}

Mixed models will be used to compare the different vaccination schedules for productivity. For absenteeism a generalized linear mixed model (logistic, poisson,..) will be used; including a fixed effect for age, gender and study group and a random study site effect.

\textbf{c. Immunogenicity endpoints}

The geometric mean titres (GMT) of antibodies binding to the RBD of the SARS-CoV-2 S protein, 28 days post third study vaccine, will be compared between the reference group and the adapted schedules. The statistical model is the same as described for the primary endpoint analysis, i.e. a linear mixed model for the logarithmic transformation (base 10) of the antibodies, including fixed effects of age, gender and study group and study site as a random factor. A Bonferroni correction (at level of the prime dose) will be used to control the Type I error. Non-inferiority of the adapted schedule compared to the standard schedule will be claimed if the lower limit of the confidence interval lies above -0.20.

GMT of antibodies binding to the RBD of SARS-CoV-2 S protein of the ancestral D614 SARS-CoV-2 virus strain, at D182 and 28 days post 3\textsuperscript{rd} COVID-19 vaccine will be presented. Summary statistics will be given for the study populations as a whole, and per brand of 3\textsuperscript{rd} COVID-19 vaccine. The change in GMT of the antibodies from D182 to 28days post 3\textsuperscript{rd} COVID-19 vaccine will be investigated by means of a linear mixed model. For each participant, the difference in log\textsubscript{10} antibodies between D182 and 28 days post 3\textsuperscript{rd} vaccine will be calculated. This difference
will be used in a linear mixed model. This model will include age, gender and brand of 3rd vaccine as fixed factors, and study site as a random factor.

After the final database lock, linear mixed models, using the log_{10} antibodies binding to the RBD of the SARS-CoV-2 S protein to Ancestral D614 SARS-CoV-2 virus strain, for

- long interval group: at days 0, 28, 84, 112, 182 and 364,
- short interval groups: at days 0, 28, 56, 112, 182 and 364,
- all groups: at day 28 post third COVID-19 vaccine, administered outside of the trial

will be employed to describe the change in GMT of these endpoints. For each cohort a separate statistical model will be fitted. The model will include fixed effects for age, gender, study group, day and the interaction term day by study group; and random study site and patient (intercept and slope) effects. Based on this model, the mean difference (adapted schedule – standard schedule) of log_{10}GMT and a 95% confidence interval for each comparison at each of the timepoints will be presented.

For the neutralizing antibodies to Ancestral D614 SARS-CoV-2 virus strain and VOCs, and the antibodies binding to the RBD of the SARS-CoV-2 S protein to VOCs, the GMT 28 days post second study vaccine, will be compared between the cohort reference group and the cohort’s adapted schedules using a linear mixed model.

For all groups, the neutralizing antibodies to Ancestral D614 SARS-CoV-2 virus strain and VOCs, and the antibodies binding to the RBD of the SARS-CoV-2 S protein to VOCs, the GMT of a subset 28 days post third COVID-19 vaccine, administered outside of the trial, will be compared between the cohort reference group and the cohort’s adapted schedules using a linear mixed model.

So, specifically, the following comparisons will be compared:

- Pfizer groups
  - group 1a versus group 1b, at day 56, at 28 days post 3rd COVID-19 vaccine
  - group 1a versus group 1c, at day 56, at 28 days post 3rd COVID-19 vaccine
  - group 1a versus group 1d, at day 56, at 28 days post 3rd COVID-19 vaccine
  - group 1a versus group 1e, at day 112, at 28 days post 3rd COVID-19 vaccine
  - group 1a versus group 1f, at day 56, at 28 days post 3rd COVID-19 vaccine

- Moderna groups
  - group 2a versus group 2b, at day 56, at 28 days post 3rd COVID-19 vaccine

For the immunogenicity subset, the groups will be compared (adapted schedule versus reference schedule) at day 0 and 28 days after second study vaccine, as well as at day 182 and 28 days after third COVID-19 vaccine, in terms of the T cell response to relevant peptide pools of SARS-CoV-2 virus strain. This comparison will also be based on a linear mixed model, T cell response will be log_{10} transformed.

For the immunogenicity-B-cell- subset, the groups will be compared (adapted schedule versus reference schedule) at days 28 after second study vaccine and 28 days post third COVID-19 vaccine in terms of the B cell memory analysis of antibody responses and B cell systems serology analysis of antibody response. This comparison will also be based on a linear mixed model, transformations will be applied if needed.
11.3.4. Exploratory outcome analyses

a. Immunogenicity

After the final database lock, linear mixed models, using the log10 antibodies binding to the RBD of the SARS-CoV-2 S protein to Ancestral D614 SARS-CoV-2 virus strain and VOCs, for

- long interval group: at days 0, 28, 84, 112, 182 and 364,
- short interval groups: at days 0, 28, 56, 112, 182 and 364,
- all groups: at day 28 post third COVID-19 vaccine, administered outside of the trial

will be employed to describe the change in GMT antibodies and to compare the average profiles between the 2 reference vaccine schedules. The model will include fixed effects for age, gender, study group, day and their interaction term; and random study site and patient (intercept and slope) effects.

For the immunogenicity subset, the groups can be compared (adapted schedule versus reference schedule) in terms of the T cell response to relevant peptide pools of SARS-CoV-2 virus strain. This comparison will also be based on a linear mixed model, T cell response will be log10 transformed.

For the immunogenicity-B-cell subset, the groups can be compared (adapted schedule versus reference schedule) in terms of the memory B cell responses to S protein of Ancestral D614 SARS-CoV-2 virus strain and VOCs. This comparison will also be based on a linear mixed model, transformations will be applied if needed.

Mixed model methodology will also be used to describe the evolution in the biophysical characteristics and Neutralizing antibodies to Ancestral D614 SARS-CoV-2 virus strain and VOCs of all vaccine schemes.

b. Efficacy

The study groups will be compared for the following binary efficacy outcome measures:

- PCR-confirmed SARS-CoV-2 infection (any variant) with COVID-19 symptoms (any severity), any time during the study
- PCR-confirmed SARS-CoV-2 infection (any variant) with severe COVID-19 (hospitalisation, death), any time during the study

Tables will present the number of participants with a PCR-confirmed SARS-CoV-2 infection. The study groups will be compared for the proportion of participants reporting a PCR-confirmed SARS-CoV-2 infection by means of generalized linear mixed models (logistic models), including a fixed study group, age and gender effect, and a random study site effect.

11.3.5. Procedure(s) to account for missing or spurious data

The amount and patterns of missing data in baseline data and endpoints will be detailed. In case of (substantial) missing data a sensitivity analyses by means of multiple imputation will be performed to investigate the sensitivity of the conclusions with respect to the assumptions about the missing data mechanism made in the
employed statistical models. An imputation model using baseline characteristics and/or imputation under MNAR (missing not at random) assumptions will be considered.

11.3.6. Other statistical considerations.

11.4. Data collection for economic evaluation

2 questions about absenteeism will completed at baseline and the four days following each study vaccination. This way effect on productivity following vaccination are captured and can be analysed by group.

One of the goals of the KCE Trials programme is to improve the efficiency of the healthcare system. This protocol has been designed with a later possible economic analysis in mind.

12. DATA HANDLING

12.1. Data collection tools and source document identification

Each participating site should keep appropriate medical and research records for this trial, in compliance with ICH E6 and regulatory and institutional requirements for the protection of confidentiality of participants. Source documents include patient records, informed consent forms, case report forms, subject diaries, laboratory data and safety data.

Data collection is the responsibility of the research staff under the supervision of the Principal Investigators. The Principal Investigator is responsible for ensuring the accuracy, completeness and timeliness of the data reported.

Individual subject data will be collected in electronic case report forms (eCRFs). Data recorded in the eCRFs derived from source documents should be consistent with the source documents or discrepancies should be explained. Only data defined by the study protocol should be captured.

12.2. Data handling and record keeping

The Principal Investigators must retain all source documents for each participant in the study, as well as any other essential trial-related documents and should make these available to monitors, auditors or regulatory authorities upon request. All hard copy documents should be kept in a secure location at the study sites.

Full details regarding the handling of data will be described in a data management plan.

Study data will be entered into eCRFs using REDCap electronic data capture system in compliance with ICH E6. Subjects will only be identified by a study ID number in the eCRF to ensure patient confidentiality.

Access to the system will be restricted through login with personal username and password to prevent unauthorized access to the data. Trial team members will be given limited user rights based on their study role and each site will only have access to records created by users within that site. An overview of up-to-date user rights will be available in the system.

Data quality will be implemented by validation checks to identify data that may appear inconsistent, incomplete, or inaccurate. If data is missing or possibly incorrect, a member of the study team will be asked to complete or verify these data by raising data queries within the system.

All data modifications will be tracked by an audit trail detailing all previous values, who changed the value at each instance, and the date and time it was changed. A complete log is available with all data and system changes.

The eCRF will be tested before moved to production status and taken into use, and the validation process will be documented. A document with guidelines for using the system will be provided to each study site.
Procedures are in place to ensure backup and long-term secure preservation of data.

A data dictionary codebook detailing the structure and contents of the eCRF will be maintained and CDASH coding standard will be used where applicable.

Data entry and quality will be the responsibility of each study site team, under supervision of the Principal Investigators. After termination of the study and cleaning and locking of the database, data will be sent to a biostatistician for statistical analysis. Data management will be performed by the study data manager.

12.3. Access to Data

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

12.4. Archiving

Access to the database or source documents will be restricted to the researchers only. The electronic database will be stored in a password protected centralized database server and the source medical records, containing identifiers, and signed informed consents, will be kept at the recruiting sites. No personal identifying information will be disclosed to anyone outside the research team. The source documents as well as the electronic database will be stored securely for the period of ten years after completion of the study and will remain available for internal audits and/or inspections of regulatory authorities.

13. MONITORING, AUDIT & INSPECTION

This study will be monitored in accordance with regulations applicable to clinical trials, including ICH-GCP and WHO-GCLP, and CTU-specific SOPs. The PI and involved site research staff will allocate adequate time and resources for such monitoring activities. The investigator will also ensure that the monitor or QA reviewer is given access to all the above noted study-related documents and study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.) and has adequate space and resources to conduct monitoring and source data verification (SDV).

A monitoring plan will be written to describe monitoring responsibilities and activities in detail (including percentage of SDV, timing and frequency of site visits, follow-up of findings and protocol deviations).

The sponsor will inform the Investigators concerned immediately upon notification of a pending study center inspection. Likewise, the investigator will inform the sponsor of any pending inspection.

Laboratory quality control and quality assurance:

All participating laboratories will ensure that all laboratory activities including specimen transport, processing, testing, result reporting and storage will be conducted in accordance with the clinical trial quality requirements. The laboratory will perform testing according to the SOPs and testing will be conducted in compliance with Good Clinical Laboratory Practice Standards (GCLP). Full validation of tests, especially tests involving new VOC, will be performed during the study. All laboratory processes and analyses of the study will be conducted in compliance with the laboratory analytical plan. Reports of laboratory test results will be forwarded to the study physician as soon as the result is available.

14. ETHICAL AND REGULATORY CONSIDERATIONS

14.1. Ethics Committee (EC) review & reports

This clinical trial (trial protocol, informed consent forms and other relevant documents) will be submitted for formal review and approval to the IEC via the CTR Pilot Project and to CA (FAMPS). No study-specific interventions will take place before written approval by the IEC has been obtained and the local regulatory requirements have
been complied with, and the signature of the clinical study protocol of each contractual party involved have been obtained.

The study will be carried out according to the principles stated in the Declaration of Helsinki, all applicable regulations and according to the most recent GCP and GCLP guidelines.

Once the final clinical study protocol has been issued and signed by the authorized signatories, it cannot be informally altered. Protocol amendments have the same legal status and must pass through the appropriate steps before being implemented. Any substantial change must be approved by all the bodies and IEC that has approved the initial protocol, prior to being implemented, unless it is due to participant’s safety concerns (in which case the immediate implementation can be necessary for the sake of participant’s protection. In case modifications to the protocol or amendment are requested by the IEC during the review process, these must be discussed and agreed upon with the Sponsor prior to any resubmission incorporating those changes.)

An annual progress report (APR), prepared by the Chief Investigator, will be submitted to the IEC within 30 days of the anniversary date on which the favorable opinion was given, and annually until the trial is declared ended. The end of the study (including in case the study was ended prematurely) will be notified to the IEC by the Chief Investigator and a final study report with the results will be submitted to the IEC within one year after the end of the study. The end of study will be defined as the last visit of the last participant.

All correspondence with the IEC will be retained in the Trial Master File/Investigator Site File.

14.2. Peer review

This protocol has been peer reviewed by:

- Experts of the sponsor site (UAntwerpen)
- Experts and investigators of the different trial sites
- Experts of KCE trials programme, KCE Prioritisation Group and KCE Trials Board
- Experts of Sciensano
- Statistical experts (Interuniversity Institute for Biostatistics and statistical Bioinformatics (I-BioStat))
- Laboratory experts (Belcovac consortium)
- Experts of a Clinical Trials Unit (ITM)
- Experts in intradermal vaccination techniques (Novosanis)

14.3. Regulatory Compliance

The trial will not commence until Clinical Trial Authorisation (CTA) is obtained from the IEC and CA (FAMPH). The protocol and trial conduct will comply with the Belgian law of May 7th 2004 regarding experiments on the human person and any relevant amendments as well as with the Clinical Trials Regulation of the European Union and the latest Belgian law of May 2017.

14.4. Protocol compliance

Protocol deviations, non-compliances, or breaches are departures from the approved protocol.
• prospective, planned deviations or waivers to the protocol are not allowed and must not be used e.g. it is not acceptable to enroll a subject if they do not meet the eligibility criteria or restrictions specified in the trial protocol

• accidental protocol deviations can happen at any time. They must be adequately documented and explained on the relevant forms and reported to the Coordinating Investigator and Sponsor immediately.

• deviations from the protocol which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach.

14.5. Notification of Serious Breaches to GCP and/or the protocol

A “serious breach” is a breach which is likely to effect to a significant degree –

• the safety or physical or mental integrity of the subjects of the trial; or

• the scientific value of the trial

In this case, the sponsor will be notified immediately of any case where the above definition applies during the trial conduct phase.

The sponsor of a clinical trial will notify the licensing authority in writing of any serious breach of the conditions and principles of GCP in connection with that trial; or the protocol relating to that trial, as amended from time to time, within 7 days of becoming aware of that breach.

14.6. Data protection and subject confidentiality

The controller is the UAntwerp with regard to the processing of the personal data in the context of this research study. The lawful basis for the processing of participant data is the public interest. A collaboration agreement concluded between all the study partners and prior to subject screening will include a section on data processing in compliance with the GDPR.

Information of trial participants will be handled confidentially. A trial participant code will be assigned to each trial participant at the earliest opportunity (pseudonymization). Any information that could lead to the identification of the participant will not be included on the eCRFs, nor on any other paper documents or electronic files used for data management. The name and contact data for each participant will be kept separately and limited to authorized staff at the sites.

All the relevant study documentation should be retained for a minimum of twenty (20) years after completion of the study, as set out by the current Belgian law.

All investigators and trial site staff must comply with the requirements of the legislation on the protection of privacy in relation to the processing of personal data (GDPR and the Belgian act of 30-JUL-2018 on the processing of personal data; see also https://www.dataprotectionauthority.be/legislation-and-standards). The Data Protection Officer is University of Antwerp.

10.4 Financial and other competing interests for the chief investigator, PIs at each site and committee members for the overall trial management

The Coordinating investigator and PIs at each site declare that they have no conflicts of interest nor competing financial interests”
14.7. Indemnity

The Sponsor of this study, the University of Antwerp, as obtained a (no-fault) study insurance to cover any injury, damage or loss to study participants and which is caused directly or indirectly by their participation in the study.

14.8. Access to the Study Data by KCE and similar institutes in the EU

This section should be read in conjunction with the research agreement, which supersedes the protocol in case of contradictory statements.

A distinction is to be made by access by KCE (and similar institutes in Europe) and access by other parties. Access to Study Data by KCE and similar institutes in the EU is fully defined in the contract between KCE and the Sponsor and the research agreement template is publicly available on the KCE website. Link: https://kce.fgov.be/fr/open-calls and then click on the last call open.

KCE and Sponsor have entered into a research agreement detailing the roles and responsibilities of each party, as well as other legal aspects of this collaboration, including the right to use and access of KCE to the Study Data.

“Background” means any intellectual property (IP), data, materials, information owned or controlled by the Sponsor or a Site, and required to run this Study. Sponsor will identify such Background including the legal restrictions of which Sponsor or Sites are aware that may affect the use of the Background for the purpose of the Study or the rights granted to KCE under this Agreement.

The Study Data consist of this protocol, including amendments, the electronic forms for data capture, including the annotations and guidance for use, the electronic database of the pseudonymized clinical and non-clinical data collected using data capture, including the log of changes from data entry to database lock, study reports based on these pseudonymized data, and any data or reports generated at a later stage, e.g. based on exploratory analyses or stored samples.

“Foreground” means any Study Data, and any tangible biological, chemical and physical material and inventions, that are generated, acquired, discovered, conceived, developed, created, exemplified or derived as a result of carrying out the Clinical Study, whatever its form or nature, whether it can be protected or not, as well as any Foreground IP. Sponsor acknowledges that the main purpose of the research performed under this Agreement is to generate results that will serve the general public interests, and specifically the interests of the subjects and public healthcare decision making bodies, and, therefore, undertakes not to exploit the Foreground in any way that is or could be detrimental to such interests.

The Sponsor owns the Study Data, but provides KCE with a copy of the pseudonymized database after database lock as well as a royalty-free unrestricted license to use the Study Data for non-commercial public health related purposes as detailed in the Agreement between KCE and the University of Antwerp. If judged appropriate, KCE will introduce the request to the competent chamber of the Information Security Committee and arrange for the data linkage. For the sake of clarity, the linked data are not part of the Study Data. However, KCE will discuss with the Sponsor the results of the analyses and the reporting of the linked data.
14.9. Access to the final trial dataset by other parties

The study results will be owned by the party who generates them. Sponsor will have access to the study data. At the end of the study, KCE will receive from Sponsor specific study data. This will only be anonymous study data or, where requested by KCE, coded personal data are made available to KCE. The study data shall not be provided to a third party without the prior written approval of KCE, which approval KCE shall not unreasonably withhold or delay and which KCE may subject to specific conditions in order to ensure that the provision of said study data does not have a negative impact on the further performance of the study, the rights granted to KCE under the research agreement and/or the benefit of the Study for the patients and/or the public payers.

15. DISSEMINATION POLICY

Dissemination policy

This section should be read in conjunction with the research agreement, which supersedes the protocol in case of contradictory statements.

The results of the study shall be owned by the party who generates them.

The results of the study owned by Sponsor and/or (where applicable) any collaborator shall be disseminated as soon as possible, by disclosing them to the public by appropriate means, including in scientific publications (in any medium). Sponsor shall inform and discuss its dissemination strategy with KCE in advance.

The final Study report should be made available for review by KCE before the results are disseminated. KCE shall be notified prior to any dissemination (including publication) (whether in oral, written or other form) of the foreground IP or results or study data or of matters arising from the study. The Chief Investigator shall send one draft copy of the proposed dissemination to KCE at least ten (10) days for an abstract and thirty (30) days for a manuscript before the date intended for dissemination. For the avoidance of doubt, this obligation continues after the end of the study. KCE may object within thirty (30) days of receiving notification, if, in its reasonable opinion, the dissemination (or the timing thereof) is not in the public interests. In the event Chief Investigator or (where applicable) any collaborator intends not to protect the results of the study it needs to formally notify KCE thereof before the dissemination takes place, Sponsor shall ensure that any dissemination is scientifically correct, objective and unbiased (taking into consideration the primary endpoint(s)).

In this multicentre study, Sponsor nor its collaborators shall independently publish or otherwise disclose any findings resulting from the study before publication of the main multicentre publication. Any dissemination shall acknowledge KCE’s financial support and carry a disclaimer as KCE may require in accordance with the clinical trial agreement.

Open access will be ensured (free of charge, online access for any user) to all peer-reviewed scientific publications relating to the results of the study owned by it and/or the collaborators. In particular, Sponsor shall: (i) As soon as possible and at the latest on publication, deposit a machine readable electronic copy of the published version or final peer-reviewed manuscript accepted for publication in a repository for scientific publications; moreover Sponsor must aim to deposit at the same time the research data needed to validate the results of the study presented in the deposited scientific publications; and; (ii) Ensure open access to the deposited publication, via the repository at the latest on publication (if an electronic version is available for free via the publisher) or, within six (6) months of publication in any other case.

We will ensure that the findings of the study will be disseminated to relevant stakeholders other than the scientific world including the general public, health care providers and policy makers. Therefore, information
about the study can be spread through websites (news sites of the universities, medical and health information sites such as gezondheid.be), newsletters and press releases. Furthermore, the results will be presented to various government bodies and policy makers and on conferences. Finally the study findings will be published in national and international journals.

In case this study proves grounds for adapting vaccination schedules, translating this evidence into practice will be the next great challenge.

15.1. Authorship eligibility guidelines and any intended use of professional writers

All reports will be written by researchers directly involved in the study and supervised by the Steering Committee. Only researchers actively involved in parts of the study will be eligible for authorship.

The results of the study will be submitted for publication in a peer reviewed journal. All centers will be entitled to one authorship for the publication of the primary outcome data, depending on the requirements and regulations of the journal. Authorships for all other publications will be depending on the contribution of an investigator to the manuscript and to the inclusion of patients. All investigators will be mentioned as members of the IMCOVAS trial team. Additional publications concerning study data will have to be approved by the Chief Investigator.
# APPENDICES

## APPENDIX 1. RISK ASSESSMENT OF THE TRIAL INTERVENTION(S)

<table>
<thead>
<tr>
<th>Risks associated with trial interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>X  A ≡ Comparable to the risk of standard medical care</td>
</tr>
<tr>
<td>□ B ≡ Somewhat higher than the risk of standard medical care</td>
</tr>
<tr>
<td>□ C ≡ Markedly higher than the risk of standard medical care</td>
</tr>
</tbody>
</table>

Justification: Briefly justify the risk category selected and your conclusions below (where the table is completed in detail the detail need not be repeated, however a summary should be given):

Subjects in this trial will all be vaccinated with COVID-19 vaccines that are approved by the Belgian authorities and used for the national vaccination campaign. Although alternative dose, interval, brand of boost and administration route will be investigated adverse events occurring in this study will be expected to be similar to the known safety profile of the used vaccines as no higher dose than standard dose will be used. To mitigate the risks of foreseen and unforeseen adverse events postvaccination observation of 30 minutes is foreseen as well as follow up of solicited and unsolicited AEs. Due to the alternative administration scheme immune response might be lower than expected. Therefore subjects of a group not meeting the primary endpoint will be offered a standard dose and administration regimen of a marketed COVID-19 vaccine and will be followed up for safety for another 28 days before leaving the study.

<table>
<thead>
<tr>
<th>What are the key risks related to therapeutic interventions you plan to monitor in this trial?</th>
<th>How will these risks be minimized?</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMP/Intervention</td>
<td>Body system/Hazard</td>
</tr>
<tr>
<td>IMP</td>
<td>Local reactions at the injection site: pain, erythema, swelling/induration and rash</td>
</tr>
<tr>
<td>IMP</td>
<td>General symptoms: Fatigue, headache, fever, chills, myalgia, arthralgia, gastrointestinal symptoms, lymphadenopathy</td>
</tr>
</tbody>
</table>
SAEs will be collected throughout the study.

DNA vaccines:
- Reactions are often milder after 2nd dose.
- To avoid the rare AE of thrombosis in combination with thrombocytopenia after vaccination with Vaxzevria: national age recommendation will be respected: subjects 18-40 will only be randomized to groups without the vaccine of AstraZeneca.

<table>
<thead>
<tr>
<th>IMP</th>
<th>Allergic reactions such as anaphylaxis</th>
<th>Close supervision of the subjects 30 min post vaccination</th>
<th>DNA vaccines: Reactions are often milder after 2nd dose. To avoid the rare AE of thrombosis in combination with thrombocytopenia after vaccination with Vaxzevria: national age recommendation will be respected: subjects 18-40 will only be randomized to groups without the vaccine of AstraZeneca.</th>
</tr>
</thead>
</table>

| ID injection | Incorrect device use causing incorrect volume or leakage | Appropriate training of administering personnel | Low |

Outline any other processes that have been put in place to mitigate risks to subject safety (e.g. DMC, independent data review, etc.)

- An ad hoc safety committee/ team will be appointed including the Investigator or his delegate(s), an independent medical monitor and the Sponsor representative(s) in case SUSAR occurs. The safety team will review the safety data and perform a risk assessment.
- Interim analysis will be performed after d28 post vaccination 2: if immune response of a group will not meet the primary endpoint subjects of that group will be offered a standard dose and regimen of a commercially available COVID 19 vaccine (brand available at that time). Additionally, they will have safety follow up until the early exit visit 28 days later.

Outline any processes (e.g. IMP labelling +/- accountability +/- trial specific temperature monitoring) that have been simplified based on the risk adapted approach.

- Open label study: therefore, physicians are aware which vaccine each subject received which facilitates review of safety issues
APPENDIX 2. AUTHORISATION OF PARTICIPATING SITES

Appendix 2.1. Required documentation

All the local documentation required prior to initiating a participating site should be collected in an Investigator Site File.

The Investigator Site File contains all essential documents held by Investigator(s) conducting a study, which individually and collectively permit the evaluation of the conduct of a study and the quality of the data produced.

For a list of all essential documents for the conduct of a clinical study, see ICH-GCP section 8

Appendix 2.2. Procedure for initiating/opening a new site

A site initiation visit (SIV) will take place via an online meeting.

During the SIV, a detailed review of all available documents in the ISF, essential to conduct a clinical study, will take place and study team is informed about all aspects related to the organization of the study. The study team will be trained on the study protocol and all required handling for executing this trial.

Appendix 2.3. Principal Investigator responsibilities

The local investigator is responsible to implement and conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the requirements for the conduct of clinical trials in the EU as provided for in "Directive 2001/20/EC" and any subsequent amendments, GCP guidelines, the Belgian law of May 7th 2004 regarding experiments on human person, the Sponsor’s SOPs, and other regulatory requirements as amended. The local investigator is bound to confidentiality and will ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation. Except where the investigator’s signature is specifically required, it is understood that the term “investigator” as used in this protocol and protocol related documents refers to the investigators and/or appropriate study personnel that the investigators designates to perform a certain duty. The investigator is ultimately responsible for the conduct of all aspects of the study. The organizing centre, Centre for the Evaluation of Vaccination from the University of Antwerp, will provide notification to the investigators of protocol and amendment approvals by regulatory authorities, if applicable.
APPENDIX 3. SAFETY REPORTING

All SAE’s whether or not deemed drug related or expected must be reported immediately or within 24 hours (one working day) using the SAE Notification Form by email to:

Clinical Trials Unit
Institute of Tropical Medicine
Nationalestraat 155
B-2000 Antwerp – Belgium
Email: pharmacovigilance@itg.be

Line listings of all reported SAE’s will be sent to the independent EC, on a yearly basis. An annual safety and status report will be sent to the Belgian Competent Authorities.

Suspected and unexpected SAE’s (SUSARs) must also be reported by the sponsor to the Belgian Competent Authority (for death and life-threatening, within 7 days, for all other SUSARs within 15 days).
# APPENDIX 4. AMENDMENT HISTORY

<table>
<thead>
<tr>
<th>Amendment No.</th>
<th>Protocol version no.</th>
<th>Date issued</th>
<th>Author(s) of changes</th>
<th>Details of changes made</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Draft version 1.0</td>
<td>30MAR2021</td>
<td>KS, IDC, KW, LB</td>
<td>Mature draft, submitted to KCE Prioritisation Group (PG) on 31MAR2021</td>
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<tr>
<td>0</td>
<td>Draft version 2.1</td>
<td>28APR2021</td>
<td>KS, IDC, KW, LB</td>
<td>Implementing feedback of the KCE trial board meeting from 20APR2021. Main points: 1/ AstraZeneca (AZ) arms: as discussed on the meeting after the TB, the investigators do still feel these are very important groups in the study and they can provide a lot of information for all the people that are already vaccinated with AZ by now and have questions about future vaccinations, as well as this can speed up vaccination programs if positive results come from this. AZ is constantly working on their vaccine and still improving it, so it can stay a big player in the market in the future and this is unique information that we need to collect now urgently. For safety reasons we respected the age limit of 41 years and up for groups that use AZ in this study. Statistically there will be corrected for this difference in age when calculating the endpoints. 2/ dose for Pfizer is adapted 3/ no device without CE-label well be used in this trial. Regular intradermal technique is possible (Mantoux technique) 4/ Moderna ID is deleted from the groups. However following the 1st point, since AZ used a different platform than Pfizer or Moderna, the AZ-intradermal group has absolutely a place in this trial. And further: - Non-inferiority margin: we adapted it to 0.2, in line with the COMCOV study running in the UK. Drop out rate has been elevated to 20% - The term cohort has been deleted. We understand it was confusing, but all participants can be randomized into all groups (depending on their age, no 18-40YOA-participants in AZ-groups)</td>
</tr>
<tr>
<td></td>
<td>Final version 1.0</td>
<td>04MAY2021</td>
<td>KS</td>
<td></td>
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<tr>
<td>0</td>
<td>Implementing feedback after the TB of 03MAY2021.</td>
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<tr>
<td></td>
<td>- Updating in/exclusion criteria</td>
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<tr>
<td></td>
<td>- Completing section 14.3, 14.10 and 14.15</td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adding protocol synopsis</td>
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<table>
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<th>KS</th>
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<td>1</td>
<td>Key Trial Contacts: contact details of ISM an TMG are added</td>
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<tr>
<td></td>
<td>- Section 4.3: updated objectives according to a more extensive early exit schedule</td>
<td></td>
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<tr>
<td></td>
<td>- Section 5 – Moderna groups: removed typo</td>
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<tr>
<td></td>
<td>- Section 7.1: incl 1: acceptable contraception</td>
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<td></td>
<td>- Section 7.2:</td>
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<tr>
<td></td>
<td>o Excl 1: clarification about how previous COVID-19 is defined</td>
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<tr>
<td></td>
<td>o Exl 8: List in appendix 8 added</td>
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<tr>
<td></td>
<td>o Excl 9 added</td>
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<tr>
<td></td>
<td>o Excl 11: more specified µ</td>
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<tr>
<td></td>
<td>o Excl 17: more specified</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Section 8.3: typo in brand name Vaxzevria® corrected</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Page</td>
<td>Final Version</td>
<td>Date</td>
<td>Authors</td>
</tr>
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<td>------</td>
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<td>---------</td>
</tr>
<tr>
<td>2</td>
<td>Final Version 2</td>
<td>10JUN2021</td>
<td>KS, LB</td>
</tr>
</tbody>
</table>

- Section 8.10.2 Early exit schedule: section is provided with more details; SoA is expanded. Follow-up is prolonged to 364 days post first study vaccine.
- Section 8.11.1: more details
- Section 8.11.3.4: extra specification
- Section 9.4 is added: information about intradermal vaccination technique
- Section 10.2: reference to appendix corrected
- Section 10.2.5 is added: details about COVID-19 infections during the trial
- Section 10.4:
  - CTU Pharmacovigilance is added
  - Independent Safety Monitor is added instead of DMC
- 11.3.2: more details added
- Appendices:
  - 4: changes made in amendment 1 are described
  - 5: birth control methods accepted in the study are corrected and updated
  - 7: list of pIMDs is added: new appendix to guide investigators in the topic of immunosuppressive medications

- Trial summary: update
- Trial flow chart: adapting group numbers and total amounts
- Section 2: explaining rationale to not to include Vaxzevria® into the trial
- Section 4.2: updating total amount of participants
- Section 4.3:
  - updating immunogenicity objective
  - updating total amount of participants
- Section 5:
  - updating total amount of participants
  - updating amount of study groups and removing group 2a, 2b, 2c and 2d
  - renaming group 3a and 3b to 2a and 2b
- Section 8.1:
  - Typo in title
  - updating total amount of participants
  - updating enrolment strategy:
    - removing predefined numbers for age and gender strata
    - explaining the unbalanced enrolment to group 1c for participants 41-55 YOA.
### Section 8.3: updating enrolment and randomisation strategy
- Section 8.4: updating blinding/unblinding
- Section 8.10.1: updating title of table 3
- Section 9.1: updating used Vaxzevria® doses in trial
- Section 9.5: updating groups
- Section 11.1: removing Vaxzevria® groups from the sample size calculation
- Section 11.2:
  - Prolonging inclusion period with 2 weeks to ensure proper inclusion
  - Updating and explaining recruitment and inclusion strategy
- Section 11.3.2:
  - Removing group 2a, 2b, 2c and 2d
  - Renaming group 3a and 3b to 2a and 2b
  - Adding gender to the analyses
- Section 11.3.3:
  - Replacing the word ‘cohort’ by ‘group’
  - Removing group 2a, 2b, 2c and 2d
  - Renaming group 3a and 3b to 2a and 2b
  - Adding gender to the analyses
- Section 11.3.4:
  - Removing group 2a, 2b, 2c and 2d
  - Adding gender to the analyses
- Appendices:
  - 4: Changes made in amendment 2 are described

### Throughout the document:
- Replace ‘COVID-19 vaccine Moderna’ by ‘Spikevax’
- Specified ‘first’ and ‘second’ vaccine dose, to avoid confusion with ‘boost dose’
- Correct some typos
- Key trial contacts: updated
- Trial Summary: updated
- List of abbreviations: added Ab, VOC and WHO
- Trial flow chart:
  - Figure 1 updated
  - Figure 2: “trial flow chart Ad hoc post 3rd dose visit” added
- Section 1: added updated information
- Section 2:
  - Added recent published information about intradermal vaccination
  - Added recent published information about mixed schedule trials
APPENDIX 5. CONTRACEPTIVE GUIDANCE AND COLLECTION OF PREGNANCY INFORMATION

Female subject of childbearing potential must follow contraceptive measures.

Definition of Woman of Childbearing Potential
Woman of Childbearing Potential
A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Woman Not of Childbearing Potential
- Premenarchal: A premenarchal state is one in which menarche has not yet occurred.
- Postmenopausal: A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
- Permanently sterile: Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Note: If the childbearing potential changes after start of the study (eg, a premenarchal woman experiences menarche) or the risk of pregnancy changes (eg, a woman who is not heterosexually active becomes active), a woman must begin a highly effective method of contraception, as described throughout the inclusion criteria.

Birth control methods which may be considered as highly effective
For the purpose of this guidance, methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods. Such methods include:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation
  (Oral/intravaginal/transdermal )
- progestogen-only hormonal contraception associated with inhibition of ovulation
  (oral/injectable/ implantable )
- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion
- vasectomised partner
- sexual abstinence from heterosexual intercourse

1Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method
2Contraception methods that in the context of this guidance are considered to have low user dependency.
3Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial subject and that the vasectomised partner has received medical assessment of the surgical success.
4In the context of this guidance sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

Acceptable birth control methods which may not be considered as highly effective
Given the nature of this clinical trial (IMP with Marketing Authorization), SmPC’s of the vaccines used in this trial can be used for contraceptive guidance. In the SmPC, no effect is expected to show on development of the fetus, based upon results from the preliminary studies. Furthermore, the most recent recommendations from
the Belgian Superior Health Council highlights the priorities for vaccinating pregnant women, women wishing to conceive and breastfeeding mothers against COVID-19. Based on this information, although it is preferred that women will not become pregnant until 1 month after last vaccination to avoid an effect on the immunogenicity data due to pregnancy, it was decided that acceptable birth control methods which may not be considered as highly effective, are also accepted in this clinical trial.

Acceptable birth control methods that result in a failure rate of more than 1% per year include:

- progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
- male or female condom with or without spermicide
- cap, diaphragm or sponge with spermicide

**Birth control methods which are considered unacceptable in clinical trials:**
Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception. Female condom and male condom should not be used together.

For additional information, see “Recommendations related to contraception and pregnancy testing in clinical trials” of the Clinical trial facilitation group (CTFG) adopted and implemented on the 21/09/2020 available on the HMA website.

### APPENDIX 6. FDA GUIDANCE FOR INDUSTRY: TOXICITY GRADING SCALE FOR HEALTHY ADULT AND ADOLESCENT VOLUNTEERS ENROLLED IN PREVENTIVE VACCINE CLINICAL TRIALS

**(SEPTEMBER 2007)**

Adapted from the FDA Guidance document “Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials” (September 2007).

#### A. Tables for Clinical Abnormalities

<table>
<thead>
<tr>
<th>Local Reaction to Injectable Product</th>
<th>Mild (Grade 1)</th>
<th>Moderate (Grade 2)</th>
<th>Severe (Grade 3)</th>
<th>Potentially Life Threatening (Grade 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain/Tenderness</td>
<td>Does not interfere with activity, easily tolerated</td>
<td>Requires use of medication or interferes with activity; Discomfort with movement</td>
<td>Requires use of narcotic pain reliever or prevents daily Activity; Significant discomfort at rest</td>
<td>Hospitalization</td>
</tr>
<tr>
<td>Erythema/Redness *</td>
<td>2.5 – 5 cm</td>
<td>5.1 – 10 cm</td>
<td>&gt; 10 cm</td>
<td>Necrosis or exfoliative dermatitis</td>
</tr>
<tr>
<td>Induration/Swelling **</td>
<td>2.5 – 5 cm and does not interfere</td>
<td>5.1 – 10 cm or interferes with activity</td>
<td>&gt; 10 cm or prevents daily activity</td>
<td>Necrosis</td>
</tr>
</tbody>
</table>
* 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.

<table>
<thead>
<tr>
<th>Vital Signs *</th>
<th>Mild (Grade 1)</th>
<th>Moderate (Grade 2)</th>
<th>Severe (Grade 3)</th>
<th>Potentially Life Threatening (Grade 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever (°C) **</td>
<td>38.0 – 38.4</td>
<td>38.5 – 38.9</td>
<td>39.0 – 40</td>
<td>&gt; 40</td>
</tr>
<tr>
<td>Tachycardia - beats per minute</td>
<td>101 – 115</td>
<td>116 – 130</td>
<td>&gt; 130</td>
<td>Hospitalization for arrhythmia</td>
</tr>
<tr>
<td>Bradycardia - beats per minute***</td>
<td>50 – 54</td>
<td>45 – 49</td>
<td>&lt; 45</td>
<td>Hospitalization for arrhythmia</td>
</tr>
<tr>
<td>Hypertension (systolic) - mm Hg</td>
<td>141 – 150</td>
<td>151 – 155</td>
<td>&gt; 155</td>
<td>Hospitalization for malignant hypertension</td>
</tr>
<tr>
<td>Hypertension (diastolic) - mm Hg</td>
<td>91 – 95</td>
<td>96 – 100</td>
<td>&gt; 100</td>
<td>Hospitalization for malignant hypertension</td>
</tr>
<tr>
<td>Hypotension (systolic) - mm Hg</td>
<td>85 – 89</td>
<td>80 – 84</td>
<td>&lt; 80</td>
<td>Hospitalization for hypotensive shock</td>
</tr>
<tr>
<td>Respiratory Rate – breaths per minute</td>
<td>17 – 20</td>
<td>21 – 25</td>
<td>&gt; 25</td>
<td>Intubation</td>
</tr>
</tbody>
</table>

* 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.

<table>
<thead>
<tr>
<th>Systemic (General)</th>
<th>Mild (Grade 1)</th>
<th>Moderate (Grade 2)</th>
<th>Severe (Grade 3)</th>
<th>Potentially Life Threatening (Grade 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea/vomiting</td>
<td>No interference with activity or 1 – 2 episodes/24 hours</td>
<td>Some interference with activity or &gt; 2 episodes/24 hours</td>
<td>Prevents daily activity, requires outsubject IV hydration</td>
<td>Hospitalization for hypotensive shock</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2 – 3 loose stools or &lt; 400 gms/24 hours</td>
<td>4 – 5 stools or 400 – 800 gms/24 hours</td>
<td>6 or more watery stools or &gt; 800gms/24 hours or requires outsubject IV hydration</td>
<td>Hospitalization</td>
</tr>
</tbody>
</table>
### APPENDIX 7. ADVERSE EVENTS OF SPECIAL INTEREST (AESI)

The US FDA defines an adverse event of special interest (serious or non-serious) as one of scientific and medical concern specific to the sponsor’s product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial sponsor to other parties (e.g., regulators) might also be warranted.47

As part of its work to harmonize safety assessment of CEPI-funded vaccines, the Safety Platform for Emergency Vaccines (SPEAC) Project has generated a list of adverse events of special interest (AESI) for safety monitoring based on one or more of the following criteria: 48

1) known association with immunization or a specific vaccine platform;
2) theoretical association based on animal models;
3) occurrence during wild-type disease as a result of viral replication and/or immunopathogenesis.

In this trial, the list of AESI defined for COVID-19 vaccines will be used as base. When this list will be updated, a new version will be submitted to the Ethical committee and Regulating Authorities, investigators will be notified of this updates and the most recent version of this list of AESI should be used:

<table>
<thead>
<tr>
<th>Condition</th>
<th>Mild (Grade 1)</th>
<th>Moderate (Grade 2)</th>
<th>Severe (Grade 3)</th>
<th>Potentially Life Threatening (Grade 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>No interference with activity</td>
<td>Some interference with activity</td>
<td>Significant; prevents daily activity</td>
<td>Hospitalization</td>
</tr>
<tr>
<td>Fatigue</td>
<td>No interference with activity</td>
<td>Some interference with activity</td>
<td>Significant; prevents daily activity</td>
<td>Hospitalization</td>
</tr>
<tr>
<td>Myalgia</td>
<td>No interference with activity</td>
<td>Some interference with activity</td>
<td>Significant; prevents daily activity</td>
<td>Hospitalization</td>
</tr>
<tr>
<td>Systemic Illness</td>
<td>Mild (Grade 1)</td>
<td>Moderate (Grade 2)</td>
<td>Severe (Grade 3)</td>
<td>Potentially Life Threatening (Grade 4)</td>
</tr>
<tr>
<td>Illness or clinical adverse event</td>
<td>No interference with activity</td>
<td>Some interference with activity not requiring medical intervention</td>
<td>Prevents daily activity and requires medical intervention</td>
<td>Hospitalization</td>
</tr>
<tr>
<td>Cardiac</td>
<td>Acute cardiac injury</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------------------------</td>
<td>------------------------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>myocarditis</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>STEMI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>arrhythmias</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>heart failure</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>endothelial dysfunction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>acute coronary syndrome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Takotsubo stress cardiomyopathy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pericarditis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>MI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurological</td>
<td>anosmia/ageusia*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Guillain-Barre Syndrome (GBS)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Acute disseminated encephalomyelitis (ADEM)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Aseptic meningitis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Peripheral facial nerve palsy</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Myelitis</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>encephalopathy</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>brain hemorrhage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>seizure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haematological</td>
<td>Thrombosis**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stroke</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Thrombocytopaenia***</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Coagulation disorder (includes coagulopathy, thrombosis, ischemia, thromboembolism, internal/external bleed and stroke)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>endothelial dysfunction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dermatological</td>
<td>Chilblain-like lesions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>cutaneous vasculitis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Erythema multiforme</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Alopecia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Acute liver injury</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ischemia/thrombosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal</td>
<td>Acute kidney injury</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>COVID-19 disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>SARS-CoV2 positivity on a validated test pIMD (see list below)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

COVID-19 AESI List 4th Update – September 2021

(in comparison with the previously included list in this protocol: No AESI added, but Brighton Case definition to be done for Long COVID and list)

*In the absence of COVID-19

** Excluding superficial thrombophlebitis (including line-associated)

*** G3 or above

List of potential immune mediated disorders (pIMDs) of interest for evaluation in clinical vaccine studies

(Note that this table is not intended to be exhaustive, but is indicative of the type of conditions that needs to be included as adverse events of special interest (AESI) in this clinical trial)

<table>
<thead>
<tr>
<th>Neuroinflammatory disorders</th>
<th>Cranial nerve inflammatory disorders, including paralyses/paresis (e.g., Bell’s palsy)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Optic neuritis</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td></td>
</tr>
<tr>
<td>----------------------------------</td>
<td></td>
</tr>
<tr>
<td>Transverse myelitis</td>
<td></td>
</tr>
<tr>
<td>Acute disseminated encephalomyelitis including site- specific VOCs: encephalitis, encephalomyelitis, myelitis, myeloradiculoneuritis, cerebellitis</td>
<td></td>
</tr>
<tr>
<td>Myasthenia gravis (including Lambert-Eaton myasthenic syndrome)</td>
<td></td>
</tr>
<tr>
<td>Immune mediated peripheral neuropathies and plexopathies, (including Guillain-Barré syndrome, Miller Fisher syndrome and other VOCs, chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy and polyneuropathies associated with monoclonal gammopathy)</td>
<td></td>
</tr>
<tr>
<td>Narcolepsy</td>
<td></td>
</tr>
</tbody>
</table>

### Musculoskeletal disorders

- Systemic lupus erythematosus
- Systemic sclerosis (with limited or diffuse cutaneous involvement)
- Dermatomyositis
- Polymyositis
- Anti-synthetase syndrome
- Rheumatoid arthritis
- Juvenile chronic arthritis (including Still’s disease)
- Polymyalgia rheumatica
- Spondyloarthritis, including ankylosing spondylitis, reactive arthritis (Reiter’s Syndrome) and undifferentiated spondyloarthritis
- Psoriatic arthropathy
- Relapsing polychondritis
- Mixed connective tissue disorder

### Skin disorders

- Psoriasis
- Vitiligo
- Erythema nodosum
- Autoimmune bullous skin diseases (including pemphigus, pemphigoid & dermatitis herpetiformis)
- Cutaneous lupus erythematosus
- Alopecia areata
- Lichen planus
- Sweet’s syndrome
- Localised Scleroderma (Morpheoa)

### Liver disorders

- Autoimmune hepatitis
- Primary biliary cirrhosis
- Primary sclerosing cholangitis
- Autoimmune cholangitis.

### Gastrointestinal disorders

- Crohn’s disease
- Ulcerative colitis
- Ulcerative proctitis
- Celiac disease

### Metabolic & endocrine disorders

- Autoimmune thyroiditis (including Hashimoto thyroiditis)
- Grave’s or Basedow’s disease
- Diabetes mellitus type I
- Addison’s disease

### Vasculitides

- Large vessels vasculitis including: giant cell arteritis such as Takayasu’s arteritis & temporal arteritis
- Medium sized and/or small vessels vasculitis including:
APPENDIX 8. LIST OF (POTENTIALLY) IMMUNOSUPPRESSIVE MEDICATIONS

Based on PUBLICATION OF THE SUPERIOR HEALTH COUNCIL No. 9158
Vaccination of immunocompromised or chronically ill children and/or adults

List of medication considered immunosuppressive
- prednisone
- Methotrexate
- 6-mercaptopurine
- Azathioprine
- Basiliximab
- Belatacept
- Cyclosporine
- Everolimus
- Fomustine
- Leflunomide
- Mitotranxone
- Mycophenolate mofenil
- Sirolimus
- Tacrolimus
- Abatacept
- Alectumab
- Anakinra
- Apremilast
- Baricitinib
- Belimumab
- Canakinumab
- Daclizumab
- Eculizumab
- Fingolimod
- Ixeizumab
- Natalizumab
- Secukinumab
- Siltuximab
- Terilunomide
- Tocilizumab
- Tofacitinib
- Ustekinumab
- Vedolizumab

**List of medication not considered immunosuppressive**

*accepted in this clinical trial

- Paracetamol, NSAID, Sulphasalazine, (hydroxy) chloroquine
- Corticosteroids
  - Short treatment with corticosteroids (< 14 days) or long-term treatment with a daily dose
    - of < 10 mg prednisone (8 mg methylprednisolone) or equivalent in adults
    - < 0.3 mg/kg/d prednisone or equivalent in children
  - Physiological doses (substitution treatment)
  - Inhalation steroids
  - Topical steroids (skin, ears, eyes)
  - Intra-articular, bursal, or intra-tendon injection of steroids
  - Budesonide enteric coating (Entocort®, etc.)
- Glatiramer acetate Copaxone® (Sanofi-Aventis) (MS)
- Selective Estrogen-receptor modulators (treatment of hormone responsive breast cancer)
  - Clomifien, tamoxifen, toremifen, raloxifen, fulvestrant
- Aromatase-Inhibitors (estrogen synthesis inhibitors; treatment of hormone responsive breast cancer)
  - Anastrozol, exemestan, letrozol
- Growth factors Hematopoietic growth factors (Granulocyte colony- stimulating factors, G-CSF)
- Antiviral therapy: HIV-drugs, ribavirin, interferon, inosine pranobex
List of medication probably not immunosuppressive**

**not accepted in this clinical trial
- Hydroxycarbamide (Hydrea*)
- Monoclonal antibodies against:
  - VEGF (vascular endothelial growth factor)
  - EGFR (epidermal growth factor)
  - Growth factor HER-2
- Anti GD2, AntiPD1, IL2 analogon
  - Aflibercept (Eylea*, Zaltrap*)
  - Aldesleukine (Proleukin*)
  - Bevacizumab (Avastin*)
  - Cetuximab (Erbitux*)
  - Dinutuximab
  - Nivolumab (Opdivo* )
  - Panitumumab (Vectibix*)
  - Pembrolizumab (Keytruda*)
  - Ramucirumab (Cyramza*)
  - Trastuzumab (Herceptin*)
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