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)

Immunogenicity after COVID-19 vaccines in Adapted Schedules

/IMCOVAS/

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
Ab	Antibody
ACE2	Angiotensin-converting enzyme 2
AE	Adverse Event
AESI	Adverse Event of Special Interest
Ag	Antigen
Ag-RDT	Antigen rapid diagnostic tests
AR	Adverse Reaction
bAb	Binding Antibody
BAU/mL	binding antibodies/mL
BLI	Biolayer Interferometry
BTI	Breakthrough Infection
CEV	Centre for the Evaluation of Vaccination
CEVAC	Centre for Vaccinology
CA	Competent Authority
CI	Chief Investigator
CMI	Cell Mediated immunity
CRF	Case Report Form
CTU	Clinical Trial Unit
CTIMP	Clinical Trial of Investigational Medicinal Product
CV	Coefficient of variation
DSUR	Development Safety Update Report
E	Envelope
EC	Ethics Committee
EDC	1-ethyl-3-[3-dimethylaminopropyl] carbodiimide hydrochloride
EMA	European Medicines Agency
EU	European Union
EUCTD	European Clinical Trials Directive
EudraCT	European Clinical Trials Database
EudraVIGILANCE	European database for Pharmacovigilance
ERA	Hôpital Erasme
FWER	family-wise error rate
GCP	Good Clinical Practice
GMFR	Geometric Mean Fold Rise
GMP	Good Manufacturing Practice
GMT	Geometric Mean Titre
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use.
IDMC	Independent Data Monitoring Committee
ID	Intradermal Dose
IEC	Independent Ethics Committee
IgG	Immuunglobuline G

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IM	Intramuscular
IMCOVAS	IMmunogenicity After COVID-19 Vaccines in Adapted Schedules
IMP	Investigational Medicinal Product
ISM	Independent Safety Monitoring
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trials
ITG	Institute of Tropical Medicine
KCE	Belgian Healthcare Knowledge Centre
LD	Low Dose (= half standard dose)
LOD	Limit of Detection
LMIC	Low- and Middle Income Countries
M	Membrane
MA	Marketing Authorisation
MAAE	Medically Attended Adverse Events
MIA	Multiplex immunoassay
MS	Member State
N	Nucleocapsid
nAb	Neutralising Antibodies
NIMP	Non-Investigational Medicinal Product
NHS	n-hydroxysuccinimide
NT	Neutralising Titer
PE	Primary Endpoint
PI	Principal Investigator
pIMD	Potential Immune Mediated Disease
PIS	Patient Information Sheet
PG	Prioritisation Group (KCE)
PNA	Pseudo Neutralization Assay
POC	Point-of-care tests
QA	Quality Assurance
QC	Quality Control
RBD	Receptor Binding Domain
RCT	Randomised Control Trial
RT-PCR	Reverse transcription polymerase chain reaction
S	Spike
S1	Spike subunit 1
S2	Spike subunit 2
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SD	Standard Dose
SDV	Source Data Verification
SI	Sub Investigator
SIV	Site Initiation Visit
SoA	Schedule of Activities
Soc	System Organ Class
SOP	Standard Operating Procedure

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SmPC	Summary of Product Characteristics
SSI	Site Specific Information
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	Trial Board (KCE)
TMG	Trial Management Group
TSC	Trial Steering Committee
TMF	Trial Master File
TTS	Thrombosis with Thrombocytopenia Syndrome
VITT	Vaccine-induced Immune Thrombotic Thrombocytopenia
UA	University of Antwerp
UZG	University Hospital Ghent
VOC	Variant of concern
WHO	World Health Organization
WOCBP	Women of child bearing potential
YOA	Years of Age

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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]. Since 2020, the pandemic caused by SARS-CoV-2 has been dominating human life on the planet and only recently in 2023 WHO announced the end of the pandemic.

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]. The clinical presentation is likely to vary by variant of the virus, pre-existing host immunity and any immunosuppression based on disease or therapy.

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]

2 Rationale, study timing and amendments in a pandemic setting

During the first half of 2021, two different mRNA vaccines (BNT162b2 (Comirnaty®; Pfizer-BioNTech) and mRNA-1273 Vaccine (Spikevax®; Moderna)) and two different DNA vaccines (COVID-19 Vaccine (ChAdOx1-S [recombinant]) (Vaxzevria®, AstraZeneca) and Ad26.COV2.S (Janssen COVID-19 vaccine®, Janssen)) showed remarkable effectiveness in preventing and minimizing impact of COVID-19 disease in adults[8,9,10,11] and were recommended by the EMA for authorization in the EU[12,13] . An efficient vaccination program was especially paramount as hospital wards filled up, particularly now knowing that SARS-CoV-2 is able to mutate.

Supply of vaccines is a delicate process and depends on a lot of factors such as the availability of raw materials, production capacity, storage capacity, packaging and transportation. Unforeseen issues in the supply of a specific brand of vaccines could cause a significant delay in the national vaccination program. Also, in case of unexpected limited availability of certain vaccines, administration of the second vaccine dose might not be possible in the prescribed timeframe. Given the anticipated challenges our population was facing with the immunization of a large part of the population, a more flexible immunization program would have had many advantages.

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The number of vaccines that could be made available for and administered to the people who need them can be doubled if administering only half a dose is proven to be as effective as administering a full (recommended) dose during both first and second vaccination. The production capacity could be increased even further when using the intradermal (ID) route, which might require only one fifth of the recommended intramuscular (IM) dose. If such an approach was found safe and the immune response was shown to be 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 willingness to be vaccinated among the general population.

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

For the BNT162b2 vaccine of Pfizer, the recommended dose is 30 µg. Higher doses were not evaluated further because side effects were observed after the BNT162b1 second dose of 50 µg[14]. For subjects 18-55 years old in the dose finding study, levels of anti-S IgG (spike protein antibodies) and the 50% neutralisation titre after two doses of 10, 20 or 30 µg did not differ significantly. Numerically, the highest response for the 50% virus neutralisation titre was actually seen for the 20 µg dose[15]. One study suggested equal immunogenicity when using a dose as low as 10 µg, compared to the recommended dose of 30 µg[16]. Building further on these promising results, we evaluated the immune response of a 20 µg dose of the BNT162b2 vaccine in this study.

For the Moderna vaccine mRNA-1273, evidence showed that a half dose regime could be effective[17] and also the FDA briefing book contains the following[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) 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."

In this study, we further evaluated whether the humoral immune response after administering half a dose of the Moderna vaccine is non-inferior compared to a full dose. Furthermore, we aimed to assess interchangeability between the mRNA vaccines by evaluating the immune response in subjects administered a Pfizer and Moderna vaccine as the first and second dose, respectively. Additionally, interchangeability for prime and boost between the Pfizer vaccine and the AstraZeneca vaccine were explored. Given the mechanistic similarities between the two mRNA vaccines (Comirnaty® and Spikevax®), the interchangeability between Spikevax ® and Vaxzevria® was not explored in this study.

Non-inferiority of one or more of the experimental schemes would provide evidence-based flexibility to the national vaccination campaign, making it less dependent on the availability of sufficient doses

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of specific brands of vaccines. Therefore, the results of this study could 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 infectious agents diminishes. Furthermore, vaccine responses are typically impaired in older individuals[19]. To prevent confounding of the study results by immunosenescence, the study was conducted in adults below the age of 55 years.

In April 2021, concerns were raised about very rare cases of blood clots with low blood platelets that occurred following vaccination (thrombosis with thrombocytopenia syndrome (TTS), also called vaccine-induced immune thrombotic thrombocytopenia (VITT)) using adenovirus vector vaccines, especially after administration of Vaxzevria®[20]. Vaxzevria® was under investigation by the EMA[21] at the time of the submission of the protocol, but we thought it would still be valuable to study the interchangeability between mRNA-vaccines and adenovirus-based vaccines. The information about immune responses against COVID-19-vaccines that were to be collected through this study, would be of important scientific value as this study had the unique possibility to investigate a large group of COVID-19-vaccine-naïve subjects. Furthermore, the EMA made following statement[22]: *"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."* To minimize the risks of the study, extra attention was paid to signs that could be related to this kind of clotting disorder. To further minimize the risk of TTS, the age-limit of 41 years-of-age and older for Vaxzevria®, recommended by the Belgian authorities, was also implemented in this trial[23].

Given the similarity between AstraZeneca (COVID-19 vaccine (ChAdOx1-S [recombinant])) and Ad26.COV2.S (Janssen COVID-19 vaccine®), the Janssen vaccine was not investigated in this study; both vaccines are adenoviral vector vaccines. Since the advice at this time was that Ad26.COV2.S can be administered in a single dose, no issues with unavailability of the second dose had to be investigated. Therefore, we focused on the 2-dose adenovirus vector vaccine Vaxzevria® in this study when evaluating interchangeability with mRNA-vaccines.

In addition to dose reduction schemes, intradermal (ID) delivery of a vaccine might pose several advantages over intramuscular (IM) delivery of the vaccine[24]. The skin is one of the largest organs of the body, providing the first line of defense against invading pathogens. It is 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. Previous studies showed that ID administration can induce a higher or equal immunogenicity compared to IM for several vaccines, especially in people with lower immunogenicity (i.e. the elderly). Studies have shown that 1/5th of the amount of antigen required for IM vaccination elicited similar immunogenic responses after ID administration of the vaccine[25]; 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[26,27,28,29,30,31]. At the time of the initiation of our trial, one publication was available about ID delivery of the COVID-19 vaccines used in this trial. This study showed promising results for the use of the ID administration of COVID-19 vaccine Spikevax® [32]. Preliminary data from this trial were supporting the evaluation of Comirnaty®, administered via the ID route. Data from other types of

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COVID-19 vaccines, delivered ID in mice, was available and promising[33]. Data from ID delivered DNA-vaccines to rhesus macaques supports the need for only 1/5th of the IM-dose[34]. ID administration of other mRNA-vaccines had been tested and proven to work[35] and also for cancer treatments with RNA-vaccines, the ID route has been successfully investigated[36,37]. Given the mechanistic similarities between the two mRNA vaccines (Comirnaty® and Spikevax®), the ID administration route for mRNA-vaccines was only explored for Comirnaty® in this study.

The study approval early in 2021 by the authorities (FAGG/AFMPS) was delayed because there were legal concerns. In particular, it was feared that the (non-public) EU joint procurement contract did not allow for academic clinical research using the vaccines procured under this contract. Clarification of this matter unfortunately took several months before finally the approval to start the trial was obtained. This made that the objective of a potential acceleration of the vaccination campaign roll-out in younger adults using a lower dose, could not be timely evaluated, very much reducing the potential impact of the trial.

Half doses of the adenovirus vector COVID-19 vaccines of Vaxzevria® (AstraZeneca) would be interesting to investigate, as up to the start of the IMCOVAS-trial (May 2021), no data for alternative vaccination schedules using Vaxzevria® were available. In the first version of the IMCOVAS trial protocol, four different vaccination schedules with different doses of the adenovirus vector COVID-19 vaccines of Vaxzevria® (AstraZeneca) ware planned to be investigated. However, Belgium imposed strict regulations for the use of Vaxzevria® in people over the age of 41 in April 2021. Since the national vaccination campaign in Belgium underwent a rapid acceleration during May and June 2021 and subject over 40 YOA received their invitation for vaccination during that time, it was difficult to recruit enough subjects in the 41-55 YOA category who had not yet been vaccinated via the national vaccination campaign in Belgium. With only limited recruitment possibilities for this age category, it was chosen to amend the protocol beginning of June 2021 and only focus on the interchangeability between mRNA-DNA-vaccines.

To this end, we amended the protocol to version 2.0, DD 10jun2021, in which we removed the Vaxzevria groups 2a (Vaxzevria reference scheme), 2b (Vaxzevria-Pfizer scheme), 2c (Vaxzevria long interval scheme) and 2d (Vaxzevria intradermal scheme). No participants had been recruited in those study groups at the time the decision was made. To be able to reach the target number of participants in each remaining group to be able to draw scientifically strong conclusions from analysis, we also had to remove the strictly defined age/gender stratification per site. In this version of the protocol, the Moderna-groups 3a and 3b were updated to be called groups 2a and 2b. However in the database and randomisation system, the Moderna-groups were already programmed as 3a and 3b, instead of 2a and 2b, since in the first version of the protocol, groups 2a-2d were the AstraZeneca groups. After amending the protocol, the name of the Moderna-groups was also adapted in the protocol. As the randomisation system was already programmed and being utilized at the time, it was not possible to modify the names of the groups in the system.
Therefore, in this Clinical Study Report, group 2a = group 3a = 'Moderna reference scheme' and group 2b = group 3b = 'Moderna low dose scheme'.

Age and/or gender stratification is in first place not common in vaccine trials in the age range between 18 and 55 and for this number of study participants. The stratification restrictions

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endangered the recruitment and therefore might have impacted scientific conclusions if statistical power would not be sufficient.
Since the distinction between 18-40 YOA and 41-55 YOA participants was still needed for randomisation because of different randomisation possibilities (7 treatment groups for 18-40 YOA and 8 treatment groups for 41-55 YOA; the consequence of the restricted age limitation for Vaxzevria), the age and gender classification was still implemented for all participants to be able to maintain a balanced representation of age and gender across the study arms. However, the maximum number of participants within each stratum was removed to allow more 18-40 YOA-participants into the trial to be able to meet the recruitment goals.

To ensure enough participants in group 1c (Pfizer-AstraZeneca scheme, only 41-55 YOA) randomisation probabilities of 41-55 YOA participants were no longer equal for all Pfizer groups following protocol version 2.0, DD 10jun2021. Participants aged 41-55 YOA and assigned to be randomized into a Pfizer-group, had a higher probability of being randomized into group 1c (Pfizer-Astrazeneca scheme) rather than into groups 1a (Pfizer reference scheme), 1b (Pfizer-Moderna scheme), 1d (Pfizer low dose scheme), 1e (Pfizer long interval scheme) or 1f (Pfizer intradermal scheme).

We needed to implement these changes as soon as possible to be able to reach the target number in the remaining groups. lf we would not have removed the stratification restrictions instantly, this would have meant sites would have to refuse certain participants based on age and/or gender, whilst not being able to recruit the remaining participants and not being able to reach the total required number of participants in a group.
lf we did not remove the Vaxzevria groups 2a (Vaxzevria reference scheme), 2b (Vaxzevria- Pfizer scheme), 2c (Vaxzevria long interval scheme) and 2d (Vaxzevria intradermal scheme) from the trial instantly, this would mean the sites would have had to start recruitment into those groups, already knowing we would not be able to reach to the total needed amounts of participants to perform an analysis or to draw any conclusion.
This would have resulted in significant loss of scientific value of the study and would have jeopardized the safety of the participants, since we would include them in the study, without being able to use their clinical study data to perform analyses.

As this was a major safety concern for the participants, we asked confirmation of the FAMPHS on 10jun2021 to immediately implement the removal of age/gender stratification and stop of recruitment in the AstraZenica study groups, even before the substantial amendment was approved. With permission of the FAMPHS, these modifications were implemented on 11jun2021.

To summarize, we have investigated in this study the non-inferiority of the immune response of marketed COVID-19 vaccines (i) after IM vaccination with lower dose first/second vaccine, (ii) when changing brand of second vaccine or prolongation of the interval between first and second vaccine and (iii) 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 practices and recommendations.

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Published data from the United Kingdom are supporting the possibility of heterologous schedules for first and second vaccine dose[38]. "Participants boosted with ChAd[1] following BNT[2] 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 trial, available in December 2021, showed 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 in the IMCOVAS trial with the 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[38], also data from two standard doses COVID-19 Vaccine (ChAdOx1-S [recombinant]) could be taken into consideration. All vaccines in that trial were administered 28 days 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 ComCov-trial elicited an antibody level that is non-inferior to the mixed schedule (30 µg BNT162b1 followed by 0,5 ml COVID-19 vaccine (ChAdOx1-S [recombinant] (BTN/ChAd) after 28 days). 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 no 'early exit schedule' (additional vaccine doses in case of unacceptable low immune response) were administered within the IMCOVAS trial.

However, in view of the rapid spread of B.1.1.529 (Omicron), an additional (third dose in case of two-dose regime) COVID-19 vaccination turned out to be of important added value for all the different IMCOVAS groups. During the 4th COVID-19-wave in Belgium (fall 2021), COVID-19 infections were observed in all different treatment arms, 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, was necessary. By closely monitoring the immune response after a third dose, the effect of an additional vaccination could be estimated better.

Given to high speed of the national vaccination campaign for the 3rd vaccine dose in Belgium, it was decided to allow the trial participants to get vaccinated via the national vaccination campaign and invite them for an additional study visit for a blood draw to evaluate immune response 4 weeks after

[1] Chad = 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))

[2] BTN = SD BNT162b2 = 0.3mL Comirnaty® (30 micrograms of COVID-19 mRNA Vaccine)

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the 3rd vaccine dose. Waiting for approval of an amended protocol that would include the 3rd vaccine dose within the trial itself would certainly have been of high scientific value but would have been highly unethical given the fact that during the Omicron wave (January 2022), study participants would have to wait for about 6 more weeks than non-participants to receive their 3rd vaccine dose. The protocol amendment 3, DD 23DEC2021, that was submitted on 23 December 2021 via the pilot to FAMPHS and EC and approved on 21 January 2022, introduced the 'ad hoc post 3rd dose visit' into the trial.

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

3 Trial objectives and primary endpoint

To demonstrate non-inferiority of the humoral immune response against SARS-Cov-2 virus of different vaccines and adapted vaccine schedules in comparison with the reference schedule, at 28 days post second study vaccine. To determine this objective, an ELISA-test measuring the SARS-CoV-2 antibodies binding to the Receptor Binding Domain was used.
The outcome of this objective is the GMT of antibodies binding to the RBD of SARS-CoV-2 S protein of the ancestral D614 SARS-CoV-2 virus strain, further referred to as 'Wuhan'.

4 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 was conducted at 4 sites in Belgium.

- 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. 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 vaccine 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 received a different brand of an approved COVID-19 vaccine on the Belgian market for the boost dose. For the group that received Vaxzevria® as a boost dose, the age range was limited to 41-55 YOA.
- 1 groups of 70 subjects have received 1/5th of the standard dose (SD) of BNT162b2 via intradermal (ID) route.

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All the vaccines used in this trial are authorized by the EMA.

There are 3 vaccine brands used in the study with 8 study groups in total. Table 1 summarizes the study groups and treatment schedules 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. *('Pfizer regular scheme')*
- Group 1b - 70 subjects received SD BNT162b2 followed by SD mRNA-1273 Vaccine administered intramuscularly 28 days apart. *('Pfizer-Moderna scheme')*
- Group 1c - 70 subjects received SD BNT162b2 followed by SD COVID-19 Vaccine (ChAdOx1-S [recombinant]) administered intramuscularly 28 days apart. *('Pfizer-AstraZeneca scheme')*
- Group 1d - 70 subjects received LD BNT162b2 followed by LD BNT162b2 administered intramuscularly 28 days apart. *('Pfizer low dose scheme')*
- Group 1e – 70 subjects received SD BNT162b2 followed by SD BNT162b2 administered intramuscularly 12 weeks apart. *('Pfizer long interval scheme')*
- Group 1f - 70 subjects received BNT162b2 followed by BNT162b2 administered intradermal 28 days apart *('Pfizer intradermal scheme')*

Moderna groups: reference group = Moderna regular scheme[3]

- Group 2a/3a - 70 subjects received SD mRNA-1273, followed by SD mRNA-1273 Vaccine administered intramuscularly 28 days apart. *('Moderna regular scheme')*
- Group 2b/3b - 70 subjects received LD mRNA-1273, followed by LD mRNA-1273 Vaccine administered intramuscularly 28 days apart. *('Moderna low dose scheme')*

Ad hoc post 3rd dose visit

Subjects were invited via the official governmental campaign to receive a third COVID-19 vaccine dose. Subjects were encouraged to accept this invitation and received this third COVID-19 vaccine dose outside of the trial. Subjects were 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 was 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.

[3] In the randomization system, the Moderna-groups are programmed as 3a and 3b, instead of 2a and 2b, because of in the first version of the protocol, groups 2a-2d were the AstraZeneca groups. After amending the protocol, the name of the Moderna-groups was also adapted in the protocol. However since the randomization system was already programmed and in use at that time, the name of the groups could not be adapted in that system. Therefore in the Clinical Study Report, group 2a = group 3a = 'Moderna reference scheme' and group 2b = group 3b = 'Moderna low dose scheme'

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Table 1: Study groups and treatment schedules administered in the study

Pfizer groups: reference group = Pfizer regular scheme

Group	Day 0	Day 28	Day84
1a *('Pfizer regular scheme')*	SD BNT162b2 [1]	SD BNT162b2	
1b *('Pfizer-Moderna scheme')*	SD BNT162b2	SD mRNA-1273 vaccine[4]	
1c *('Pfizer-AstraZeneca scheme')*	SD BNT162b2	SD COVID-19 Vaccine (ChAdOx1-S [recombinant]) [5]	
1d *('Pfizer low dose scheme')*	LD BNT162b2 [2]	LD BNT162b2	
1e *('Pfizer long interval scheme')*	SD BNT162b2		SD BNT162b2
1f *('Pfizer intradermal scheme')*	*Intradermal* BNT162b2[3]	*Intradermal* BNT162b2	

Moderna groups: reference group = Moderna regular scheme

Group	Day 0	Day 28	Day84
2a *('Moderna regular scheme')*	SD mRNA-1273 vaccine	SD mRNA-1273 vaccine	
2b[6] *('Moderna low dose scheme')*	LD mRNA-1273 vaccine[6]	LD mRNA-1273 vaccine	

[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 COVID-19 Vaccine Moderna® (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 COVID-19 Vaccine Moderna® (50 microgram mRNA)

5 Trial population

The study was carried out in 4 study centers, specialised in vaccination trials, in Belgium. Study participants were recruited in Hôpital Erasme, Institute of Tropical Medicine, University of Antwerp, Centre for the Evaluation of Vaccination (CEV) and University Hospital Ghent, Centre for Vaccinology. Only the study centrs Hôpital Erasme and University of Antwerp, CEV, had the capacity to process PBMC-samples, therefore only in those 2 study centers subject for the immunogenicity subset were recruited.

Eligible participants had to meet all inclusion criteria and none of the exclusion criteria at the time of enrollment.

Inclusion criteria

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 a 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.

Exclusion criteria

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)

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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: 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.

6 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 of the Wuhan SARS-CoV-2 virus strain, comparing the reference schedule ('group a') with each of the adapted vaccine strategies ('group b' and following).

Available data from published and ongoing COVID-19 trails[39] at the time of the protocol development 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 data available at the time of the protocol development.
- The true difference of GMT on $\log_{10}$ scale is 0.

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- 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 of -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[40,41].

Based on these assumptions, the comparison needs 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%.

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

We assumed that 20% of the participants would be excluded from the primary analysis due a seropositive RBD-antibody-test in the blood draw at baseline, due to experiencing COVID-19 disease during the trial or due to loss of follow-up during the study, therefore the sample size was increased to 70 per group.

However, the number of participants that experienced a COVID-19-infection during the trial, was in fact a lot higher due to a very strong Delta and especially Omicron wave that turned out to be extremely contagious, even for vaccinated people. The impact of this high amount of COVID-19 infections during the trial became only of significant impact after the primary end-point data (28 days after 2nd vaccination) was collected. Especially visits 5, 6 and the ad hoc post 3rd dose visit experience a big impact from the COVID-19 infections. Therefore, the long-term vaccine effect on the immune system became less clear to evaluate over the 8 different study groups.

7 Trial randomisation and subset-identification

Subject randomisation was conducted using a randomisation 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, 3a and 3b). Subjects aged 41-55YOA were randomly allocated to one of 8 groups as shown in Table 1, but after the first protocol amendment, 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 process aimed to have a balanced representation of age and gender distribution across the study groups but this was not a mandatory condition.

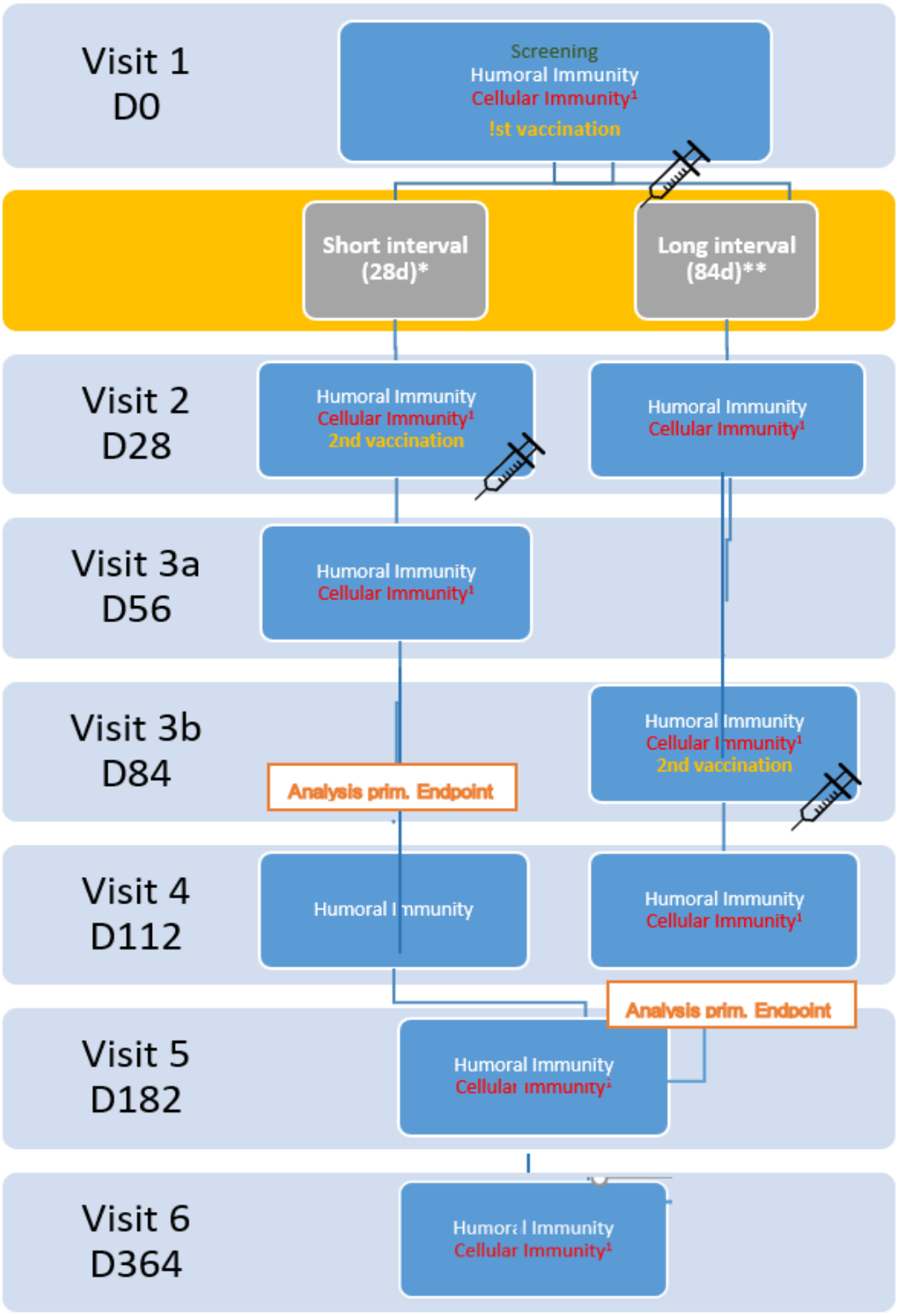
30 subjects per group were allocated to the **immunogenicity subset for analysis of the cellular immunity**. Subject for this subset were only recruited in 2 of the 4 trial sites, due to limited availability of PBMC-capacity. At the trial sites that randomized subjects for the immunogenicity subset,

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participants were allocated first to subset groups, and participants could only be allocated to a non-subset group once the predefined number of subset participants for that group for that study center was reached. It was foreseen in the protocol to perform testing for cellular immunity (T-cel analysis and B-cel analysis) on the samples of this immunogenicity subset. However due to shifting of priorities to more in depth analysis of cellular immunity and a rapidly changing scientific landscape and new insights and evolution with regards to the COVID-19 pandemic, it was decided in May 2022 after a meeting with BelcCoVac Consortium and KCE, to not to perform the originally planned cellular immunity tests, and to store all PBMC samples in the biobank.

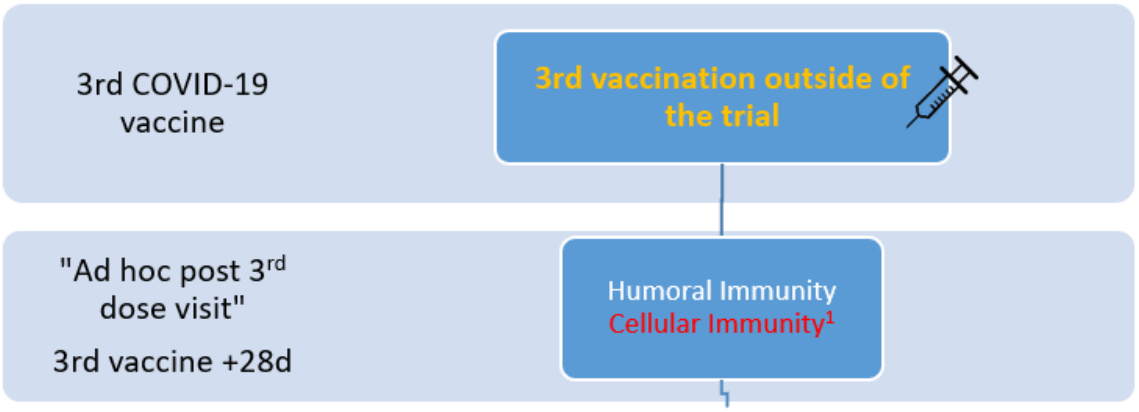
Next to the immunogenicity subset for cellular immunity testing, also a subset of 30 subjects per group were identified for the analysis of more detailed humoral immunity analysis such as the determination of neutralizing antibodies against Delta and Omicron variants at the primary endpoint and against Wuhan and Delta and Omicron variants on the timepoints after the primary endpoint, as well as avidity testing. For the selection of this **humoral immunity subset**, only participants who reached the primary end-point per protocol (i.e. correct visit-windows and no COVID-19 infections as far as we knew at that time based on the adverse event reporting) were eligible. The goal was to select 30 participants per study group such that the groups are comparable in terms of the GMT of antibodies binding to the RBD of SARS-CoV-2 S protein of the Wuhan SARS-CoV-2 virus strain, 28 days post second study vaccine. Priority was given to participants who were allocated to the cellular immunogenicity subset, complemented with the other participants from the trial. Participants of this humoral immunity subset originate from all four study centers.

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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



[1] Subset only

Figure 2: Trial flow chart, ad hoc post 3rd dose visit

8 Methods

8.1 Laboratory measurements

i. Antibodies binding to the RBD of SARS-CoV-2 S protein

Antibody responses at baseline and after vaccination were assessed using an enzyme-linked immunosorbent assay (ELISA) for the quantitative detection of IgG-class antibodies to RBD (Receptor Binding Domain, Wuhan strain)(Wantai SARS-CoV-2 IgG ELISA (Quantitative); CE-marked; WS-1396; Beijing Wantai Biological Pharmacy Enterprise Co., Ltd, China). For quantification of antibodies, diluted serum samples were tested with an internal standard, calibrated against NIBSC 20/136 (First WHO International Standard Anti-SARS-CoV-2 Immunoglobulin), and an external positive control sample included on each plate. Diluted samples were incubated (37°C, 30 min.) with pre-coated micro wells and washed five times. Next, plates were incubated (37°C, 30 min) with horseradish peroxidase (HRP)-conjugated anti-human IgG antibodies and washed five times before adding a TMB and urea peroxide solution for 15 min (37°C, dark). After incubation, a stop solution (0.5 M H2SO4) was added and optical density was measured at 450 nm using a microplate reader. Antibody measurements were adjusted for any sample dilution and converted to Binding Antibody Units/ml (BAU/ml). Lower limit of quantification (LLQ) was 5 BAU/ml. For this test, the manufacturer obtained %CV values of <15% for repeatability (intra-assay precision) and for reproducibility (inter-assay precision). During the in house validation (DOC 15-3-07), %CV values were found to be consistently below 15% for both parameters. In each ELISA-run, a kit-independent external positive control was added, controlling for inter-assay and -batch precision. The value for this external positive control was monitored using QC charts.

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It was foreseen in the protocol to also test all samples for antibodies binding to the RBD of SARS-CoV-2 VOCs. However, due to the high workload and cost of this test, and the rather low added scientific value, it was eventually decided not to perform this test. This was especially the case since resources were scarce, and analyzing labs were totally overloaded with COVID-19 related analysis.

ii. Neutralizing antibodies

We have assessed the levels of neutralising antibodies (nAb) against the original lineage B (Wuhan-Hu-1), Delta (B.1.617.2) and Omicron (B.1.1.529-BA.1 and B.1.1.529-BA.5) variant of concern (VOC) in the eight different study groups. Further in the document, we will refer to these different lineages with the terms 'Wuhan', Delta, Omicron BA.1 and Omicron BA.5 respectively. Delta and Omicron BA.1 were chosen as this were the most relevant VOCs during the course of the trial. Omicron BA.5 was chosen as this was the dominant variant circulation in Belgium during summer 2022, as can be seen in Figure 3 that presents a general update on SARS-CoV-2 genomic surveillance for Belgium[42]. By testing the neutralizing antibody capacity against Omicron BA.5 this could give us insights in the levels of antibodies circulating within the national population one year after first vaccination, with or without BTIs and provide guidance in the need for additional vaccinations.

SARS-CoV-2 neutralizing antibodies were quantified by incubating serial dilutions of heat-inactivated serum (1/50–1/25,600 in EMEM supplemented with 2mM L-glutamine, 100 U/ml–100 µg/ml of Penicillin–Streptomycin and 2% foetal bovine serum) during 1 h (37 °C, 7% CO2) with 3xTCID100 of wild type (WT) lineage B (2019-nCoV-Italy-INMI1, reference 008 V-03893), 83DJ-1 (B.1.617.2, Delta) or VLD20211207 (B.1.1.529, Omicron). One hundred µl of sample-virus mixtures and virus/cell controls were added to 100 µl of Vero cells (18,000 cells/well) in a 96-well plate and incubated for five days (37 °C, 7% CO2). The cytopathic effect (CPE) caused by viral growth was scored microscopically. The Reed–Muench method was used to calculate the nAb titre that reduced the number of infected wells by 50% (NT50), which was used as a proxy for the nAb concentration in the sample[43], [44]. In accordance with WHO guidance, an internal reference standard was included in each nAb assay run. This internal standard was calibrated against the International Standard 21/234 (NIBSC) and NT50 values were recalculated to International Units per ml (IU/ml) for each variant.

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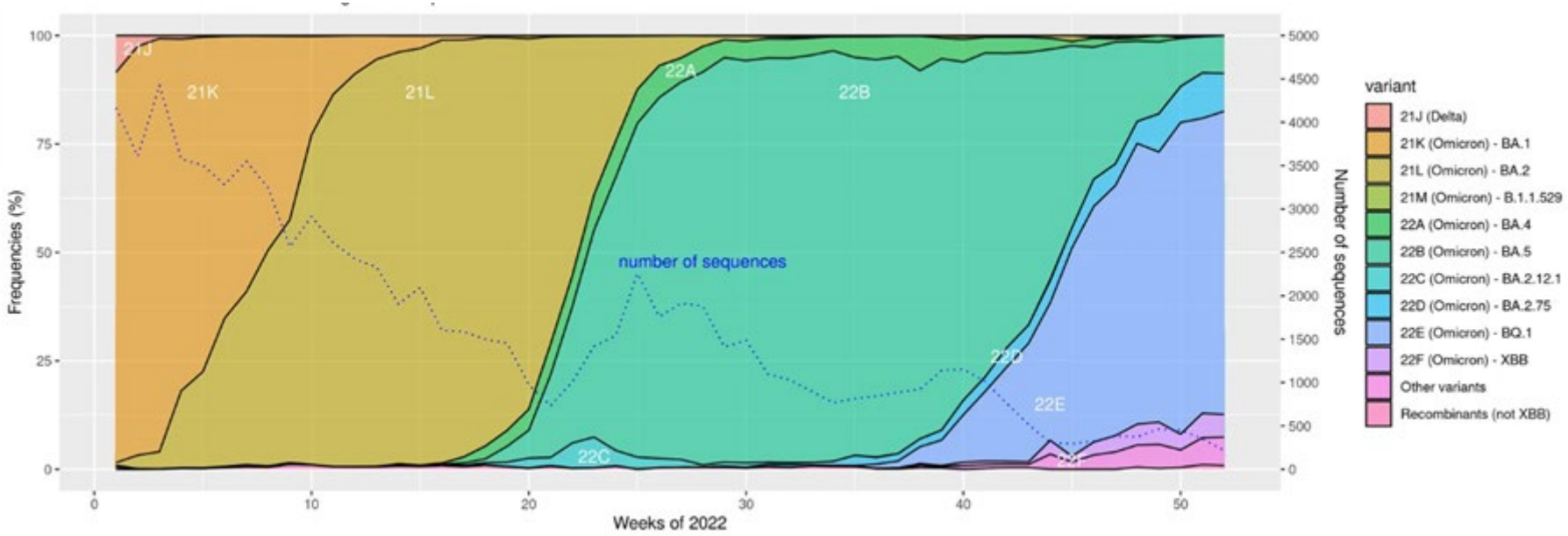


Figure 3: General update on SARS-CoV-2 genomic surveillance for Belgium: Frequency of SARS-CoV-2 variants in Belgium, 1 January 2022 (week 1) to 31 December 2022 (week 52) based on 83733 SARS-CoV-2 whole genome sequences[45]

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iii. Avidity

Antibody avidity reflects the strength of the interaction of polyclonal antibodies with their specific antigen. Antibody avidity is an important parameter which provides information about the quality of the humoral immune response. Indeed, somatic hypermutations which occur in the germinal center during the adaptative immune response is a crucial step which allows to improve the affinity of an antibody to its specific antigen. Thus, to obtain a global view of the humoral immune response, it is important to focus on the polyclonal antibody response and consequently on the antibody avidity which refers to the overall strength of binding between the antigen and antibodies, whereas affinity refers to the binding strength of a single interaction, i.e. for a single epitope.

Biolayer Interferometry (BLI) is a technology which allows to obtain real-time kinetics parameters on the association and dissociation phases of the antibody-antigen interaction without the use of chaotropic agents. Because the dissociation rate (the k_{off}, its unit is 1/second) is concentration independent, it is used to determine the antibody avidity for polyclonal antibodies, for which the concentration of antigen-specific antibodies is unknow among the entire polyclonal antibodies. Thereby, the koff reflects the stability of the antibodies-antigen complex and it is inversely proportional to the stability of the interaction. In this way, a low dissociation of the complex means a high stability of the interaction, and consequently suggests high antibody avidity.

In the analysis done, we measured the koff and calculated the antibody avidity from this as $1/k_{off}$, so this represents the level of stability.

BLI measurements were performed with the Sartorius HTX Octet instrument and Sartorius AR2G biosensors. Data analysis was performed using Sartorius Data Analysis 12.0 software. Kinetic assays were performed at 25-30˚C at a sample plate agitation speed of 1000 rpm. The use of AR2G biosensors involves several steps before kinetic measurements. First, a sensor activation step is performed by immersing the biosensors in a solution containing 20 mM EDC (1-ethyl-3-[3-dimethylaminopropyl] carbodiimide hydrochloride) and 10 mM NHS (n-hydroxysuccinimide). Then, 0.05 mg/ml of RBD antigen (Sanyou Bio; cat# PNA004) in 10 mM sodium acetate pH 6 was loaded for 600 sec onto AR2G sensors. After antigen loading, the biosensors were immersed in a solution of 1 M ethanolamine pH 8.5 to inactivate the remaining sites on the biosensors to prevent possible non-specific interactions. The antigen loaded on AR2G sensors were then immersed in a PBS solution (20 mM pH 7.5) to establish a baseline time curve, and then immersed for 600 sec in wells containing the analytes (polyclonal IgG antibodies purified from serum with the Melon™ gel purification kit (Thermo Scientific™) at different dilutions (diluted in 20 mM PBS pH 7.5) to achieve association. The dissociation step was performed by replating the antibody-bound sensors for 600 sec in the wells used to collect the baseline time course. Two negative controls were performed. A first one where the ligand is loaded and not the analyte, to ensure the correct loading of the antigen. And a second control without ligand and in the presence of analyte to ensure that there is no non-specific interaction between IgG and AR2G biosensors. Because the concentration of anti-RBD antibody is unknown in a polyclonal antibody solution, samples containing purified IgG solutions were analyzed at three dilutions (3x, 5x, and 8x). To monitor variability of the results, diluted samples were not analyzed during the same experiment. Moreover, previous preliminary works were done to verify variability between experiments and no significant differences were observed. Kinetic parameters were determined by global fitting of the association and dissociation phases of the binding curves following a 1:1 binding model.

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iv. COVID-19 infections

SARS-CoV-2 is a Betacoronavirus belonging to the Sarbecovirus subgenus, like SARS-CoV. Coronaviruses have a positive-sense RNA genome of 26–32 kilobases. This genome encodes four structural proteins: Spike (S), Nucleocapsid (N), Envelope (E) and Membrane (M). The most important for protective immunity is the glycoprotein Spike, which forms a trimeric structure on the virus surface and comprises two subunits. Spike subunit 1 (S1) contains the receptor-binding domain (RBD) responsible for binding to the angiotensin-converting enzyme 2 (ACE2) receptor on the host cell, while Spike subunit 2 (S2) permits the fusion of the viral and cellular membranes. Nucleocapsid plays an important role in transcription enhancement and viral assembly[46].

COVID-19 infections can be confirmed in several ways. On the one hand, a current infection in an (a)symptomatic individual can be diagnosed. Reverse transcription polymerase chain reaction (RT-PCR) from naso-oropharyngeal swabs is considered the gold standard for detection of COVID-19[47]. As the COVID-19 pandemic continued around the globe, during the second half of 2021 the antigen rapid diagnostic tests (AgRDTs) (also called point-of-care tests, POC) for SARS-CoV-2 are became also important diagnostic tool[48], allowing individuals to get a faster test result. Ag-RDTs for SARS-CoV-2 aim to detect infection by recognizing viral proteins. Most AgRDTs use specific labeled antibodies attached to a nitrocellulose matrix strip, to capture the virus antigen. Successful binding of the antibodies to the antigen either is detected visually (through the appearance of a line on the matrix strip [lateral flow assay]) or requires a specific reader for fluorescence detection. Microfluidic enzyme-linked immunosorbent assays have also been developed. Ag-RDTs typically provide results within 10 to 30 minutes[49].

On the other hand, COVID-19 infections in the recent past can be diagnosed by looking into the antibody responses of the participants. Measurement of anti-N IgG are being used to distinguish naturally acquired from vaccine-induced immunity, although this is limited by the short duration of anti-N IgG antibodies. In this trial however, given the rather short interval between timepoints for sample collection, the impact of this limitation is rather small. Also an important point to take into account, is the time it takes after infection before the anti-N-antibodies appear in the serum (about 2-3 weeks), so it is possible that when an infection that took place shortly before a study visit, anti_N-IgG was only identified on the blood sample during study visit thereafter.

In this trial we identified anti-N-antibodies in two different ways. To be able to exclude participants with an undiagnosed COVID-19 infection before the study start from the primary endpoint analyses, the antibody responses at baseline were tested with an in house multiplex immunoassay (MIA). The V1-samples of participants with an anti-RBD-IgG level at visit 1 between 5BAU/ml and 50 BAU/ml, were selected for this additional test. In this test, IgG antibodies to SARS-CoV-2 antigens RBD, S1, S2 and N (Wuhan strain) were measured simultaneously in one assay run. In short, purified antigens RBD (cat n° PX-COV-P046, ProteoGenix, Schiltigheim, France), S1 (cat n° PHA002, Sanyou Biopharmaceuticals, China), S2 (cat n° 40590-V08H1, Sino Biological, China) and N (cat n° PNA006, Sanyou Biopharmaceuticals, China) were coupled covalently to distinct color-coded activated carboxylated beads (Luminex, Austin, Texas, USA). Diluted serum samples (1/100, 1/400, 1/1600 and 1/6400, 1/25600) were measured with the international standard (NIBSC 20/136; first WHO International

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Standard Anti-SARS-CoV-2 Immunoglobulin), control sera and blanks included on each plate and MFI was converted to BAU/mL by interpolation from a five-parameter logistic standard curve.

If the result of the anti-RBD-IgG at V1 were below the limit of detection, the sample was classified as seronegative for COVID-19. If the result of the anti-RBD-IgG at V1 were higher than 50 BAU/ml, the sample was classified as seropositive for COVID-19, without additional testing.

During the trial, undiagnosed COVID-19 infections were identified by using an anti-N Elecsys Anti-SARS-CoV-2 immunoassay (Cobas, Roche diagnostics) according to the instructions of the manufacturer. The assay determines the presence of antibodies against a recombinant protein representing the nucleocapsid (N) antigen of SARS-CoV-2 and provides a qualitative outcome (non-reactive versus reactive) indicating the presence or absence of anti-SARS-CoV-2 antibodies in the sample. Note that this assay was used to confirm the exposure to COVID-19, but is not capable of quantifying antibody titers.

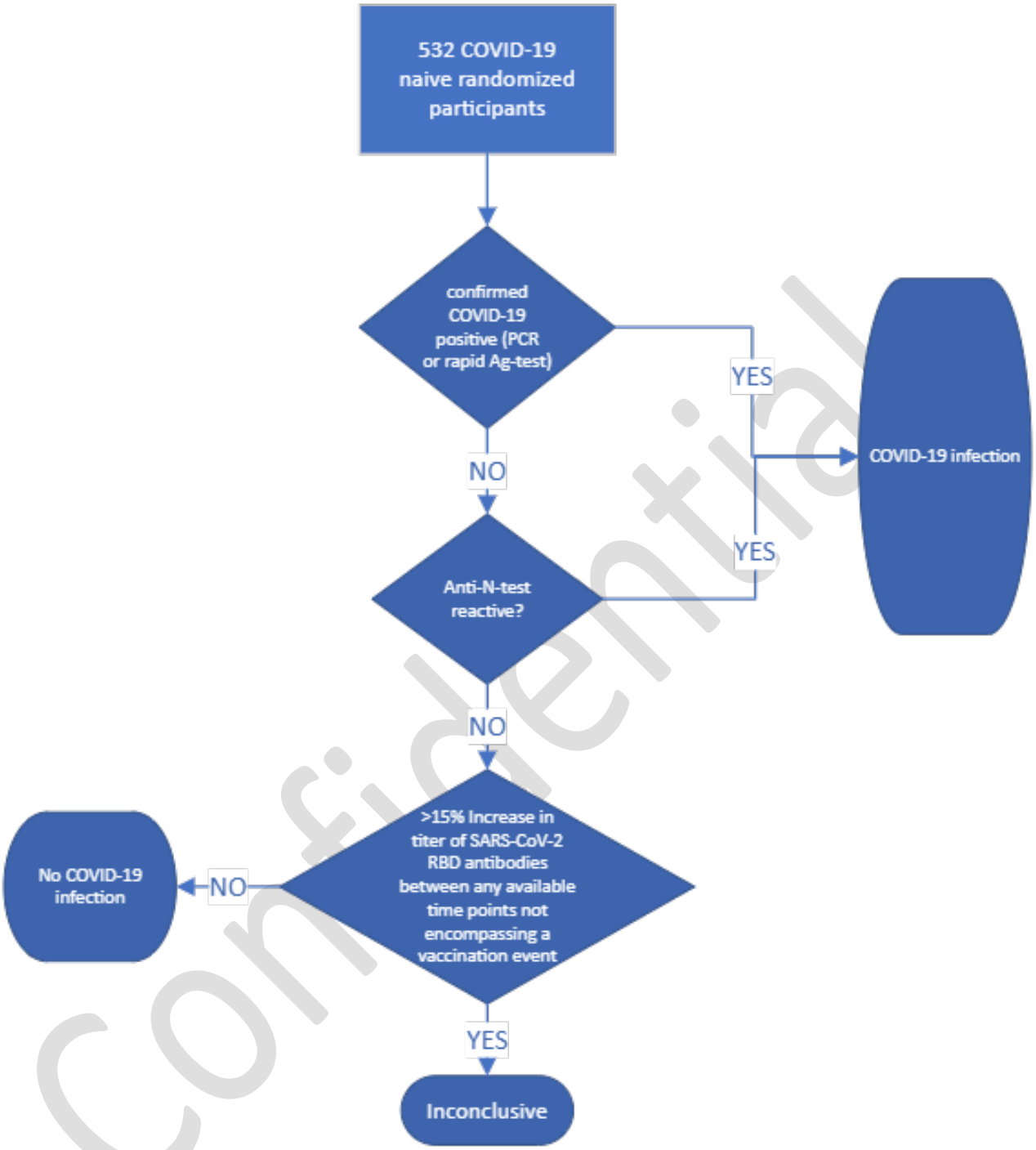
A breakthrough infection (BTI) in this trial is defined as a COVID-19 infection that occurs in a study participant who received a full basic vaccination schedule against COVID-19, this is 2 COVID-19 vaccinations, plus 28days. (in this trial, the visit date of visit 3 (D56) for the short interval groups and visit 4 (D112) for the long interval groups is used as start date for possible BTIs).

In this trial COVID-19 infections were identified using a combination of three parameters.

- First, confirmed COVID-19 infections were reported as adverse events by subjects to study site personnel, those COVID-19 infections were confirmed by either a AgRDT or a RT-PCR-test. Those COVID-19 infections were registered as AESI's (adverse events of special interest) in the eCFR. As start date of the infection, either the first day of the symptoms is used or in case of asymptomatic positive test, the date of the test is used.
- Secondly, at the end of the trial the collected samples of all participants, all study timepoints, were analyzed by using an anti-N Elecsys Anti-SARS-CoV-2 immunoassay. When positive for anti-N, the first visit on which the test became positive was used as the moment of infection, unless an infection before this visit was also reported by the participant as described in the first point, then the exact start date of the infection was used.
- Finally, when despite no AE-reporting and the anti-N Elecsys Anti-SARS-CoV-2 immunoassay being negative, an increase was observed of 15% or more in RBD antibody titers between subsequent visits not encompassing a vaccination, those results were classified as 'inconclusive' with regard to a possible BTI. *This cut-off was used because for the anti-RBD IgG ELISA, used in the present study, the manufacturer obtained %CV values of <15% for repeatability (intra-assay precision) and for reproducibility (inter-assay precision). During the in house validation, %CV values were found to be consistently below 15% for both parameters. With this knowledge at hand, it was estimated that an increase of anti-RBD IgG between two time points was meaningful if exceeding 15%.*

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This methodology is shown in



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Figure 4.

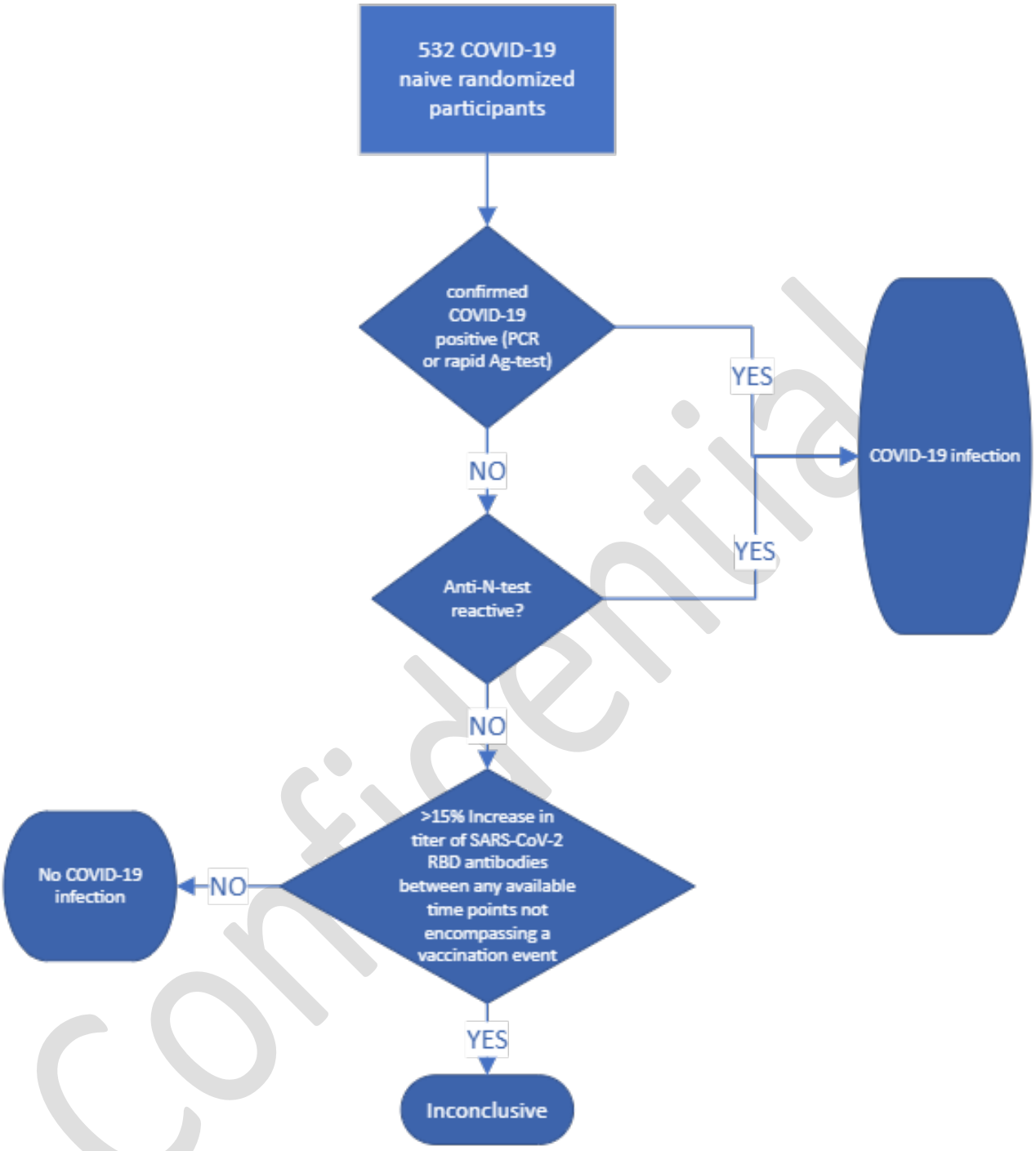


Figure 4: Identification of COVID-19 infections after visit 1

8.2 Safety

i. Adverse events

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

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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)), and medically attended adverse events (MAAE).

(a) Solicited Injection Site (Local) Adverse Events

Subjects were asked to note in a 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 were measured and recorded daily.

Event that are asked for:

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

(b) Solicited Systemic Adverse Events

Subjects were instructed on how to record daily temperature using a thermometer provided for home use. Subject recorded the temperature diary starting from 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 were 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

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- 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.

(c) 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)), 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 the dates when meeting the serious criteria.

Unsolicited AEs that happened in the 14days after vaccination and solicited AEs were collected via an eDiary after vaccination 1. Due to technical complexities, it was not in all cases straightforward to link the correct eDiary entries to the correct participants and this turned out to be very time consuming. To make sure all safety data of the participant would be timely available after second vaccinations, it was decided to capture information from participants diaries into a paper diary instead of electronically after vaccination 2.

AESIs, MAAEs and SAEs were collected by the sites throughout the trial when the participant notified the investigator. All reportable events were entered in the eCRF and were processed after database lock into MEDRA-terms.

8.3 Health economics

To assess the impact of all different vaccination schedules on productivity, participants were asked to provide information regarding absenteeism from work within five days after the first and second study vaccination.

First, they were asked whether they have a job, only paid work was included in this evaluation. If the participant answered positive on the first question, it was established whether the subject had to work on that specific diary day, and if so, whether the side effects from the vaccine made going to work possible or not. For those participants who were not required to go to work on a particular day, they were asked if it would have been feasible for them to go to work if it had been necessary.

9 Statistical Analysis

9.1 Study populations

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i. Immune response to the COVID-19 vaccine

The analysis of the humoral immune response against SARS-Cov2 infections of different vaccines schedules was carried out on a ***modified-intention-to-treat*** (mITT) population.

- For the evaluation of the humoral immune response at the **primary endpoint visit** (visit 3 (D56) for the short interval groups and visit 4 (D112) for the long interval groups) the mITT population comprised eligible participants who where still in the study at the primary endpoint visit, who were seronegative for COVID-19 at baseline, had received both study vaccines, did not receive a vaccine outside the study 14 days after each study vaccination, did not receive a COVID-19 vaccine outside the study, and had not been identified with a COVID-19 infection before or on the primary endpoint evaluation visit.

- For the evaluation of the humoral immune response at ***visits after the primary endpoint visit*** the mITT population comprised those participants of the mITT population for the primary endpoint evaluation; but responses (bAb, nAb, and avidity) collected from visits after a participant received a subsequent COVID-19 vaccination outside the study other than the vaccine registered at the ad hoc post 3rd dose visit or experienced a breakthrough infection, are not included in the statistical analyses. For example, if a participant experienced a breakthrough infection between visit 4 and visit 5, then the responses observed at visits 5, ad hoc post 3rd dose visit and visit 6 are be treated as to missing. A similar approach is be followed in case the conclusion about a possible BTI was unclear (see 'inconclusive results' in Figure 4).

In addition to the mITT analyses also a ***per-protocol*** analysis is conducted.

- The per-protocol population at the ***primary endpoint visit*** consists of participants included in the modified-intention-to-treat population for whom the visits took place within the foreseen time window specified in the protocol.
- The per-protocol population ***28 days post 3rd study vaccine*** consists of participants included in the modified-intention-to-treat population (see above) for this visit for whom the ad hoc post 3rd dose visit took place within the foreseen time window specified in the protocol.

ii. Levels of antibodies after 3 vaccines, comparing COVID-19 infected and non-infected participants

The antibody levels (RBD-Ab and nAb) at the ad hoc post-3rd dose visit and D364-visit between participants with and without a COVID-19 infection (during the study) who received three COVID-19 vaccines within the study are also studyied. This comparison is restricted to the participants of the mITT primary endpoint population who received three COVID-19 vaccinations as described in the study protocol and no other COVID-19 vaccine outside of it. Their levels of RBD-Ab and nAb collected at the last two study visits were used for this comparison. It is worth noting this analysis differs (in how COVID-19 infected participants are dealt with) from the one used to assess the humoral immune

response reaction to the vaccine, as those analyses excluded participants with a COVID-19 infection prior to the study visit.

9.2 Participant's baseline characteristics

Descriptive summaries of age, gender, and race are provided for all participants in the modified-intention-to-treat population, stratified by study arm. Baseline differences between different schedules are assessed using a chi-square test (or Fisher's exact test) for categorical variables, and an ANOVA model (or Kruskal-Wallis test) for continuous variables.

9.3 Antibodies binding to the RBD of SARS-CoV-2 S protein

i. Descriptive statistics

Descriptive statistics of the observed IgG values (antibodies binding to the RBD of SARS-CoV-2 S protein) are presented for the modified-intention-to-treat population, and per randomisation group and visit.

ii. Primary objective: non-inferiority of adapted schedules compared to reference schedule in IgG levels 28 days post second vaccine

Assessment of non-inferiority of the humoral immune response against SARS-CoV2 infection of different vaccines and adapted vaccine schedules in comparison with the reference schedule, 28 days post 2nd vaccine dose is performed using linear mixed models.

A logarithmic transformation (base 10) is applied to the antibodies binding to the RBD of SARS-CoV-2 S protein. For each prime dose group separately (Pfizer groups 1a, 1b, 1c, 1d, 1e, 1f and Moderna groups 3a, 3b), a linear mixed model is fitted to the $\log_{10}$-IgG data. The data at 28 days post second study vaccine are used; for the short interval groups this is visit 3 and for the long interval group this is visit 4. The model includes age (continuous), gender and study group as fixed factors, and study site as a random factor. By incorporating age and gender as explanatory variables in the model, age/gender imbalances between groups are corrected for.

Based on this model, age and gender adjusted geometric mean titres are obtained, and presented with 95% two-sided confidence intervals.

The geometric mean ratio, obtained by applying the antilog on the mean difference (adapted schedule – standard schedule) of $\log_{10}$-IgG for each comparison is presented with a 97.5% (FWER at the level of prime dose group) one-sided confidence interval. A Bonferroni correction (at level of the prime dose) is used to control the Type I error. This implies that 99.5% one-sided CI intervals are presented for the Pfizer prime dose comparisons, and a 97.5% CI interval for the Moderna comparison.

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Non-inferiority of the adapted schedule compared to the standard schedule is claimed if the lower limit of the confidence interval of the geometric mean ratio lies above 0.63. Inferiority of the adapted schedule compared to the reference schedule is claimed if the upper limit of the confidence interval of the geometric mean ratio lies below 0.63. An inconclusive result, presented as 'not non-inferior', is claimed if the confidence interval of the geometric mean ratio includes a ratio of 0.63, which represents the non-inferiority margin.

The given p-values are for one-sided (upper) tests. For the Moderna comparison a p-value < 0.025 implies non-inferiority, for the Pfizer comparisons a p-value < 0.005 implies non-inferiority.

The primary analysis is conducted on the modified-intention-to-treat population. As a sensitivity analysis, the model is also applied to the per-protocol-population.

iii. Non-inferiority of adapted schedules compared to reference schedule in IgG levels 28 days post 3rd dose

Assessment of non-inferiority of the humoral immune response against SARS-CoV2 infection of different vaccines and adapted vaccine schedules in comparison with the reference schedule, 28 days post 3rd vaccine is performed using the linear mixed models described in Section 9.3.ii. However, the following two modifications are made:

- The data collected at 28 days post third COVID-19 vaccine (i.e., ad hoc post 3rd dose visit) is used.
- The model includes fixed factors for the brand and dose of the third COVID-19 vaccine in addition to age, gender and study group.

The analysis is conducted on the modified-intention-to-treat population, as defined in Section 9.1, for visits after the primary endpoint evaluation.

As a sensitivity analysis, the model is also fitted to the data, excluding visits that took place out-of-window (not within 28 +/- 5 days after the third vaccine, n=82). A reason why this number of ad hoc post 3rd dose visits that took place out-of-window is very high, is due to the accelerated roll-out of the administration of the 3rd dose COVID-19 vaccine via the national vaccination campaign in December 2021-January 2022 and the delayed approval for protocol amendment 3, as explained in "Rationale, study timing and amendments in a pandemic setting" . The earliest ad hoc post 3rd dose visit could therefore only take place on 24 Jan 2022, whereas the earliest 3rd COVID-19 vaccine was already administered on 02DEC2021. The latest dose of a 3rd COVID-19 vaccine that was still included in the analysis 28 days post 3rd vaccine, was administered on 09MAR2023.

Due to the smaller sample size for this secondary objective, it is expected that the confidence interval of the GMR will be wider than that of the primary objective. Also note that no power calculations were conducted for this objective, as a result, the study may be underpowered to evaluate non-inferiority.

iv. IgG levels of the 8 study groups, average evolution till visit 5 (D182)

A repeated measurement model is fitted to the log_{10}-IgGdata of visits 2, 3, 4 and 5; including both prime dose group (Pfizer groups 1a, 1b, 1c, 1d, 1e, 1f and Moderna groups 3a, 3b). The model includes age (continuous), gender and study group as fixed factors. An unstructured variance covariance matrix for the residuals is used to allow for correlation between the different IgG values of the same participant. By incorporating age and gender as explanatory variables in the model, age/gender imbalances between groups are corrected for.

Based on this model, age and gender adjusted geometric mean titres are obtained for the study groups at the different visits, and presented with 95% two-sided confidence intervals.

At each visit, the comparisons between (1) an adapted schedule and the standard schedule of the prime dose group and (2) the two standard schedules are made. The geometric mean ratio, obtained by applying the antilog on the mean difference (adapted schedule – standard schedule) of log_{10}GMT for each comparison is presented with a 95% two-sided confidence interval and a two-sided p value. No correction for multiple testing was implemented.

The analysis is conducted on the modified-intention-to-treat population, as defined in Section 9.1.

v. Changes in IgG level, 28 days post vaccination versus vaccination

For each participant, the change in log_{10}-IgG, comparing the level at the time of vaccination with those at 28 days post vaccination, is obtained. As for the 3rd COVID-19 vaccine dose, no sample of the day of vaccination is available, the sample of V5, D182 is used as this visit happened the closest before the 3rd COVID-19 vaccination. Thus, the following changes in log_{10}-IgG are evaluated for the two cohort groups.

So, for the short cohort groups:

- visit 2 (D28) – visit 1 (D0)
- visit 3 (D56) – visit 2 (D28)
- Ad hoc post 3rd dose visit – visit 5 (D182)

and for the long cohort group:

- visit 2 (D28) – visit 1 (D0)
- visit 4 (D112) – visit 3 (D84)
- Ad hoc post 3rd dose visit – visit 5 (D182)

To compare the study groups with respect to the change in log_{10}-IgG, ***28 days post first and second study vaccine***, a linear mixed model is used. Corrections for gender and age (linear) are done by incorporating them as fixed effects, center is included as a fixed effect. The model is fitted to the change 28 days post first and second vaccine separately, and for the Pfizer groups and Moderna together. Using data of the 8 groups together allows for the formal comparison of the two reference groups (1a and 3a).

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To compare the study groups with respect to the change in log_{10}-IgG, ***28 days post third COVID-19 vaccine and D182***, a linear mixed model is used. Corrections for gender and age (linear) were done by incorporating them as fixed effects, center was included as a fixed effect. The brand and dose of the third vaccine is also included in the model as a fixed effect. Based on this model, the 8 study groups will be compared, but also the two brands and 2 doses administered as third vaccine.

Based on these model, adjusted (for age, gender and brand/dose of third vaccine for the change after the third vaccine) mean changes for each study group are obtained, and presented with 95% two-sided confidence intervals. Also, the difference in mean change between two study groups is given together with a 95% CI for this difference and the p value. The change in log_{10}-IgG of the adapted vaccine schedule is compared with the change in log_{10}-IgG of the reference schedule. The changes in log_{10}-IgG of the two reference schedules are also compared. Testing for differences between vaccine schedules was done at a 5% level of significance and no correction for multiple testing was implemented.

These analyses were conducted on the modified-intention-to-treat population.

vi. Comparison of IgG levels of participants with and without COVID-19 breakthrough infection during the study

A repeated measurement model is utilized to compare the IgG levels of participants who received three vaccinations and had a breakthrough infection after the primary endpoint visit with those who did not experience a breakthrough infection. The measurements taken at the ad hoc post 3rd dose visit and at the final study visit, i.e. visit 6 are used for this purpose.
The model incorporates fixed effects for gender, age, visit, and a factor indicating whether a breakthrough infection had occurred prior to visit 6. An unstructured variance-covariance matrix is applied for the residuals. Using this model, geometric least square means were calculated and used to compare the two groups (those who previously had a breakthrough infection and those who did not).

The analysis is conducted on the population defined in Section 9.1.ii

9.4 Neutralizing antibodies

i. Number of samples analyzed

Wuhan is measured for all participants, Delta and Omicron BA.1 and Omicron BA.5 are only measured for the participants in the humoral immunity subset (n=240). Neutralizing antibodies are available at the primary endpoint visit, the ad hoc post 3rd dose visit and for visit 6 (D364).

ii. International units

For international comparisons, the titers are presented in IU/ml. For participants in the subset, the NT50 was provided in IU/ml by the analyzing lab. For the participants not part of the humoral immunity

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subset, the Wuhan NT50 was re-calculated in IU/ml by multiplying the NT50 by a factor 1.544206053. This calculation was provided and validated by the analyzing lab.

iii. Titer values below the limit of detection

Titer values 'below the limit of detection' (<LOD) are replaced by half of the LOD. The percentage of participants with a titer below the limit of detection for each study group and study visit is presented. Since only a few participants in the humoral immunity subset had detectable titers for Omicron BA.1, the data of Omicron BA.1 is not explored.

iv. Descriptive statistics

Descriptive statistics of the observed nAb values (Wuhan NT50 and Delta NT50), 28 days post second vaccination are presented for the modified-intention-to-treat population, and are presented per randomisation group.

v. Non-inferiority of adapted schedules compared to reference schedule in nAb levels 28 days post second vaccine

Assessment of non-inferiority of Wuhan NT50 and Delta NT50 of different vaccines and adapted vaccine schedules in comparison with the reference schedule, 28 days post 2rd COVID-19 vaccine is performed using the linear mixed models described in Section 9.3.ii.

The analysis is conducted on the subset of the modified-intention-to-treat population, as defined in Section 9.1.

As a sensitivity analysis, the model is also applied to subset of the per-protocol-population.

Due to the smaller sample size for Delta NT50, it is expected that the confidence interval of the GMR will be wider than that of Wuhan NT50. Also note that no power calculations were conducted for this objective, as a result, the study may be underpowered to evaluate non-inferiority of Nab levels 28 days post second study vaccine.

vi. Comparison of study groups for the proportion of participants with detectable nAb titres, 28 days post second vaccine

A significant number of participants had NT50 levels below the limit of detection for Delta and Omicron. To address this issue, these values were imputed by half of the LOD. However, when imputing values for the majority of the observations the statistical models that use these levels as continuous responses should be interpreted with caution.

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Therefore, the variables were transformed into binary variables, nAb levels below and above the LOD. Logistic regression with a Firth correction was used to compare the study groups in terms of the percentage of participants below LOD. Gender and age were adjusted for in the analysis.

vii. Non-inferiority of adapted schedules compared to reference schedule in nAb levels 28 days days post 3rd vaccine

Assessment of non-inferiority 28 days post 3rd COVID-19 vaccine is performed using the linear mixed models described in Section 9.3.ii. However, the following two modifications are made:

- The Wuhan NT50 and Delta NT50 data collected at 28 days post third study vaccine (i.e., ad hoc post 3rd dose visit) are used.
- The model includes fixed factors for the brand and dose of the third vaccine in addition to age, gender and study group.

The analysis is conducted on the subset of the modified-intention-to-treat population, as defined in Section 9.1 , for visits after the primary endpoint evaluation.

As a sensitivity analysis, the model is also fitted to the data, excluding visits that took place out-of window (not within 28 +/- 5 days after the third COVID-19 vaccine)

Due to the smaller sample size for this objective, it is expected that the confidence interval of the GMR will be wide. Also note that no power calculations were conducted for this objective, as a result, the study may be underpowered to evaluate non-inferiority.

viii. Comparison of nAb levels of participants with and without COVID-19 breakthrough infection during the study

A repeated measurement model is utilized to compare the nAb levels of participants who received three vaccinations and had a breakthrough infection after the primary endpoint visit with those who did not experience a BTI. The values measured on the ad hoc post 3rd dose visit and on the final study visit, i.e. visit 6, are used for this purpose.
The model incorporates fixed effects for gender, age, visit, and a factor indicating whether a breakthrough infection had occurred prior to visit 6. An unstructured variance-covariance matrix is applied for the residuals. Using this model, geometric least square means were calculated and used to compare the two groups (those who previously had a breakthrough infection and those who did not).

The analysis is conducted on the population defined in Section 9.1.ii, “Levels of antibodies after 3 vaccines, comparing COVID-19 infected and non-infected participants”

ix. Conversion factors: neutralizing and receptor binding antibodies

For each participant the following ratios (note that these are ratios of the $\log_{10}$ transformed values) are calculated

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- RATIO_WH_NT50_IU_IgG_log10 = WUHAN_NT50_IU_log10/IgG_log10
- RATIO_DE_NT50_IU_IgG_log10 = DELTA_NT50_IU_log10/IgG_log10
- RATIO_DE_WU_IU_NT50_log10 = DELTA_NT50_IU_log10/WUHAN_NT50_IU_log10

Due to a high proportion of participants in study groups 1C and 1F having Delta NT50 levels below the limit of detection, the ratios involving Delta NT50 are not calculated for these groups. Moreover, the statistical analyses for the conversion factor related to Delta NT50 are limited to participants who have measurable Delta NT50 levels.

A linear mixed model is used to formally test whether there is a significant difference in the average conversion factor across the 8 groups. The model incorporated a fixed treatment effect (i.e., 8 groups) and a random center effect.

9.5 Avidity

i. Number of samples analyzed

Based on the preliminary results of the primary endpoint analysis of the RBD and Nab, and the conversion factor observed from it, it was decided that the avidity analysis would focuse on group 1e (Pfizer long interval scheme). During visits 2, 3, and 4, avidity results were obtained for all participants in groups 1a (Pfizer regular scheme) and 1e (Pfizer long interval scheme), as well as for the participants of the subsets from all study groups. Laboratory results were excluded for participants who had experienced a COVID-19 infection or received a COVID-19 vaccination outside of the study prior to this timepoint.

ii. Descriptive statistics

Descriptive statistics of the observed avidity values (in seconds) and log10 transformed avidity values are provided per randomisation group and visit. Statistics are presented for the modified-intention-to-treat population.

iii. Comparison of adapted schedules compared to reference schedule in avidity 28 days post second vaccine

Assessment of differences in avidity of different vaccines and adapted vaccine schedules in comparison with the reference schedule, 28 days post 2nd COVID-19 vaccine is performed using the linear mixed models described in Section 9.3.ii, but no corrections for multiple testing were implemented.

The analysis is conducted on data described in Section 9.5.i; as a sensitivity analysis, the model is also applied to the data excluding the participants having out-of-window visits (i.e. not belonging to the per-protocol-population).

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iv. Avidity of the 8 study groups, average evolution till visit 4 (D112)

A repeated measurement model is fitted to the log_{10}-avidity data of visits 2, 3, and 4; including all study groups (Pfizer groups 1a, 1b, 1c, 1d, 1e, 1f and Moderna groups 3a, 3b). The model includes age (continuous), gender and study group as fixed factors. An unstructured variance covariance matrix for the residuals is used to allow for correlation between the different avidity values of the same participant. By incorporating age and gender as explanatory variables in the model, age/gender imbalances between groups are corrected for.

Based on this model, age and gender adjusted geometric means are obtained for the study groups at the different visits, and presented with 95% two-sided confidence intervals.

At each visit, the comparisons between (1) an adapted schedule and the standard schedule of the prime dose group and (2) the two standard schedules are made. The geometric mean ratio, obtained by applying the antilog on the mean difference (adapted schedule – standard schedule) of log_{10} avidity for each comparison is presented with a 95% two-sided confidence interval and a two-sided p value. No correction for multiple testing was implemented.
The analysis is conducted on the data described in Section 9.5.i

v. Changes in avidity, 28 days post second vaccination versus vaccination

For each participant, the change in log_{10}-avidity, comparing the avidity at the time of second vaccination with those 28 days post second vaccination, is obtained. In addition, in the log_{10}-avidity difference between visit 4 and visit 3 is assessed for the short interval groups (excluding group 1e (Pfizer long interval scheme)). Thus, the following changes in log_{10}-avidity are evaluated:

So, for the short interval groups:

- visit 3 – visit 2
- visit 4 – visit 3.

and for the long interval group:

- visit 4 – visit 3

To compare the study groups with respect to these change in log_{10}-avidity a linear mixed model is used. Corrections for gender and age (linear) are done by incorporating them as fixed effects, center is included as a random effect. The model is fitted to the change 28 days post second vaccine and the change at visit 4 versus visit 3 separately, and for the Pfizer groups and Moderna together. Using data of the 8 groups together allows for the formal comparison of the two reference groups (1a and 3a).
Based on these models, adjusted (for age, gender) mean changes for each study group are obtained, and presented with 95% two-sided confidence intervals. Also, the difference in mean change between two study groups is given together with a 95% CI for this difference and the p value. The change in log_{10}-avidity of the adapted vaccine schedule is compared with the change in log_{10}-avidity of the reference schedule. The changes in log_{10}-avidity of the two reference schedules are also compared. Testing for differences between vaccine schedules was done at a 5% level of significance and no correction for multiple testing was implemented.

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The analysis is conducted on data described in Section 9.5.i

9.6 COVID-19 infections

i. Total amount of break through infections

The number of participants of the mITT population, experiencing a breakthrough infection after the primary endpoint evaluation is presented per study group. Information is provided on the time of breakthrough infection and the method used to determine the BTI (AE reported by participant or anti-N test).

ii. Covid-19 infections as reported by the participant

The number of participants of the mITT population reporting a COVID-19 infection after the primary endpoint evaluation, are given per study group. Information is provide on the time of infection.

9.7 Safety

The results presented in this section are obtained by analyzing the AEs as reported in the eCRF.

i. Adverse events reported by the eligible participants

Provided is a table summarizing all adverse events that were reported during the study, based on the 566 ***eligible participants***. The table includes the following information: the total number of adverse events, the number of eligible participants who experienced at least one adverse event, the severity of the adverse events and their relationship to the treatment, as well as the number of adverse events that required medical attention, the number of adverse events of special interest, and the number of serious adverse events.

ii. COVID-19 infections (as reported by the participant) – mITT population

COVID-19 infections were classified in the protocol as adverse events of special interest (AESIs) and required to be reported throughout the study period. A table containing information about the reported COVID-19 infections is provided for the 506 participants in the ***modified-intention-to-treat*** (mITT) population. This table includes the total number of reported COVID-19 infections, the number of mITT participants who experienced at least one COVID-19 infection after receiving the second vaccine dose, the severity of the infection, and its relationship to the treatment. Additionally, the table presents the number of COVID-19 infections that required medical attention and the number of serious adverse events.

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A graph is provided to illustrate the infection rate over the course of the study, showing the cumulative number of COVID-19 infections since a participants' baseline visit (D1).

iii. Solicited and unsolicited AEs reported after 1st and 2nd study vaccination

For the ***mITT population***, the number of solicited (local of systemic) and unsolicited AEs reported after 1st and 2nd study vaccination and the percentage of participants experiencing at least one of these AEs is presented. The number and percentage of participants who experienced at least one AE of a specific type are tabulated. Information of the type of AE (PT term), the severity, relationship to treatment, MAAE, AESI and SAE are provided.

Graphical representation of the severity of the solicited AEs is also provided, depicting the percentage of participants who experienced at least one adverse event categorized by treatment group and severity. If a participant encountered multiple adverse events of the same type, only the most severe event is considered.

9.8 Health economics

An indicator is created to assess the impact of different vaccination schedules on productivity. This indicator is based on three questions from the eCRF and determines whether the participant missed a day of work or would have missed a day in the days following the vaccination. The indicator only applies to participants who were employed at the time of completing the questionnaire.

The percentage of participants who missed at least one day of work is presented for each study group, and for the first and second vaccination separately.

To formally compare the eight groups, a logistic mixed model is used, with fixed effects for gender and age. The study center was included as a random effect, or as a fixed effect if non-convergence occurred.

For these analyses, only participants in the mITT population who have paid work are included.

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10 Trial results

10.1 Participants and populations

i. Inclusion rate

A total of 580 participants were screened for the trial after signing ICF. A total of 14 individuals were deemed ineligible to partake in the IMCOVAS trial. Of this group, 8 failed to meet the inclusion criteria while 7 met one of the exclusion criteria. These screen failure criteria are listed in Table 2**Fout! Verwijzingsbron niet gevonden.**.

Table 2: Screen failure criteria

in/excl	Criterium	N
Incl 1	Male, female, or X (non-binary gender) subjects, 18-55y inclusive on the day of signing of the ICF	1
Incl 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.	1
Incl 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.	4
Incl 5	Willing and able to comply with all study procedures	1
Excl 3	Unstable, severe, progressive disease in the past 3 months.	2
Excl 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').	1
Excl 7	Primary or secondary immunodeficiency disorders (e.g. immunosuppressive disease or therapy, human immunodeficiency virus (HIV) infection…).	2
Excl 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.	1
Excl 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.	1

This implies a total of 566 eligible participants, as shown in Table 3.

Table 3: Total participants randomized in each treatment arm

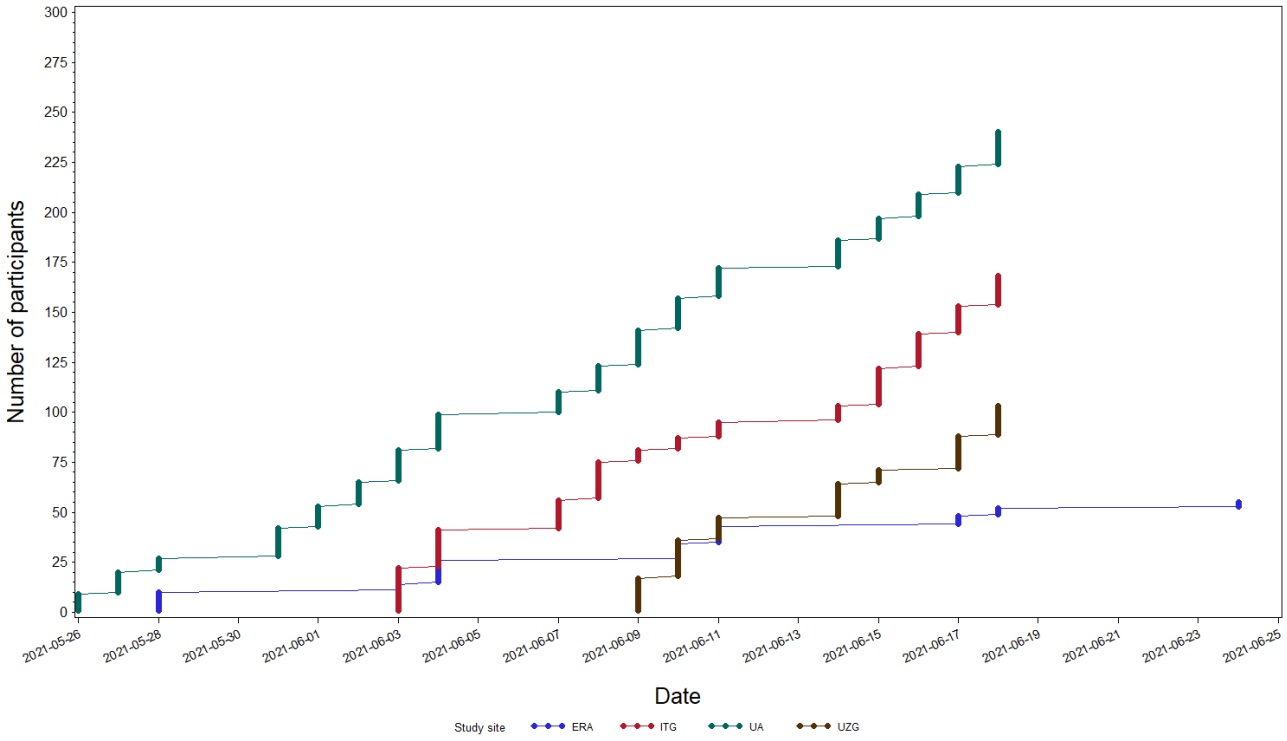
1a = 'Pfizer regular scheme'; 1b = 'Pfizer-Moderna scheme'; 1c ='Pfizer-AstraZeneca scheme'; 1d='Pfizer low dose scheme'; 1e = 'Pfizer long interval scheme'; 1f= 'Pfizer intradermal scheme'; 3a='Moderna regular scheme'; 3b='Moderna low dose scheme'

Randomisation group	Number of eligible participants (%)
1a Pfizer + Pfizer	67 (11.84%)
1b Pfizer + Moderna	77 (13.60%)
1c Pfizer + AstraZeneca	63 (11.13%)
1d Pfizer + Pfizer (low dose)	72 (12.72%)
1e Pfizer + Pfizer (long interval)	72 (12.72%)
1f Pfizer + Pfizer (intradermal)	72 (12.72%)
3a Moderna + Moderna	70 (12.37%)
3b Moderna + Moderna (low dose)	73 (12.90%)
Total	566 (100.00%)

Participant recruitment started on 26th of May 2021 By the 9th of June 2021 all 4 study sites across Belgium where recruiting participants. The final participant was included on 24th of June 2021. In total, 240 participants (42%) were included at the University of Antwerp, 168 (30%) at the Institute of Tropical Medicine Antwerp, 103 (18%) at the University Hospital of Ghent and 55 (10%) at the Erasmus Hospital in Brussels. As expected, based on the randomized design, inclusion rates of participants were similar across the different treatment arms (Figure 5, Figure 6).

Figure 5: Inclusion rate per study center of eligible participants

ERA = Hôpital Erasme; ITG = Institute of Tropical Medicine; UA = University of Antwerp, Centre for the Evaluation of Vaccination (CEV); UZG = University Hospital Ghent, Centre for Vaccinology

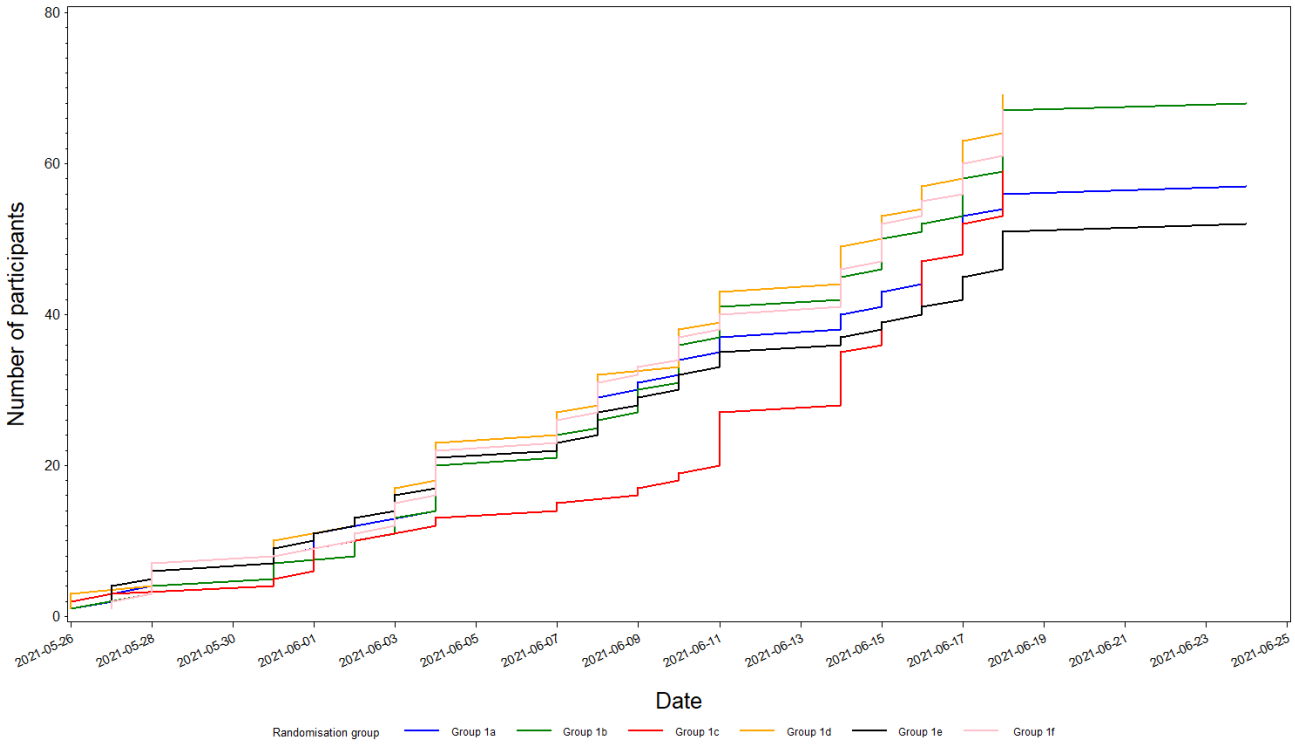


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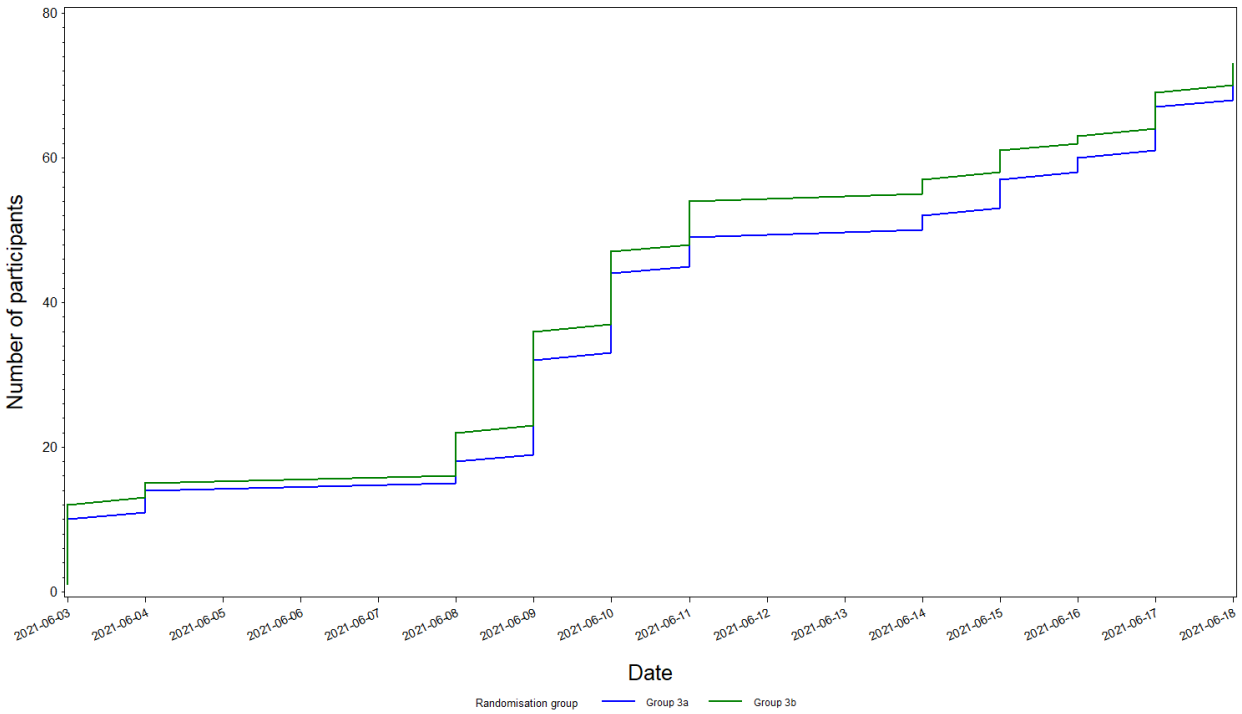
Figure 6: Inclusion rate per study group of eligible participants

1a = 'Pfizer regular scheme'; 1b = 'Pfizer-Moderna scheme'; 1c ='Pfizer-AstraZeneca scheme'; 1d='Pfizer low dose scheme'; 1e = 'Pfizer long interval scheme'; 1f= 'Pfizer intradermal scheme'; 3a='Moderna regular scheme'; 3b='Moderna low dose scheme'

a) Pfizer prime dose group



b)Moderna prime dose groups



10.2 Populations for the primary endpoint analyses

Of the 566 eligible participants, 34 (6.01%) were classified as **seropositive for COVID-19 at visit 1** (Table 4). Collected data for these subjects is excluded from all statistical analyses.

Furthermore, an additional 26 participants (4.42% of the eligible study population) were excluded from the analyses of the primary endpoint because of the following reasons:

- Leaving the study before the evaluation of the primary endpoint (visit 3 (day 56) for the short interval groups and visit 4 (day 112) for the long interval group) (n=12).
- Not receiving two study vaccines (n=17).
- Receiving a COVID-19 vaccine outside the study before the evaluation of the primary endpoint (n=7).
- Receiving a vaccine outside the study 14 days before or within 14 days after each study vaccination (28 days for live attenuated vaccines) (n=1).
- Experiencing a COVID-19 infection before the evaluation of the primary endpoint (n=6). For these 6 participants who experienced a COVID-19 infection before the evaluation of the PE, Table 5 shows whether the decision with respect to a COVID-19 infection was based on the COVID AE reported by the participant, the anti-N test or both. The basis for the decision is marked in bold.

Table 4: Seropositivity at baseline (eligible participants)

1a = 'Pfizer regular scheme'; 1b = 'Pfizer-Moderna scheme'; 1c ='Pfizer-AstraZeneca scheme'; 1d='Pfizer low dose scheme'; 1e = 'Pfizer long interval scheme'; 1f= 'Pfizer intradermal scheme'; 3a='Moderna regular scheme'; 3b='Moderna low dose scheme'

	Seropositivity at baseline				Total
	seronegative		seropositive		
	N	%	N	%	N
Randomisation Group					
Group 1a	58	86.57	9	13.43	67
Group 1b	71	92.21	6	7.79	77
Group 1c	62	98.41	1	1.59	63
Group 1d	70	97.22	2	2.78	72
Group 1e	66	91.67	6	8.33	72
Group 1f	70	97.22	2	2.78	72
Group 3a	67	95.71	3	4.29	70
Group 3b	68	93.15	5	6.85	73
Total	532	93.99	34	6.01	566

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Table 5: Identification of COVID-19 infections before or on the evaluation of the primary endpoint

1a = 'Pfizer regular scheme'; 1b = 'Pfizer-Moderna scheme'; 1c ='Pfizer-AstraZeneca scheme'; 1d='Pfizer low dose scheme'; 1e = 'Pfizer long interval scheme'; 1f= 'Pfizer intradermal scheme'; 3a='Moderna regular scheme'; 3b='Moderna low dose scheme'

Randomisation Group	Visit impacted by the COVID-19 infection	Reported COVID-19 AE	Anti N test reactive
Group 1a	V2		**V2**
Group 1e	V4	**V4**	V6
Group 1e	V3		**V3**
Group 1e	V3	**V3**	**V3**
Group 1e	V3	**V3**	V4
Group 1f	V2	**V2**	**V2**

Table 6: Eligible seronegative participants excluded from the modified-intention-to-treat population

1a = 'Pfizer regular scheme'; 1b = 'Pfizer-Moderna scheme'; 1c ='Pfizer-AstraZeneca scheme'; 1d='Pfizer low dose scheme'; 1e = 'Pfizer long interval scheme'; 1f= 'Pfizer intradermal scheme'; 3a='Moderna regular scheme'; 3b='Moderna low dose scheme'

Randomisation group	Dropout before PE				Two study vaccins in the trial				COVID-19 vaccine or other vaccin outside study				Other vaccine within 14days before or after study-vaccine				BTI before PE				Total
	No		Yes		Yes		No		No		Yes		No		Yes		No		Yes		
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N
Group 1a	58	100.0	.	.	58	100.0	.	.	58	100.0	.	.	58	100.0	.	.	57	98.3	1	1.7	58
Group 1b	69	97.2	2	2.8	70	98.6	1	1.4	71	100.0	.	.	71	100.0	.	.	71	100.0	.	.	71
Group 1c	60	96.8	2	3.2	60	96.8	2	3.2	61	98.4	1	1.6	62	100.0			62	100.0	.	.	62
Group 1d	70	100.0	.	.	70	100.0	.	.	70	100.0			69	98.6	1	1.4	70	100.0	.	.	70
Group 1e	60	90.9	6	9.1	55	83.3	11	16.7	62	93.9	4	6.1	66	100.0			62	93.9	4	6.1	66
Group 1f	69	98.6	1	1.4	68	97.1	2	2.9	69	98.6	1	1.4	70	100.0			69	98.6	1	1.4	70
Group 3a	66	98.5	1	1.5	66	98.5	1	1.5	66	98.5	1	1.5	67	100.0			67	100.0	.	.	67
Group 3b	68	100.0	.	.	68	100.0	.	.	68	100.0	.	.	68	100.0	.	.	68	100.0	.	.	68
Total	520	97.7	12	2.3	515	96.8	17	3.2	525	98.7	7	1.3	524	99.8	1	0.2	526	98.9	6	1.1	532

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Table 7: modified-intention-to-treat population per study center

1a = 'Pfizer regular scheme'; 1b = 'Pfizer-Moderna scheme'; 1c ='Pfizer-AstraZeneca scheme'; 1d='Pfizer low dose scheme'; 1e = 'Pfizer long interval scheme'; 1f= 'Pfizer intradermal scheme'; 3a='Moderna regular scheme'; 3b='Moderna low dose scheme' ERA = Hôpital Erasme; ITG = Institute of Tropical Medicine; UA = University of Antwerp, Centre for the Evaluation of Vaccination (CEV); UZG = University Hospital Ghent, Centre for Vaccinology

	Study site								Total	
	ERA		ITG		UA		UZG			
	N	%	N	%	N	%	N	%	N	%
Randomisation Group										
Group 1a	7	12.28	22	38.60	20	35.09	8	14.04	57	100.00
Group 1b	7	10.29	20	29.41	25	36.76	16	23.53	68	100.00
Group 1c	.	.	13	22.03	41	69.49	5	8.47	59	100.00
Group 1d	8	11.59	20	28.99	28	40.58	13	18.84	69	100.00
Group 1e	7	13.46	15	28.85	21	40.38	9	17.31	52	100.00
Group 1f	10	14.93	20	29.85	22	32.84	15	22.39	67	100.00
Group 3a	3	4.55	17	25.76	33	50.00	13	19.70	66	100.00
Group 3b	3	4.41	21	30.88	30	44.12	14	20.59	68	100.00
Total	45	8.89	148	29.25	220	43.48	93	18.38	506	100.00

Table 8: Distribution of the participants per analyzed population

1a = 'Pfizer regular scheme'; 1b = 'Pfizer-Moderna scheme'; 1c ='Pfizer-AstraZeneca scheme'; 1d='Pfizer low dose scheme'; 1e = 'Pfizer long interval scheme'; 1f= 'Pfizer intradermal scheme'; 3a='Moderna regular scheme'; 3b='Moderna low dose scheme'

	Modified IIT population		Per protocol population			
	Included		Excluded		Included	
	N	%	N	%	N	%
Randomisation Group						
Group 1a	57	100.00	1	1.75	56	98.25
Group 1b	68	100.00	6	8.82	62	91.18
Group 1c	59	100.00	1	1.69	58	98.31
Group 1d	69	100.00	5	7.25	64	92.75
Group 1e	52	100.00	4	7.69	48	92.31
Group 1f	67	100.00	4	5.97	63	94.03
Group 3a	66	100.00	4	6.06	62	93.94
Group 3b	68	100.00	4	5.88	64	94.12
Total	506	100.00	29	5.73	477	94.27

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10.3 Participants' baseline characteristics

Participant's characteristics are given in Table 9 and Table 10. In the 2 treatment arms encompassing the Moderna vaccinations, gender (p = 0.8566), race (p = 0.7130) and age (p = 0.2058) did not differ. In the 6 treatment arms encompassing the Pfizer vaccinations, gender (p = 0.8566) and race (p = 0.6764) were similar between groups. Because of safety concerns, only participants > 40 years could be randomized to the Pfizer + AstraZeneca (1c) treatment arm, resulting in a higher mean age in this group. Excluding this group, age did not differ between the other 5 treatments arms (p = 0.7734).

At baseline, IgG antibodies binding to the RBD of the SARS-CoV-2 S protein were above the limit of detection (5 BAU/mL) in 9 participants (1.78%) but tested negative for previous COVID-19 infectionon the MIA. An overview per treatment arm is given in Table 11.

Table 9: Participants' characteristics (gender, age-group and race), per randomization group – mITT population

1a = 'Pfizer regular scheme'; 1b = 'Pfizer-Moderna scheme'; 1c ='Pfizer-AstraZeneca scheme'; 1d='Pfizer low dose scheme'; 1e = 'Pfizer long interval scheme'; 1f= 'Pfizer intradermal scheme'; 3a='Moderna regular scheme'; 3b='Moderna low dose scheme'

	Seks				Age group				Race						Total
	Male		Female		–8 - 40 yrs		–1 - 55 yrs		Unknown		Other		White		
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N
Randomisation group															
Group 1a	29	50.88	28	49.12	43	75.44	14	24.56	.	.	2	3.51	55	96.49	57
Group 1b	38	55.88	30	44.12	51	75.00	17	25.00	.	.	3	4.41	65	95.59	68
Group 1c	26	44.07	33	55.93	.	.	59	100.00	1	1.69	2	3.39	56	94.92	59
Group 1d	38	55.07	31	44.93	56	81.16	13	18.84	.	.	3	4.35	66	95.65	69
Grou[p] 1e	24	46.15	28	53.85	41	78.85	11	21.15	.	.	.	.	52	100.00	52
Group 1f	36	53.73	31	46.27	56	83.58	11	16.42	.	.	1	1.49	66	98.51	67
Group 3a	31	46.97	35	53.03	58	87.88	8	12.12	.	.	3	4.55	63	95.45	66
Group 3b	33	48.53	35	51.47	58	85.29	10	14.71	1	1.47	4	5.88	63	92.65	68
Total	255	50.40	251	49.60	363	71.74	143	28.26	2	0.40	18	3.56	486	96.05	506

Table 10: Age distribution per randomization group -mITT population

1a = 'Pfizer regular scheme'; 1b = 'Pfizer-Moderna scheme'; 1c ='Pfizer-AstraZeneca scheme'; 1d='Pfizer low dose scheme'; 1e = 'Pfizer long interval scheme'; 1f= 'Pfizer intradermal scheme'; 3a='Moderna regular scheme'; 3b='Moderna low dose scheme'

	Age					
	N	Mean	P50	Std	Min	Max
Randomisation group						
Group 1a	57	31.12	28.00	9.43	18.00	50.00
Group 1b	68	31.71	30.00	9.91	18.00	53.00
Group 1c	59	45.78	45.00	4.11	41.00	55.00
Group 1d	69	30.19	28.00	9.36	18.00	52.00
Grou[p] 1e	52	31.62	32.00	9.56	18.00	52.00
Group 1f	67	30.01	29.00	9.09	18.00	54.00
Group 3a	66	29.73	27.50	8.46	18.00	53.00
Group 3b	68	31.57	31.00	8.34	18.00	49.00
Total	506	32.57	31.00	9.94	18.00	55.00

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Table 11: IgG (in BAU/ml) at baseline, per randomization gro–p - mITT population

1a = 'Pfizer regular scheme'; 1b = 'Pfizer-Moderna scheme'; 1c ='Pfizer-AstraZeneca scheme'; 1d='Pfizer low dose scheme'; 1e = 'Pfizer long interval scheme'; 1f= 'Pfizer intradermal scheme'; 3a='Moderna regular scheme'; 3b='Moderna low dose scheme'; BAU=binding antibody units, a standardized unit based on the WHO international standard for SARS-CoV-2 immunoglobulins.

	IgG at baseline				Total
	>5BAU/ml		<5BAU/ml		
	N	%	N	%	N
Randomisation group					
Group 1a	1	1.75	56	98.25	57
Group 1b	1	1.47	67	98.53	68
Group 1c	.	.	59	100.00	59
Group 1d	1	1.45	68	98.55	69
Grou[p] 1e	1	1.92	51	98.08	52
Group 1f	1	1.49	66	98.51	67
Group 3a	2	3.03	64	96.97	66
Group 3b	2	2.94	66	97.06	68
Total	9	1.78	497	98.22	506

10.4 Antibodies binding to the RBD of SARS-CoV-2 S protein

i. Descriptive statistics for IgG

Observed IgG values (antibodies binding to the RBD of SARS-CoV-2 S protein), p55andomizationion group and visit, are presented in Table 12 and Figure 7.

ii. Descriptive statistics for IgG at primary endpoint evaluation

Table 133 presents descriptive statistics for log_{10}-IgG at the primary endpoint visit (visit 3 for the short interval groups and visit 4 for the long interval-group 1e).

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Table 12: Observed IgG values in BAU/ml (antibodies binding to the RBD of SARS-CoV-2 S protein), per randomisation group and visit, mITT population

1a = 'Pfizer regular scheme'; 1b = 'Pfizer-Moderna scheme'; 1c ='Pfizer-AstraZeneca scheme'; 1d='Pfizer low dose scheme'; 1e = 'Pfizer long interval scheme'; 1f= 'Pfizer intradermal scheme'; 3a='Moderna regular scheme'; 3b='Moderna low dose scheme

'The visit highlighted in yellow is the PE visit.

Prime vaccin group	Randomisation group	Visit	N	Mean	Std Dev	50th Pctl	25th Pctl	75th Pctl	Minimum	Maximum
Pfizer groups	Group 1a (Pfizer regular scheme)	visit 2	57	396.45	322.93	277.00	190.00	557.33	56.00	1649.00
		visit 3	57	4158.83	2814.32	3476.00	2255.12	5288.00	834.00	17354.00
		visit 4	54	1719.22	1932.87	1065.13	811.00	1842.00	446.00	11068.42
		visit 5	45	562.72	503.85	401.31	256.89	752.19	109.82	2299.64
		ad hoc post 3rd dose visit	30	4002.99	2580.14	3257.75	1680.84	6593.29	927.22	9699.87
		visit 6	16	1320.74	799.47	1142.72	597.05	2113.28	362.55	2574.92
	Group 1b (Pfizer-Moderna scheme)	visit 2	68	437.98	381.05	336.22	198.00	537.61	19.76	1696.00
		visit 3	68	5516.84	3381.21	5273.00	3226.87	7536.00	820.77	17160.00
		visit 4	67	2185.18	1847.51	1738.00	936.00	2817.79	250.00	10217.00
		visit 5	58	829.90	630.83	633.68	430.47	934.88	97.12	2556.09
		ad hoc post 3rd dose visit	31	4458.79	2921.46	3620.96	2194.49	6282.81	1050.59	14275.84
		visit 6	11	1341.08	1118.85	1117.44	492.28	1640.54	299.52	4128.31
	Group 1c (Pfizer-AstraZeneca scheme)	visit 2	59	367.51	276.51	319.00	180.00	479.00	15.00	1393.00
		visit 3	59	1193.65	789.67	1025.37	602.00	1547.00	200.00	3433.29
		visit 4	58	510.54	352.53	459.12	249.00	686.00	98.00	1818.00
		visit 5	44	230.66	176.52	191.45	87.30	316.95	39.33	799.07
		ad hoc post 3rd dose visit	34	3121.67	2342.55	2256.54	1751.38	3084.07	904.85	10908.14
		visit 6	21	1238.50	1126.16	733.81	514.86	1349.36	308.73	3946.31
	Group 1d (Pfizer low dose scheme)	visit 2	69	346.32	327.30	237.00	148.00	444.69	24.26	2066.00
		visit 3	69	3656.11	2534.02	3010.93	2016.00	4005.00	444.98	11132.00
		visit 4	68	1251.17	974.79	948.69	664.00	1582.97	190.00	6127.39
		visit 5	54	468.86	323.19	411.76	286.33	542.54	83.22	2238.69
		ad hoc post 3rd dose visit	35	3971.19	3175.63	2892.68	2232.89	3908.82	626.59	13543.40
		visit 6	12	2134.46	1941.72	1035.54	921.82	3646.94	724.68	5572.11

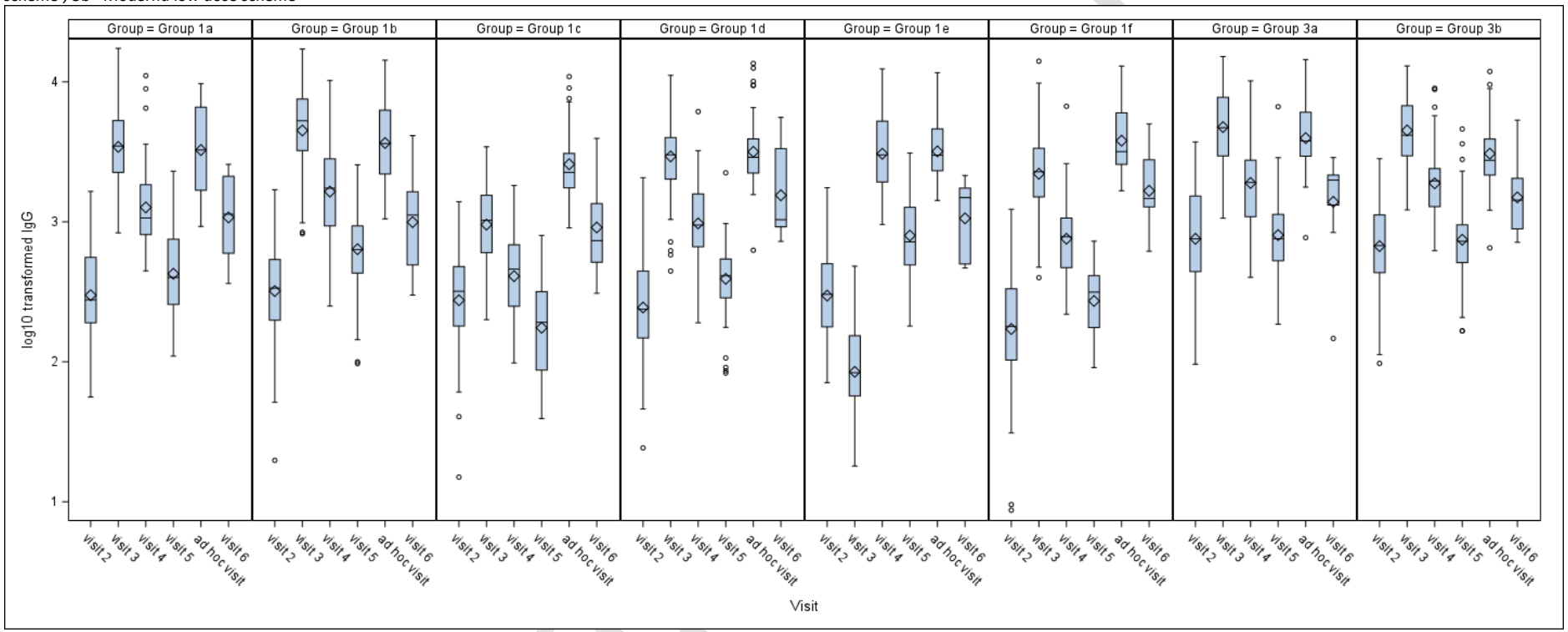
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Prime vaccin group	Randomisation group	Visit	N	Mean	Std Dev	50th Pctl	25th Pctl	75th Pctl	Minimum	Maximum
Moderna groups	Group 1e (Pfizer long interval scheme)	visit 2	52	387.38	323.95	303.50	177.50	502.47	71.00	1754.00
		visit 3	52	114.78	100.21	83.61	56.94	153.50	18.00	482.00
		visit 4	51	3802.79	2658.62	3008.62	1927.00	5235.25	957.00	12375.00
		visit 5	49	1011.32	759.95	719.34	491.46	1268.69	180.02	3097.04
		ad hoc post 3rd dose visit	29	3632.29	2098.42	2992.82	2316.01	4614.66	1421.49	11621.53
		visit 6	7	1240.07	673.35	1488.96	499.56	1743.12	467.88	2144.62
	Group 1f (Pfizer intradermal scheme)	visit 2	67	249.34	225.06	179.00	102.97	332.35	8.69	1231.03
		visit 3	67	2755.14	2133.84	2279.00	1508.00	3356.00	398.91	14042.00
		visit 4	65	962.57	901.44	782.00	470.60	1063.00	218.75	6692.34
		visit 5	47	313.52	158.60	314.35	175.62	412.91	90.88	726.96
		ad hoc post 3rd dose visit	35	4399.25	2641.44	3176.00	2572.60	6004.25	1667.63	12975.76
		visit 6	20	1932.57	1127.40	1474.26	1278.85	2778.36	616.83	4999.62
	Group 3a (Moderna regular scheme)	visit 2	66	1054.07	876.75	756.31	440.90	1526.00	96.12	3720.00
		visit 3	66	5803.12	3522.39	4725.13	2955.00	7762.00	1061.32	15167.00
		visit 4	64	2499.87	2106.72	1908.05	1089.58	2757.11	401.63	10164.71
		visit 5	56	1048.66	1001.14	756.97	527.04	1129.82	185.79	6644.72
		ad hoc post 3rd dose visit	35	4592.97	2705.55	3779.18	2938.76	6071.67	770.92	14436.53
		visit 6	10	1708.82	790.58	1988.99	1317.79	2154.98	146.80	2877.35
	Group 3b (Moderna low dose scheme)	visit 2	68	833.17	548.76	676.07	433.32	1121.50	97.44	2826.00
		visit 3	68	5313.32	3141.95	4159.92	2962.48	6757.00	1216.00	13002.00
		visit 4	66	2270.74	1677.94	1960.95	1282.00	2398.41	621.27	9009.81
		visit 5	55	958.94	831.98	725.98	511.15	951.53	166.22	4602.45
		ad hoc post 3rd dose visit	42	3644.67	2425.51	2749.94	2156.49	3908.00	651.73	11856.67
		visit 6	18	1752.17	1142.58	1431.12	889.70	2045.52	714.22	5326.31

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Figure 7: log_{10}-IgG values, per randomisation group and visit- mITT population

1a = 'Pfizer regular scheme'; 1b = 'Pfizer-Moderna scheme'; 1c ='Pfizer-AstraZeneca scheme'; 1d='Pfizer low dose scheme'; 1e = 'Pfizer long interval scheme'; 1f= 'Pfizer intradermal scheme'; 3a='Moderna regular scheme'; 3b='Moderna low dose scheme'



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Table 13: Descriptive statistics for log10-IgG at primary endpoint evaluation - mITT population

1a = 'Pfizer regular scheme'; 1b = 'Pfizer-Moderna scheme'; 1c ='Pfizer-AstraZeneca scheme'; 1d='Pfizer low dose scheme'; 1e = 'Pfizer long interval scheme'; 1f= 'Pfizer intradermal scheme'; 3a='Moderna regular scheme'; 3b='Moderna low dose scheme'

Randomisation Group	log_{10} -IgG					
	N	Mean	Std	P50	P25	P75
Group 1a	57	3.54	0.27	3.54	3.35	3.72
Group 1b	68	3.65	0.30	3.72	3.51	3.88
Group 1c	59	2.98	0.31	3.01	2.78	3.19
Group 1d	69	3.47	0.30	3.48	3.30	3.60
Group 1e	51	3.49	0.29	3.48	3.28	3.72
Group 1f	67	3.34	0.29	3.36	3.18	3.53
Group 3a	66	3.68	0.29	3.67	3.47	3.89
Group 3b	68	3.65	0.25	3.62	3.47	3.83

iii. Primary endpoint analysis: non-inferiority of adapted schedules compared to reference schedule in IgG levels 28 days post second vaccine

The results of the non-inferiority analysis for IgG levels of different vaccines and adapted vaccine schedules compared to the reference schedule, 28 days post 2 vaccine doses, are displayed in Table 14 and Figure 8.

Age and gender adjusted geometric mean titres with 95% two-sided confidence intervals and the geometric mean ratio (adapted schedule/reference schedule) with 97.5% (FWER at the level of prime dose group) one-sided confidence interval are presented. Non-inferiority of the adapted schedule compared to the reference schedule is claimed if the lower limit of the confidence interval of the geometric mean ratio lies above 0.63. Inferiority of the adapted schedule compared to the reference schedule is claimed if the upper limit of the confidence interval of the geometric mean ratio lies below 0.63. An inconclusive result, presented as 'not non-inferior', is claimed if the confidence interval of the geometric mean ratio includes a ratio of 0.63, which represents the non-inferiority margin.

The reported p-values are for one-sided (upper) tests. For the Pfizer comparisons a p-value <0.005 implies non-inferiority, for the Moderna comparison a p-value <0.025 implies non-inferiority.

Results for the heterologous vaccination schedules were ambivalent. The Pfizer-Moderna schedule (group 1b) was shown to be non-inferior to the standard Pfizer-Pfizer schedule (group 1a) (p<0.0001). In contrast, the Pfizer-AstraZeneca (group 1c) (p>0.999) was inferior to the standard Pfizer-Pfizer schedule (group 1a).

Non-inferiority could not be demonstrated for the Pfizer vaccination schedule with lower doses (groups 1d) (p=0.008) and Pfizer intradermal schedules (group 1f) ([=0.564).

An increased time interval between the first and second Pfizer dose (group 1e) led to a decrease in IgG levels that was non-inferior to those observed for the standard Pfizer schedule (p=0.002).

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Finally, lower doses of the Moderna vaccination schedule (group 3b) resulted in an IgG response that was non-inferior to the standard Moderna-Moderna schedule (group 3a) ($p<0.001$).

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Table 14: GMT and GMR of IgG-RBD at primary endpoint, comparison of the adapted schedules with the reference schedule

Non-inferior comparisons marked in yellow

1a = 'Pfizer regular scheme'; 1b = 'Pfizer-Moderna scheme'; 1c ='Pfizer-AstraZeneca scheme'; 1d='Pfizer low dose scheme'; 1e = 'Pfizer long interval scheme'; 1f= 'Pfizer intradermal scheme'; 3a='Moderna regular scheme'; 3b='Moderna low dose scheme'

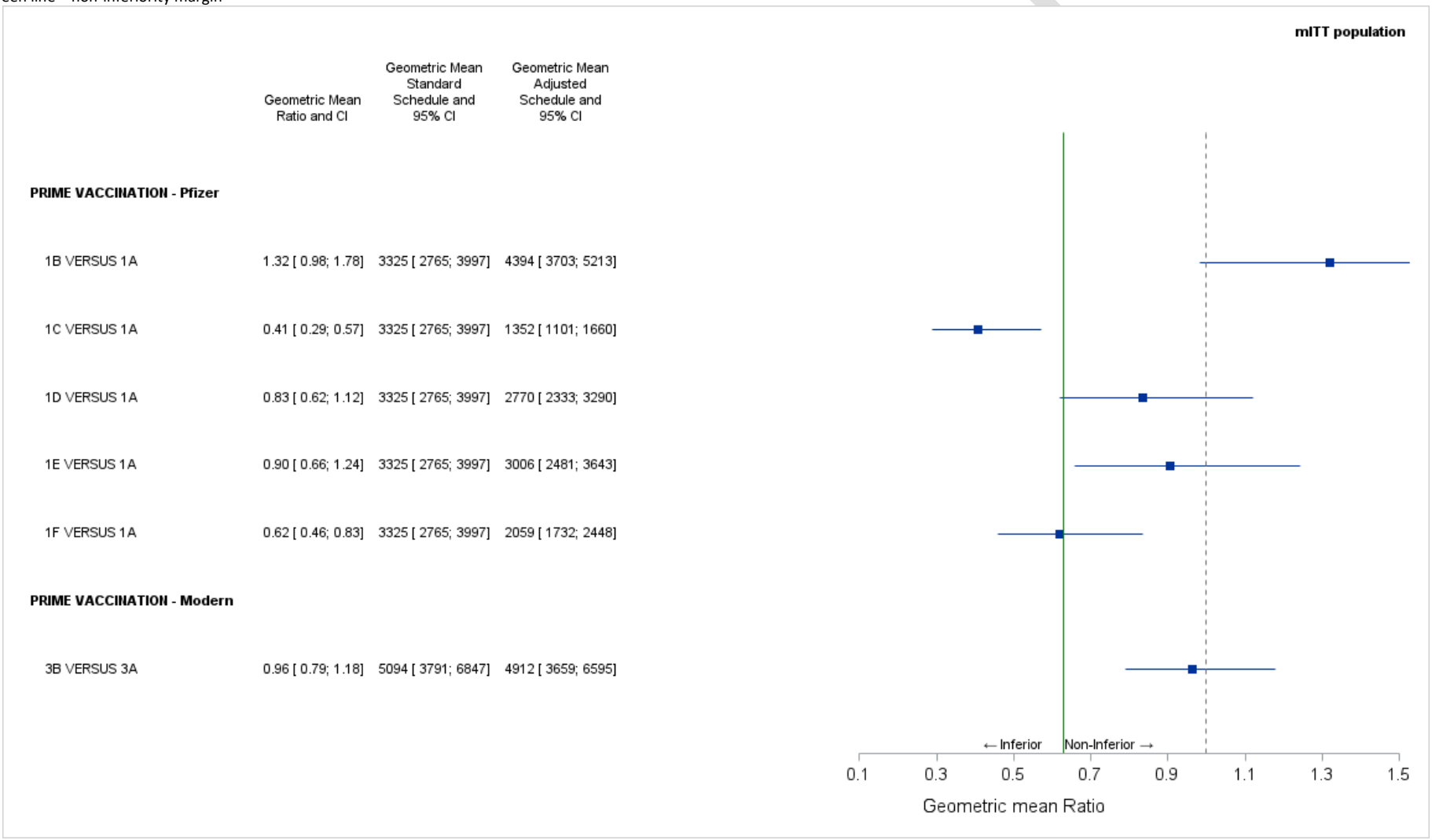
Analysis Population	Comparison	Geometric Mean of Standard Schedule and 95% CI	Geometric Mean of Adjusted Schedule and 95% CI	Geometric Mean Ratio and CI	p value (one sided test)	Conclusion
mITT	1B VERSUS 1A	3325 [2765; 3997]	4394 [3703; 5213]	1.32 [0.98;+inf]	0.000	Non-inferior
Per-protocol	1B VERSUS 1A	3337 [2795; 3986]	4407 [3717; 5224]	1.32 [0.97;+inf]	0.000	Non-inferior
mITT	1C VERSUS 1A	3325 [2765; 3997]	1352 [1101; 1660]	0.41 [0.29;+inf]	1.000	Inferior
Per-protocol	1C VERSUS 1A	3337 [2795; 3986]	1318 [1080; 1609]	0.39 [0.28;+inf]	1.000	Inferior
mITT	1D VERSUS 1A	3325 [2765; 3997]	2770 [2333; 3290]	0.83 [0.62;+inf]	0.008	Not non-inferior
Per-protocol	1D VERSUS 1A	3337 [2795; 3986]	2724 [2301; 3226]	0.82 [0.60;+inf]	0.014	Not non-inferior
mITT	1e VERSUS 1A	3325 [2765; 3997]	3006 [2481; 3643]	0.90 [0.66;+inf]	0.002	Non-inferior
Per-protocol	1e VERSUS 1A	3337 [2795; 3986]	2845 [2349; 3446]	0.85 [0.61;+inf]	0.009	Not non-inferior
mITT	1F VERSUS 1A	3325 [2765; 3997]	2059 [1732; 2448]	0.62 [0.46;+inf]	0.564	Not non-Inferior
Per-protocol	1F VERSUS 1A	3337 [2795; 3986]	2052 [1733; 2431]	0.61 [0.45;+inf]	0.587	Not non-Inferior
mITT	3B VERSUS 3A	5094 [3791; 6847]	4912 [3659; 6595]	0.96 [0.79;+inf]	0.000	Non-inferior
Per-protocol	3B VERSUS 3A	5083 [3733; 6922]	4886 [3594; 6642]	0.96 [0.78;+inf]	0.000	Non-inferior

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Figure 8: GMT and GMR of IgG-RBD at primary endpoint, comparison of the adapted schedules with the reference schedule – mITT population

1a = 'Pfizer regular scheme'; 1b = 'Pfizer-Moderna scheme'; 1c ='Pfizer-AstraZeneca scheme'; 1d='Pfizer low dose scheme'; 1e = 'Pfizer long interval scheme'; 1f= 'Pfizer intradermal scheme'; 3a='Moderna regular scheme'; 3b='Moderna low dose scheme'

Green line = non-inferiority margin



iv. Non-inferiority of Pfizer schedules compared to the Pfizer-AstraZeneca scheme in IgG levels 28 days post second vaccine

Com-COV[50] is a participant-blinded, randomised, non-inferiority trial evaluating vaccine safety, reactogenicity, and immunogenicity. Adults aged 50 years and older with no or well controlled comorbidities and no previous SARS-CoV-2 infection by laboratory confirmation were eligible and were recruited at eight sites across the UK. The majority of eligible participants were enrolled into the general cohort (28-day or 84-day prime-boost intervals), who were randomly assigned (1:1:1:1:1:1:1:1) to receive ChAd[4]/ChAd, ChAd/BNT[5], BNT/BNT, or BNT/ChAd, administered at either 28-day or 84-day prime-boost intervals. The primary endpoint was the geometric mean ratio (GMR) of serum SARS-CoV-2 anti-spike IgG concentration (measured by ELISA) at 28 days after boost, when comparing ChAd/BNT with ChAd/ChAd, and BNT/ChAd with BNT/BNT. The heterologous schedules were considered non-inferior to the approved homologous schedules if the lower limit of the one-sided 97·5% CI of the GMR of these comparisons was greater than 0·63. Inferiority of the adapted schedule compared to the reference schedule is claimed if the upper limit of the confidence interval of the geometric mean ratio lies below 0.63. An inconclusive result, presented as not non-inferior, is claimed if the confidence interval of the geometric mean ratio includes a ratio of 0.63, which represents the non-inferiority margin.

Participants boosted with ChAd following BNT prime (BNT/ChAd) had significantly higher SARS-CoV-2 anti-spike IgG ($p<0.0001$) and Pseudo Neutralization Assay (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.

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. Along with the higher immunogenicity of ChAd/BNT compared with ChAD/ChAd, these data support flexibility in the use of heterologous prime-boost vaccination using ChAd and BNT COVID-19 vaccines.

Supported by this publication, an exploratory analysis with a different reference group for the Pfizer groups was done and is presented below. The linear mixed model described Section 9.3.i was used; but **comparison is with respect to the Pfizer-AstraZeneca scheme (group 1c)** instead of the Pfizer regular scheme (group 1a).

We conclude that all Pfizer schedules are non-inferior to group 1c, for the level of RBD-IgG (Table 15).

[4] Chad = 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))

[5] BTN = SD BNT162b2 = 0.3mL Comirnaty® (30 micrograms of COVID-19 mRNA Vaccine)

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Table 15: GMT and GMR of IgG-RBD at primary endpoint, comparison of the Pfizer schedules with group 1c as comparator

1a = 'Pfizer regular scheme'; 1b = 'Pfizer-Moderna scheme'; 1c ='Pfizer-AstraZeneca scheme'; 1d='Pfizer low dose scheme'; 1e = 'Pfizer long interval scheme'; 1f= 'Pfizer intradermal scheme'; 3a='Moderna regular scheme'; 3b='Moderna low dose scheme'

Analysis population	Comparison	Geometric Mean of Schedule 1C and 95% CI	Geometric Mean of Adjusted Schedule and 95% CI	Geometric Mean Ratio	p value (one sided test)	Conclusion
mITT	1A VERSUS 1C	1352 [1101; 1660]	3325 [2765; 3997]	2.46 [1.75;+inf]	0.000	Non-inferior
Per-protocol	1A VERSUS 1C	1318 [1080; 1609]	3337 [2795; 3986]	2.53 [1.80;+inf]	0.000	Non-inferior
mITT	1B VERSUS 1C	1352 [1101; 1660]	4394 [3703; 5213]	3.25 [2.34;+inf]	0.000	Non-inferior
Per-protocol	1B VERSUS 1C	1318 [1080; 1609]	4407 [3717; 5224]	3.34 [2.39;+inf]	0.000	Non-inferior
mITT	1D VERSUS 1C	1352 [1101; 1660]	2770 [2333; 3290]	2.05 [1.47;+inf]	0.000	Non-inferior
Per-protocol	1D VERSUS 1C	1318 [1080; 1609]	2724 [2301; 3226]	2.07 [1.47;+inf]	0.000	Non-inferior
mITT	1e VERSUS 1C	1352 [1101; 1660]	3006 [2481; 3643]	2.22 [1.57;+inf]	0.000	Non-inferior
Per-protocol	1e VERSUS 1C	1318 [1080; 1609]	2845 [2349; 3446]	2.16 [1.52;+inf]	0.000	Non-inferior
mITT	1F VERSUS 1C	1352 [1101; 1660]	2059 [1732; 2448]	1.52 [1.09;+inf]	0.000	Non-inferior
Per-protocol	1F VERSUS 1C	1318 [1080; 1609]	2052 [1733; 2431]	1.56 [1.11;+inf]	0.000	Non-inferior

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v. Non-inferiority of adapted schedules compared to reference schedule in IgG levels 28 days post 3rd COVID-19 vaccine

This non-inferiority analysis is performed on the mITT population, which includes participants who received three COVID-19 vaccines as per study protocol, did not experience a BTI, and did not receive a COVID-19 vaccine outside of the study (n=271). Therefore, this analysis investigates the pure vaccine effect 28 days after the third COVID-19 vaccine.

A total of 460 mITT-participants attended the ad hoc post 3rd dose visit, but 189 of them experienced a BTI diagnosed before or on this visit. This correlates with the high incidence of COVID-19-infections that is observed in the Belgian population in the period October 2021 – February 2022, as shown in the red square in Figure 9.

Table 16 presents an overview of the brand and dose of the 3rd COVID-19 vaccine that the 271 mITT participants included in this non-inferiority analysis received. Note that this info was collected via the Belgian COVID-19 vaccine registration system Vaccinet. In case there was no specification added to the Spikevax-vaccine, it was registered in our database as 0.5mL, although the registered dose for booster is only 0.25mL. It is known that in some vaccination centra, 0.5mL was given anyway. Therefore, when no specification was available, the standard dose was chosen to register.

The results of the non-inferiority analysis for IgG levels of different vaccines and adapted vaccine schedules compared to the reference schedule, 28 days post 3rd vaccine dose, are displayed in Table 17 and Figure 10.

Geometric mean titres - adjusted for age, gender and brand and dose of the third study vaccine - with 95% two-sided confidence intervals and the geometric mean ratio (adapted schedule/reference schedule) with 97.5% (FWER at the level of prime dose group) one-sided confidence interval are presented. Non-inferiority of the adapted schedule compared to the reference schedule is claimed if the lower limit of the confidence interval of the geometric mean ratio lies above 0.63. Inferiority of the adapted schedule compared to the reference schedule is claimed if the upper limit of the confidence interval of the geometric mean ratio lies below 0.63. An inconclusive result, presented as not non-inferior, is claimed if the confidence interval of the geometric mean ratio includes a ratio of 0.63, which represents the non-inferiority margin.

The reported p-values are for one-sided (upper) tests. For the Moderna comparison a p-value < 0.025 implies non-inferiority, for the Pfizer comparisons a p-value < 0.005 implies non-inferiority.

As a sensitivity analysis, the model is also fitted to the data, excluding visits that took place out-of-window at ad hoc 3rd dose visit (not within 28 +/-5 days after the third vaccine). The per-protocol analysis is based on 189 participants, excluding 82 out of window visits.

Non-inferiority of the IgG-response could be demonstrated in COVID-19 naïve participant, for all the 6 adapted vaccination schedules used for the first and second COVID-19 vaccination, after a 3rd COVID-19 vaccine is administered, when compared to their reference schedule. This is independent of the brand or dose that was used as third COVID-19 vaccine.

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Figure 9: Incidence of COVID-19-infections in Belgium during the IMCOVAS-trial[51]

Red square = high incidence of COVID-19-infections that is observed in the Belgian population in the period October 2021 – February 2022

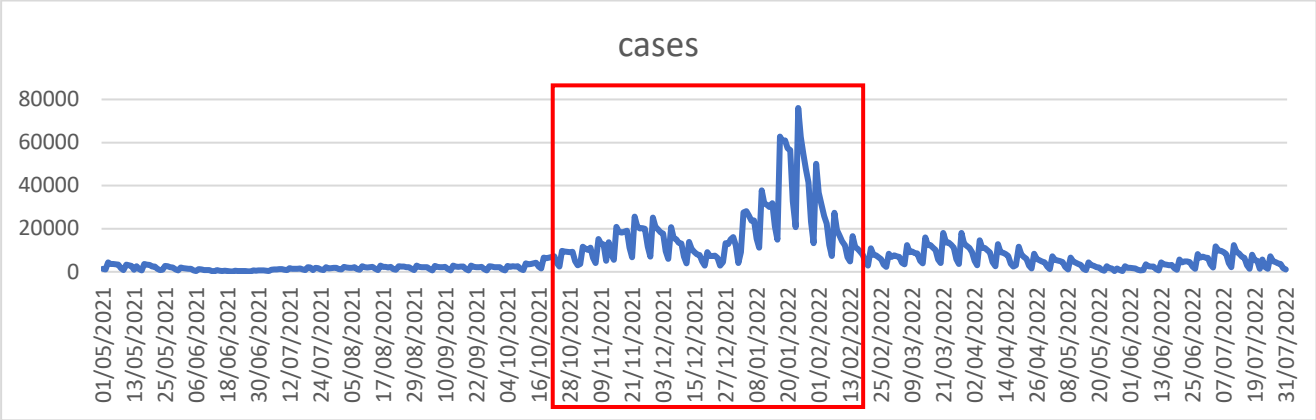


Table 16: Brand and dose of the 3rd COVID-19 vaccine, per study group – mITT population

1a = 'Pfizer regular scheme'; 1b = 'Pfizer-Moderna scheme'; 1c ='Pfizer-AstraZeneca scheme'; 1d='Pfizer low dose scheme'; 1e = 'Pfizer long interval scheme'; 1f= 'Pfizer intradermal scheme'; 3a='Moderna regular scheme'; 3b='Moderna low dose scheme'

Only participants who did not had a breakthrough infection before this visit and did not receive COVID-19 vaccines outside of the study before September 2021 are taken into account.

Which vaccine did the subject receive?	**Randomisation group**								
N (%)	**Group 1a**	**Group 1b**	**Group 1c**	**Group 1d**	**Group 1e**	**Group 1f**	**Group 3a**	**Group 3b**	**Total**
Comirnaty 0.3 mL	4 (13.3%)	4(12.9%)	8 (23.5%)	6 (17.1%)	2 (6.9%)	3 (8.6%)	1 (2.9%)	3 (7.1%)	31
Spikevax 0.25 mL	24 (80.0%)	23(74.2)%	22 (64.7%)	27 (77.1%)	25 (86.2%)	28 (80.0%)	33 (94. %)	36 (85.7%)	218
Spikevax 0.5 mL	2(6.7%)	4 (12.9%)	4 (11.7%)	2 (5.7%)	2 (6.9%)	4 (11.4%)	1 (2.9%)	3 (7.1%)	22
Total	30	31	34	35	29	35	35	42	271

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Table 17: GMT and GMR of IgG-RBD at 28 days post third vaccine, comparison of the adapted schedules with the reference schedule

1a = 'Pfizer regular scheme'; 1b = 'Pfizer-Moderna scheme'; 1c ='Pfizer-AstraZeneca scheme'; 1d='Pfizer low dose scheme'; 1e = 'Pfizer long interval scheme'; 1f= 'Pfizer intradermal scheme'; 3a='Moderna regular scheme'; 3b='Moderna low dose scheme'

Analyses set	Comparison	Geometric Mean of Standard Schedule and 95% CI	Geometric Mean of Adjusted Schedule and 95% CI	Geometric Mean Ratio and CI	p value (one sided test)	Conclusion
mITT	1B VERSUS 1A	3011 [2399; 3780]	3433 [2758; 4274]	1.14 [0.78;+inf]	0.000048	Non-inferior
Per-protocol	1B VERSUS 1A	2888 [2201; 3790]	3468 [2661; 4519]	1.20 [0.75;+inf]	0.000256	Non-inferior
mITT	1C VERSUS 1A	3011 [2399; 3780]	3305 [2593; 4213]	1.10 [0.72;+inf]	0.000378	Non-inferior
Per-protocol	1C VERSUS 1A	2888 [2201; 3790]	3243 [2387; 4406]	1.12 [0.67;+inf]	0.002092	Non-inferior
mITT	1D VERSUS 1A	3011 [2399; 3780]	2990 [2419; 3697]	0.99 [0.68;+inf]	0.000894	Non-inferior
Per-protocol	1D VERSUS 1A	2888 [2201; 3790]	2984 [2293; 3883]	1.03 [0.65;+inf]	0.002738	Non-inferior
mITT	1e VERSUS 1A	3011 [2399; 3780]	2980 [2357; 3768]	0.99 [0.67;+inf]	0.001486	Non-inferior
Per-protocol	1e VERSUS 1A	2888 [2201; 3790]	3149 [2387; 4155]	1.09 [0.68;+inf]	0.001295	Non-inferior
mITT	1F VERSUS 1A	3011 [2399; 3780]	3350 [2707; 4145]	1.11 [0.77;+inf]	0.000053	Non-inferior
Per-protocol	1F VERSUS 1A	2888 [2201; 3790]	3519 [2689; 4605]	1.22 [0.77;+inf]	0.000148	Non-inferior
mITT	3B VERSUS 3A	4107 [3068; 5499]	3392 [2546; 4521]	0.83 [0.66;+inf]	0.010742	Non-inferior
Per-protocol	3B VERSUS 3A	4220 [3160; 5636]	3315 [2494; 4407]	0.79 [0.60;+inf]	0.057579	Not non-inferior

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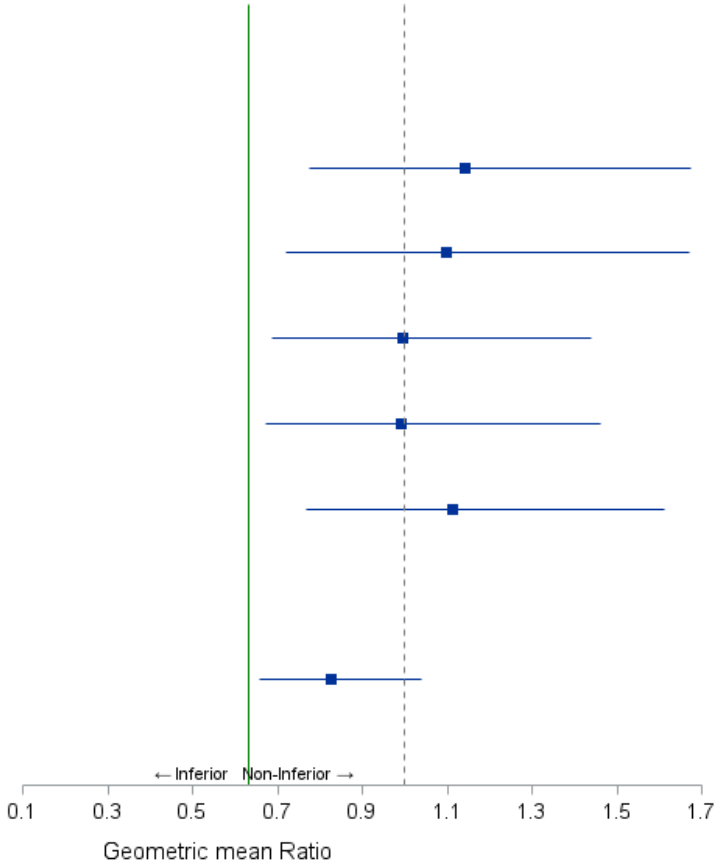
Figure 10: GMT and GMR of IgG-RBD at 28 days post third vaccine, comparison of adapted schedules with the reference schedule - mITT

1a = 'Pfizer regular scheme'; 1b = 'Pfizer-Moderna scheme'; 1c ='Pfizer-AstraZeneca scheme'; 1d='Pfizer low dose scheme'; 1e = 'Pfizer long interval scheme'; 1f= 'Pfizer intradermal scheme'; 3a='Moderna regular scheme'; 3b='Moderna low dose scheme'

Green line = non-inferiority margin

mITT population

	Geometric Mean Ratio and CI	Geometric Mean Standard Schedule and 95% CI	Geometric Mean Adjusted Schedule and 95% CI
PRIME VACCINATION - Pfizer			
1B VERSUS 1A	1.14 [0.78; 1.68]	3011 [2399; 3780]	3433 [2758; 4274]
1C VERSUS 1A	1.10 [0.72; 1.67]	3011 [2399; 3780]	3305 [2593; 4213]
1D VERSUS 1A	0.99 [0.68; 1.44]	3011 [2399; 3780]	2990 [2419; 3697]
1E VERSUS 1A	0.99 [0.67; 1.46]	3011 [2399; 3780]	2980 [2357; 3768]
1F VERSUS 1A	1.11 [0.77; 1.61]	3011 [2399; 3780]	3350 [2707; 4145]
PRIME VACCINATION - Modern			
3B VERSUS 3A	0.83 [0.66; 1.04]	4107 [3068; 5499]	3392 [2546; 4521]



vi. IgG levels of the 8 study groups, average evolution till visit 5 (D182)

The results of the repeated measurements model on the IgG levels if visits 2, 3, 4 and 5 are displayed in Table 18 and Figure 11.

Age and gender adjusted geometric mean titres with 95% two-sided confidence intervals for the standard and adapted schedules are presented. At each visit, the geometric mean ratio for the adapted schedule versus the standard schedule and the GMR of the two standard schedules is also given with a 95% two-sided confidence interval and a two-sided p value. No correction for multiple testing is implemented.

The geometric mean IgG-RBD titres of the Pfizer-Moderna scheme (group 1b), Pfizer long interval scheme (group 1e), and Moderna regular scheme (group 3a) are higher than those of the Pfizer regular scheme (group 1a). On the other hand, the geometric mean IgG-RBD titres of the Pfizer-AstraZeneca scheme (group 1c) and Pfizer intradermal scheme (group 1f) are lower compared to the Pfizer regular scheme (group 1a). Although the differences with respect to the Pfizer regular scheme decrease over time, they are still statistically significant during visit 5.

In contrast, there are no significant differences between the Moderna regular scheme (group 3a) and the Moderna low dose scheme (group b) during the 182-day follow-up period.

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Table 18: GMT and GMR of IgG-RBD at study visits 2, 3, 4, and 5, comparison of the adapted schedules with the reference schedule – mITT population

1a = 'Pfizer regular scheme'; 1b = 'Pfizer-Moderna scheme'; 1c ='Pfizer-AstraZeneca scheme'; 1d='Pfizer low dose scheme'; 1e = 'Pfizer long interval scheme'; 1f= 'Pfizer intradermal scheme'; 3a='Moderna regular scheme'; 3b='Moderna low dose scheme'

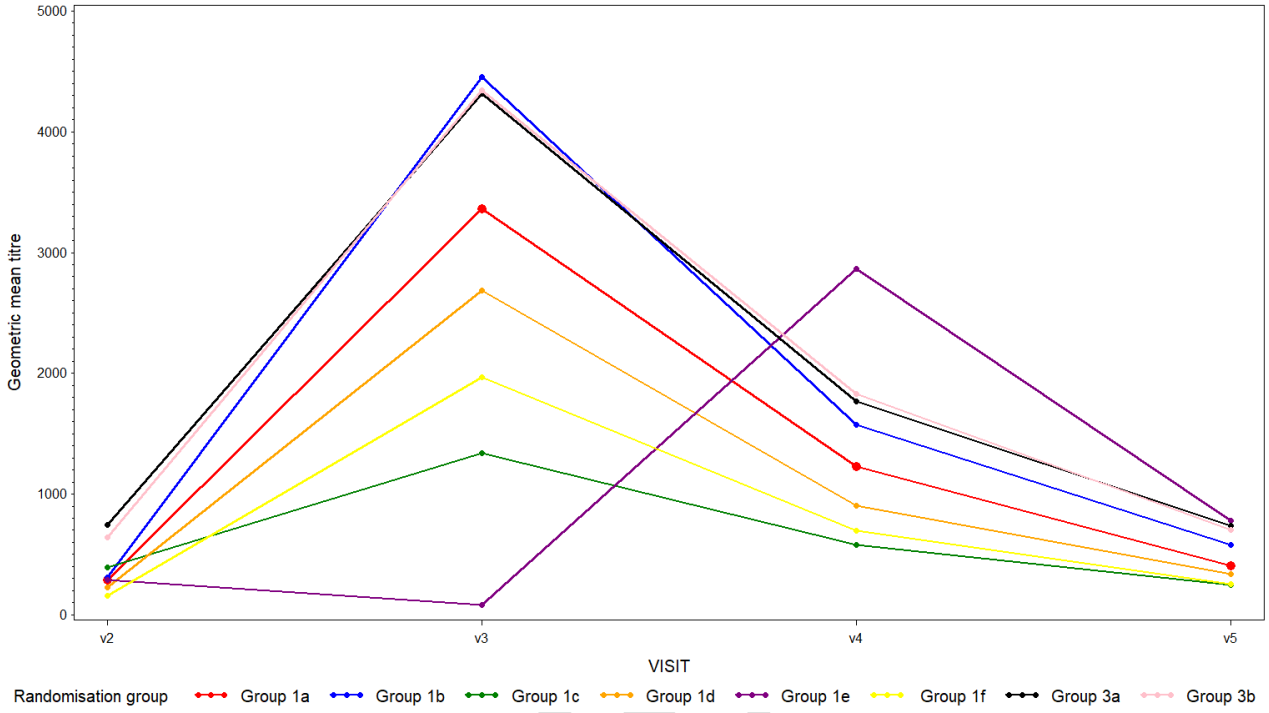
Comparison	Standard Schedule	Adapted Schedule	Geometric Mean of Standard Schedule and 95% CI	Geometric Mean of Adapted Schedule and 95% CI	Geometric Mean Ratio and 95% CI	pvalue
VISIT2: 1B VERSUS 1A	Group 1a	Group 1b	288 [237; 351]	309 [255; 375]	1.07 [0.81; 1.41]	0.6225
VISIT2: 1C VERSUS 1A	Group 1a	Group 1c	288 [237; 351]	390 [315; 483]	1.35 [1.01; 1.81]	0.0439
VISIT2: 1D VERSUS 1A	Group 1a	Group 1d	288 [237; 351]	227 [189; 272]	0.79 [0.60; 1.03]	0.0795
VISIT2: 1e VERSUS 1A	Group 1a	Group 1e	288 [237; 351]	289 [234; 358]	1.00 [0.75; 1.34]	0.9797
VISIT2: 1F VERSUS 1A	Group 1a	Group 1f	288 [237; 351]	155 [128; 188]	0.54 [0.41; 0.71]	<.0001
VISIT2: 3A VERSUS 1A	Group 1a	Group 3a	288 [237; 351]	746 [616; 902]	2.59 [1.97; 3.40]	<.0001
VISIT2: 3B VERSUS 3A	Group 3a	Group 3b	746 [616; 902]	643 [533; 774]	0.86 [0.66; 1.12]	0.2724
VISIT3: 1B VERSUS 1A	Group 1a	Group 1b	3362 [2841; 3978]	4457 [3778; 5258]	1.33 [1.05; 1.68]	0.0192
VISIT3: 1C VERSUS 1A	Group 1a	Group 1c	3362 [2841; 3978]	1339 [1111; 1614]	0.40 [0.31; 0.51]	<.0001
VISIT3: 1D VERSUS 1A	Group 1a	Group 1d	3362 [2841; 3978]	2689 [2300; 3144]	0.80 [0.64; 1.01]	0.0561
VISIT3: 1e VERSUS 1A	Group 1a	Group 1e	3362 [2841; 3978]	81 [67; 96]	0.02 [0.02; 0.03]	<.0001
VISIT3: 1F VERSUS 1A	Group 1a	Group 1f	3362 [2841; 3978]	1966 [1673; 2311]	0.58 [0.46; 0.74]	<.0001
VISIT3: 3A VERSUS 1A	Group 1a	Group 3a	3362 [2841; 3978]	4314 [3669; 5074]	1.28 [1.02; 1.62]	0.0361
VISIT3: 3B VERSUS 3A	Group 3a	Group 3b	4314 [3669; 5074]	4343 [3706; 5090]	1.01 [0.80; 1.26]	0.9537
VISIT4: 1B VERSUS 1A	Group 1a	Group 1b	1226 [1028; 1462]	1576 [1326; 1872]	1.29 [1.00; 1.64]	0.0460
VISIT4: 1C VERSUS 1A	Group 1a	Group 1c	1226 [1028; 1462]	576 [475; 699]	0.47 [0.36; 0.61]	<.0001
VISIT4: 1D VERSUS 1A	Group 1a	Group 1d	1226 [1028; 1462]	905 [769; 1064]	0.74 [0.58; 0.94]	0.0130
VISIT4: 1e VERSUS 1A	Group 1a	Group 1e	1226 [1028; 1462]	2863 [2372; 3455]	2.34 [1.80; 3.02]	<.0001
VISIT4: 1F VERSUS 1A	Group 1a	Group 1f	1226 [1028; 1462]	698 [590; 826]	0.57 [0.45; 0.73]	<.0001
VISIT4: 3A VERSUS 1A	Group 1a	Group 3a	1226 [1028; 1462]	1764 [1489; 2089]	1.44 [1.13; 1.84]	0.0036
VISIT4: 3B VERSUS 3A	Group 3a	Group 3b	1764 [1489; 2089]	1830 [1551; 2159]	1.04 [0.82; 1.31]	0.7601
VISIT5: 1B VERSUS 1A	Group 1a	Group 1b	407 [337; 490]	578 [483; 692]	1.42 [1.10; 1.84]	0.0077
VISIT5: 1C VERSUS 1A	Group 1a	Group 1c	407 [337; 490]	249 [203; 306]	0.61 [0.46; 0.81]	0.0006
VISIT5: 1D VERSUS 1A	Group 1a	Group 1d	407 [337; 490]	339 [285; 403]	0.83 [0.65; 1.07]	0.1575
VISIT5: 1e VERSUS 1A	Group 1a	Group 1e	407 [337; 490]	781 [644; 948]	1.92 [1.47; 2.51]	<.0001
VISIT5: 1F VERSUS 1A	Group 1a	Group 1f	407 [337; 490]	251 [209; 302]	0.62 [0.48; 0.80]	0.0003
VISIT5: 3A VERSUS 1A	Group 1a	Group 3a	407 [337; 490]	740 [620; 882]	1.82 [1.41; 2.35]	<.0001
VISIT5: 3B VERSUS 3A	Group 3a	Group 3b	740 [620; 882]	703 [591; 837]	0.95 [0.74; 1.22]	0.6892

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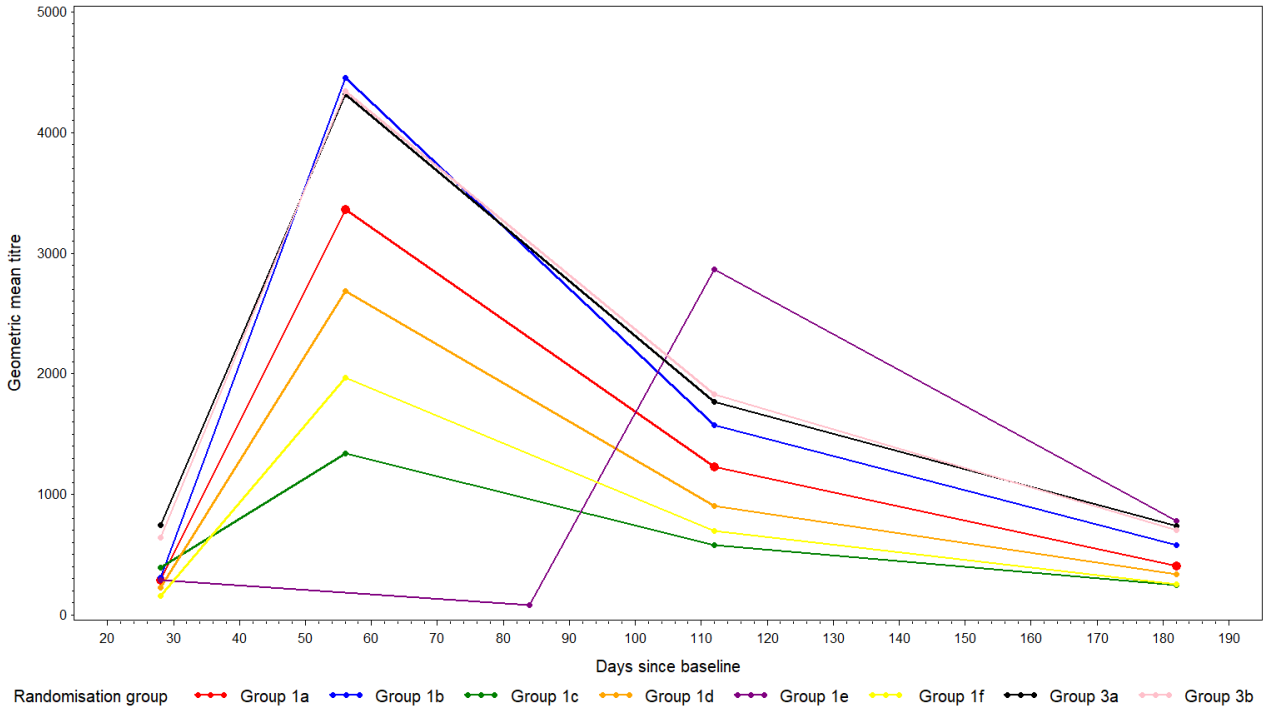
Figure 11: Evolution in GMT of IgG-RBD - mITT population

1a = 'Pfizer regular scheme'; 1b = 'Pfizer-Moderna scheme'; 1c ='Pfizer-AstraZeneca scheme'; 1d='Pfizer low dose scheme'; 1e = 'Pfizer long interval scheme'; 1f= 'Pfizer intradermal scheme'; 3a='Moderna regular scheme'; 3b='Moderna low dose scheme'

a) GMT of IgG-RBD per study visit



b) GMT of IgG-RBD versus time since baseline



vii. Change in IgG level, 28 days post vaccination versus vaccination

For each participant, the change in log_{10}-IgG, comparing the level at the time of vaccination with those at 28 days post vaccination, is obtained.
As for the 3rd COVID-19 vaccine dose, no sample of the day of vaccination is available, the sample of V5 is used. On average the ad hoc post 3rd dose visit took place 32 days (ranging from 21-65 days) after administering the 3rd dose and 63 days (ranging 34-120 days) after visit 5 (D182). There are differences between the study groups (Table 19), on average groups 1c and 3a had a longer period between 3rd COVID-19 vaccine dose and the ad hoc post 3rd dose visit, group 1e had a longer period between the ad hoc post 3rd dose visit and visit 5 (D182).

Info about the third vaccine is available for 460 participants of the mITT population (Table 20). The majority of them received Spikevax 0.25 ml (n=370, 80%), and about one of 10 participants received Comirnaty 0.3 ml (n=57, 12%) or Spikevax 0.5 ml (n=33, 7%).

Descriptive statistics for the change in log_{10}-IgG per study group and vaccination are presented in Table 21 and Figure 12. The change after the 3rd vaccine (i.e. difference 'visit post 3rd dose – visit 5 (D182)') is obtained for 267 participants.

Table 22 and Table 24 present the average log_{10}-IgG change (adjusted for age and gender, and brand/dose of third vaccine in case of the 28 days post third vaccine) and 95% two-sided confidence intervals per study group and vaccination. The change in log_{10}-IgG of the adapted vaccine schedule is compared with the change in log10-IgG of the reference schedule. The changes in log_{10}-IgG of the two reference schedules are also compared. These results are given in Table 24/Table 25, the difference in mean change between two study groups is given together with a 95% CI for this difference and the p value.

Compared to the Pfizer reference schedule (group 1a), Pfizer-AstraZeneca (group 1c) and Moderna regular schedules (group 3a) exhibit a larger increase in log_{10}-IgG 28 days after the first vaccination. However, the increase in log_{10}-IgG observed in these study groups is smaller than that of the Pfizer regular schedule (group 1a), 28 days after the second vaccination.

The Pfizer intradermal scheme (group 1f) shows a smaller increase in log_{10}-IgG 28 days after the first vaccination compared to the Pfizer reference schedule (group 1a); 28 days after the second vaccination, Pfizer long interval scheme (group 1e) exhibits a larger increase in log_{10}-IgG compared to the Pfizer reference schedule (group 1a)

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Table 19: Time between visits

1a = 'Pfizer regular scheme'; 1b = 'Pfizer-Moderna scheme'; 1c ='Pfizer-AstraZeneca scheme'; 1d='Pfizer low dose scheme'; 1e = 'Pfizer long interval scheme'; 1f= 'Pfizer intradermal scheme'; 3a='Moderna regular scheme'; 3b='Moderna low dose scheme'

Randomisation group	Time interval	N	Mean	Std Dev	Minimum	Maximum
Group 1a	Days between ad hoc visit and administration of 3rd dose	55	31.16	6.48	24.00	62.00
	Days between visit 5 (D182) and ad hoc visit	55	61.60	14.84	40.00	107.00
Group 1b	Days between ad hoc visit and administration of 3rd dose	57	30.53	5.80	23.00	55.00
	Days between visit 5 (D182) and ad hoc visit	57	61.89	12.13	41.00	91.00
Group 1c	Days between ad hoc visit and administration of 3rd dose	54	33.94	8.57	21.00	60.00
	Days between visit 5 (D182) and ad hoc visit	54	58.80	12.04	36.00	90.00
Group 1d	Days between ad hoc visit and administration of 3rd dose	64	31.17	5.63	22.00	47.00
	Days between visit 5 (D182) and ad hoc visit	64	64.22	14.50	40.00	120.00
Group 1e	Days between ad hoc visit and administration of 3rd dose	48	30.19	5.95	21.00	52.00
	Days between visit 5 (D182) and ad hoc visit	48	71.19	17.93	48.00	114.00
Group 1f	Days between ad hoc visit and administration of 3rd dose	60	31.80	5.91	23.00	51.00
	Days between visit 5 (D182) and ad hoc visit	60	61.23	13.03	41.00	95.00
Group 3a	Days between ad hoc visit and administration of 3rd dose	60	34.65	9.02	23.00	65.00
	Days between visit 5 (D182) and ad hoc visit	59	65.20	16.26	42.00	120.00
Group 3b	Days between ad hoc visit and administration of 3rd dose	62	31.48	5.31	24.00	45.00
	Days between visit 5 (D182) and ad hoc visit	62	61.58	16.05	34.00	101.00

Table 20: Brand and dose of third COVID-19 vaccine

Brand/dose	N	%
Comirnaty 0.3 mL	57	12.39
Spikevax 0.25 mL	370	80.43
Spikevax 0.5 mL	33	7.17

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Table 21: Change in log_{10} -IgG, 28 days post vaccination compared to vaccination -mITT population

As for the 3rd COVID-19 vaccine dose, no sample of the day of vaccination is available, the sample of V5, D182 is used as this visit happened the closest before the 3rd COVID-19 vaccination.
1a = 'Pfizer regular scheme'; 1b = 'Pfizer-Moderna scheme'; 1c ='Pfizer-AstraZeneca scheme'; 1d='Pfizer low dose scheme'; 1e = 'Pfizer long interval scheme'; 1f= 'Pfizer intradermal scheme'; 3a='Moderna regular scheme'; 3b='Moderna low dose scheme'

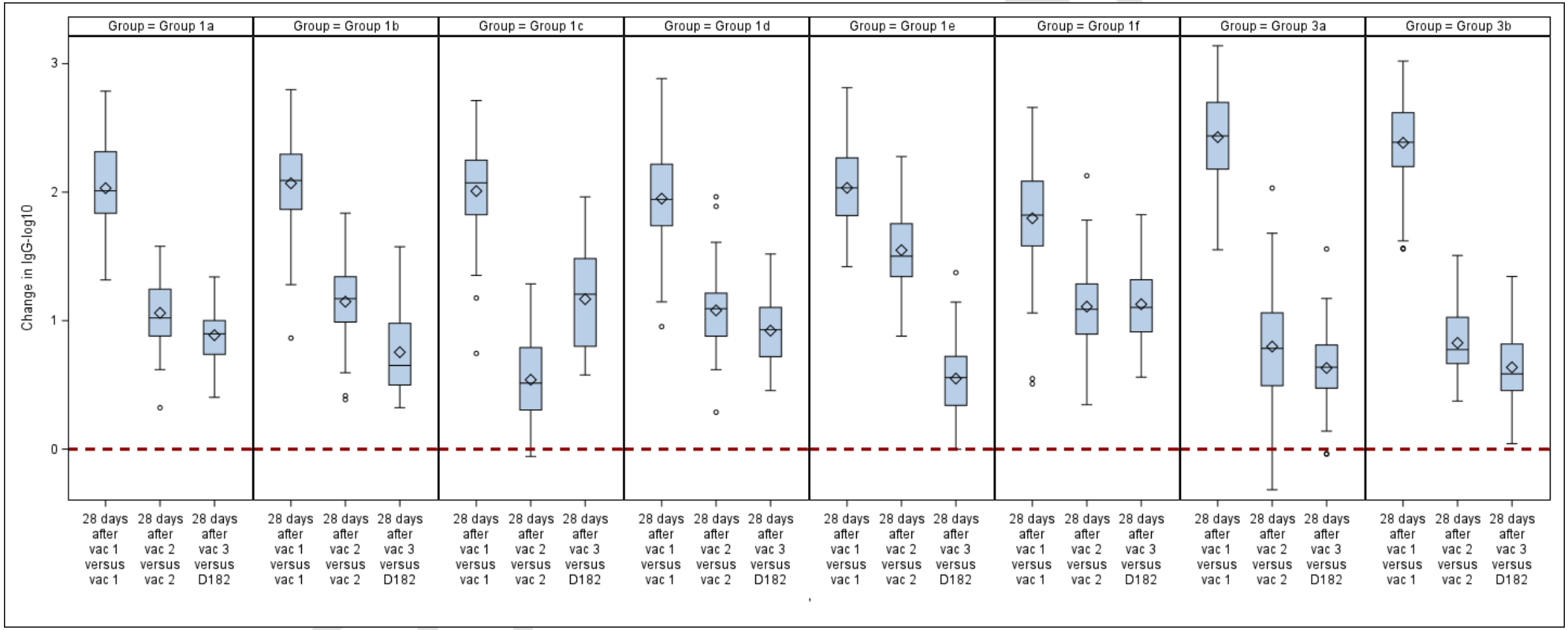
Difference in log_{10}-IgG										
Randomisation group	**Comparison**		**N**	**Mean**	**Std Dev**	**Median**	**25th Pctl**	**75th Pctl**	**Minimum**	**Maximum**
Group 1a	28 days after vac 1 versus vac 1		57	2.03	0.34	2.01	1.84	2.31	1.32	2.79
	28 days after vac 2 versus vac 2		57	1.06	0.26	1.02	0.88	1.24	0.32	1.58
	28 days after vac 3 versus D182		30	0.89	0.22	0.90	0.74	1.00	0.40	1.34
Group 1b	28 days after vac 1 versus vac 1		68	2.07	0.36	2.09	1.87	2.30	0.86	2.80
	28 days after vac 2 versus vac 2		68	1.15	0.28	1.17	0.99	1.34	0.39	1.84
	28 days after vac 3 versus D182		31	0.75	0.34	0.65	0.50	0.98	0.32	1.58
Group 1c	28 days after vac 1 versus vac 1		59	2.01	0.37	2.07	1.82	2.25	0.74	2.71
	28 days after vac 2 versus vac 2		59	0.54	0.31	0.51	0.31	0.79	-0.06	1.29
	28 days after vac 3 versus D182		32	1.17	0.38	1.21	0.80	1.48	0.58	1.96
Group 1d	28 days after vac 1 versus vac 1		69	1.95	0.39	1.94	1.74	2.22	0.95	2.88
	28 days after vac 2 versus vac 2		69	1.08	0.29	1.09	0.88	1.21	0.29	1.96
	28 days after vac 3 versus D182		35	0.92	0.26	0.93	0.72	1.10	0.46	1.52
Group 1e	28 days after vac 1 versus vac 1		52	2.03	0.31	2.03	1.82	2.27	1.42	2.81
	28 days after vac 2 versus vac 2		51	1.55	0.28	1.50	1.34	1.76	0.88	2.28
	28 days after vac 3 versus D182		29	0.55	0.31	0.56	0.34	0.72	-0.00	1.37
Group 1f	28 days after vac 1 versus vac 1		67	1.80	0.40	1.82	1.58	2.08	0.51	2.66
	28 days after vac 2 versus vac 2		67	1.11	0.33	1.09	0.90	1.29	0.35	2.13
	28 days after vac 3 versus D182		35	1.13	0.28	1.10	0.91	1.32	0.56	1.82
Group 3a	28 days after vac 1 versus vac 1		66	2.43	0.37	2.44	2.18	2.70	1.55	3.14
	28 days after vac 2 versus vac 2		66	0.80	0.40	0.78	0.49	1.06	-0.32	2.03
	28 days after vac 3 versus D182		34	0.63	0.34	0.64	0.48	0.81	-0.04	1.56
Group 3b	28 days after vac 1 versus vac 1		68	2.38	0.31	2.39	2.20	2.62	1.56	3.02
	28 days after vac 2 versus vac 2		68	0.83	0.26	0.77	0.67	1.03	0.37	1.51
	28 days after vac 3 versus D182		41	0.64	0.26	0.59	0.46	0.82	0.04	1.34

Figure 12: Change in log10-IgG, 28 days post vaccination compared to vaccination -mITT population

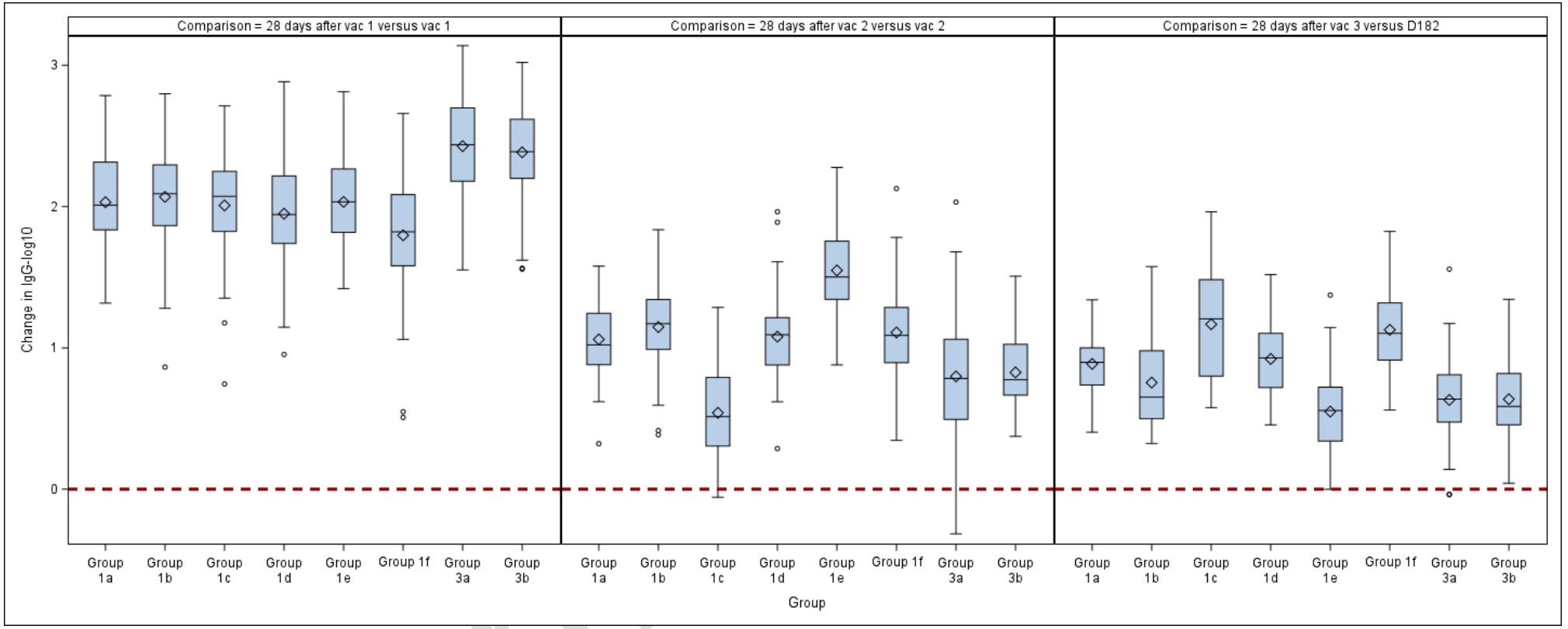
1a = 'Pfizer regular scheme'; 1b = 'Pfizer-Moderna scheme'; 1c ='Pfizer-AstraZeneca scheme'; 1d='Pfizer low dose scheme'; 1e = 'Pfizer long interval scheme'; 1f= 'Pfizer intradermal scheme'; 3a='Moderna regular scheme'; 3b='Moderna low dose scheme'

As for the 3rd COVID-19 vaccine dose, no sample of the day of vaccination is available, the sample of V5, D182 is used as this visit happened the closest before the 3rd COVID-19 vaccination

a) Per study group

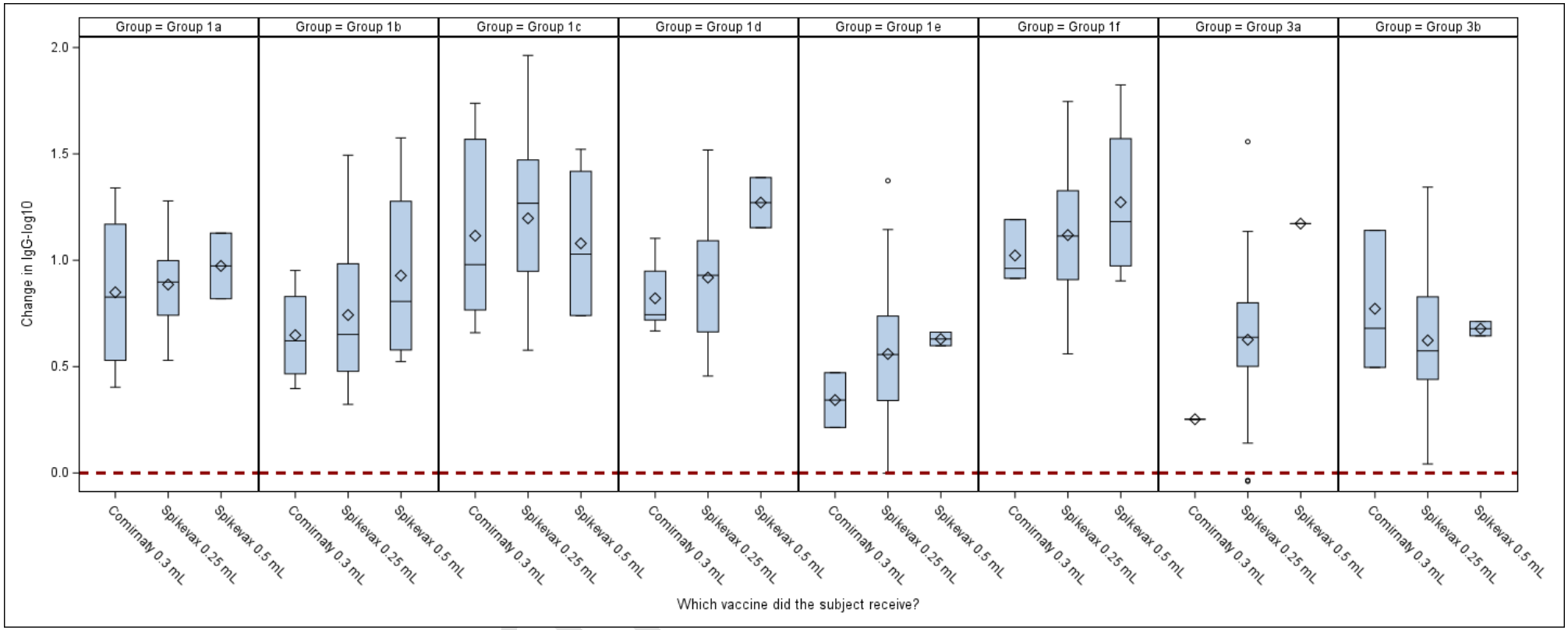


b) Per study visit



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c)Per vaccine brand/dose for the 3rd COVID-19 vaccine



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Table 22: Average change in log_{10}-IgG, 28 days post vaccination compared to vaccination for 1st and 2nd vaccination – mITT population

1a = 'Pfizer regular scheme'; 1b = 'Pfizer-Moderna scheme'; 1c ='Pfizer-AstraZeneca scheme'; 1d='Pfizer low dose scheme'; 1e = 'Pfizer long interval scheme'; 1f= 'Pfizer intradermal scheme'; 3a='Moderna regular scheme'; 3b='Moderna low dose scheme'

Randomisation group	Comparison	Mean change in log_{10}-IgG	Lower limit 95%CI	Upper limit 95%CI
Group 1a	28 days after vac 1 versus vac 1	2.0130	[1.9253;	2.1007]
Group 1b	28 days after vac 1 versus vac 1	2.0608	1.9804	2.1412
Group 1c	28 days after vac 1 versus vac 1	2.2181	2.1190	2.3172
Group 1d	28 days after vac 1 versus vac 1	1.9193	1.8389	1.9996
Group 1e	28 days after vac 1 versus vac 1	2.0191	1.9280	2.1102
Group 1f	28 days after vac 1 versus vac 1	1.7611	1.6805	1.8417
Group 3a	28 days after vac 1 versus vac 1	2.3847	2.3006	2.4687
Group 3b	28 days after vac 1 versus vac 1	2.3700	2.2881	2.4519
Group 1a	28 days after vac 2 versus vac 2	1.0896	1.0109	1.1683
Group 1b	28 days after vac 2 versus vac 2	1.1649	1.0928	1.2370
Group 1c	28 days after vac 2 versus vac 2	0.4910	0.4022	0.5799
Group 1d	28 days after vac 2 versus vac 2	1.1121	1.0400	1.1842
Group 1e	28 days after vac 2 versus vac 2	1.5765	1.4941	1.6590
Group 1f	28 days after vac 2 versus vac 2	1.1367	1.0644	1.2090
Group 3a	28 days after vac 2 versus vac 2	0.8486	0.7732	0.9240
Group 3b	28 days after vac 2 versus vac 2	0.8594	0.7859	0.9328

Table 23: Average change in log_{10}-IgG, 28 days post vaccination compared to vaccination for 1st and 2nd vaccination, mITTpopulation

1a = 'Pfizer regular scheme'; 1b = 'Pfizer-Moderna scheme'; 1c ='Pfizer-AstraZeneca scheme'; 1d='Pfizer low dose scheme'; 1e = 'Pfizer long interval scheme'; 1f= 'Pfizer intradermal scheme'; 3a='Moderna regular scheme'; 3b='Moderna low dose scheme'

Randomisation groups being compared			Difference in change in log_{10}-IgG	Lower limit 95%CI	Upper limit 95%CI	p value
Group 1b	Group 1a	28 days after vac 1 versus vac 1	0.04780	-0.06882	0.1644	0.4210
Group 1c	Group 1a	28 days after vac 1 versus vac 1	0.2051	0.07417	0.3360	0.0022
Group 1d	Group 1a	28 days after vac 1 versus vac 1	-0.09376	-0.2099	0.02239	0.1134
Group 1e	Group 1a	28 days after vac 1 versus vac 1	0.006080	-0.1183	0.1304	0.9235
Group 1f	Group 1a	28 days after vac 1 versus vac 1	-0.2519	-0.3689	-0.1349	<.0001
Group 3a	Group 1a	28 days after vac 1 versus vac 1	0.3716	0.2537	0.4896	<.0001
Group 3a	Group 3b	28 days after vac 1 versus vac 1	0.01464	-0.09750	0.1268	0.7976
Group 1b	Group 1a	28 days after vac 2 versus vac 2	0.07526	-0.02931	0.1798	0.1580
Group 1c	Group 1a	28 days after vac 2 versus vac 2	-0.5986	-0.7160	-0.4812	<.0001
Group 1d	Group 1a	28 days after vac 2 versus vac 2	0.02249	-0.08166	0.1266	0.6716
Group 1e	Group 1a	28 days after vac 2 versus vac 2	0.4869	0.3748	0.5991	<.0001
Group 1f	Group 1a	28 days after vac 2 versus vac 2	0.04706	-0.05783	0.1519	0.3785
Group 3a	Group 1a	28 days after vac 2 versus vac 2	-0.2410	-0.3468	-0.1353	<.0001
Group 3a	Group 3b	28 days after vac 2 versus vac 2	-0.01079	-0.1113	0.08976	0.8331

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Table 24: Average change in log_{10} -IgG, 28 days post third vaccine and D182 – mITT population

1a = 'Pfizer regular scheme'; 1b = 'Pfizer-Moderna scheme'; 1c ='Pfizer-AstraZeneca scheme'; 1d='Pfizer low dose scheme'; 1e = 'Pfizer long interval scheme'; 1f= 'Pfizer intradermal scheme'; 3a='Moderna regular scheme'; 3b='Moderna low dose scheme'

a)Per study group

Randomisation group	Comparison	Mean change in log_{10}-IgG	Lower limit 95%CI	Upper limit 95%CI
Group 1a	28 days after vac 3 versus D182	0.9216	0.8032	1.0401
Group 1b	28 days after vac 3 versus D182	0.7831	0.6642	0.9019
Group 1c	28 days after vac 3 versus D182	1.1732	1.0377	1.3086
Group 1d	28 days after vac 3 versus D182	0.9628	0.8492	1.0763
Group 1e	28 days after vac 3 versus D182	0.5737	0.4509	0.6964
Group 1f	28 days after vac 3 versus D182	1.1623	1.0501	1.2744
Group 3a	28 days after vac 3 versus D182	0.6565	0.5362	0.7767
Group 3b	28 days after vac 3 versus D182	0.6690	0.5584	0.7796

b)per brand and dose of the 3rd COVID-19 vaccine

Brand and dose of 3rd COVID-19 vaccine	Comparison	Mean difference in log_{10}-IgG	Lower limit 95%CI	Upper limit 95%CI
Comirnaty 0.3 mL	28 days after vac 3 versus D182	0.7692	0.6580	0.8804
Spikevax 0.25 mL	28 days after vac 3 versus D182	0.8649	0.8102	0.9195
Spikevax 0.5 mL	28 days after vac 3 versus D182	0.9542	0.8139	1.0944

Table 25: Difference in average change in log10-IgG, 28 days post third vaccine and D182, mITT population

1a = 'Pfizer regular scheme'; 1b = 'Pfizer-Moderna scheme'; 1c ='Pfizer-AstraZeneca scheme'; 1d='Pfizer low dose scheme'; 1e = 'Pfizer long interval scheme'; 1f= 'Pfizer intradermal scheme'; 3a='Moderna regular scheme'; 3b='Moderna low dose scheme'

a) per study group

Randomisation groups being compared			Difference in change in log_{10}-IgG	Lower limit 95%CI	Upper limit 95%CI	p value
Group 1b	Group 1a	28 days after vac 3 versus D182	-0.1386	-0.2908	0.01366	0.0742
Group 1c	Group 1a	28 days after vac 3 versus D182	0.2515	0.08585	0.4172	0.0031
Group 1d	Group 1a	28 days after vac 3 versus D182	0.04111	-0.1060	0.1883	0.5826
Group 1e	Group 1a	28 days after vac 3 versus D182	-0.3480	-0.5016	-0.1943	<.0001
Group 1f	Group 1a	28 days after vac 3 versus D182	0.2406	0.09281	0.3884	0.0015
Group 3a	Group 1a	28 days after vac 3 versus D182	-0.2652	-0.4139	-0.1164	0.0005
Group 3a	Group 3b	28 days after vac 3 versus D182	-0.01255	-0.1498	0.1247	0.8573

b)per brand and dose of 3rd COVID-19 vaccine

3rd vaccine groups being compared			Difference in change in log_{10}-IgG	Lower limit 95%CI	Upper limit 95%CI	p value
Comirnaty 0.3 mL	Spikevax 0.25 mL	28 days after vac 3 versus D182	-0.09564	-0.2173	0.02604	0.1229
Comirnaty 0.3 mL	Spikevax 0.5 mL	28 days after vac 3 versus D182	-0.1849	-0.3612	-0.00862	0.0399
Spikevax 0.25 mL	Spikevax 0.5 mL	28 days after vac 3 versus D182	-0.08929	-0.2300	0.05140	0.2125

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viii. Comparison of IgG levels of participants with and without COVID-19 breakthrough infection during the study

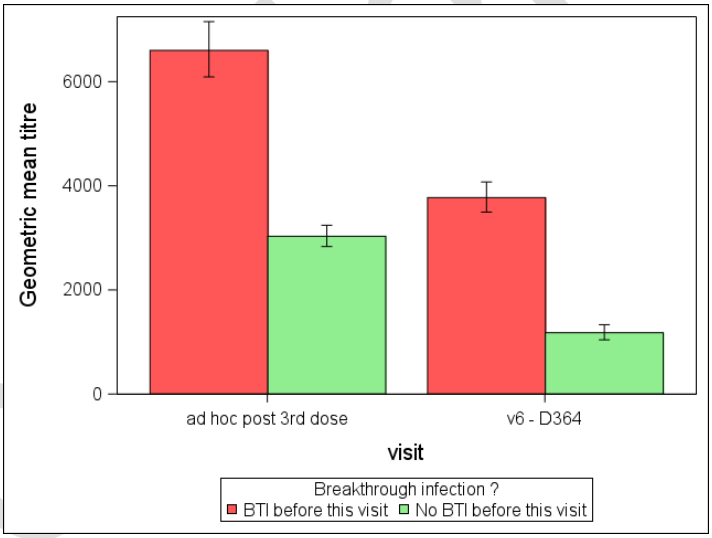
For the participants that received three vaccinations, IgG-RBD levels for those experiencing a breakthrough infection after the second vaccination were compared with the levels of participants without a COVID-19 infection.

Figure 13 displays the graphical representation of the results of the statistical analysis, while Table 26 presents the geometric mean ratios comparing the geometric mean titres for participants with and without a breakthrough infection. The difference is statistically significant for both visits, higher IgG levels are observed for participants with a COVID-19 infection, with a geometric mean ratio of 2.18 for the ad hoc post 3rd dose visit and of 3.20 for visit 6.

Table 26: GMR of IgG-RBD levels at ad hoc post 3rd dose visit and visit 6 comparing participants with a previous BTI and without a BTI

Comparison	Geometric mean Ratio and 95% CI	p value
Ad hoc post 3rd dose visite : BTI versus no BTI	2.18 [1.98; 2.40]	<.0001
Visit 6: BTI versus no BTI	3.20 [2.80; 3.66]	<.0001

Figure 13: GMR of the IgG-RBD levels at ad hoc post 3rd dose visit and visit 6 comparing participants with a previous BTI and without a BTI



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10.5 Neutralizing antibodies

At the primary endpoint (28 days after second vaccination) we tested for neutralizing antibody capacity against Wuhan in a whole-virus neutralisation assay on all available serum samples. Delta and Omicron BA.1 variants of SARS-CoV-2 in a whole-virus neutralisation assay were assessed on the humoral immunity subset of 30 samples per study group. At the ad hoc post third dose visit, neutralizing antibody capacity against Wuhan, Delta and Omicron BA.1 variants of SARS-CoV-2 in a whole-virus neutralisation assay were assessed on the same humoral immunity subset as used for the primary end-point, however all samples that tested positive for a recent COVID-19 infection at that timepoint, as confirmed using the Elecsys Anti-SARS-CoV-2assay, were excluded from the testing. The goal of the evaluation at this timepoint was to evaluate the effect of a third COVID-19-vaccine dose in the eight different study groups, without impact of a COVID-19-infection. Given the high incidence of Omicron BA.1 VOC at that moment, the Elecsys Anti-SARS-CoV-2 assay was necessary to use to identify the asymptomtically and undiagnosed COVID-19 infected subjects.

At visit 6 (D364), one year after the first COVID-19 vaccination of the study participants, we tested for neutralizing antibody capacity against Wuhan and Omicron BA.5 variant of SARS-CoV-2 in a whole-virus neutralisation assay in the subset of 30 samples per study group.

i. Titer values below the limit of detection

Table 27 displays the number of participants included in the statistical analysis for neutralizing antibodies (nAb) at each visit (primary endpoint visit, ad hoc post 3rd dose visit, or visit 6 (D364)). Additionally, the table provides the percentage of observations with a nAb level below the limit of detection, calculated based on these numbers. At the primary endpoint visit and the ad hoc post 3rd dose visit the Omicron strain presented in the table is BA.1, at visit 6 the Omicron strain presented in the table is BA.5.

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Table 28 displays the percentage of participants with nAb level below the limit of detection, for each study group at the primary endpoint visit. For the Wuhan strain we see that group 1c (Pfizer-AstraZeneca scheme) has relatively more participants with titers <LOD for NT90. For the Delta strain, groups 1c (Pfizer-AstraZeneca scheme) and 1f (Pfizer intradermal scheme) have more participants with titers <LOD (NT50 and NT90). Only a few participants in the subset have detectable titers for Omicron. The data of Omicron will not be explored any further.

ii. Descriptive statistics for nAb-levels 28 days post second vaccination and at adhoc post 3rd dose

Descriptive statistics (on the original scale IU/ml) and graphical displays (on the log_{10}-scale) are presented in Table 29/Table 30 and Figure 14/Figure 15.

Table 27: Participants with nAb levels below LOD – mITT population

1a = 'Pfizer regular scheme'; 1b = 'Pfizer-Moderna scheme'; 1c ='Pfizer-AstraZeneca scheme'; 1d='Pfizer low dose scheme'; 1e = 'Pfizer long interval scheme'; 1f= 'Pfizer intradermal scheme'; 3a='Moderna regular scheme'; 3b='Moderna low dose scheme'

Visit	nAb	N	% <LOD
visit 3/visit 4 PE	WUHAN NT50	503	0.40
	WUHAN NT90	503	2.58
	DELTA NT50	237	28.69
	DELTA NT90	237	48.95
	OMICRON NT50	237	96.20
	OMICRON NT90	237	98.31
ad hoc post 3rd dose	WUHAN NT50	139	0.00
	WUHAN NT90	139	1.44
	DELTA NT50	139	1.44
	DELTA NT90	139	5.04
	OMICRON NT50	139	8.63
	OMICRON NT90	139	41.73
visit 6	WUHAN NT50	54	0.00
	WUHAN NT90	54	3.70
	DELTA NT50	0	0
	DELTA NT90	0	0
	OMICRON NT50	54	44.44
	OMICRON NT90	54	68.52

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Table 28: Neutralizing antibodies at primary endpoint, per study group , % below LOD - mITT population

1a = 'Pfizer regular scheme'; 1b = 'Pfizer-Moderna scheme'; 1c ='Pfizer-AstraZeneca scheme'; 1d='Pfizer low dose scheme'; 1e = 'Pfizer long interval scheme'; 1f= 'Pfizer intradermal scheme'; 3a='Moderna regular scheme'; 3b='Moderna low dose scheme'

Randomisation group	nAB	N	% < LOD
Group 1a	WUHAN NT50	57	0.00
	WUHAN NT90	57	0.00
	DELTA NT50	29	24.14
	DELTA NT90	29	51.72
	OMICRON NT50	29	100.00
	OMICRON NT90	29	100.00
Group 1b	WUHAN NT50	66	0.00
	WUHAN NT90	66	0.00
	DELTA NT50	30	13.33
	DELTA NT90	30	33.33
	OMICRON NT50	30	96.67
	OMICRON NT90	30	96.67
Group 1c	WUHAN NT50	59	3.39
	WUHAN NT90	59	15.25
	DELTA NT50	30	76.67
	DELTA NT90	30	90.00
	OMICRON NT50	30	100.00
	OMICRON NT90	30	100.00
Group 1d	WUHAN NT50	69	0.00
	WUHAN NT90	69	1.45
	DELTA NT50	30	26.67
	DELTA NT90	30	56.67
	OMICRON NT50	30	100.00
	OMICRON NT90	30	100.00
Group 1e	WUHAN NT50	51	0.00
	WUHAN NT90	51	0.00
	DELTA NT50	28	3.57
	DELTA NT90	28	14.29
	OMICRON NT50	28	71.43
	OMICRON NT90	28	89.29
Group 1f	WUHAN NT50	67	0.00
	WUHAN NT90	67	4.48
	DELTA NT50	30	63.33
	DELTA NT90	30	83.33
	OMICRON NT50	30	100.00
	OMICRON NT90	30	100.00
Group 3a	WUHAN NT50	66	0.00
	WUHAN NT90	66	0.00
	DELTA NT50	30	10.00
	DELTA NT90	30	33.33
	OMICRON NT50	30	100.00
	OMICRON NT90	30	100.00
Group 3b	WUHAN NT50	68	0.00
	WUHAN NT90	68	0.00
	DELTA NT50	30	10.00
	DELTA NT90	30	26.67
	OMICRON NT50	30	100.00
	OMICRON NT90	30	100.00

Table 29: nAb-levels 28 days post second vaccination – mITT population

1a = 'Pfizer regular scheme'; 1b = 'Pfizer-Moderna scheme'; 1c ='Pfizer-AstraZeneca scheme'; 1d='Pfizer low dose scheme'; 1e = 'Pfizer long interval scheme'; 1f= 'Pfizer intradermal scheme'; 3a='Moderna regular scheme'; 3b='Moderna low dose scheme'

Randomisation group	nAb	N	Mean	Std Dev	50th Pctl	25th Pctl	75th Pctl	Minimum	Maximum
Group 1a	Wuhan NT50	57	783	528	618	378	1011	189	2628
	Delta NT50	29	123	77	104	84	177	39	362
Group 1b	Wuhan NT50	66	961	596	755	526	1450	126	3038
	Delta NT50	30	149	93	119	104	198	39	505
Group 1c	Wuhan NT50	59	297	179	236	177	404	39	859
	Delta NT50	30	56	41	39	39	39	39	237
Group 1d	Wuhan NT50	69	692	493	519	390	874	116	2471
	Delta NT50	30	118	79	109	39	154	39	416
Group 1e	Wuhan NT50	51	1604	897	1450	925	1935	396	4199
	Delta NT50	28	249	175	192	134	332	39	831
Group 1f	Wuhan NT50	67	566	467	459	245	789	89	3131
	Delta NT50	30	80	101	39	39	97	39	576
Group 3a	Wuhan NT50	66	1141	713	967	618	1510	236	4217
	Delta NT50	30	171	99	148	97	245	39	465
Group 3b	Wuhan NT50	68	1024	538	828	644	1278	213	2599
	Delta NT50	30	172	109	134	109	208	39	505

Table 30: nAb levels 28 days post third vaccination -mITT population

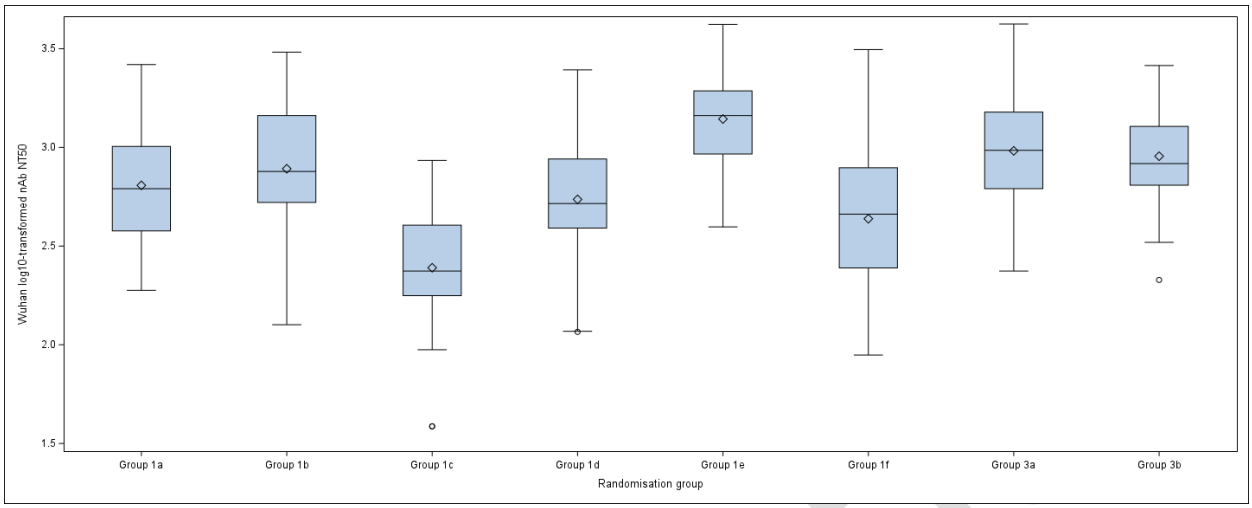
1a = 'Pfizer regular scheme'; 1b = 'Pfizer-Moderna scheme'; 1c ='Pfizer-AstraZeneca scheme'; 1d='Pfizer low dose scheme'; 1e = 'Pfizer long interval scheme'; 1f= 'Pfizer intradermal scheme'; 3a='Moderna regular scheme'; 3b='Moderna low dose scheme'

Randomisation group	nAb	N	Mean	Std Dev	50th Pctl	25th Pctl	75th Pctl	Minimum	Maximum
Group 1a	Wuhan NT50	17	2595	1845	2571	1586	3018	406	8449
	Delta NT50	17	758	572	586	424	927	132	2223
Group 1b	Wuhan NT50	19	2310	1764	1976	1245	2864	368	8293
	Delta NT50	19	648	570	604	198	766	143	2572
Group 1c	Wuhan NT50	16	2763	1985	1974	1212	3957	899	7374
	Delta NT50	16	907	738	750	329	1283	189	2832
Group 1d	Wuhan NT50	15	2648	1866	2486	1497	3360	247	7782
	Delta NT50	15	971	609	981	401	1220	39	1973
Group 1e	Wuhan NT50	15	2306	1429	2285	1076	3589	385	4426
	Delta NT50	15	682	546	643	278	916	222	2173
Group 1f	Wuhan NT50	16	2408	1521	2195	1230	3226	654	6277
	Delta NT50	16	753	553	483	398	948	245	2115
Group 3a	Wuhan NT50	19	3313	2660	2546	1272	4598	829	11372
	Delta NT50	19	821	612	560	396	1044	211	2088
Group 3b	Wuhan NT50	22	2133	1478	1734	942	3003	287	5627
	Delta NT50	22	563	480	438	244	705	39	2152

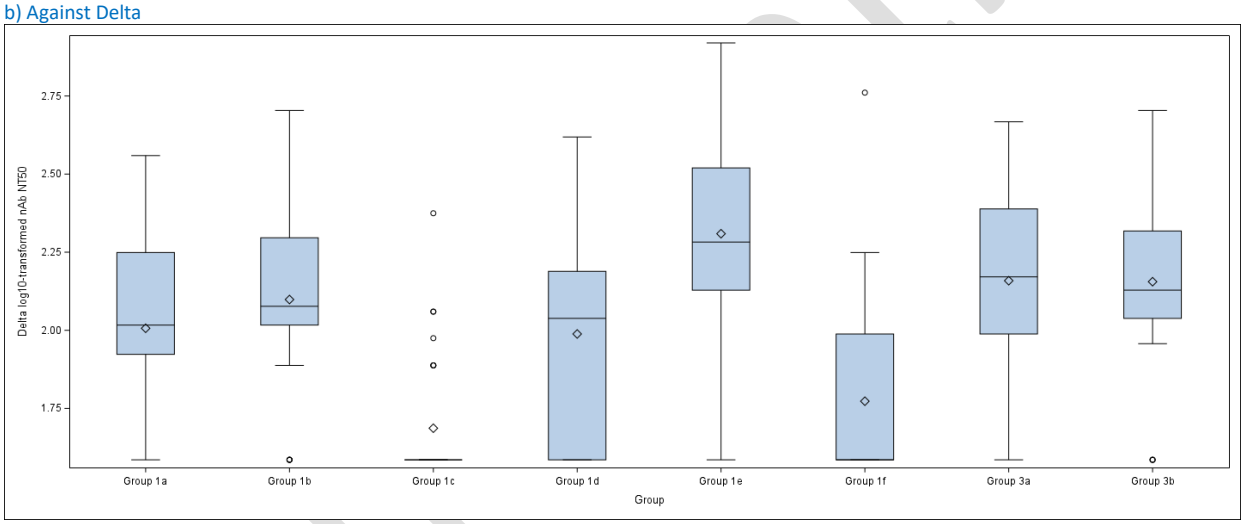
Figure 14 : log_{10} nAb levels 28 days post second vaccination -mITT population

1a = 'Pfizer regular scheme'; 1b = 'Pfizer-Moderna scheme'; 1c ='Pfizer-AstraZeneca scheme'; 1d='Pfizer low dose scheme'; 1e = 'Pfizer long interval scheme'; 1f= 'Pfizer intradermal scheme'; 3a='Moderna regular scheme'; 3b='Moderna low dose scheme'

a) Against Wuhan



b) Against Delta

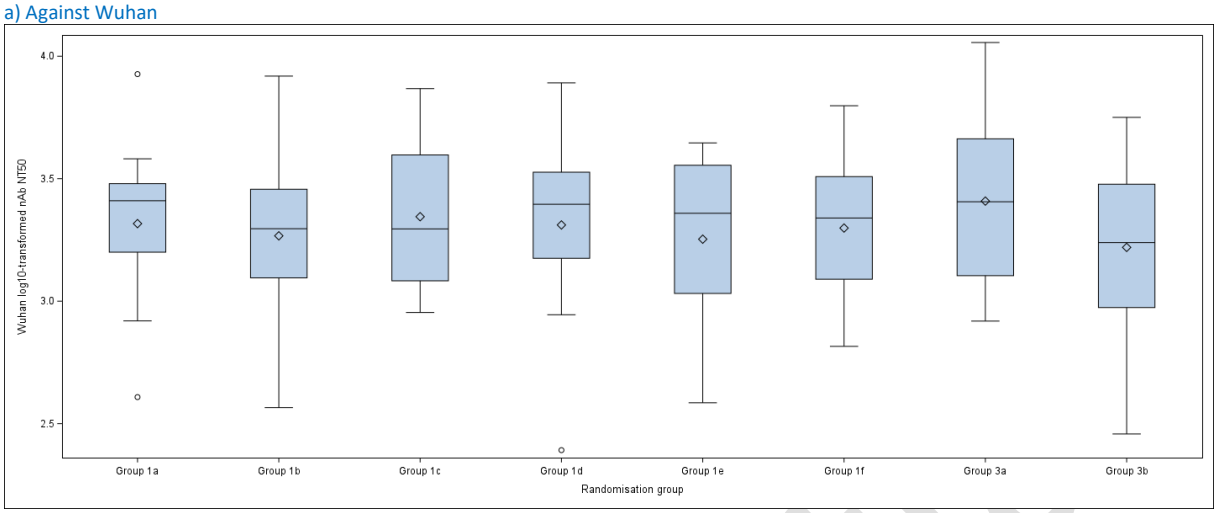


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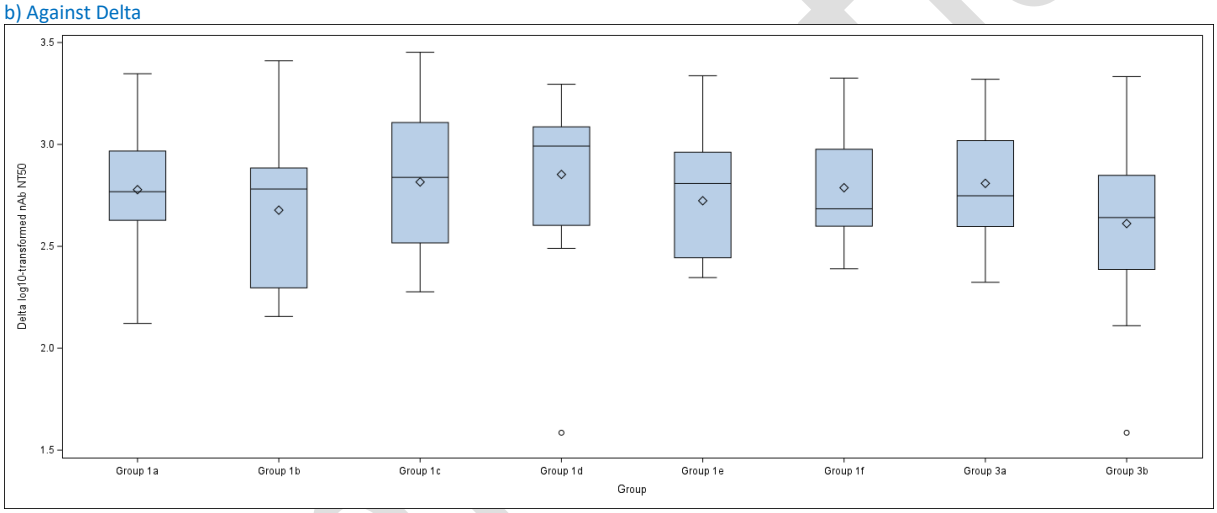
Figure 15: log_{10} nAb levels 28 days post third vaccination -mITT population

1a = 'Pfizer regular scheme'; 1b = 'Pfizer-Moderna scheme'; 1c ='Pfizer-AstraZeneca scheme'; 1d='Pfizer low dose scheme'; 1e = 'Pfizer long interval scheme'; 1f= 'Pfizer intradermal scheme'; 3a='Moderna regular scheme'; 3b='Moderna low dose scheme'

a) Against Wuhan



b) Against Delta



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iii. Non-inferiority of adapted schedules compared to reference schedule in nAb levels 28 days post second vaccine

The results of the non-inferiority analysis for Wuhan NT50 and Delta NT50 of different vaccines and adapted vaccine schedules compared to the reference schedule, 28 days post 2 vaccine doses, are displayed in Table 31 / Table 32 and Figure 16/Figure 17.

Age and gender adjusted geometric mean titres with 95% two-sided confidence intervals and the geometric mean ratio (adapted schedule/reference schedule) with 97.5% (FWER at the level of prime dose group) one-sided confidence interval are presented. Non-inferiority of the adapted schedule compared to the reference schedule is claimed if the lower limit of the confidence interval of the geometric mean ratio lies above 0.63. Inferiority of the adapted schedule compared to the reference schedule is claimed if the upper limit of the confidence interval of the geometric mean ratio lies below 0.63. An inconclusive result, presented as 'not non-inferior', is claimed if the confidence interval of the geometric mean ratio includes a ratio of 0.63, which represents the non-inferiority margin.

The reported p-values are for one-sided (upper) tests. For the Moderna comparison a p-value < 0.025 implies non-inferiority, for the Pfizer comparisons a p-value < 0.005 implies non-inferiority.

Adapted schedules Pfizer-Moderna (group 1b), Pfizer low dose (group 1d), and 'Pfizer long interval (group 1e) are found to be non-inferior to the standard Pfizer schedule (group 1a) for both Wuhan NT50 and Delta NT50 nAb levels. Furthermore, Moderna regular (group 3A) was also non-inferior to the standard Pfizer schedule (group 1a). Interestingly, 'Pfizer long interval (group 1e) showed significantly higher nAb levels for both Wuhan NT50 and Delta NT50 compared to the standard Pfizer schedule (group 1a).

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Table 31: GMT and GMR of nAb Wuhan NT50 at primary endpoint, comparison of the adapted schedules with the reference schedule

1a = 'Pfizer regular scheme'; 1b = 'Pfizer-Moderna scheme'; 1c ='Pfizer-AstraZeneca scheme'; 1d='Pfizer low dose scheme'; 1e = 'Pfizer long interval scheme'; 1f= 'Pfizer intradermal scheme'; 3a='Moderna regular scheme'; 3b='Moderna low dose scheme'

Analysis Population	Comparison	Geometric Mean of Standard Schedule and 95% CI	Geometric Mean of Adjusted Schedule and 95% CI	Geometric Mean Ratio	p value (one sided test)	Conclusion
mITT	1B VERSUS 1A	643 [521; 794]	815 [666; 997]	1.27 [0.95;+inf]	0.00000	Non-inferior
Per-protocol	1B VERSUS 1A	644 [522; 795]	808 [658; 992]	1.25 [0.93;+inf]	0.00000	Non-inferior
mITT	1C VERSUS 1A	643 [521; 794]	388 [305; 492]	0.60 [0.43;+inf]	0.64204	Not non-Inferior
Per-protocol	1C VERSUS 1A	644 [522; 795]	379 [298; 482]	0.59 [0.42;+inf]	0.70576	Not non-Inferior
mITT	1D VERSUS 1A	643 [521; 794]	541 [443; 661]	0.84 [0.63;+inf]	0.00455	Non-inferior
Per-protocol	1D VERSUS 1A	644 [522; 795]	537 [438; 658]	0.83 [0.62;+inf]	0.00712	Not non-inferior
mITT	1e VERSUS 1A	643 [521; 794]	1451 [1168; 1803]	2.26 [1.66;+inf]	0.00000	Non-inferior
Per-protocol	1e VERSUS 1A	644 [522; 795]	1400 [1121; 1747]	2.17 [1.59;+inf]	0.00000	Non-inferior
mITT	1F VERSUS 1A	643 [521; 794]	432 [353; 527]	0.67 [0.50;+inf]	0.28896	Not non-inferior
Per-protocol	1F VERSUS 1A	644 [522; 795]	445 [364; 545]	0.69 [0.52;+inf]	0.20847	Not non-inferior
mITT	3B VERSUS 3A	958 [797; 1152]	932 [776; 1119]	0.97 [0.81;+inf]	0.00000	Non-inferior
Per-protocol	3B VERSUS 3A	947 [786; 1142]	943 [783; 1135]	0.99 [0.83;+inf]	0.00000	Non-inferior

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Figure 16: GMT and GMR of nAb Wuhan NT50 at primary endpoint, comparison of the adapted schedules with the reference schedule - mITT population

1a = 'Pfizer regular scheme'; 1b = 'Pfizer-Moderna scheme'; 1c ='Pfizer-AstraZeneca scheme'; 1d='Pfizer low dose scheme'; 1e = 'Pfizer long interval scheme'; 1f= 'Pfizer intradermal scheme'; 3a='Moderna regular scheme'; 3b='Moderna low dose scheme'

Green line = non-inferiority margin

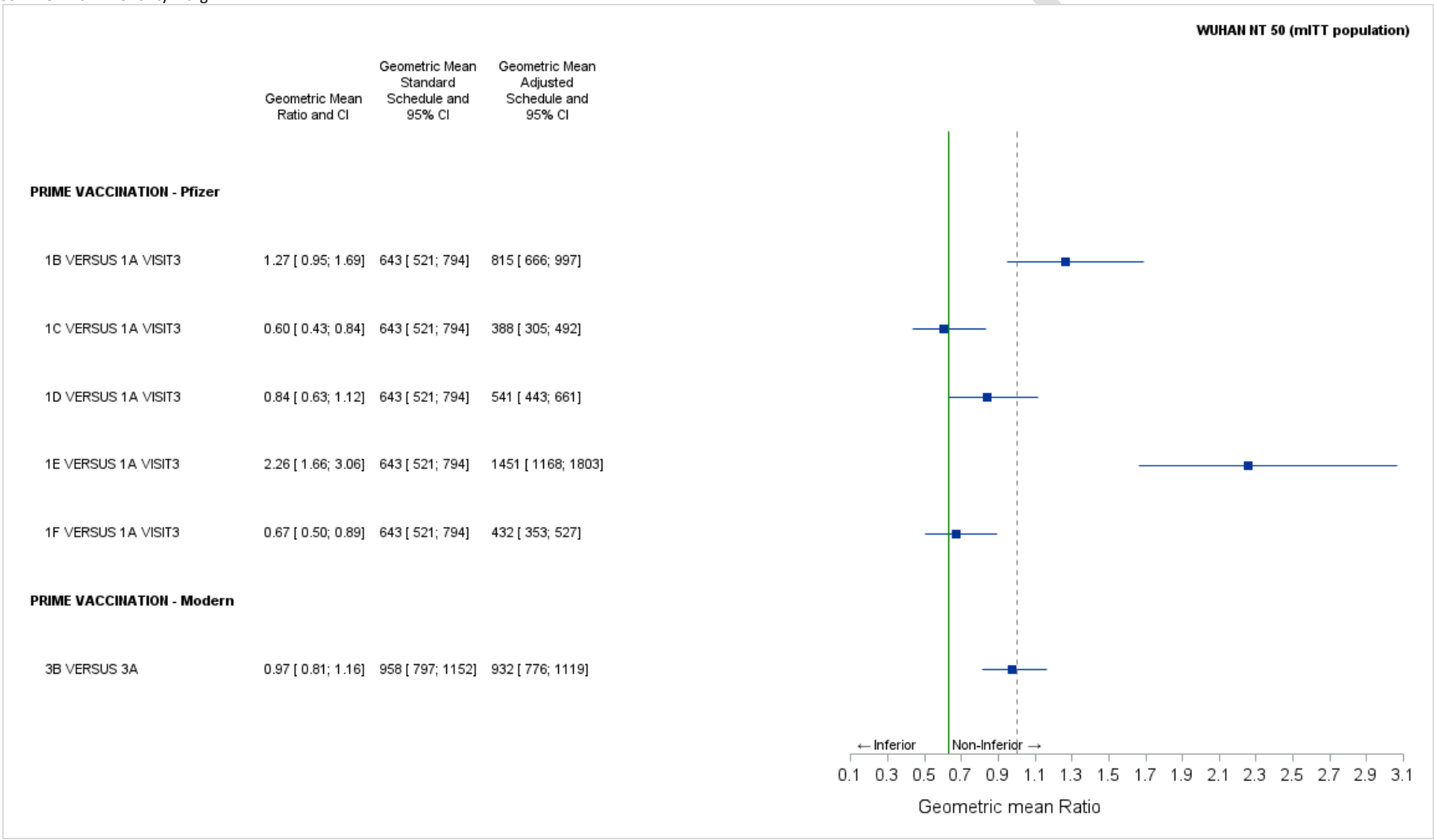


Table 32: GMT and GMR of the nAb Delta NT50 at primary endpoint, comparison of the adapted schedules with the reference schedule

1a = 'Pfizer regular scheme'; 1b = 'Pfizer-Moderna scheme'; 1c ='Pfizer-AstraZeneca scheme'; 1d='Pfizer low dose scheme'; 1e = 'Pfizer long interval scheme'; 1f= 'Pfizer intradermal scheme'; 3a='Moderna regular scheme'; 3b='Moderna low dose scheme'

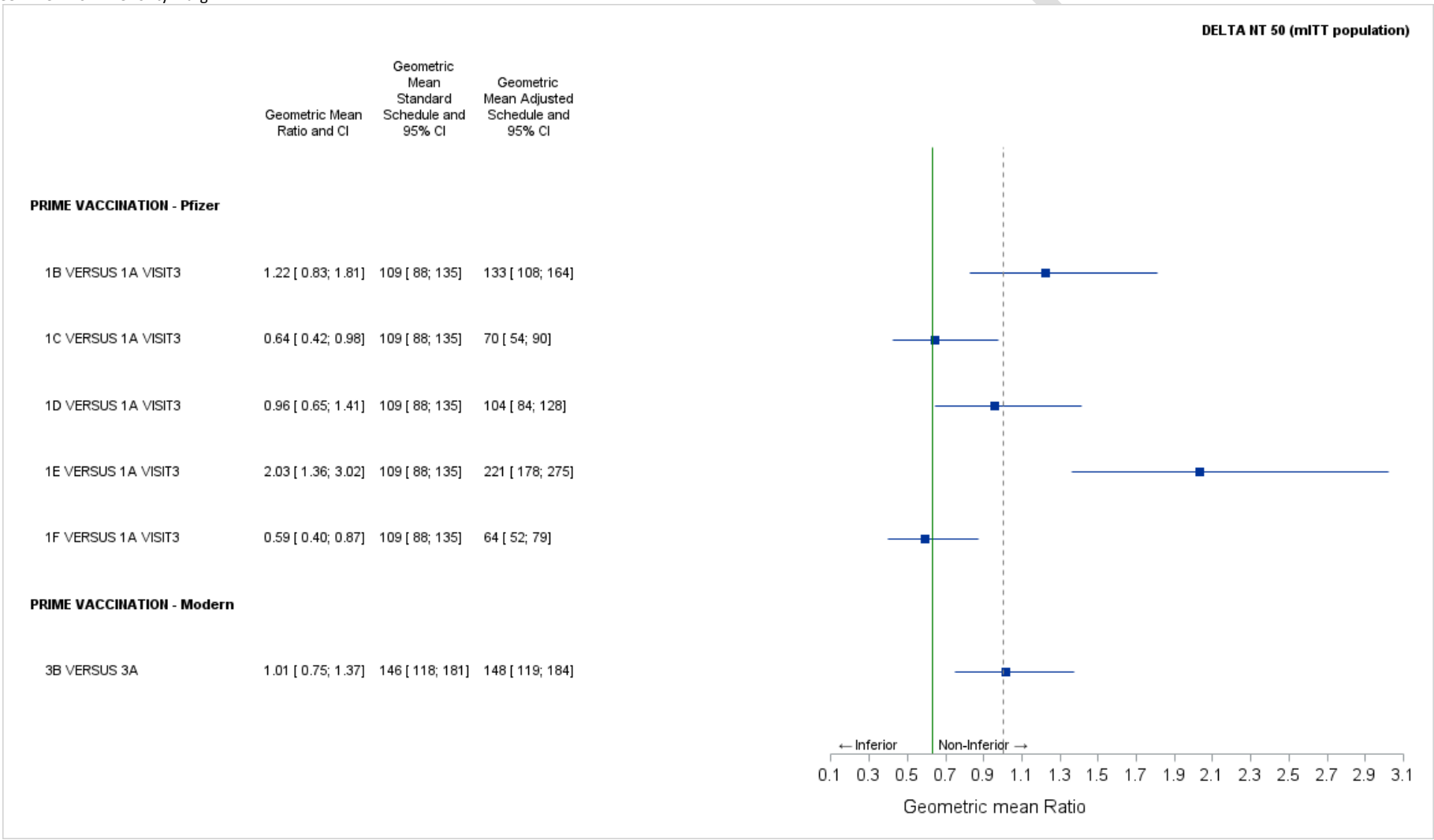
Analysis Population	Comparison	Geometric Mean of Standard Schedule and 95% CI	Geometric Mean of Adjusted Schedule and 95% CI	Geometric Mean Ratio and CI	p value (one sided test)	Conclusion
mITT	1B VERSUS 1A	109 [88; 135]	133 [108; 164]	1.22 [0.83;+inf]	0.00001	Non-inferior
Per-protocol	1B VERSUS 1A	109 [88; 135]	133 [108; 164]	1.22 [0.83;+inf]	0.00001	Non-inferior
mITT	1C VERSUS 1A	109 [88; 135]	70 [54; 90]	0.64 [0.42;+inf]	0.45626	Not non-inferior
Per-protocol	1C VERSUS 1A	109 [88; 135]	70 [54; 90]	0.64 [0.42;+inf]	0.45626	Not non-inferior
mITT	1D VERSUS 1A	109 [88; 135]	104 [84; 128]	0.96 [0.65;+inf]	0.00313	Non-inferior
Per-protocol	1D VERSUS 1A	109 [88; 135]	104 [84; 128]	0.96 [0.65;+inf]	0.00313	Non-inferior
mITT	1e VERSUS 1A	109 [88; 135]	221 [178; 275]	2.03 [1.36;+inf]	0.00000	Non-inferior
Per-protocol	1e VERSUS 1A	109 [88; 135]	221 [178; 275]	2.03 [1.36;+inf]	0.00000	Non-inferior
mITT	1F VERSUS 1A	109 [88; 135]	64 [52; 79]	0.59 [0.40;+inf]	0.67547	Not non-Inferior
Per-protocol	1F VERSUS 1A	109 [88; 135]	64 [52; 79]	0.59 [0.40;+inf]	0.67547	Not non-Inferior
mITT	3B VERSUS 3A	146 [118; 181]	148 [119; 184]	1.01 [0.75;+inf]	0.00146	Non-inferior
Per-protocol	3B VERSUS 3A	146 [118; 181]	148 [119; 184]	1.01 [0.75;+inf]	0.00146	Non-inferior

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Figure 17 : GMT and GMR of the nAb Delta NT50 at primary endpoint, comparison of the adapted schedules with the reference schedule – mITT population

1a = 'Pfizer regular scheme'; 1b = 'Pfizer-Moderna scheme'; 1c ='Pfizer-AstraZeneca scheme'; 1d='Pfizer low dose scheme'; 1e = 'Pfizer long interval scheme'; 1f= 'Pfizer intradermal scheme'; 3a='Moderna regular scheme'; 3b='Moderna low dose scheme'

Green line = non-inferiority margin



iv. Comparison of study groups for the proportion of participants with detectable nAb titres, 28 days post second vaccine

A significant number of participants had NT50 levels below the limit of detection (LOD) for Delta and Omicron. Therefore, the variables are also transformed into binary variables, nAb levels below and above the LOD and the study groups are compared in terms of the percentage of participants below LOD.

Table 33 displays the (for age and gender adjusted) odds ratios for nAb levels below the limit of detection. These odds ratios are presented for both the adapted schedules compared to the reference schedule, as well as for the comparison between the two reference schedules (groups 1a and 3a).

At the primary endpoint visit (28 days after second vaccination), the odds of having a Delta NT50 value below the limit of detection are greater in Pfizer-AstraZeneca scheme (group 1c), Pfizer low dose scheme (group 1d) and Pfizer intradermal scheme (group 1f) than in Pfizer regular scheme (group 1a). However, there is no significant difference in odds observed between the Moderna regular scheme (group 3a) and Moderna low dose scheme (group 3b). Additionally, the Pfizer long interval scheme (group 1e) exhibits higher odds of having an Omicron NT50 value below the limit of detection compared to the Pfizer reference scheme (group 1a).

Table 33: Odds-Ratios of having a nAb value below the limit of detection, at primary endpoint, comparison of the adapted schedules with the reference schedule and comparison of the reference schedules

1a = 'Pfizer regular scheme'; 1b = 'Pfizer-Moderna scheme'; 1c ='Pfizer-AstraZeneca scheme'; 1d='Pfizer low dose scheme'; 1e = 'Pfizer long interval scheme'; 1f= 'Pfizer intradermal scheme'; 3a='Moderna regular scheme'; 3b='Moderna low dose scheme'

nAb	Comparison	Odds-Ratio (95%CI)	p value
DELTA NT50	Group 1B versus 1A	0.5 [0.1; 1.9]	0.2976
DELTA NT50	Group 1C versus 1A	4.6 [1.3; 16.4]	0.0172
DELTA NT50	Group 1D versus 1A	1.2 [0.3; 3.9]	0.8186
DELTA NT50	Group 1e versus 1A	0.1 [0.0; 1.0]	0.0498
DELTA NT50	Group 1F versus 1A	5.9 [1.8; 19.6]	0.0033
DELTA NT50	Group 3A versus 1A	0.5 [0.1; 2.0]	0.2918
DELTA NT50	Group 3B versus 3A	0.9 [0.2; 4.8]	0.9337
OMICRON NT	Group 1B versus 1A	0.4 [0.0; 11.6]	0.6266
OMICRON NT	Group 1C versus 1A	0.1 [0.0; 6.8]	0.2615
OMICRON NT	Group 1D versus 1A	1.3 [0.0; 66.3]	0.9119
OMICRON NT	Group 1e versus 1A	0.0 [0.0; 0.5]	0.0155
OMICRON NT	Group 1F versus 1A	1.2 [0.0; 66.3]	0.9191
OMICRON NT	Group 3A versus 1A	1.3 [0.0; 65.3]	0.9093
OMICRON NT	Group 3B versus 3A	1.0 [0.0; 53.3]	0.9920

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v. Non-inferiority of adapted schedules compared to reference schedule in nAb levels 28 days post 3rd vaccine

Results of the non-inferiority analyses 28 days post 3rd COVID-19 vaccine of the adapted vaccine schedules in comparison with the standard schedule, are presented in Table 34/Table 35 and Figure 18/Figure 19. Note that only COVID-19 naïve participants (in the subset) are included in this analysis, and thus the amount of available data is rather limited. Results should be interpreted with caution.

Geometric mean titres - adjusted for age, gender and brand and dose of the third study vaccine - with 95% two-sided confidence intervals and the geometric mean ratio (adapted schedule/reference schedule) with 97.5% (FWER at the level of prime dose group) one-sided confidence interval are presented. Non-inferiority of the adapted schedule compared to the reference schedule is claimed if the lower limit of the confidence interval of the geometric mean ratio lies above 0.63. Inferiority of the adapted schedule compared to the reference schedule is claimed if the upper limit of the confidence interval of the geometric mean ratio lies below 0.63. An inconclusive result, presented as not non-inferior, is claimed if the confidence interval of the geometric mean ratio includes a ratio of 0.63, which represents the non-inferiority margin.

The reported p-values are for one-sided (upper) tests. For the Moderna comparison a p-value < 0.025 implies non-inferiority, for the Pfizer comparisons a p-value < 0.005 implies non-inferiority.

As a sensitivity analysis, the model is also fitted to the data, excluding visits that took place out-of-window at ad hoc 3rd dose visit (not within 28 +/-5 days after the third vaccine).

Twenty-eight days post 3rd COVID-19 vaccine, non-inferiority could only be demonstrated for group 1C as compared to group 1A.

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Table 34 : GMT and GMR of nAb Wuhan NT50 28 days post 3rd vaccine, comparison of the adapted schedules with the reference schedule

1a = 'Pfizer regular scheme'; 1b = 'Pfizer-Moderna scheme'; 1c ='Pfizer-AstraZeneca scheme'; 1d='Pfizer low dose scheme'; 1e = 'Pfizer long interval scheme'; 1f= 'Pfizer intradermal scheme'; 3a='Moderna regular scheme'; 3b='Moderna low dose scheme'

Analysis Population	Comparison	Geometric Mean of Standard Schedule and 95% CI	Geometric Mean of Adjusted Schedule and 95% CI	Geometric Mean Ratio and CI	p value (one sided test)	Conclusion
mITT voor PE and having 3rd dose	1B VERSUS 1A	1990 [1328; 2981]	1730 [1163; 2574]	0.87 [0.47;+inf]	0.08971	Not non-inferior
Ad hoc visit in window	1B VERSUS 1A	1983 [1233; 3190]	1623 [979; 2691]	0.82 [0.39;+inf]	0.17614	Not non-inferior
mITT voor PE and having 3rd dose	1C VERSUS 1A	1990 [1328; 2981]	2947 [1824; 4763]	1.48 [0.73;+inf]	0.00112	Non-inferior
Ad hoc visit in window	1C VERSUS 1A	1983 [1233; 3190]	2974 [1745; 5066]	1.50 [0.69;+inf]	0.00202	Non-inferior
mITT voor PE and having 3rd dose	1D VERSUS 1A	1990 [1328; 2981]	1948 [1266; 2996]	0.98 [0.51;+inf]	0.04197	Not non-inferior
Ad hoc visit in window	1D VERSUS 1A	1983 [1233; 3190]	2154 [1310; 3541]	1.09 [0.50;+inf]	0.03429	Not non-inferior
mITT voor PE and having 3rd dose	1e VERSUS 1A	1990 [1328; 2981]	1682 [1104; 2563]	0.85 [0.44;+inf]	0.12448	Not non-inferior
Ad hoc visit in window	1e VERSUS 1A	1983 [1233; 3190]	1892 [1171; 3057]	0.95 [0.44;+inf]	0.08192	Not non-inferior
mITT voor PE and having 3rd dose	1F VERSUS 1A	1990 [1328; 2981]	1907 [1274; 2853]	0.96 [0.50;+inf]	0.04843	Not non-inferior
Ad hoc visit in window	1F VERSUS 1A	1983 [1233; 3190]	1976 [1197; 3263]	1.00 [0.46;+inf]	0.06045	Not non-inferior
mITT voor PE and having 3rd dose	3B VERSUS 3A	2721 [1220; 6067]	1640 [793; 3394]	0.60 [0.37;+inf]	0.57356	Not non-inferior
Ad hoc visit in window	3B VERSUS 3A	3232 [1375; 7596]	2340 [1005; 5449]	0.72 [0.38;+inf]	0.33100	Not non-inferior

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Figure 18: GMT and GMR of nAb Wuhan NT50 28 days post 3rd vaccine, comparison of the adapted schedules with the reference schedule

1a = 'Pfizer regular scheme'; 1b = 'Pfizer-Moderna scheme'; 1c ='Pfizer-AstraZeneca scheme'; 1d='Pfizer low dose scheme'; 1e = 'Pfizer long interval scheme'; 1f= 'Pfizer intradermal scheme'; 3a='Moderna regular scheme'; 3b='Moderna low dose scheme'

Green line = non-inferiority margin

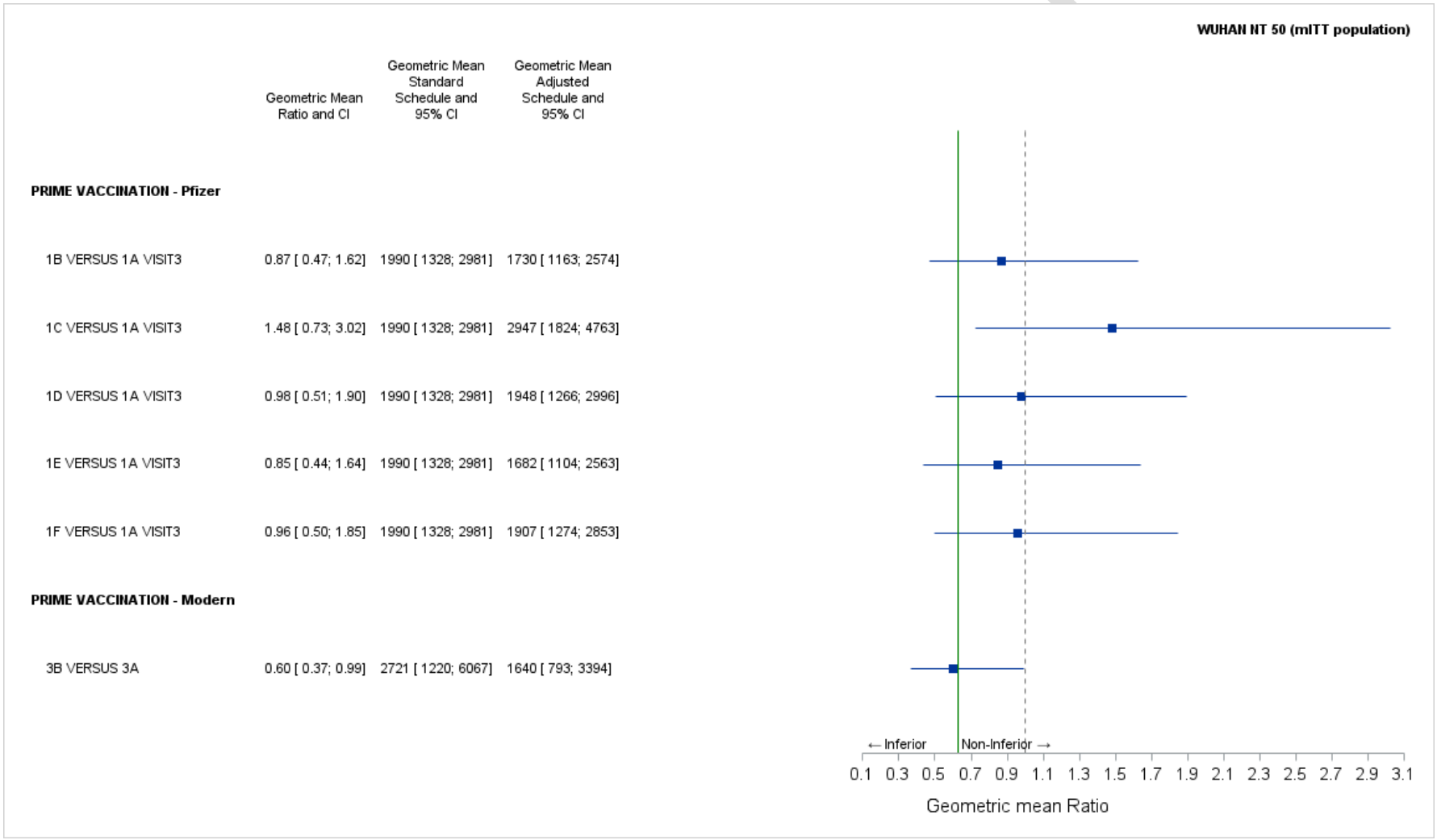


Table 35: GMT and GMR of nAb Delta NT50 28 days post 3rd vaccine, comparison of the adapted schedules with the reference schedule

1a = 'Pfizer regular scheme'; 1b = 'Pfizer-Moderna scheme'; 1c ='Pfizer-AstraZeneca scheme'; 1d='Pfizer low dose scheme'; 1e = 'Pfizer long interval scheme'; 1f= 'Pfizer intradermal scheme'; 3a='Moderna regular scheme'; 3b='Moderna low dose scheme'

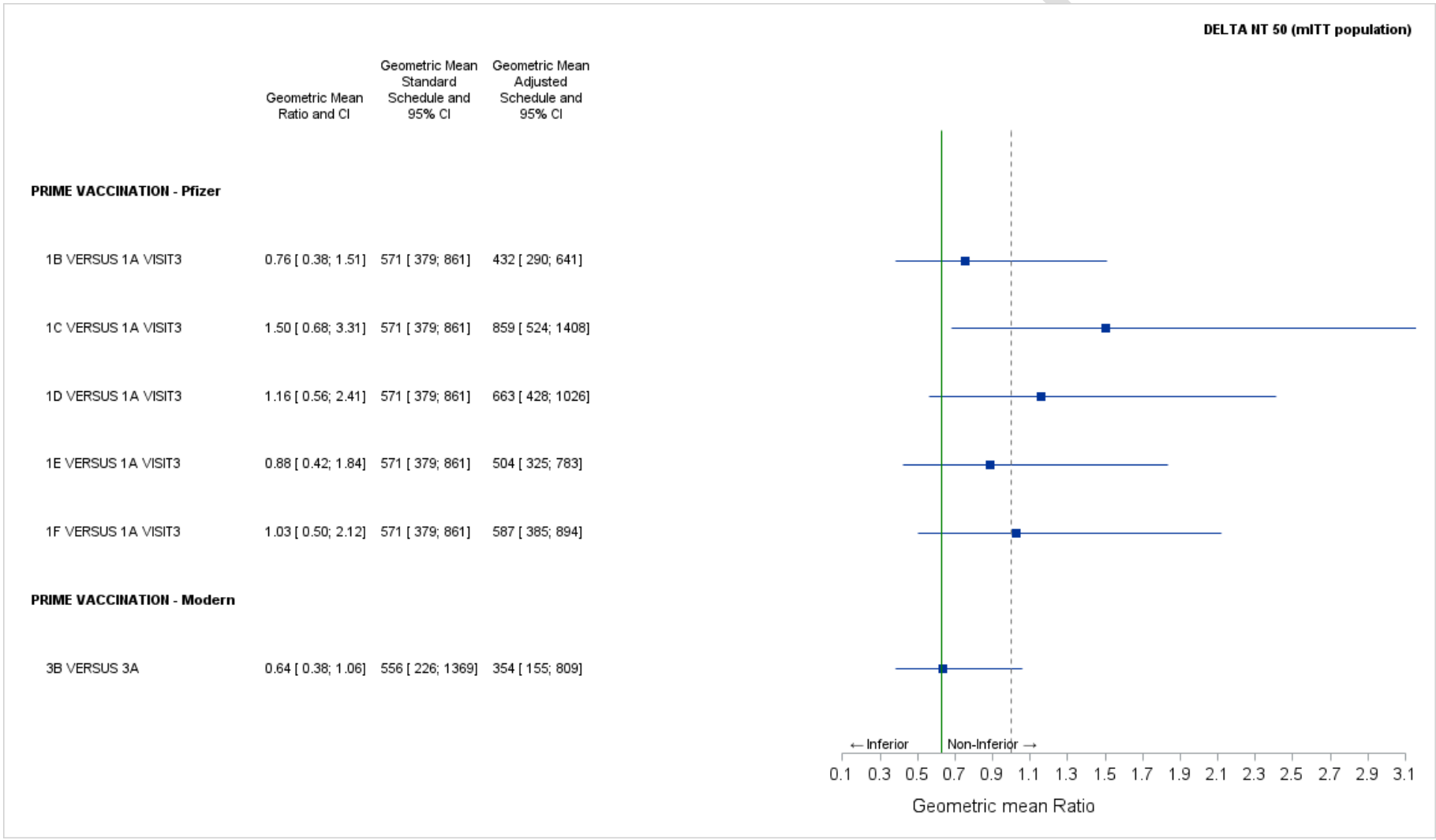
Analysis Population	Comparison	Geometric Mean of Standard Schedule and 95% CI	Geometric Mean of Adjusted Schedule and 95% CI	Geometric Mean Ratio and CI	p value (one sided test)	Conclusion
mITT voor PE and having 3rd dose	1B VERSUS 1A	571 [379; 861]	432 [290; 641]	0.76 [0.38;+inf]	0.24595	Not non-inferior
Ad hoc visit in window	1B VERSUS 1A	550 [340; 890]	413 [252; 678]	0.75 [0.33;+inf]	0.28493	Not non-inferior
mITT voor PE and having 3rd dose	1C VERSUS 1A	571 [379; 861]	859 [524; 1408]	1.50 [0.68;+inf]	0.00238	Non-inferior
Ad hoc visit in window	1C VERSUS 1A	550 [340; 890]	821 [476; 1416]	1.49 [0.64;+inf]	0.00462	Non-inferior
mITT voor PE and having 3rd dose	1D VERSUS 1A	571 [379; 861]	663 [428; 1026]	1.16 [0.56;+inf]	0.01548	Not non-inferior
Ad hoc visit in window	1D VERSUS 1A	550 [340; 890]	734 [446; 1209]	1.34 [0.57;+inf]	0.01171	Not non-inferior
mITT voor PE and having 3rd dose	1e VERSUS 1A	571 [379; 861]	504 [325; 783]	0.88 [0.42;+inf]	0.11509	Not non-inferior
Ad hoc visit in window	1e VERSUS 1A	550 [340; 890]	553 [335; 912]	1.00 [0.43;+inf]	0.07695	Not non-inferior
mITT voor PE and having 3rd dose	1F VERSUS 1A	571 [379; 861]	587 [385; 894]	1.03 [0.50;+inf]	0.03962	Not non-inferior
Ad hoc visit in window	1F VERSUS 1A	550 [340; 890]	585 [346; 987]	1.06 [0.45;+inf]	0.05469	Not non-inferior
mITT voor PE and having 3rd dose	3B VERSUS 3A	556 [226; 1369]	354 [155; 809]	0.64 [0.38;+inf]	0.48837	Not non-inferior
Ad hoc visit in window	3B VERSUS 3A	753 [313; 1812]	525 [221; 1244]	0.70 [0.36;+inf]	0.37633	Not non-inferior

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Figure 19: GMT and GMR of nAb Delta NT50 28 days post 3rd vaccine, comparison of the adapted schedules with the reference schedule

1a = 'Pfizer regular scheme'; 1b = 'Pfizer-Moderna scheme'; 1c ='Pfizer-AstraZeneca scheme'; 1d='Pfizer low dose scheme'; 1e = 'Pfizer long interval scheme'; 1f= 'Pfizer intradermal scheme'; 3a='Moderna regular scheme'; 3b='Moderna low dose scheme'

Green line = non-inferiority margin



vi. Comparison of nAb levels of participants with and without a COVID-19 breakthrough infection during the study.

For the participants that received three COVID-19 vaccinations as described in the protocol, nAb levels for those experiencing a breakthrough infection after the second vaccination were compared with the levels of participants without a COVID-19 infection. Table 36 shows the percentage of participants, included in this comparison, with levels of the Delta nAb below the limit of detection (<LOD). All Wuhan nAb levels at the ad hoc post 3rd dose visit and at visit 6 were above the LOD.

Figure 20 displays the graphical representation of the results of the statistical analysis, while Table 37 presents the geometric mean ratios comparing the geometric means for participants with and without a breakthrough infection. For Wuhan-Hu-1 and Delta (B.1.617.2) variant of concern (VOC) the difference is statistically significant for both visits, higher nAb levels are observed for participants with a COVID-19 infection, with geometric mean ratio's lager than 1 and the GMR for the ad hoc post 3rd dose visit smaller than the GMR at visit 6.

Table 36: *Delta NT50,* % < LOD

1a = 'Pfizer regular scheme'; 1b = 'Pfizer-Moderna scheme'; 1c ='Pfizer-AstraZeneca scheme'; 1d='Pfizer low dose scheme'; 1e = 'Pfizer long interval scheme'; 1f= 'Pfizer intradermal scheme'; 3a='Moderna regular scheme'; 3b='Moderna low dose scheme'

DELTA NT50			
Visit	**Randomisation group**	**N**	**% < LOD**
ad hoc post 3rd dose	Group 1a	18	0.00
	Group 1b	21	0.00
	Group 1c	16	0.00
	Group 1d	17	5.88
	Group 1e	17	0.00
	Group 1f	20	0.00
	Group 3a	21	0.00
	Group 3b	23	4.35

Table 37: GMR of nAb levels at ad hoc post 3rd dose and 6 visit comparing participants with a previous BTI and without a BTI

1a = 'Pfizer regular scheme'; 1b = 'Pfizer-Moderna scheme'; 1c ='Pfizer-AstraZeneca scheme'; 1d='Pfizer low dose scheme'; 1e = 'Pfizer long interval scheme'; 1f= 'Pfizer intradermal scheme'; 3a='Moderna regular scheme'; 3b='Moderna low dose scheme'

a)Wuhan NT50

Comparison	**Geometric mean Ratio (95% CI)**	**pvalue**
Ad hoc post 3rd dose visite : BTI versus no BTI	2.05 [1.35; 3.09]	0.0007
Visit 6: BTI versus no BTI	3.65 [2.94; 4.53]	<.0001

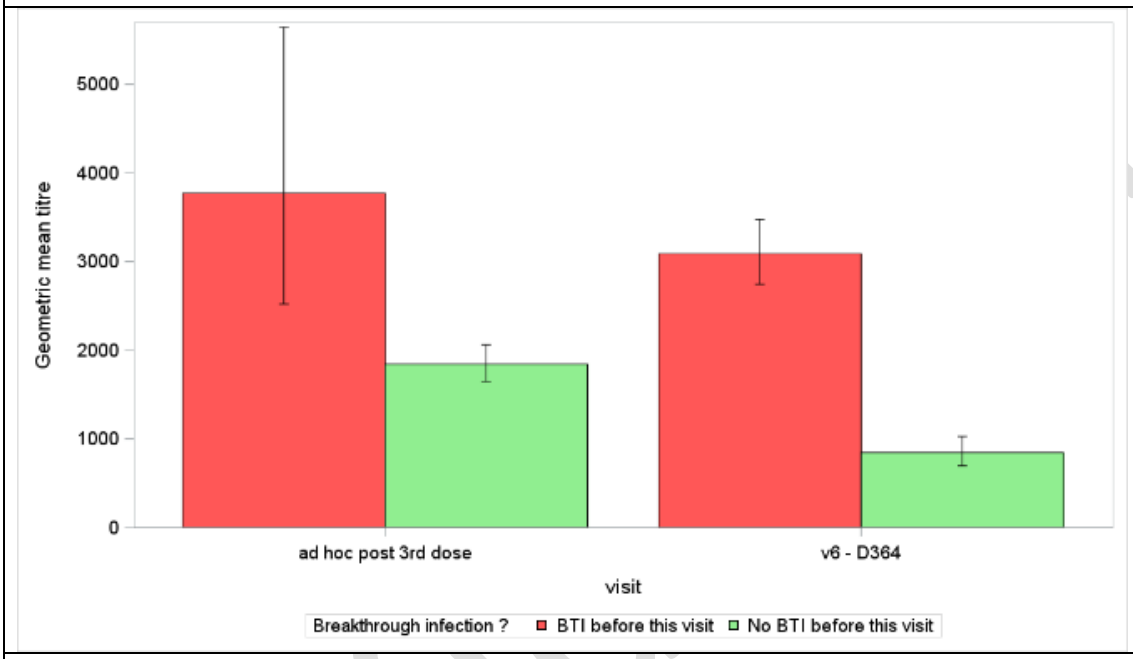
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b)DeltaNT50

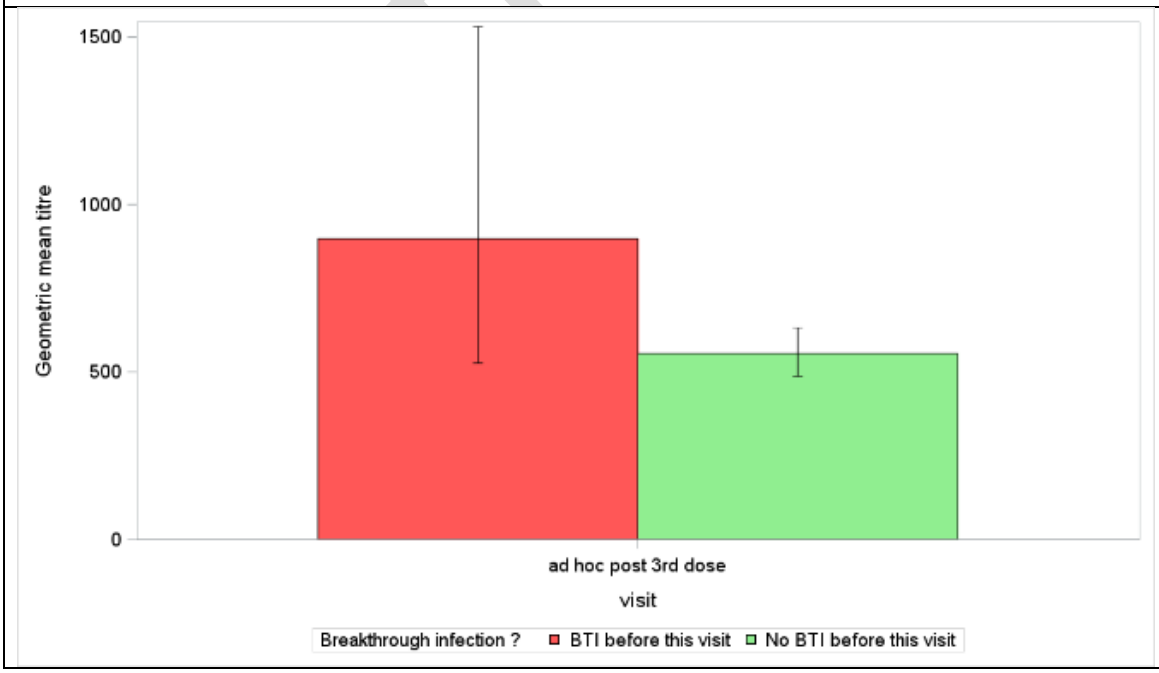
Comparison	Geometric mean Ratio (95% CI)	pvalue
ad hoc post 3rd dose	1.62 [0.93; 2.81]	0.0865

Figure 20: GMT of nAb levels at ad hoc post 3rd dose visit and visit 6 comparing participants with a previous BTI and without a BTI

Wuhan NT50



Delta NT50



vii. Conversion factors: neutralizing and receptor binding antibodies

For the nAb titers evaluated at the primary endpoint visit, scatterplots are used to display the association between IgG level and Nab level.

In general, there is a strong correlation between IgG levels and the titers of the Wuhan and Delta strain.

Due to a high proportion of participants in study groups 1C and 1F having Delta NT50 levels below the limit of detection, the conversion factors involving Delta NT50 are not calculated for these groups. Moreover, the statistical analyses for the conversion factor related to Delta NT50 are limited to participants who have measurable Delta NT50 levels.

Table 38 and Figure 22 illustrate the participant-to-participant variability in the conversion factors. The conversion factor for Wuhan-nAb/anti-RBD-IgG is around 1.33 times the conversion factor for Delta-nAb/ anti-RBD-IgG across different study groups. Differences in the conversion factors among the study groups are observed.

Table 39 presents the mean values obtained from the mixed models. Table 40 highlights the statistically significant pairwise comparisons between the treatment groups at a 5% significance level.

Focusing on the comparison between the adapted schedule and the reference schedules, and the comparison of the two reference schedules we observe that:

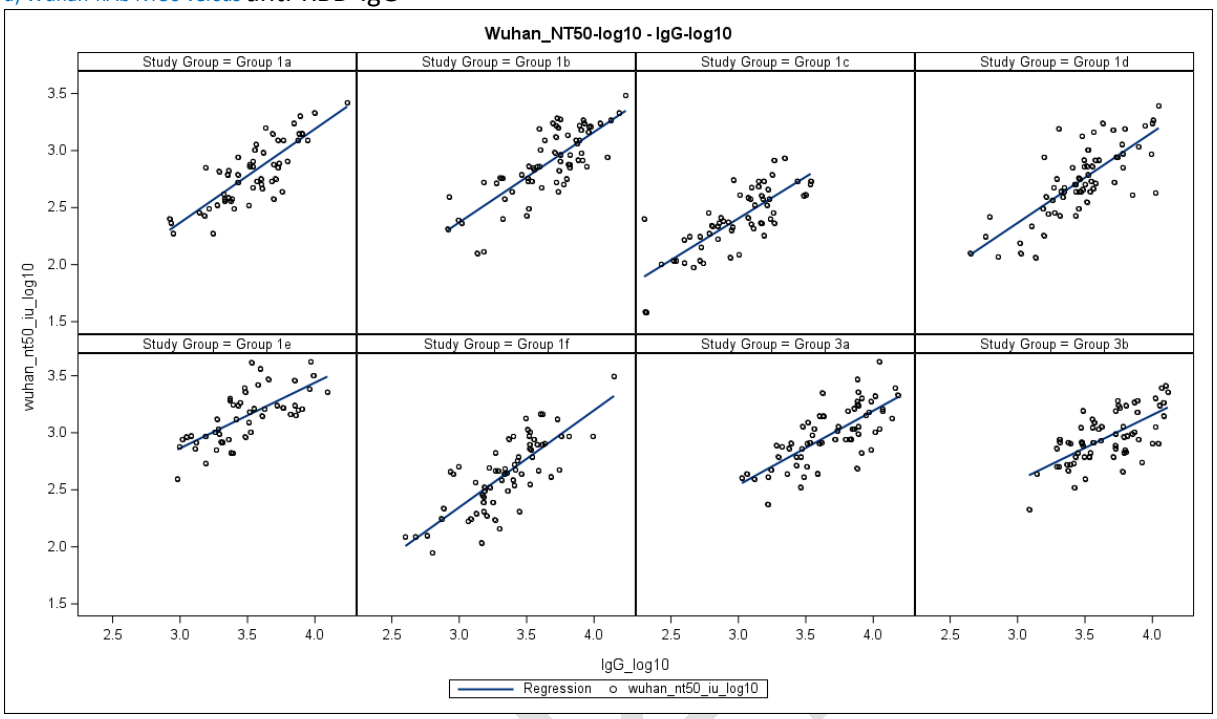
- For the Wuhan-nAb/anti-RBD-IgG conversion factor, study group 1e (Pfizer long interval scheme) has a higher conversion value than 1A (Pfizer regular scheme), also study group 3A (Moderna regular scheme) has a (slightly) higher value than 1A (Pfizer regular scheme). The Moderna groups do not show any significant differences from eachother.
- For the Delta-nAb/anti-RBD-IgG conversion factor, study group 1e (Pfizer long interval scheme) has a higher value than 1A (Pfizer regular scheme). Similar to the Wuhan-IgG conversion factor, the Moderna groups do not exhibit any significant differences.
- Not statistically significant differences are found for the Delta-nAb to Wuhan-nAb NT50 conversion.

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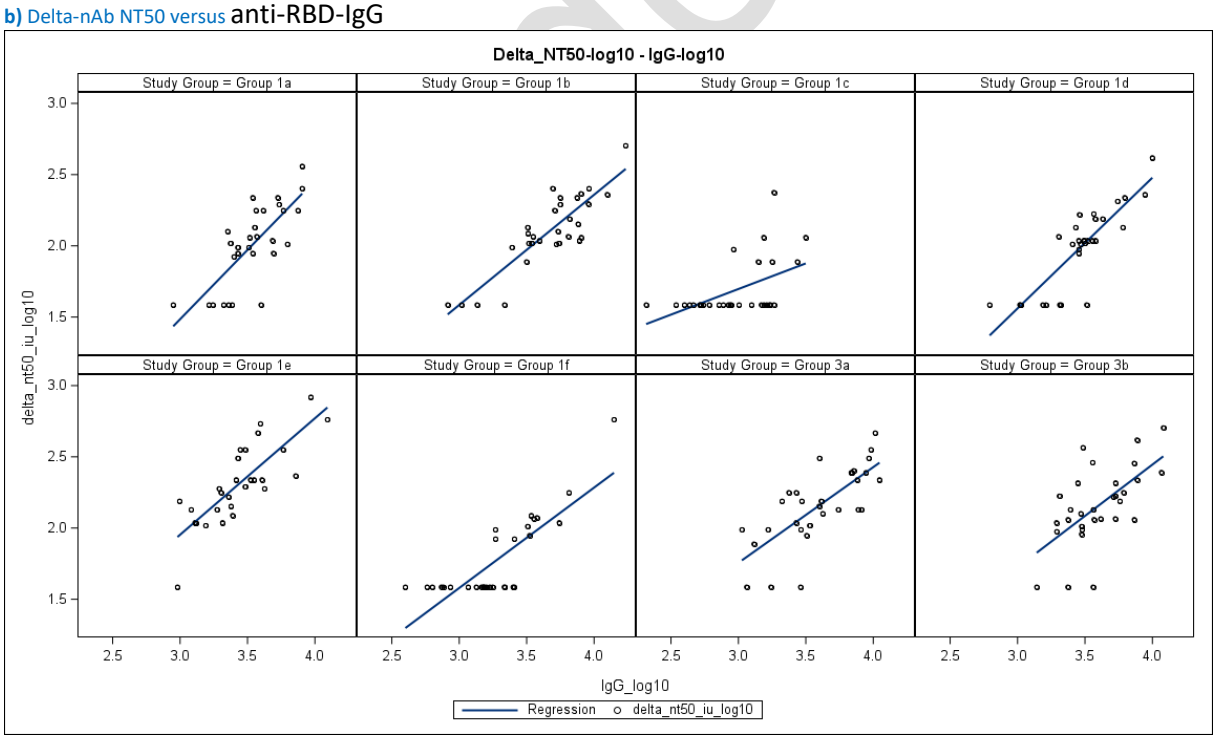
Figure 21 : Association between anti-RBD-IgG and nAb, at primary endpoint

1a = 'Pfizer regular scheme'; 1b = 'Pfizer-Moderna scheme'; 1c ='Pfizer-AstraZeneca scheme'; 1d='Pfizer low dose scheme'; 1e = 'Pfizer long interval scheme'; 1f= 'Pfizer intradermal scheme'; 3a='Moderna regular scheme'; 3b='Moderna low dose scheme'

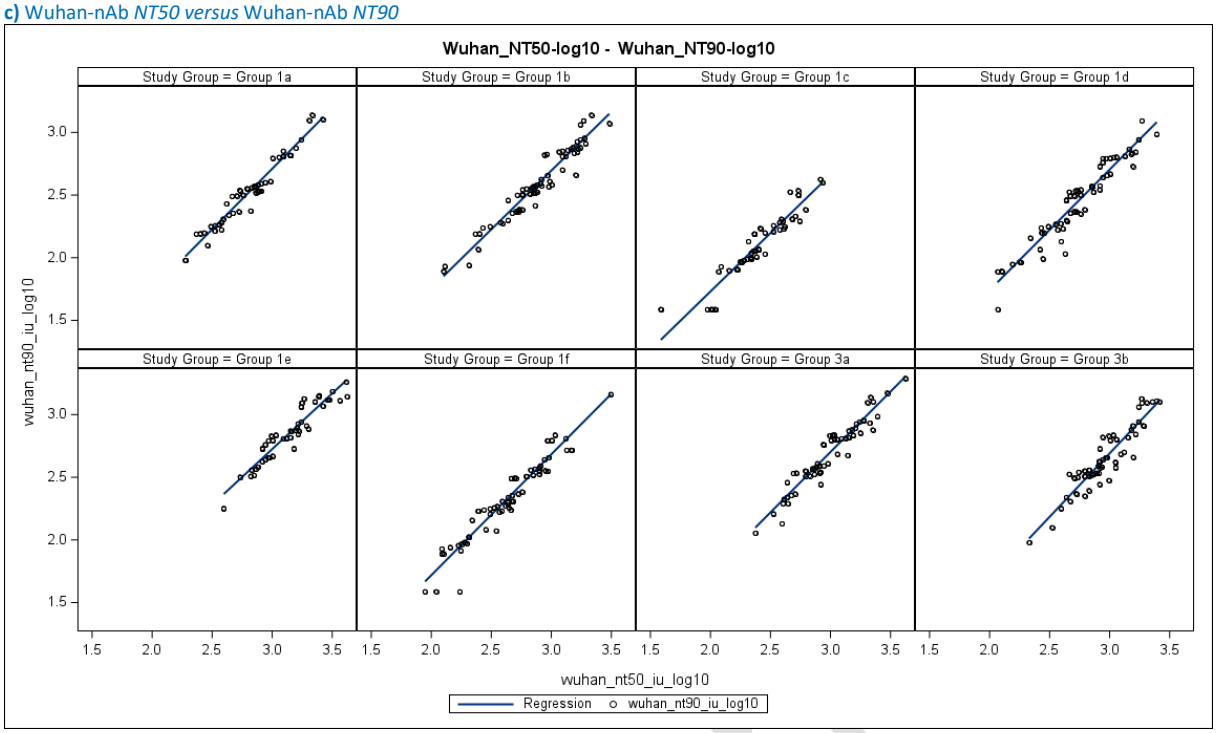
a) Wuhan-nAb NT50 versus anti-RBD-IgG



b) Delta-nAb NT50 versus anti-RBD-IgG



c) Wuhan-nAb *NT50 versus* Wuhan-nAb *NT90*



d) Wuhan-nAb *NT50 vs* Delta-nAb *NT50*

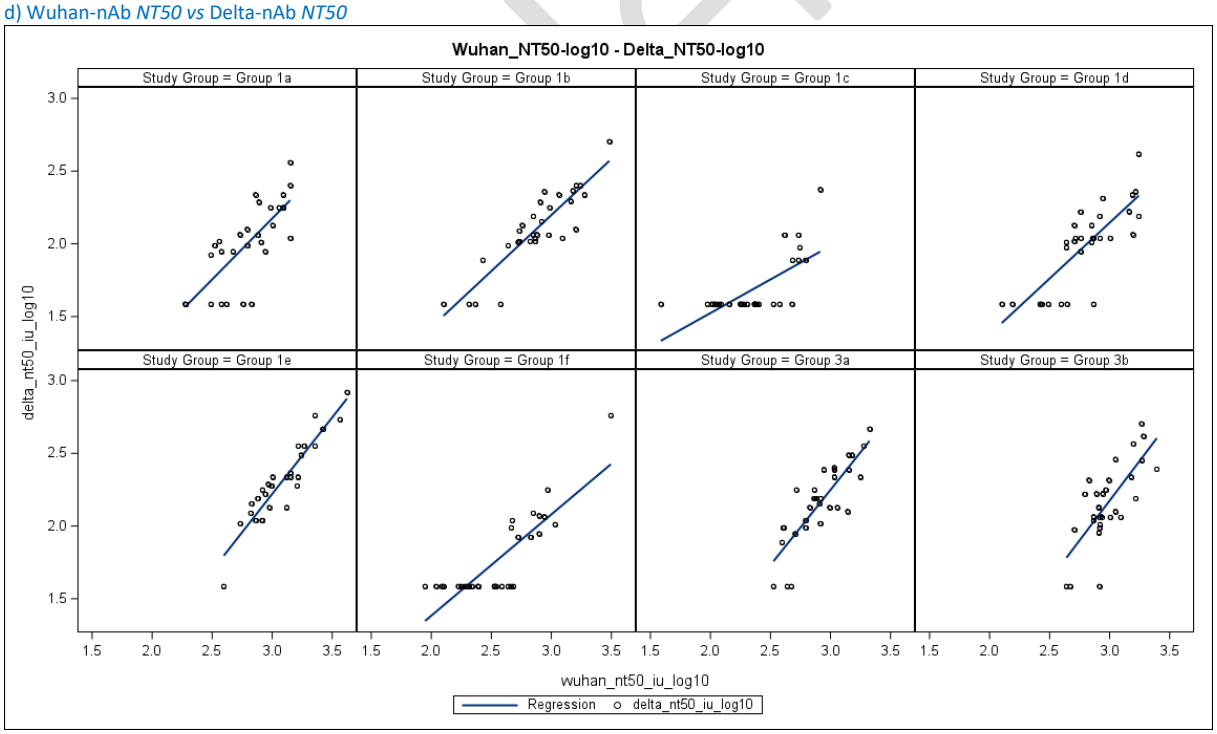


Table 38: descriptive statistics for the ratios, at primary endpoint

1a = 'Pfizer regular scheme'; 1b = 'Pfizer-Moderna scheme'; 1c ='Pfizer-AstraZeneca scheme'; 1d='Pfizer low dose scheme'; 1e = 'Pfizer long interval scheme'; 1f= 'Pfizer intradermal scheme'; 3a='Moderna regular scheme'; 3b='Moderna low dose scheme'

Randomisation group	Variable	N	Mean	Std Dev	50th Pctl	Minimum	Maximum
Group 1a	RATIO_WH_NT50_IU_IgG_log10	57	0.7939616	0.0449013	0.7940001	0.6981046	0.8938642
	RATIO_DE_NT50_IU_IgG_log10	22	0.5924001	0.0367961	0.5913622	0.5276506	0.6609613
	RATIO_DE_WU_NT50_IU_log10	22	0.7439078	0.0441522	0.7531540	0.6470324	0.8178423
Group 1b	RATIO_WH_NT50_IU_IgG_log10	66	0.7905981	0.0517273	0.7959637	0.6644003	0.8883031
	RATIO_DE_NT50_IU_IgG_log10	26	0.5803666	0.0337340	0.5782900	0.5236594	0.6507165
	RATIO_DE_WU_NT50_IU_log10	26	0.7379697	0.0359861	0.7400085	0.6563436	0.8026173
Group 1c	RATIO_WH_NT50_IU_IgG_log10	59	0.8028290	0.0633801	0.8087687	0.6850888	1.0440279
	RATIO_DE_NT50_IU_IgG_log10	0					
	RATIO_DE_WU_NT50_IU_log10	0					
Group 1d	RATIO_WH_NT50_IU_IgG_log10	69	0.7891774	0.0577502	0.7890479	0.6533952	0.9660002
	RATIO_DE_NT50_IU_IgG_log10	22	0.5971844	0.0259790	0.5902559	0.5629620	0.6547653
	RATIO_DE_WU_NT50_IU_log10	22	0.7333244	0.0418455	0.7360368	0.6470058	0.8076797
Group 1e	RATIO_WH_NT50_IU_IgG_log10	51	0.9038154	0.0536635	0.9054552	0.8172604	1.0248545
	RATIO_DE_NT50_IU_IgG_log10	27	0.6763376	0.0434727	0.6642212	0.6135576	0.7598393
	RATIO_DE_WU_NT50_IU_log10	27	0.7518162	0.0337811	0.7594965	0.6817965	0.8222595
Group 1f	RATIO_WH_NT50_IU_IgG_log10	67	0.7887594	0.0600634	0.7914350	0.6439283	0.9068634
	RATIO_DE_NT50_IU_IgG_log10	0					
	RATIO_DE_WU_NT50_IU_log10	0					
Group 3a	RATIO_WH_NT50_IU_IgG_log10	66	0.8121385	0.0493257	0.8145408	0.6938881	0.9254973
	RATIO_DE_NT50_IU_IgG_log10	27	0.6114697	0.0390523	0.6060061	0.5441454	0.6914545
	RATIO_DE_WU_NT50_IU_log10	27	0.7540661	0.0390770	0.7605202	0.6688692	0.8281734
Group 3b	RATIO_WH_NT50_IU_IgG_log10	68	0.8101444	0.0477560	0.8151228	0.6986360	0.9169900
	RATIO_DE_NT50_IU_IgG_log10	27	0.6124970	0.0466165	0.6001604	0.5328618	0.7359076
	RATIO_DE_WU_NT50_IU_log10	27	0.7371364	0.0487721	0.7309003	0.6661801	0.8283641

Figure 22: boxplots of the ratios, at primary endpoint

1a = 'Pfizer regular scheme'; 1b = 'Pfizer-Moderna scheme'; 1c ='Pfizer-AstraZeneca scheme'; 1d='Pfizer low dose scheme'; 1e = 'Pfizer long interval scheme'; 1f= 'Pfizer intradermal scheme'; 3a='Moderna regular scheme'; 3b='Moderna low dose scheme'Ratio

Wuhan Nab vs RBD, Ratio Delta Nab vs RBD, Ratio Wuhan Nab vs Delta Nab

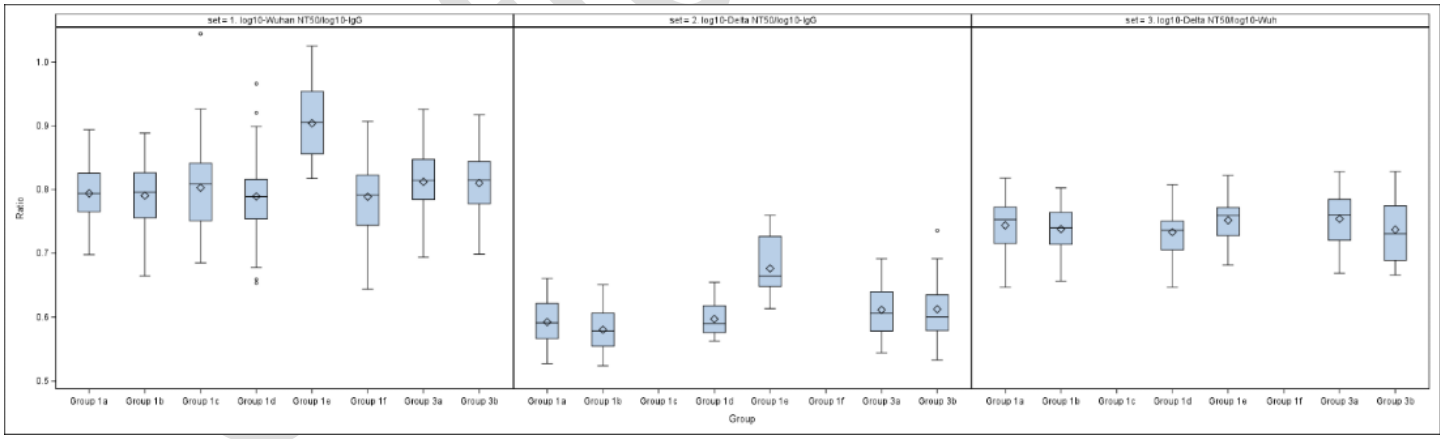


Table 39: Average conversion factors, based on linear mixed models, at primary endpoint

1a = 'Pfizer regular scheme'; 1b = 'Pfizer-Moderna scheme'; 1c ='Pfizer-AstraZeneca scheme'; 1d='Pfizer low dose scheme'; 1e = 'Pfizer long interval scheme'; 1f= 'Pfizer intradermal scheme'; 3a='Moderna regular scheme'; 3b='Moderna low dose scheme'

Randomisation group	log10-Wuhan NT50/log10-IgG	log10-Delta NT50/log10-IgG	log10-Delta NT50/log10-Wuhan NT50
Group 1a	0.78466	0.59240	0.74391
Group 1b	0.78687	0.58037	0.73797
Group 1c	0.79154		
Group 1d	0.78344	0.59718	0.73332
Group 1e	0.89816	0.67634	0.75182
Group 1f	0.78505		
Group 3a	0.80606	0.61147	0.75407
Group 3b	0.80362	0.61250	0.73714

Table 40: Statistical significance of the pairwise comparisons

1a = 'Pfizer regular scheme'; 1b = 'Pfizer-Moderna scheme'; 1c ='Pfizer-AstraZeneca scheme'; 1d='Pfizer low dose scheme'; 1e = 'Pfizer long interval scheme'; 1f= 'Pfizer intradermal scheme'; 3a='Moderna regular scheme'; 3b='Moderna low dose scheme'

Ratio	Randomisation group	Randomisation group	pvalue
log10-Wuhan NT50/log10-IgG	Group 1a	Group 1e	<.0001
log10-Wuhan NT50/log10-IgG	Group 1a	Group 3a	0.0178
log10-Wuhan NT50/log10-IgG	Group 1a	Group 3b	0.0341
log10-Wuhan NT50/log10-IgG	Group 1b	Group 1e	<.0001
log10-Wuhan NT50/log10-IgG	Group 1b	Group 3a	0.0267
log10-Wuhan NT50/log10-IgG	Group 1c	Group 1e	<.0001
log10-Wuhan NT50/log10-IgG	Group 1d	Group 1e	<.0001
log10-Wuhan NT50/log10-IgG	Group 1d	Group 3a	0.0084
log10-Wuhan NT50/log10-IgG	Group 1d	Group 3b	0.0176
log10-Wuhan NT50/log10-IgG	Group 1e	Group 1f	<.0001
log10-Wuhan NT50/log10-IgG	Group 1e	Group 3a	<.0001
log10-Wuhan NT50/log10-IgG	Group 1e	Group 3b	<.0001
log10-Wuhan NT50/log10-IgG	Group 1f	Group 3a	0.0154
log10-Wuhan NT50/log10-IgG	Group 1f	Group 3b	0.0306
log10-Delta NT50/log10-IgG	Group 1a	Group 1e	<.0001
log10-Delta NT50/log10-IgG	Group 1b	Group 1e	<.0001
log10-Delta NT50/log10-IgG	Group 1b	Group 3a	0.0039
log10-Delta NT50/log10-IgG	Group 1b	Group 3b	0.0029
log10-Delta NT50/log10-IgG	Group 1d	Group 1e	<.0001
log10-Delta NT50/log10-IgG	Group 1e	Group 3a	<.0001
log10-Delta NT50/log10-IgG	Group 1e	Group 3b	<.0001

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10.6 Avidity

After analyzing the results of the primary endpoint, specific timepoints and subjects were chosen for the avidity analysis. The correlation between RBD-nAb was found to be significantly different for participants in group 1e (Pfizer long interval scheme) compared to other groups, as was also observed for the primary endpoint analysis. Therefore, it was decided that the avidity analysis focused on this group. During visits 2, 3, and 4, avidity results were obtained for all participants in groups 1a (Pfizer regular scheme) and 1e (Pfizer long interval scheme), as well as for the participants of the humoral immunity subsets of all other study groups. Laboratory results were excluded for participants who had experienced a COVID-19 infection or received a COVID-19 vaccination outside of the study prior to this timepoint.

A logarithmic transformation (base 10) was be applied to the avidity measurements.

i. Descriptive statistics for avidity

Descriptive statistics for the observed avidity results, measured in seconds, are presented in Table 41. Figure 23shows a spaghetti plot displaying individual avidity evolutions, while the box plot in Figure 24 represents the $\log_{10}$ transformed avidity values per study group and visit.

ii. Comparison of adapted schedules compared to reference schedule in avidity 28 days post second vaccine

Descriptive statistics for $\log_{10}$-avidity at the primary endpoint visit (visit 3 for the short interval and visit 4 for the long interval-group 1e) are presented in Table 42.

The results of the linear mixed model for avidity of different vaccines and adapted vaccine schedules compared to the reference schedule, 28 days post 2 vaccine doses, are displayed inTable 43 and Figure 25.

Age and gender adjusted geometric means and the geometric mean ratios (adapted schedule/reference schedule) with 95% two-sided confidence intervals are presented. The reported p-values are for two-sided tests, no correction for multiple testing is used.

At the primary endpoint visit, the avidity levels of adapted schedules 1c (Pfizer-AstraZeneca scheme) and 1f (Pfizer Intradermal scheme) were found to be lower than that of the reference schedule (1a, Pfizer regular scheme). On the other hand, the avidity level of adapted schedule 1e (Pfizer-long interval scheme) was higher than that of the reference schedule. Additionally, the avidity level of Moderna group 3B (Moderna low dose scheme) was found to be higher than that of group 3A (Moderna regular scheme).

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Table 41: Avidity at visits 2, 3 and 4

1a = 'Pfizer regular scheme'; 1b = 'Pfizer-Moderna scheme'; 1c ='Pfizer-AstraZeneca scheme'; 1d='Pfizer low dose scheme'; 1e = 'Pfizer long interval scheme'; 1f= 'Pfizer intradermal scheme'; 3a='Moderna regular scheme'; 3b='Moderna low dose scheme'

	Randomisation group	VISIT	N	Mean	Std Dev	50th Pctl	25th Pctl	75th Pctl	Minimum	Maximum
Pfizer groups	Group 1a	v2	57	1621	783	1580	1070	2086	319	4458
		v3	51	13092	6137	11646	8881	16565	3804	29744
		v4	54	5437	2637	4732	3778	6892	831	12644
	Group 1b	v2	29	1747	947	1521	1226	2184	342	4448
		v3	29	11386	5515	11174	9141	12219	4234	31114
		v4	29	6252	3448	5701	3887	7593	1427	18918
	Group 1c	v2	30	1798	768	1737	1310	2206	393	3821
		v3	30	4830	2714	4400	2614	6592	1274	10868
		v4	29	2864	1985	2333	1443	3483	754	8375
	Group 1d	v2	30	1879	888	1753	1197	2592	255	3812
		v3	30	11545	4534	10725	8681	13994	3890	21182
		v4	30	5586	2724	5118	3876	6757	1069	11936
	Group 1e	v2	52	1765	929	1617	1113	2225	260	4933
		v3	45	990	678	847	514	1344	116	3288
		v4	51	15338	8157	14704	10526	18379	4836	56786
	Group 1f	v2	30	1304	755	1160	708	1653	148	3020
		v3	30	8614	5702	7368	4340	11740	3130	27548
		v4	29	4086	2670	3063	2261	5040	1471	13040
Moderna groups	Group 3a	v2	30	2859	1317	2640	1697	3664	735	5382
		v3	30	8283	2195	7829	6596	9872	4570	13294
		v4	30	6833	2790	6207	4664	9083	2740	12149
	Group 3b	v2	30	2560	867	2505	1806	3453	1068	4093
		v3	30	12041	3060	11251	9891	14550	7194	18372
		v4	30	8508	3383	8262	6468	9141	2070	19044

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Figure 23: *Spaghetti plots for log_{10}-avidity*

1a = 'Pfizer regular scheme'; 1b = 'Pfizer-Moderna scheme'; 1c ='Pfizer-AstraZeneca scheme'; 1d='Pfizer low dose scheme'; 1e = 'Pfizer long interval scheme'; 1f= 'Pfizer intradermal scheme'; 3a='Moderna regular scheme'; 3b='Moderna low dose scheme'

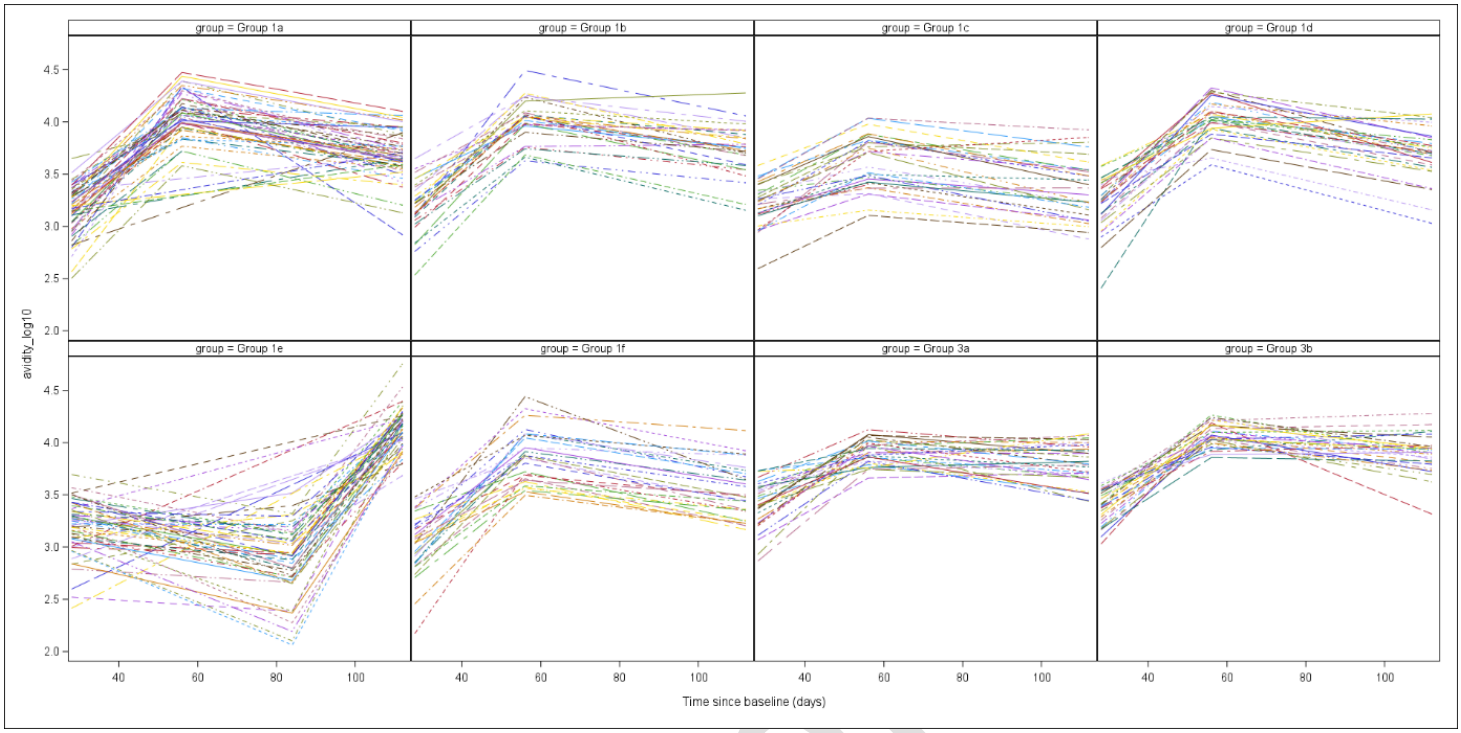


Figure 24: *Boxplots for log_{10}-avidity*

1a = 'Pfizer regular scheme'; 1b = 'Pfizer-Moderna scheme'; 1c ='Pfizer-AstraZeneca scheme'; 1d='Pfizer low dose scheme'; 1e = 'Pfizer long interval scheme'; 1f= 'Pfizer intradermal scheme'; 3a='Moderna regular scheme'; 3b='Moderna low dose scheme'

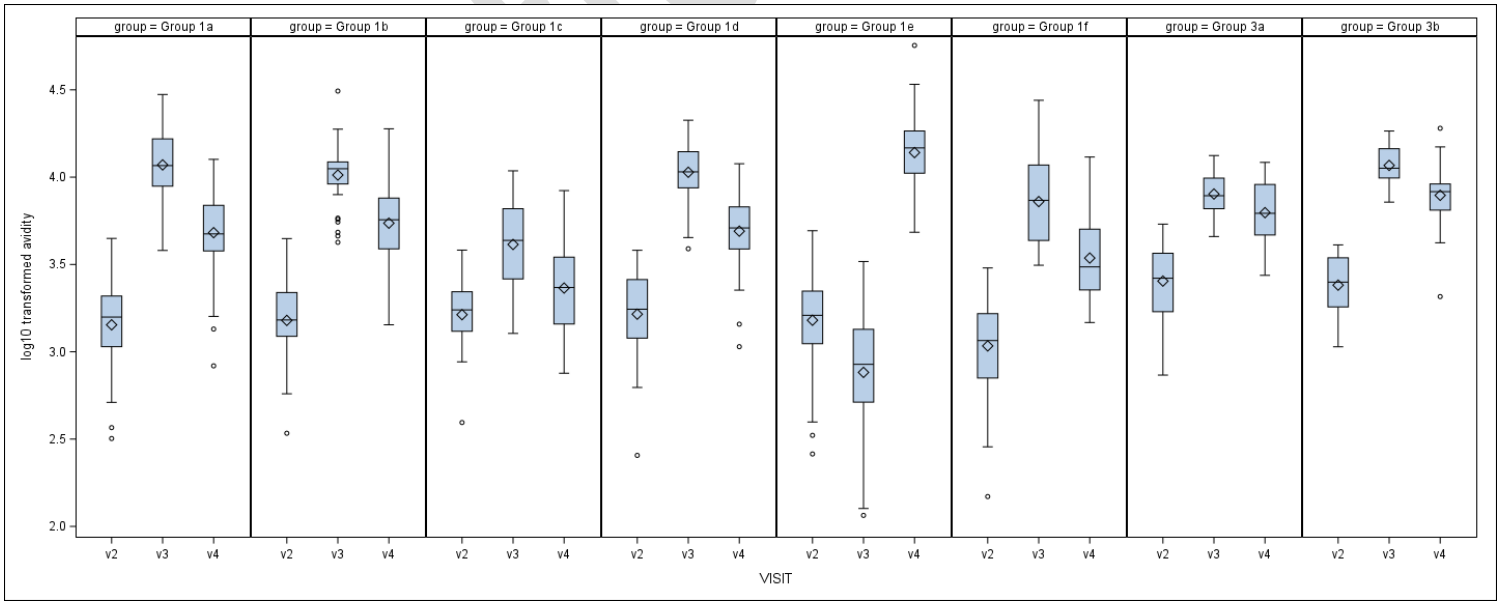


Table 42: log10-avidity 28 days post second vaccination

1a = 'Pfizer regular scheme'; 1b = 'Pfizer-Moderna scheme'; 1c ='Pfizer-AstraZeneca scheme'; 1d='Pfizer low dose scheme'; 1e = 'Pfizer long interval scheme'; 1f= 'Pfizer intradermal scheme'; 3a='Moderna regular scheme'; 3b='Moderna low dose scheme'

Randomisation group	N	Mean	Std Dev	Minimum	Maximum
Group 1a	51	4.07	0.21	3.58	4.47
Group 1b	29	4.01	0.20	3.63	4.49
Group 1c	30	3.61	0.26	3.11	4.04
Group 1d	30	4.03	0.18	3.59	4.33
Group 1e	51	4.14	0.19	3.68	4.75
Group 1f	30	3.86	0.25	3.50	4.44
Group 3a	30	3.90	0.12	3.66	4.12
Group 3b	30	4.07	0.11	3.86	4.26

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Table 43: GM and GMR ratio of avidity at primary endpoint, comparison of the adapted schedules with the reference schedule

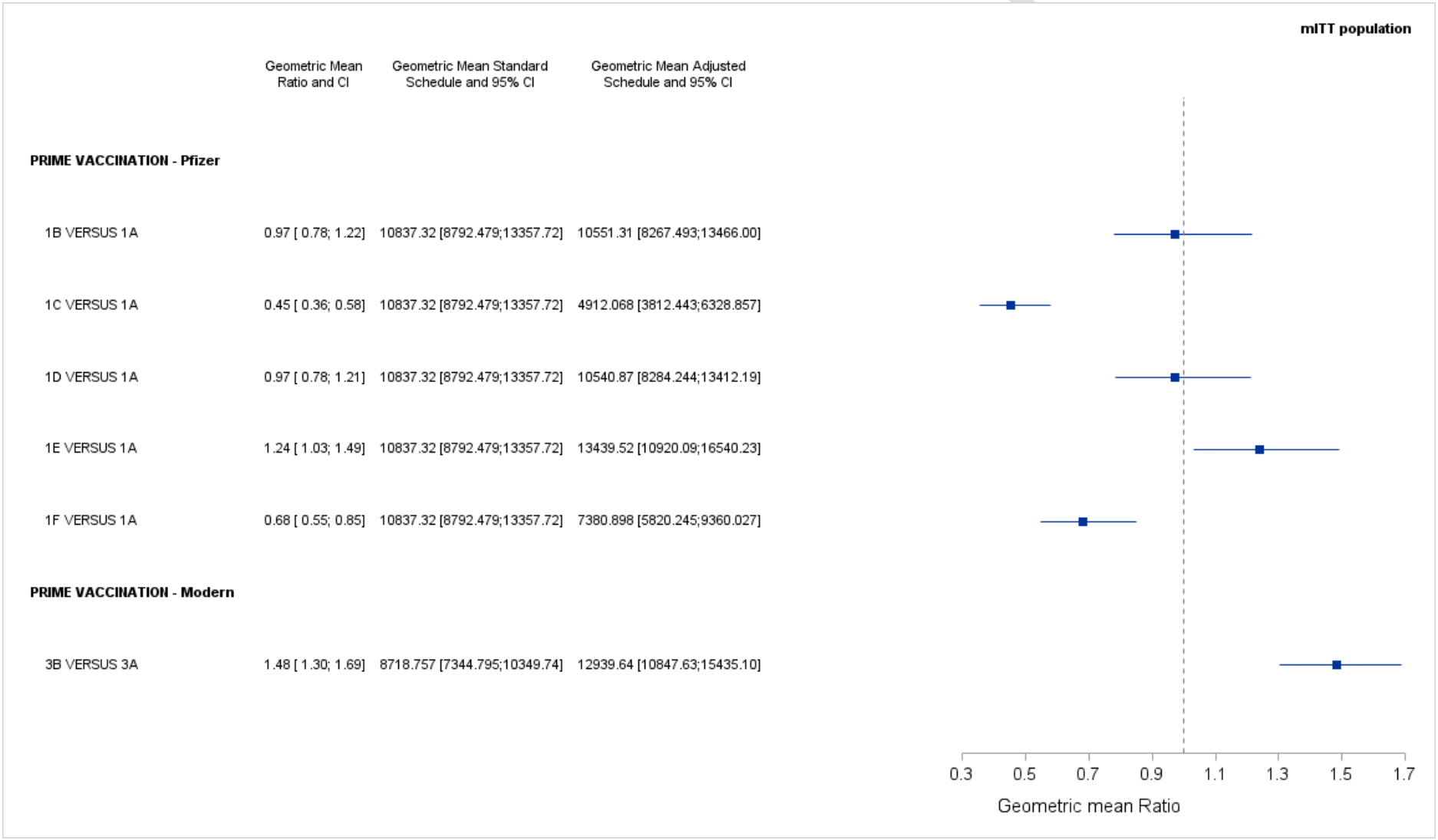
1a = 'Pfizer regular scheme'; 1b = 'Pfizer-Moderna scheme'; 1c ='Pfizer-AstraZeneca scheme'; 1d='Pfizer low dose scheme'; 1e = 'Pfizer long interval scheme'; 1f= 'Pfizer intradermal scheme'; 3a='Moderna regular scheme'; 3b='Moderna low dose scheme'

Analysis Population	Comparison	Geometric Mean of Standard Schedule and 95% CI	Geometric Mean of Adjusted Schedule and 95% CI	Geometric Mean Ratio and 95%CI	p value (two sided test)
mITT	1B VERSUS 1A	10837 [8792; 13358]	10551 [8267; 13466]	0.97 [0.78; 1.22]	0.81392
Per-protocol	1B VERSUS 1A	10748 [8708; 13265]	10558 [8261; 13492]	0.98 [0.78; 1.23]	0.87647
mITT	1C VERSUS 1A	10837 [8792; 13358]	4912 [3812; 6329]	0.45 [0.36; 0.58]	0.00000
Per-protocol	1C VERSUS 1A	10748 [8708; 13265]	4919 [3812; 6348]	0.46 [0.36; 0.59]	0.00000
mITT	1D VERSUS 1A	10837 [8792; 13358]	10541 [8284; 13412]	0.97 [0.78; 1.21]	0.80308
Per-protocol	1D VERSUS 1A	10748 [8708; 13265]	10547 [8279; 13437]	0.98 [0.79; 1.22]	0.86698
mITT	1e VERSUS 1A	10837 [8792; 13358]	13440 [10920; 16540]	1.24 [1.03; 1.49]	0.02284
Per-protocol	1e VERSUS 1A	10748 [8708; 13265]	13341 [10793; 16489]	1.24 [1.02; 1.50]	0.02713
mITT	1F VERSUS 1A	10837 [8792; 13358]	7381 [5820; 9360]	0.68 [0.55; 0.85]	0.00071
Per-protocol	1F VERSUS 1A	10748 [8708; 13265]	7390 [5821; 9382]	0.69 [0.55; 0.86]	0.00109
mITT	3B VERSUS 3A	8719 [7345; 10350]	12940 [10848; 15435]	1.48 [1.30; 1.69]	0.00000
Per-protocol	3B VERSUS 3A	8719 [7345; 10350]	12940 [10848; 15435]	1.48 [1.30; 1.69]	0.00000

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Figure 25: GM and GMR of avidity at primary endpoint, comparison of the adapted schedules with the reference schedule

1a = 'Pfizer regular scheme'; 1b = 'Pfizer-Moderna scheme'; 1c ='Pfizer-AstraZeneca scheme'; 1d='Pfizer low dose scheme'; 1e = 'Pfizer long interval scheme'; 1f= 'Pfizer intradermal scheme'; 3a='Moderna regular scheme'; 3b='Moderna low dose scheme'



iii. Avidity of the 8 study groups, average evolution

The results of the repeated measurements model on (log_{10}-)avidity of visits 2, 3, and 4 and 5 are displayed in Table 44, a graphical presentation of the evolution in geometric log_{10}-avidity means is given in Figure 26.

Age and gender adjusted geometric means with 95% two-sided confidence intervals for the standard and adapted schedules are presented. At each visit, the geometric mean ratio for the adapted schedule versus the standard schedule and the GMR of the two standard schedules is also given with a 95% two-sided confidence interval and a two-sided p value. No correction for multiple testing is implemented.

Table 44: Geometric means and geometric mean ratio of avidity at study visits 2, 3 and 4, comparisons between adapted schedules and reference schedule and comparison of the two reference schedules

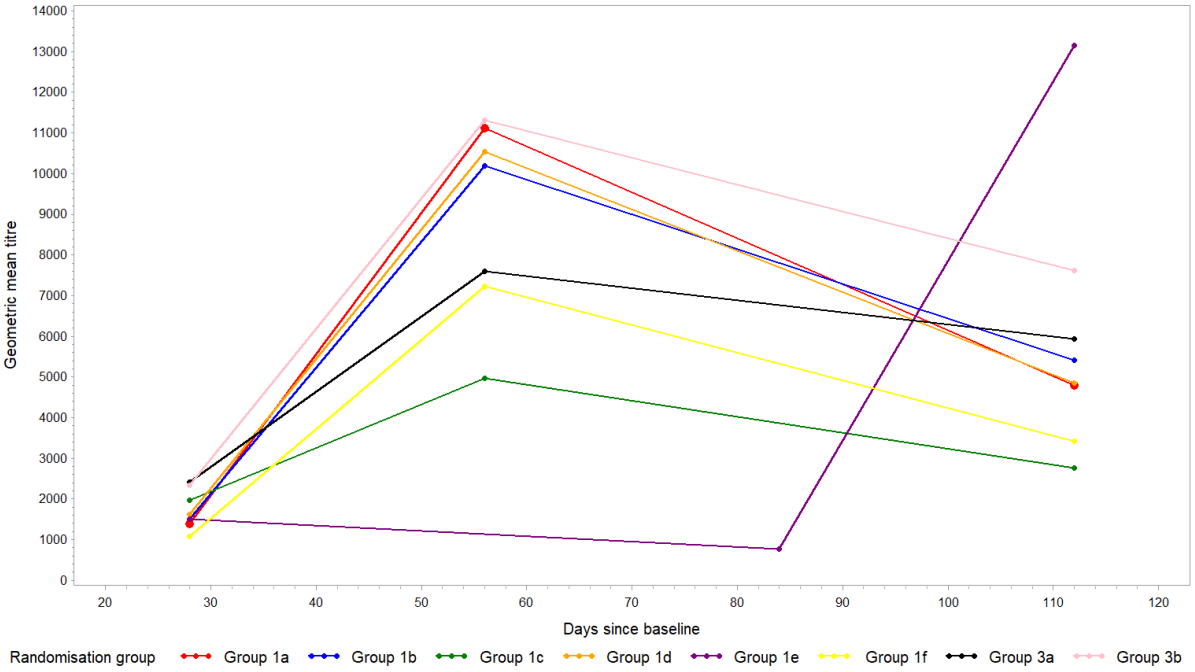
1a = 'Pfizer regular scheme'; 1b = 'Pfizer-Moderna scheme'; 1c ='Pfizer-AstraZeneca scheme'; 1d='Pfizer low dose scheme'; 1e = 'Pfizer long interval scheme'; 1f= 'Pfizer intradermal scheme'; 3a='Moderna regular scheme'; 3b='Moderna low dose scheme'

Comparison	Standard Schedule	Adapted Schedule	Geometric Mean of Standard Schedule and 95% CI	Geometric Mean of Adapted Schedule and 95% CI	Geometric Mean Ratio of Adapted Schedule versus Standard Schedule	pvalue
VISIT2: 1B VERSUS 1A	Group 1a	Group 1b	1395 [1214; 1603]	1499 [1239; 1814]	1.07 [0.85; 1.36]	0.5480
VISIT2: 1C VERSUS 1A	Group 1a	Group 1c	1395 [1214; 1603]	1971 [1618; 2399]	1.41 [1.11; 1.80]	0.0055
VISIT2: 1D VERSUS 1A	Group 1a	Group 1d	1395 [1214; 1603]	1621 [1344; 1956]	1.16 [0.92; 1.47]	0.2058
VISIT2: 1e VERSUS 1A	Group 1a	Group 1e	1395 [1214; 1603]	1496 [1290; 1736]	1.07 [0.88; 1.31]	0.4958
VISIT2: 1F VERSUS 1A	Group 1a	Group 1f	1395 [1214; 1603]	1079 [894; 1301]	0.77 [0.61; 0.98]	0.0309
VISIT2: 3A VERSUS 1A	Group 1a	Group 3a	1395 [1214; 1603]	2409 [1995; 2908]	1.73 [1.37; 2.18]	<.0001
VISIT2: 3B VERSUS 3A	Group 3a	Group 3b	2409 [1995; 2908]	2331 [1932; 2812]	0.97 [0.74; 1.26]	0.8069
VISIT3: 1B VERSUS 1A	Group 1a	Group 1b	11117 [9624; 12842]	10193 [8430; 12325]	0.92 [0.72; 1.16]	0.4739
VISIT3: 1C VERSUS 1A	Group 1a	Group 1c	11117 [9624; 12842]	4973 [4088; 6051]	0.45 [0.35; 0.57]	<.0001
VISIT3: 1D VERSUS 1A	Group 1a	Group 1d	11117 [9624; 12842]	10531 [8735; 12696]	0.95 [0.75; 1.20]	0.6514
VISIT3: 1e VERSUS 1A	Group 1a	Group 1e	11117 [9624; 12842]	772 [660; 902]	0.07 [0.06; 0.09]	<.0001
VISIT3: 1F VERSUS 1A	Group 1a	Group 1f	11117 [9624; 12842]	7236 [6004; 8722]	0.65 [0.51; 0.82]	0.0004
VISIT3: 3A VERSUS 1A	Group 1a	Group 3a	11117 [9624; 12842]	7592 [6294; 9159]	0.68 [0.54; 0.86]	0.0016
VISIT3: 3B VERSUS 3A	Group 3a	Group 3b	7592 [6294; 9159]	11304 [9376; 13628]	0.97 [0.74; 1.26]	0.8069
VISIT4: 1B VERSUS 1A	Group 1a	Group 1b	4793 [4198; 5473]	5403 [4514; 6467]	1.13 [0.90; 1.41]	0.2922
VISIT4: 1C VERSUS 1A	Group 1a	Group 1c	4793 [4198; 5473]	2771 [2295; 3346]	0.58 [0.46; 0.73]	<.0001
VISIT4: 1D VERSUS 1A	Group 1a	Group 1d	4793 [4198; 5473]	4844 [4058; 5782]	1.01 [0.81; 1.26]	0.9257
VISIT4: 1e VERSUS 1A	Group 1a	Group 1e	4793 [4198; 5473]	13157 [11428; 15146]	2.74 [2.26; 3.33]	<.0001
VISIT4: 1F VERSUS 1A	Group 1a	Group 1f	4793 [4198; 5473]	3428 [2867; 4099]	0.72 [0.57; 0.89]	0.0033
VISIT4: 3A VERSUS 1A	Group 1a	Group 3a	4793 [4198; 5473]	5937 [4971; 7092]	1.24 [0.99; 1.54]	0.0575
VISIT4: 3B VERSUS 3A	Group 3a	Group 3b	5937 [4971; 7092]	7620 [6384; 9096]	1.28 [1.00; 1.65]	0.0506

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Figure 26: Geometric avidity means at study visits 2, 3, and 4

1a = 'Pfizer regular scheme'; 1b = 'Pfizer-Moderna scheme'; 1c ='Pfizer-AstraZeneca scheme'; 1d='Pfizer low dose scheme'; 1e = 'Pfizer long interval scheme'; 1f= 'Pfizer intradermal scheme'; 3a='Moderna regular scheme'; 3b='Moderna low dose scheme'



iv. Changes in avidity, 28 days post second vaccination versus vaccination

For each participant, the change in log_{10}-avidity, comparing the avidity at the time of second vaccination with those at 28 days post second vaccination, is obtained calculated. In addition, the change in log-avidity between the visit 4 and visit 3 is assessed for the short interval.

Descriptive statistics for these changes in log_{10}-avidity per study group are presented in Table 45 and Figure 27.

Table 46 presents the average log_{10}-avidity change (adjusted for age and gender) and 95% two-sided confidence intervals per study group. The change in log_{10}-avidity of the adapted vaccine schedule is compared with the change in log_{10}-avidity of the reference schedule. The changes in log_{10}-avidity of the two reference schedules are also compared. These pairwise comparisons are presented Table 47. Testing for a difference was done at a 5% level of significance and no correction for multiple testing is done. The difference in change between two study groups is given together with a 95% CI for this difference and the p value.

All study groups showed an increase in avidity 28 days after receiving their second vaccination. However, the increase observed in group 1e was greater than that seen in group 1a. On the other

hand, the increase in group 1c was smaller than the increase observed in group 1a. Additionally, group 3a had a smaller increase in avidity compared to groups 1a and 3b.

In the short interval groups, there is a decrease in avidity observed from visit 3 to visit 4. The magnitude of these decreases is similar among the short interval study groups, except for group 3a, which has a relatively weaker decrease compared to group 1a.

In the short interval groups, we observed that antibody avidity waned significantly over the 2 months following the second dose for all adult participants. This is in stark contrast to findings in the literature which describes healthy adults where anti-spike IgG avidity increased from 2 weeks to 6 months following the second vaccine dose. However in literature often is looked at only a limited amount of timepoints (often only 1 or 2), therefore it is possible that the peak we observe in this trial is not necessarily captured in other trial due to choosing different timepoint, and in IMCOVAS we see avidity at day 112 still remains higher that it was at the start for all 8 groups. Also an important consideration to make, is that in the IMCOVAS-results only COVID-naïf samples are included, where as we know a higher avidity and more sustainable plateau can be reached in pre-infected individuals.

Table 45: Changes in log-avidity, 28 days post second vaccination compared to vaccination and visit 4 compared to visit 3

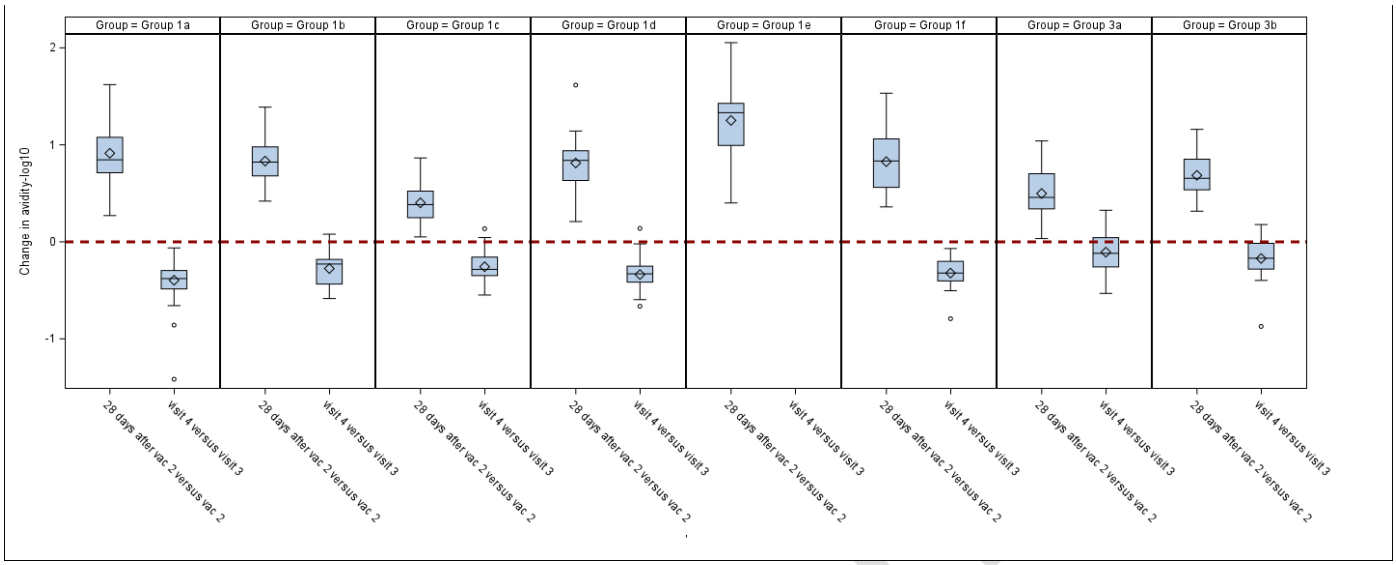
1a = 'Pfizer regular scheme'; 1b = 'Pfizer-Moderna scheme'; 1c ='Pfizer-AstraZeneca scheme'; 1d='Pfizer low dose scheme'; 1e = 'Pfizer long interval scheme'; 1f= 'Pfizer intradermal scheme'; 3a='Moderna regular scheme'; 3b='Moderna low dose scheme'3a='Moderna regular scheme'; 3b='Moderna low dose scheme'

Randomisation group	Comparison	N	Mean	Std Dev	Median	25th Pctl	75th Pctl	Minimum	Maximum
Group 1a	28 days after vac 2 versus vac 2	51	0.91	0.27	0.85	0.71	1.08	0.27	1.62
	visit 4 versus visit 3	48	-0.40	0.22	-0.38	-0.49	-0.30	-1.42	-0.06
Group 1b	28 days after vac 2 versus vac 2	29	0.83	0.23	0.82	0.68	0.98	0.42	1.39
	visit 4 versus visit 3	29	-0.28	0.17	-0.23	-0.44	-0.18	-0.58	0.08
Group 1c	28 days after vac 2 versus vac 2	30	0.40	0.19	0.38	0.25	0.52	0.05	0.86
	visit 4 versus visit 3	29	-0.26	0.17	-0.28	-0.35	-0.16	-0.55	0.14
Group 1d	28 days after vac 2 versus vac 2	30	0.81	0.26	0.84	0.63	0.94	0.21	1.62
	visit 4 versus visit 3	30	-0.34	0.16	-0.33	-0.41	-0.25	-0.66	0.14
Group 1e	28 days after vac 2 versus vac 2	44	1.25	0.37	1.33	0.99	1.43	0.40	2.05
	visit 4 versus visit 3	0							
Group 1f	28 days after vac 2 versus vac 2	30	0.83	0.32	0.83	0.56	1.06	0.36	1.53
	visit 4 versus visit 3	29	-0.32	0.15	-0.32	-0.40	-0.20	-0.79	-0.07
Group 3a	28 days after vac 2 versus vac 2	30	0.50	0.24	0.46	0.34	0.70	0.03	1.04
	visit 4 versus visit 3	30	-0.11	0.18	-0.12	-0.26	0.04	-0.53	0.33
Group 3b	28 days after vac 2 versus vac 2	30	0.69	0.20	0.66	0.54	0.85	0.32	1.16
	visit 4 versus visit 3	30	-0.17	0.20	-0.17	-0.28	-0.02	-0.87	0.18

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Figure 27: Change in log_{10}-avidity, 28 days post second vaccination compared to vaccination and visit 4 compared to visit 3

1a = 'Pfizer regular scheme'; 1b = 'Pfizer-Moderna scheme'; 1c ='Pfizer-AstraZeneca scheme'; 1d='Pfizer low dose scheme'; 1e = 'Pfizer long interval scheme'; 1f= 'Pfizer intradermal scheme'; 3a='Moderna regular scheme'; 3b='Moderna low dose scheme'



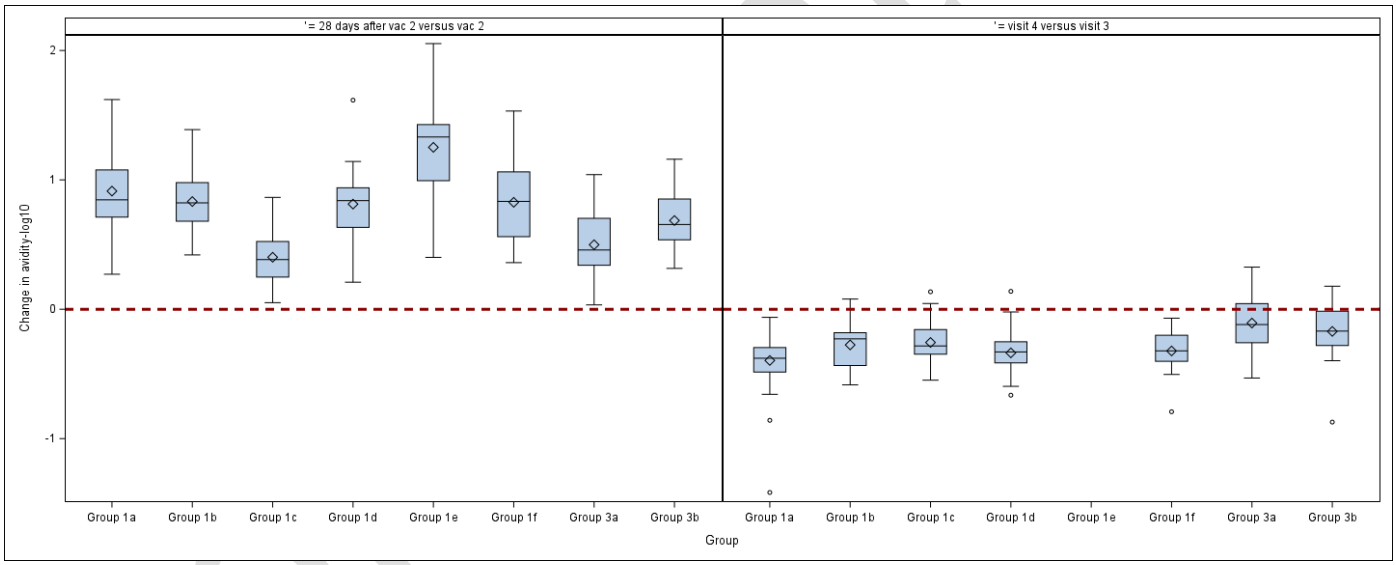


Table 46: Average change (least square means) in log_{10}-avidity

1a = 'Pfizer regular scheme'; 1b = 'Pfizer-Moderna scheme'; 1c ='Pfizer-AstraZeneca scheme'; 1d='Pfizer low dose scheme'; 1e = 'Pfizer long interval scheme'; 1f= 'Pfizer intradermal scheme';
3a='Moderna regular scheme'; 3b='Moderna low dose scheme'

a) 28 days after vac 2 versus vac 2

Randomisation group	Comparison	Mean change in log_{10}-avidity	Lower limit 95%CI	Upper limit 95%CI
Group 1a	28 days after vac 2 versus vac 2	0.90	0.83	0.98
Group 1b	28 days after vac 2 versus vac 2	0.85	0.75	0.95
Group 1c	28 days after vac 2 versus vac 2	0.37	0.26	0.48
Group 1d	28 days after vac 2 versus vac 2	0.83	0.73	0.93
Group 1e	28 days after vac 2 versus vac 2	1.25	1.18	1.33
Group 1f	28 days after vac 2 versus vac 2	0.87	0.77	0.96
Group 3a	28 days after vac 2 versus vac 2	0.54	0.44	0.64
Group 3b	28 days after vac 2 versus vac 2	0.72	0.61	0.82

b) visit 4 versus visit 3

Randomisation group	Comparison	Mean change in log_{10}-avidity	Lower limit 95%CI	Upper limit 95%CI
Group 1a	visit 4 versus visit 3	-0.40	-0.44	-0.35
Group 1b	visit 4 versus visit 3	-0.35	-0.41	-0.28
Group 1c	visit 4 versus visit 3	-0.31	-0.38	-0.24
Group 1d	visit 4 versus visit 3	-0.39	-0.45	-0.33
Group 1f	visit 4 versus visit 3	-0.38	-0.44	-0.31
Group 3a	visit 4 versus visit 3	-0.20	-0.26	-0.13
Group 3b	visit 4 versus visit 3	-0.24	-0.31	-0.18

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Table 47: Difference in average change in log_{10}-avidity

1a = 'Pfizer regular scheme'; 1b = 'Pfizer-Moderna scheme'; 1c ='Pfizer-AstraZeneca scheme'; 1d='Pfizer low dose scheme'; 1e = 'Pfizer long interval scheme'; 1f= 'Pfizer intradermal scheme';
3a='Moderna regular scheme'; 3b='Moderna low dose scheme'

a) 28 days after vac2 versus vac 2

Randomisation group being compared		Comparison	Difference in change in log_{10}-avidity	Lower limit 95%CI	Upper limit 95%CI	p value
Group 1b	Group 1a	28 days after vac 2 versus vac 2	-0.05	-0.18	0.07	0.3895
Group 1c	Group 1a	28 days after vac 2 versus vac 2	-0.53	-0.67	-0.40	<.0001
Group 1d	Group 1a	28 days after vac 2 versus vac 2	-0.07	-0.19	0.05	0.2297
Group 1e	Group 1a	28 days after vac 2 versus vac 2	0.35	0.25	0.46	<.0001
Group 1f	Group 1a	28 days after vac 2 versus vac 2	-0.03	-0.16	0.09	0.5822
Group 3a	Group 1a	28 days after vac 2 versus vac 2	-0.36	-0.48	-0.24	<.0001
Group 3a	Group 3b	28 days after vac 2 versus vac 2	-0.17	-0.31	-0.04	0.0104

b) Visit 4 versus visit 3

Randomisation group being compared		Comparison	Difference in change in log_{10}-avidity	Lower limit 95%CI	Upper limit 95%CI	p value
Group 1b	Group 1a	visit 4 versus visit 3	0.05	-0.03	0.13	0.2315
Group 1c	Group 1a	visit 4 versus visit 3	0.09	-0.00	0.17	0.0564
Group 1d	Group 1a	visit 4 versus visit 3	0.00	-0.07	0.08	0.8993
Group 1f	Group 1a	visit 4 versus visit 3	0.02	-0.06	0.10	0.6593
Group 3a	Group 1a	visit 4 versus visit 3	0.20	0.12	0.28	<.0001
Group 3a	Group 3b	visit 4 versus visit 3	0.05	-0.04	0.13	0.2601

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10.7 COVID-19 infections

i. Breakthrough infections

Of the 506 subjects in the mITT population, 364 subjects (72%) experienced a breakthrough infection (BTI) after the primary endpoint evaluation while enrolled in the study (Table 48). However, because not all participants remained in the study until the final visit (visit 6), it is possible that the percentage of breakthrough infections has been underestimated.

Among those who experienced breakthrough infections, 62% (224/364) had both a COVID-19 AE and a reactive anti-N test, 8% (30/364) had only a COVID-19 AE reported, and 30% (110/364) had only a reactive anti-N test. This is presented in Table 49.

The majority of breakthrough infections occurred after visit 5 (D182), , with 298 subjects experiencing their initial breakthrough infection during that time period (Table 50). Among them, 113 subjects experienced a breakthrough infection between visit 5 and the ad hoc post 3rd dose visit, that was executed 28 days after receiving a 3rd COVID-19 vaccine via the national vaccination campaign (though not all subjects choose to receive a 3rd COVID-19 vaccine and/or to come to the study center for this additional study visit). Additionally, 185 participants had their first breakthrough infection between the ad hoc post 3rd dose visit and visit 6 (D364), or between visit 5 and visit 6 if they had no ad hoc post 3rd dose visit.

Out of the 506 participants, 446 participants remained in the study until the final visit (visit 6, D364) and received the third COVID-19 vaccine after September 2021, and no additional COVID-19 vaccines outside the study. To correct for the underestimation described earlier, when we only look at those participants (Table 51/Table 52/Figure 1Figure 28), we see that~~,~~ 330 participants had a breakthrough infection ***before the end of the study (visit 6).*** Study group 1c (Pfizer-AstraZeneca scheme) had the lowest breakthrough rate (61%), while study group 1e (Pfizer long interval scheme) had the highest breakthrough rate (85%), closely followed by group 3a (Moderna regular scheme) (83%) and group 1b (Pfizer-Moderna scheme) (82%).

ii. COVID-19 infections as reported by the participant

Of the 506 patients in the ITT population, 256 reported a COVID-19 infection while enrolled in the study. However, because not all participants remained in the study until the final visit (visit 6), it is possible that the percentage of COVID-19 infections has been underestimated.

Out of the 446 participants who remained in the study until the final visit (visit 6, D364) and received the third COVID-19 vaccine after September 2021, and no additional COVID-19 vaccine outside the study~~)~~, 231 had a COVID-19 infection ***before the end of the study (visit 6).*** Study group 1a (Pfizer-regular scheme) had the lowest breakthrough rate (43%), while study group 3a (Moderna standard dose scheme) had the highest breakthrough rate (65%) (Table 53/Figure 29).

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Table 48: Number of participants without BTIs after PE, per randomisation group

1a = 'Pfizer regular scheme'; 1b = 'Pfizer-Moderna scheme'; 1c ='Pfizer-AstraZeneca scheme'; 1d='Pfizer low dose scheme'; 1e = 'Pfizer long interval scheme'; 1f= 'Pfizer intradermal scheme'; 3a='Moderna regular scheme'; 3b='Moderna low dose scheme'

	Randomisation group								
N (%)	**Group 1a**	**Group 1b**	**Group 1c**	**Group 1d**	**Group 1e**	**Group 1f**	**Group 3a**	**Group 3b**	**Total**
No BTI	20 (35.1%)	16 (23.5%)	23 (39.0%)	16 (23.2%)	8 (15.4%)	24 (35.8%)	14 (21.2%)	21 (30.9%)	142 (28,1%)
BTI	37 (64.9%)	52 (76.5%)	36 (61.0%)	53 (76.8%)	44 (84.6%)	43 (64.2%)	52 (78.8%)	47 (69.1%)	364 (71.9%)
Total	57	68	59	69	52	67	66	68	506

Table 49: Identification of the BTIs

BTI diagnosis defined based on	**N**	**Percent**
COVID-19 AE only	30	8.24%
COVID-19 AE and Reactive Anti-N	224	61.54%
Reactive Anti-N only	110	30.22%

Table 50: Number of participants and visit timepoint influenced by BTIs after PE, per randomization group

1a = 'Pfizer regular scheme'; 1b = 'Pfizer-Moderna scheme'; 1c ='Pfizer-AstraZeneca scheme'; 1d='Pfizer low dose scheme'; 1e = 'Pfizer long interval scheme'; 1f= 'Pfizer intradermal scheme'; 3a='Moderna regular scheme'; 3b='Moderna low dose scheme'

Visit impacted by the first BTI	**Randomisation group**								
N (%)	**Group 1a**	**Group 1b**	**Group 1c**	**Group 1d**	**Group 1e**	**Group 1f**	**Group 3a**	**Group 3b**	**Total**
v4	2 (3.51%)	0 (0.00%)	1 (1.69%)	0 (0.00%)	0 (0.00%)	1 (1.49%)	0 (0.00%)	1 (1.47%)	5
v5	7 (12.28%)	5 (7.35%)	6 (10.17%)	12 (17.39%)	2 (3.85%)	15 (22.39%)	6 (9.09%)	8 (11.76%)	61
Ad hoc post 3rd dose visit	14 (24.56%)	18 (26.47%)	11 (18.64%)	16 (23.19%)	17 (32.69%)	7 (10.45%)	19 (28.79%)	11 (16.18%)	113
v6	14 (24.56%)	29 (42.65%)	18 (30.51%)	25 (36.23%)	25 (48.08%)	20 (29.85%)	27 (40.91%)	27 (39.71%)	185
Total	**37 (64,91%)**	**52 (76,47%)**	**36 (61,02%)**	**53 (76,81%)**	**44 (84,62%)**	**43 (64,18%)**	**52 (78,79%)**	**47 (69,12%)**	**364 (71,94%)**

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Table 51: Number of participants without BTIs after PE, per randomisation group for subjects who remained in the study until the final visit (visit 6, D364) and received the third COVID-19 vaccine after September 2021, and no additional COVID-19 vaccines outside the study

1a = 'Pfizer regular scheme'; 1b = 'Pfizer-Moderna scheme'; 1c ='Pfizer-AstraZeneca scheme'; 1d='Pfizer low dose scheme'; 1e = 'Pfizer long interval scheme'; 1f= 'Pfizer intradermal scheme'; 3a='Moderna regular scheme'; 3b='Moderna low dose scheme'

	Randomisation group								
N (%)	**Group 1a**	**Group 1b**	**Group 1c**	**Group 1d**	**Group 1e**	**Group 1f**	**Group 3a**	**Group 3b**	**Total**
No BTI	19 (34,6%)	10 (18,2%)	20 (39,2%)	13 (20,6%)	7 (15.2%)	19 (32,8%)	10 (17,2%)	18 (30,0%)	116 (26,0%)
BTI	36 (64,4%)	45 (81,8%)	31 (60,8%)	50 (79,4%)	39 (84,8%)	39 (67,2%)	48 (82,8%)	42 (70,0%)	330 (74,0%)
Total	55	55	51	63	46	58	58	60	446

Table 52: Number of participants and visit timepoint influenced by BTIs after PE, per randomization group, for subjects who remained in the study until the final visit (visit6, D364) and received the third COVID-19 vaccine after September 2021, and not additional COVID-19 vaccines outside the study

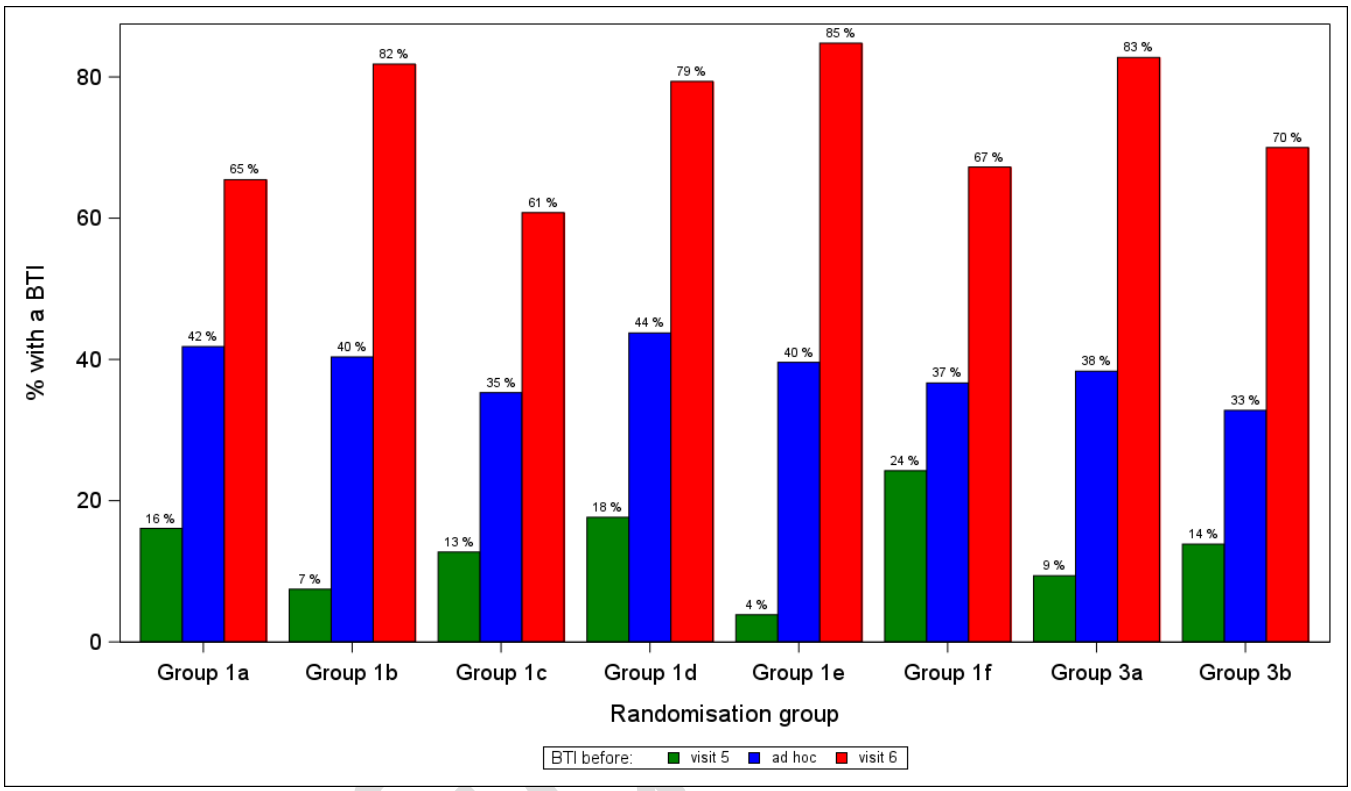
1a = 'Pfizer regular scheme'; 1b = 'Pfizer-Moderna scheme'; 1c ='Pfizer-AstraZeneca scheme'; 1d='Pfizer low dose scheme'; 1e = 'Pfizer long interval scheme'; 1f= 'Pfizer intradermal scheme'; 3a='Moderna regular scheme'; 3b='Moderna low dose scheme

Visit impacted by the first BTI	**Randomisation group**								
N (%)	**Group 1a**	**Group 1b**	**Group 1c**	**Group 1d**	**Group 1e**	**Group 1f**	**Group 3a**	**Group 3b**	**Total**
v4	2 (3.64%)	0 (0.00%)	1 (1.96%)	0 (0.00%)	0 (0.00%)	1 (1.72%)	0 (0.00%)	1 (1.67%)	5
v5	7 (12.73%)	5 (9.09%)	6 (11.76%)	12 (19.05%)	1 (2.17%)	14 (24.14%)	4 (6.90%)	8 (13.33%)	57
Ad hoc post 3rd dose visit	14 (25.45%)	18 (32.73%)	11 (21.57%)	16 (25.40%)	17 (36.96%)	7 (12.07%)	18 (31.03%)	11 (18.33%)	112
v6	13 (23.64%)	22 (40.00%)	13 (25.49%)	22 (34.92%)	21 (45.65%)	17 (29.31%)	26 (44.83%)	22 (36.67%)	156
Total	**36 (64,45%)**	**45 (81,82%)**	**31 (60,78%)**	**50 (79,37%)**	**39 (84,78%)**	**39 (67,24%)**	**48 (82,76%)**	**42 (70,00%)**	**330 (74,00%)**

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Figure 28: Number of participants and visit timepoint influenced by BTIs after PE, per randomisation group, for subjects who remained in the study until the final visit (visit 6, D364) and received the third COVID-19 vaccine after September 2021, and no additional COVID-19 vaccines outside the study

1a = 'Pfizer regular scheme'; 1b = 'Pfizer-Moderna scheme'; 1c ='Pfizer-AstraZeneca scheme'; 1d='Pfizer low dose scheme'; 1e = 'Pfizer long interval scheme'; 1f= 'Pfizer intradermal scheme'; 3a='Moderna regular scheme'; 3b='Moderna low dose scheme'



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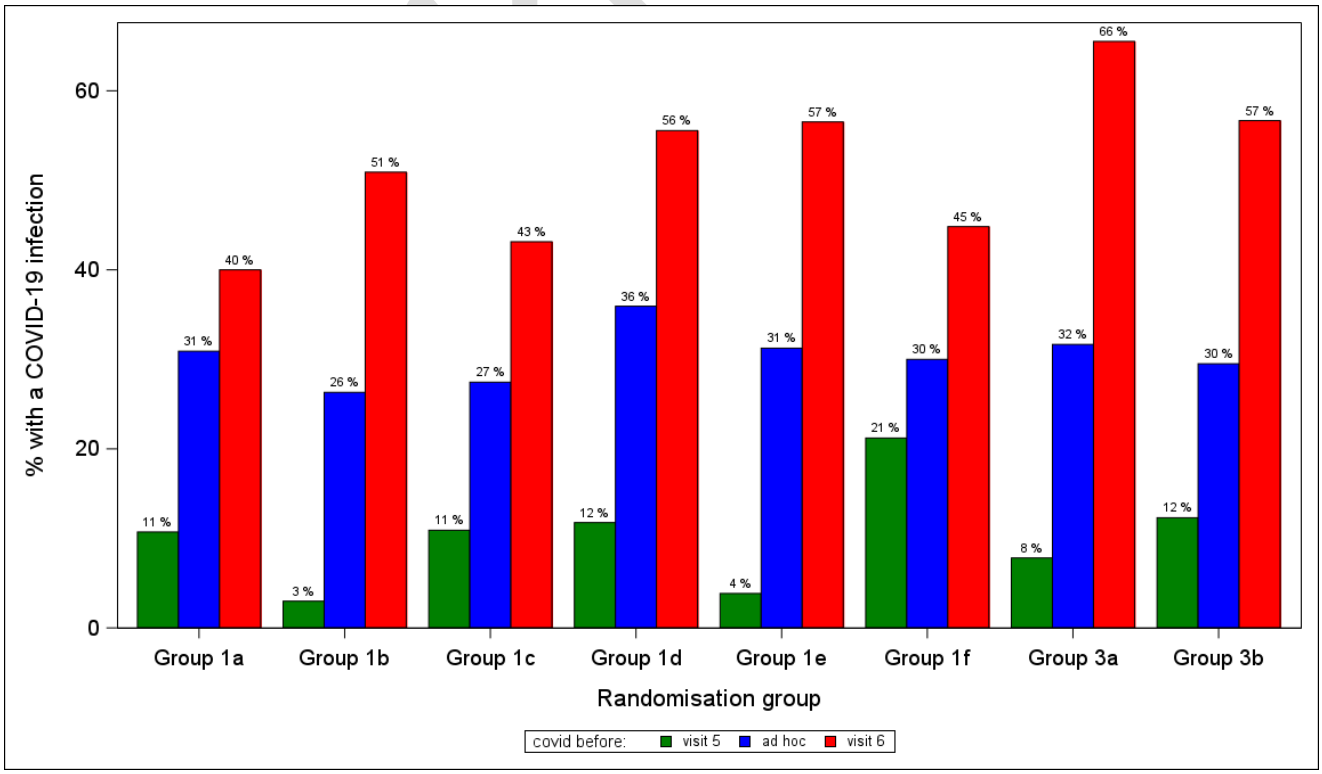
Table 53: Number of participants reporting a COVID-19 infection, for subjects who remained in the study until the final visit (visit 6, D364) and received the third COVID-19 vaccine after September 2021, and no additional COVID-19 vaccines outside the study

1a = 'Pfizer regular scheme'; 1b = 'Pfizer-Moderna scheme'; 1c ='Pfizer-AstraZeneca scheme'; 1d='Pfizer low dose scheme'; 1e = 'Pfizer long interval scheme'; 1f= 'Pfizer intradermal scheme'; 3a='Moderna regular scheme'; 3b='Moderna low dose scheme'

First COVID-19 infection reported before or on visit 6	**Randomisation group**								
N (%)	Group 1a	Group 1b	Group 1c	Group 1d	Group 1e	Group 1f	Group 3a	Group 3b	Total
No COVID-19 infection reported before or on visit 6	33 (60.00 %)	27 (49.09 %)	29 (56.86 %)	28 (44.44%)	20 (43.48%)	32 (55.17%)	20 (34.48%)	26 (43.33%)	215
v4	1 (1.82 %)	0 (0.00 %)	1 (1.96 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.67%)	3
v5	5 (9.09 %)	2 (3.64 %)	5 (9.80 %)	8 (12.70%)	1 (2.17%)	13 (22.41%)	4 (6.90%)	7 (11.67%)	45
Ad hoc	11 (20.00 %)	13 (23.64 %)	8 (15.69 %)	15 (23.81%)	13 (28.26%)	5 (8.62%)	15 (25.86%)	10 (16.67%)	90
v6	5 (9.09 %)	13 (23.64 %)	8 (15.69 %)	12 (19.05%)	12 (26.09 %)	8 (13.79	19 (32.76 %)	16 (26.67%)	93
Total	55	55	51	63	46	58	58	60	446

Figure 29: Proportion of participants reporting a COVID-19 infection, for subjects who remained in the study until the final visit (visit 6, D364) and received the third COVID-19 vaccine after September 2021, and no additional COVID-19 vaccines outside the study

1a = 'Pfizer regular scheme'; 1b = 'Pfizer-Moderna scheme'; 1c ='Pfizer-AstraZeneca scheme'; 1d='Pfizer low dose scheme'; 1e = 'Pfizer long interval scheme'; 1f= 'Pfizer intradermal scheme'; 3a='Moderna regular scheme'; 3b='Moderna low dose scheme'



10.8 Safety

i. Adverse events reported by the eligible participants

Table 54 summarizes all AEs that were reported by the eligible participants (n=566). Almost all of the participants (98%) reported at least one AE during the study, with a total of 5426 AEs reported, including 26 serious adverse events. Approximately 1 in 10 AEs required medical attention, and a bit more then 5% were categorized as AEs of special interest. The majority (94%) of AEs were classified as mild to moderate. 26 AEs were categorized as Serious Adverse Event, of which one life-threatening AE was reported, more details can be found under iv.

Table 54: Summary of ALL AEs reported during the study reported by all eligible participants

		Total
Participants with at least one adverse event		557/566(98.41%)
Number of adverse events		5426
Severity	1- Mild	3293 (60.69%)
	2- Moderate	1813 (33.41%)
	3- Severe	319 (5.88%)
	4- Life threatening	1 (0.02%)
Relationship treatment	Not related	1000 (18.43%)
	Related	4426 (81.57%)
Medically attended event	No	4849 (89.37%)
	yes	577 (10.63%)
AE of special interest	No	5141 (94.75%)
	yes	285 (5.25%)
Serious adverse event	No	5400 (99.52%)
	yes	26 (0.48%)

ii. COVID-19 infections (as reported in the eCRF) – mITT population

Of the 506 participants included in the modified-intention-to-treat (mITT) population, 256 participants reported a total of 260 COVID-19 infections after the second vaccine dose, as shown in Table 55. The majority of the infections were classified as severity mild to moderate, while 55 of them required medical attention. Only 6 of the reported COVID-19 infections were classified as severe, and happened divided over 6 different study groups.
The onset of COVID-19 infections since baseline is illustrated in Figure 30

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Table 55: Summary of COVID-19 infections reported during the study by the mITT population

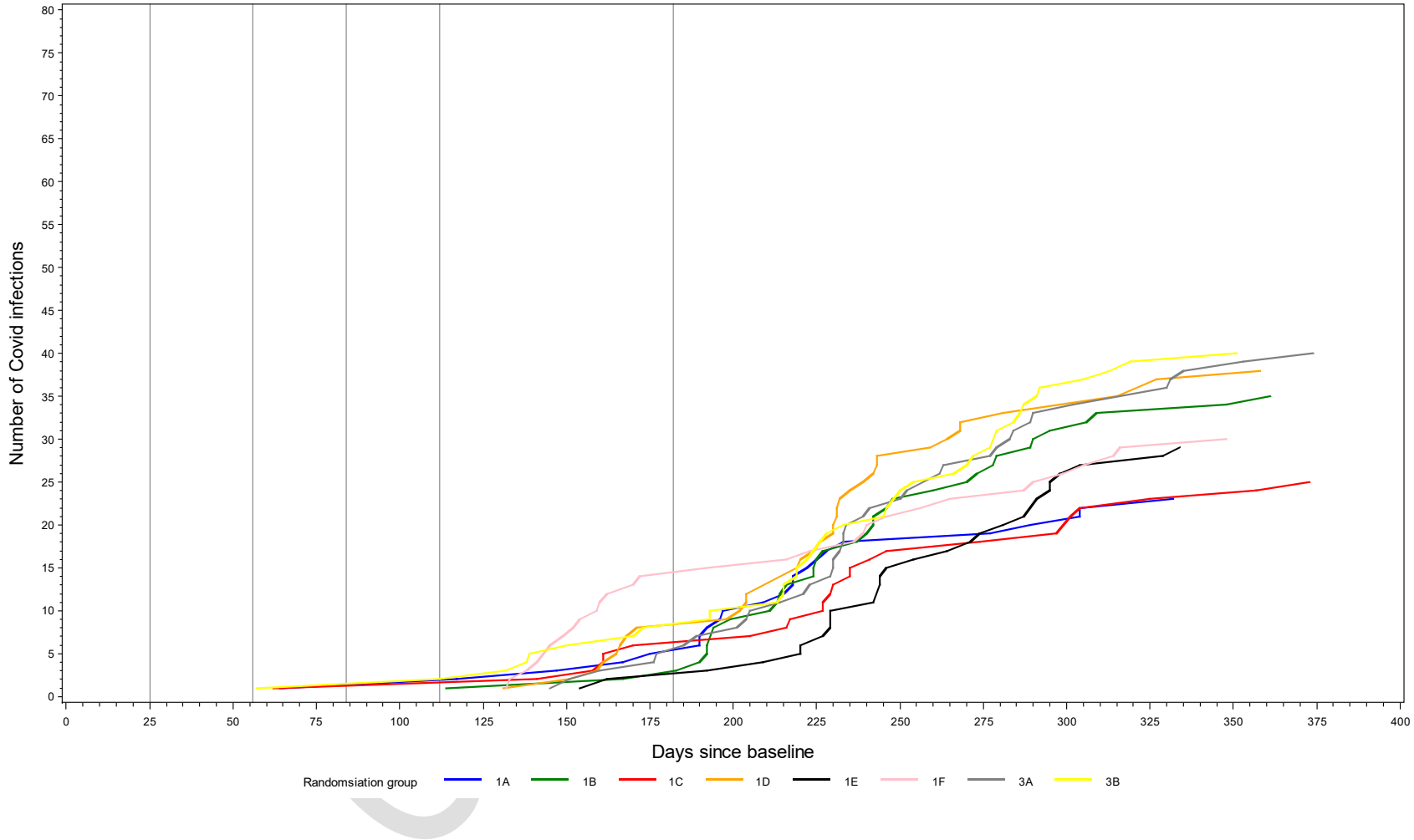
1a = 'Pfizer regular scheme'; 1b = 'Pfizer-Moderna scheme'; 1c ='Pfizer-AstraZeneca scheme'; 1d='Pfizer low dose scheme'; 1e = 'Pfizer long interval scheme'; 1f= 'Pfizer intradermal scheme'; 3a='Moderna regular scheme'; 3b='Moderna low dose scheme'

		1A	**1B**	**1C**	**1D**	**1e**	**1F**	**3A**	**3B**	**Total**
Participants with at least one COVID-19 infection		22/57 (38.60%)	33/68 (48.53%)	25/59 (42.37%)	38/69 (55.07%)	29/52 (55.77%)	30/67 (44.78%)	40/66 (60.61%)	39/68 (57.35%)	256/506 (50.59%)
Number of COVID-19 infections		23	35	25	38	29	30	40	40	260
Severity	1- Mild	19 (82.61%)	21 (60.00%)	11 (44.00%)	22 (57.89%)	17 (58.62%)	17 (56.67%)	21 (52.50%)	25 (62.50%)	153 (58.85%)
	2- Moderate	3 (13.04%)	13 (37.14%)	13 (52.00%)	15 (39.47%)	12 (41.38%)	12 (40.00%)	19 (47.50%)	14 (35.00%)	101 (38.85%)
	3- Severe	1 (4.35%)	1 (2.86%)	1 (4.00%)	1 (2.63%)		1 (3.33%)		1 (2.50%)	6 (2.31%)
Relationship treatment	Not related	23 (100.00%)	35 (100.00%)	25 (100.00%)	38 (100.00%)	28 (96.55%)	29 (96.67%)	40 (100.00%)	40 (100.00%)	258 (99.23%)
	Related					1 (3.45%)	1 (3.33%)			2 (0.77%)
Medically attended event	No	19 (82.61%)	32 (91.43%)	14 (56.00%)	34 (89.47%)	23 (79.31%)	18 (60.00%)	34 (85.00%)	31 (77.50%)	205 (78.85%)
	yes	4 (17.39%)	3 (8.57%)	11 (44.00%)	4 (10.53%)	6 (20.69%)	12 (40.00%)	6 (15.00%)	9 (22.50%)	55 (21.15%)
AE of special interest	yes	23 (100.00%)	35 (100.00%)	25 (100.00%)	38 (100.00%)	29 (100.00%)	30 (100.00%)	40 (100.00%)	40 (100.00%)	260 (100.00%)
Serious adverse event	No	23 (100.00%)	35 (100.00%)	25 (100.00%)	38 (100.00%)	29 (100.00%)	30 (100.00%)	40 (100.00%)	40 (100.00%)	260 (100.00%)

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Figure 30: Covid-19 infections based on AE-reporting, days since 1st vaccine, mITT population

1a = 'Pfizer regular scheme'; 1b = 'Pfizer-Moderna scheme'; 1c ='Pfizer-AstraZeneca scheme'; 1d='Pfizer low dose scheme'; 1e = 'Pfizer long interval scheme'; 1f= 'Pfizer intradermal scheme'; 3a='Moderna regular scheme'; 3b='Moderna low dose scheme'



iii. Solicited and unsolicited AEs reported after 1st and 2nd study vaccination

The mITT population, consisting of 506 participants, reported a total of 4278 AEs (Table 56). Of these, 84% (3612) were solicited AEs, with 1642 local AEs and 1970 systemic AEs. The remaining 666 (16%) AEs were unsolicited. Most AEs (94%) were mild to moderate in severity and related to the study treatment. Medical attention was required for 59 AEs, with 4 considered AEs of special interest and 1 reported as a serious adverse event.

Among the reported solicited local AEs (

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Table 57/Table 58), injection site pain tenderness accounted for almost 3 out of 4 of the local AEs (72%). Overall, 98% of participants experienced this local AE, the 'Pfizer intradermal scheme' (group 1f) had the highest proportion of participants reporting any type of local AE.

Regarding solicited systemic AEs (Table 59/Table 60), fatigue was the most common type (27%). Overall, 73% of participants experienced this systemic AE, with 88% of group 1b participants (Pfizer-Moderna scheme) and 48% of group 1e participants (Pfizer intradermal scheme) reporting it.

Unsolicited AEs were reported by 54% of participants (Table 61) , with 42% ITT participants in group 1d (Pfizer low dose scheme) experiencing them, while 72% of group 1f (Pfizer intradermal) reported them.

Figure 31 and Figure 32 illustrate the percentage of participants who experience at least one adverse event, categorized by treatment group and severity. If a participant experiences multiple adverse events of the same type, the most severe event is considered.

In the appendix, Table 65 and Table 66 provide identical information, but they present the adverse events separately for those reported after the first study-vaccination and those reported after the second study-vaccination. There is a higher number of reported adverse events (AEs) following the second study-vaccination compared to the first (2687 after second vaccination versus 1591 after first vaccination). Specifically, there is a greater frequency of systemic AEs reported after the second study-vaccination (1482 after second vaccination versus 488 after first vaccination).

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Table 56: Summary of (solicited and unsolicited) AEs reported within 14 days after 1st and 2nd vaccination, per study group, mITT population

1a = 'Pfizer regular scheme'; 1b = 'Pfizer-Moderna scheme'; 1c ='Pfizer-AstraZeneca scheme'; 1d='Pfizer low dose scheme'; 1e = 'Pfizer long interval scheme'; 1f= 'Pfizer intradermal scheme'; 3a='Moderna regular scheme'; 3b='Moderna low dose scheme'

		RANDOMISATION GROUP								
		1A	**1B**	**1C**	**1D**	**1e**	**1F**	**3A**	**3B**	**Total**
Participants with at least one adverse event		56/57(98.25%)	68/68(100.00%)	59/59(100.00%)	68/69(98.55%)	51/52(98.08%)	67/67(100.00%)	66/66(100.00%)	68/68(100.00%)	503/506(99.41%)
Number of adverse events		417	693	524	428	287	666	661	602	4278
Number of solicited AE		361 (86.57%)	596 (86.00%)	449 (85.69%)	366 (85.51%)	240 (83.62%)	518 (77.78%)	571 (86.38%)	511 (84.88%)	3612 (84.43%)
..... local AE		164 (39.33%)	220 (31.75%)	143 (27.29%)	163 (38.08%)	130 (45.30%)	365 (54.80%)	242 (36.61%)	215 (35.71%)	1642 (38.38%)
..... systemic AE		197 (47.24%)	376 (54.26%)	306 (58.40%)	203 (47.43%)	110 (38.33%)	153 (22.97%)	329 (49.77%)	296 (49.17%)	1970 (46.05%)
Number of un solicited AE		56 (13.43%)	97 (14.00%)	75 (14.31%)	62 (14.49%)	47 (16.38%)	148 (22.22%)	90 (13.62%)	91 (15.12%)	666 (15.57%)
Severity	1- Mild	295 (70.74%)	398 (57.43%)	322 (61.45%)	297 (69.39%)	184 (64.11%)	484 (72.67%)	401 (60.67%)	376 (62.46%)	2757 (64.45%)
	2- Moderate	108 (25.90%)	222 (32.03%)	156 (29.77%)	119 (27.80%)	87 (30.31%)	171 (25.68%)	226 (34.19%)	194 (32.23%)	1283 (29.99%)
	3- Severe	14 (3.36%)	73 (10.53%)	46 (8.78%)	12 (2.80%)	16 (5.57%)	11 (1.65%)	34 (5.14%)	32 (5.32%)	238 (5.56%)
Relationship treatment	Not related	22 (5.28%)	43 (6.20%)	22 (4.20%)	43 (10.05%)	28 (9.76%)	40 (6.01%)	29 (4.39%)	36 (5.98%)	263 (6.15%)
	Related	395 (94.72%)	650 (93.80%)	502 (95.80%)	385 (89.95%)	259 (90.24%)	626 (93.99%)	632 (95.61%)	566 (94.02%)	4015 (93.85%)
Medically attended event	No	407 (97.60%)	685 (98.85%)	516 (98.47%)	424 (99.07%)	282 (98.26%)	661 (99.25%)	651 (98.49%)	593 (98.50%)	4219 (98.62%)
	yes	10 (2.40%)	8 (1.15%)	8 (1.53%)	4 (0.93%)	5 (1.74%)	5 (0.75%)	10 (1.51%)	9 (1.50%)	59 (1.38%)
AE of special interest	No	413 (99.04%)	693 (100.00%)	524 (100.00%)	428 (100.00%)	287 (100.00%)	666 (100.00%)	661 (100.00%)	602 (100.00%)	4274 (99.91%)
	yes	4 (0.96%)								4 (0.09%)
Serious adverse event	No	416 (99.76%)	693 (100.00%)	524 (100.00%)	428 (100.00%)	287 (100.00%)	666 (100.00%)	661 (100.00%)	602 (100.00%)	4277 (99.98%)
	yes	1 (0.24%)								1 (0.02%)

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Table 57:Summary of solicited local AEs reported within 14 days after 1st and 2nd vaccination, per study group, mITT population

1a = 'Pfizer regular scheme'; 1b = 'Pfizer-Moderna scheme'; 1c ='Pfizer-AstraZeneca scheme'; 1d='Pfizer low dose scheme'; 1e = 'Pfizer long interval scheme'; 1f= 'Pfizer intradermal scheme'; 3a='Moderna regular scheme'; 3b='Moderna low dose scheme'

		RANDOMISATION GROUP								
		1A	**1B**	**1C**	**1D**	**1e**	**1F**	**3A**	**3B**	**Total**
Participants with at least one local adverse event		56/57(98.25%)	68/68(100.00%)	59/59(100.00%)	68/69(98.55%)	50/52(96.15%)	66/67(98.51%)	66/66(100.00%)	68/68(100.00%)	501/506(99.01%)
Number of local adverse events		164	220	143	163	130	365	242	215	1642
PT term	Injection site erythema	5 (3.05%)	12 (5.45%)	7 (4.90%)	2 (1.23%)	2 (1.54%)	121 (33.15%)	25 (10.33%)	15 (6.98%)	189 (11.51%)
	Injection site induration	8 (4.88%)	26 (11.82%)	8 (5.59%)	7 (4.29%)	6 (4.62%)	36 (9.86%)	30 (12.40%)	22 (10.23%)	143 (8.71%)
	Injection site pain tenderness	148 (90.24%)	171 (77.73%)	124 (86.71%)	152 (93.25%)	118 (90.77%)	141 (38.63%)	171 (70.66%)	163 (75.81%)	1188 (72.35%)
	Injection site swelling	3 (1.83%)	11 (5.00%)	4 (2.80%)	2 (1.23%)	4 (3.08%)	67 (18.36%)	16 (6.61%)	15 (6.98%)	122 (7.43%)
Severity	1- Mild	129 (78.66%)	133 (60.45%)	116 (81.12%)	133 (81.60%)	93 (71.54%)	259 (70.96%)	140 (57.85%)	135 (62.79%)	1138 (69.31%)
	2- Moderate	35 (21.34%)	73 (33.18%)	27 (18.88%)	29 (17.79%)	34 (26.15%)	97 (26.58%)	94 (38.84%)	73 (33.95%)	462 (28.14%)
	3- Severe		14 (6.36%)		1 (0.61%)	3 (2.31%)	9 (2.47%)	8 (3.31%)	7 (3.26%)	42 (2.56%)
Relationship treatment	Not related						1 (0.27%)			1 (0.06%)
	Related	164 (100.00%)	220 (100.00%)	143 (100.00%)	163 (100.00%)	130 (100.00%)	364 (99.73%)	242 (100.00%)	215 (100.00%)	1641 (99.94%)
MAAE	No	164 (100.00%)	220 (100.00%)	143 (100.00%)	163 (100.00%)	130 (100.00%)	365 (100.00%)	242 (100.00%)	215 (100.00%)	1642 (100.00%)
AESI	No	164 (100.00%)	220 (100.00%)	143 (100.00%)	163 (100.00%)	130 (100.00%)	365 (100.00%)	242 (100.00%)	215 (100.00%)	1642 (100.00%)
SAE	No	164 (100.00%)	220 (100.00%)	143 (100.00%)	163 (100.00%)	130 (100.00%)	365 (100.00%)	242 (100.00%)	215 (100.00%)	1642 (100.00%)

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Table 58: Percentage of participants reporting (at least one) solicited local AE within 14 days after 1st and 2nd vaccination, per study group, mITT population

1a = 'Pfizer regular scheme'; 1b = 'Pfizer-Moderna scheme'; 1c ='Pfizer-AstraZeneca scheme'; 1d='Pfizer low dose scheme'; 1e = 'Pfizer long interval scheme'; 1f= 'Pfizer intradermal scheme'; 3a='Moderna regular scheme'; 3b='Moderna low dose scheme'	Randomisation group								
	Group 1a	**Group 1b**	**Group 1c**	**Group 1d**	**Group 1e**	**Group 1f**	**Group 3a**	**Group 3b**	**Total**
	% of participants	**% of participants**	**% of participants**	**% of participants**	**% of participants**	**% of participants**	**% of participants**	**% of participants**	**% of participants**
Preferred term									
Injection site erythema	7.02	14.71	11.86	2.90	3.85	97.01	30.30	20.59	24.51
Injection site induration	8.77	29.41	11.86	5.80	9.62	38.81	33.33	26.47	21.15
Injection site pain tenderness	98.25	100.00	100.00	98.55	94.23	92.54	100.00	100.00	98.02
Injection site swelling	5.26	14.71	6.78	1.45	5.77	67.16	21.21	17.65	18.18

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Table 59: Summary of solicited systemic AEs reported within 14 days after 1st and 2nd vaccination, per study group, mITT population

1a = 'Pfizer regular scheme'; 1b = 'Pfizer-Moderna scheme'; 1c ='Pfizer-AstraZeneca scheme'; 1d='Pfizer low dose scheme'; 1e = 'Pfizer long interval scheme'; 1f= 'Pfizer intradermal scheme'; 3a='Moderna regular scheme'; 3b='Moderna low dose scheme'

		RANDOMISATION GROUP								
		1A	**1B**	**1C**	**1D**	**1e**	**1F**	**3A**	**3B**	**Total**
Participants with at least one systemic adverse event		52/57 (91.23%)	64/68 (94.12%)	54/59 (91.53%)	57/69 (82.61%)	33/52 (63.46%)	55/67 (82.09%)	64/66 (96.97%)	58/68 (85.29%)	437/506 (86.36%)
Number of systemic adverse events		197	376	306	203	110	153	329	296	1970
PT term	Arthralgia	14 (7.11%)	24 (6.38%)	24 (7.84%)	15 (7.39%)	7 (6.36%)	4 (2.61%)	20 (6.08%)	16 (5.41%)	124 (6.29%)
	Chest pain	1 (0.51%)	5 (1.33%)	7 (2.29%)	3 (1.48%)	2 (1.82%)	2 (1.31%)	5 (1.52%)	6 (2.03%)	31 (1.57%)
	Chills	9 (4.57%)	32 (8.51%)	27 (8.82%)	8 (3.94%)	3 (2.73%)	4 (2.61%)	32 (9.73%)	23 (7.77%)	138 (7.01%)
	Dyspnoea	4 (2.03%)	6 (1.60%)	5 (1.63%)	2 (0.99%)	2 (1.82%)	1 (0.65%)	3 (0.91%)	7 (2.36%)	30 (1.52%)
	Fatigue	63 (31.98%)	85 (22.61%)	65 (21.24%)	70 (34.48%)	35 (31.82%)	63 (41.18%)	81 (24.62%)	77 (26.01%)	539 (27.36%)
	Headache	44 (22.34%)	75 (19.95%)	62 (20.26%)	44 (21.67%)	26 (23.64%)	41 (26.80%)	60 (18.24%)	63 (21.28%)	415 (21.07%)
	Malaise	21 (10.66%)	45 (11.97%)	40 (13.07%)	23 (11.33%)	8 (7.27%)	15 (9.80%)	37 (11.25%)	37 (12.50%)	226 (11.47%)
	Myalgia	27 (13.71%)	48 (12.77%)	30 (9.80%)	23 (11.33%)	10 (9.09%)	14 (9.15%)	43 (13.07%)	32 (10.81%)	227 (11.52%)
	Nausea	7 (3.55%)	24 (6.38%)	20 (6.54%)	10 (4.93%)	12 (10.91%)	8 (5.23%)	23 (6.99%)	23 (7.77%)	127 (6.45%)
	Neurological symptom	1 (0.51%)	2 (0.53%)	3 (0.98%)	1 (0.49%)	2 (1.82%)		1 (0.30%)	1 (0.34%)	11 (0.56%)
	Petechiae		1 (0.27%)							1 (0.05%)
	Pyrexia	5 (2.54%)	26 (6.91%)	19 (6.21%)	3 (1.48%)	2 (1.82%)		22 (6.69%)	10 (3.38%)	87 (4.42%)
	Vomiting	1 (0.51%)	3 (0.80%)	4 (1.31%)	1 (0.49%)	1 (0.91%)	1 (0.65%)	2 (0.61%)	1 (0.34%)	14 (0.71%)
Severity	1- Mild	125 (63.45%)	203 (53.99%)	155 (50.65%)	129 (63.55%)	61 (55.45%)	112 (73.20%)	200 (60.79%)	186 (62.84%)	1171 (59.44%)
	2- Moderate	64 (32.49%)	117 (31.12%)	107 (34.97%)	66 (32.51%)	37 (33.64%)	40 (26.14%)	108 (32.83%)	87 (29.39%)	626 (31.78%)
	3- Severe	8 (4.06%)	56 (14.89%)	44 (14.38%)	8 (3.94%)	12 (10.91%)	1 (0.65%)	21 (6.38%)	23 (7.77%)	173 (8.78%)
Relationship treatment	Not related	4 (2.03%)	9 (2.39%)	3 (0.98%)	14 (6.90%)	6 (5.45%)	3 (1.96%)	8 (2.43%)	8 (2.70%)	55 (2.79%)
	Related	193 (97.97%)	367 (97.61%)	303 (99.02%)	189 (93.10%)	104 (94.55%)	150 (98.04%)	321 (97.57%)	288 (97.30%)	1915 (97.21%)
MAAE	No	197 (100.00%)	376 (100.00%)	304 (99.35%)	203 (100.00%)	110 (100.00%)	153 (100.00%)	327 (99.39%)	293 (98.99%)	1963 (99.64%)
	yes			2 (0.65%)				2 (0.61%)	3 (1.01%)	7 (0.36%)
AESI	No	197 (100.00%)	376 (100.00%)	306 (100.00%)	203 (100.00%)	110 (100.00%)	153 (100.00%)	329 (100.00%)	296 (100.00%)	1970 (100.00%)
SAE	No	197 (100.00%)	376 (100.00%)	306 (100.00%)	203 (100.00%)	110 (100.00%)	153 (100.00%)	329 (100.00%)	296 (100.00%)	1970 (100.00%)

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Table 60: Percentage of participants reporting (at least one) solicited systemic AE within 14 days after 1st and 2nd vaccination, per study group, mITT population

1a = 'Pfizer regular scheme'; 1b = 'Pfizer-Moderna scheme'; 1c ='Pfizer-AstraZeneca scheme'; 1d='Pfizer low dose scheme'; 1e = 'Pfizer long interval scheme'; 1f= 'Pfizer intradermal scheme'; 3a='Moderna regular scheme'; 3b='Moderna low dose scheme'

	Randomisation group								
	Group 1a	Group 1b	Group 1c	Group 1d	Group 1e	Group 1f	Group 3a	Group 3b	Total
	% of participants	% of participants	% of participants	% of participants	% of participants	% of participants	% of participants	% of participants	% of participants
Preferred term									
Arthralgia	22.81	33.82	35.59	20.29	11.54	4.48	28.79	22.06	22.53
Chest pain	1.75	5.88	10.17	4.35	3.85	2.99	7.58	5.88	5.34
Chills	15.79	45.59	45.76	11.59	3.85	5.97	46.97	33.82	26.68
Dyspnoea	7.02	8.82	8.47	2.90	1.92	1.49	4.55	8.82	5.53
Fatigue	80.70	88.24	79.66	73.91	48.08	68.66	71.21	72.06	73.32
Headache	68.42	77.94	79.66	50.72	36.54	49.25	60.61	63.24	61.07
Malaise	33.33	63.24	64.41	30.43	13.46	19.40	51.52	51.47	41.50
Myalgia	43.86	61.76	45.76	30.43	17.31	17.91	51.52	42.65	39.33
Nausea	10.53	32.35	32.20	11.59	21.15	8.96	31.82	30.88	22.53
Neurological symptom	1.75	2.94	5.08	1.45	3.85	0.00	1.52	1.47	2.17
Petechiae	0.00	1.47	0.00	0.00	0.00	0.00	0.00	0.00	0.20
Pyrexia	8.77	38.24	28.81	4.35	3.85	0.00	31.82	14.71	16.60
Vomiting	1.75	4.41	6.78	1.45	1.92	1.49	3.03	1.47	2.77

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Table 61: Summary of unsolicited AEs reported within 14 days after 1st and 2nd vaccination, per study group, mITT population

Unsolicited AE reported less than 10 times are grouped under the category 'Others'.

1a = 'Pfizer regular scheme'; 1b = 'Pfizer-Moderna scheme'; 1c ='Pfizer-AstraZeneca scheme'; 1d='Pfizer low dose scheme'; 1e = 'Pfizer long interval scheme'; 1f= 'Pfizer intradermal scheme'; 3a='Moderna regular scheme'; 3b='Moderna low dose scheme'

		RANDOMISATION GROUP								
		1A	**1B**	**1C**	**1D**	**1e**	**1F**	**3A**	**3B**	**Total**
Participants with at least one unsolicited adverse event		28/57(49.12%)	36/68(52.94%)	29/59(49.15%)	29/69(42.03%)	26/52(50.00%)	48/67(71.64%)	36/66(54.55%)	40/68(58.82%)	272/506(53.75%)
Number of unsolicited adverse events		56	97	75	62	47	148	90	91	666
PT term	Abdominal pain	2 (3.57%)	9 (9.28%)	5 (6.67%)	3 (4.84%)	2 (4.26%)	2 (1.35%)	3 (3.33%)	6 (6.59%)	32 (4.80%)
	Cough		3 (3.09%)	3 (4.00%)		2 (4.26%)	1 (0.68%)		1 (1.10%)	10 (1.50%)
	Diarrhoea	2 (3.57%)	3 (3.09%)	3 (4.00%)	2 (3.23%)	1 (2.13%)	8 (5.41%)	1 (1.11%)	3 (3.30%)	23 (3.45%)
	Dizziness	2 (3.57%)	4 (4.12%)	1 (1.33%)	3 (4.84%)	2 (4.26%)		2 (2.22%)	4 (4.40%)	18 (2.70%)
	Fatigue	2 (3.57%)	1 (1.03%)	3 (4.00%)		1 (2.13%)	2 (1.35%)	1 (1.11%)		10 (1.50%)
	Headache	5 (8.93%)	8 (8.25%)	9 (12.00%)	5 (8.06%)	6 (12.77%)	9 (6.08%)	6 (6.67%)	4 (4.40%)	52 (7.81%)
	Injection site erythema					1 (2.13%)	14 (9.46%)	9 (10.00%)	3 (3.30%)	27 (4.05%)
	Injection site haematoma	1 (1.79%)	2 (2.06%)	1 (1.33%)	2 (3.23%)		1 (0.68%)		3 (3.30%)	10 (1.50%)
	Injection site haemorrhage		2 (2.06%)				5 (3.38%)	4 (4.44%)	3 (3.30%)	14 (2.10%)
	Injection site movement impairment	5 (8.93%)	6 (6.19%)	5 (6.67%)	7 (11.29%)	3 (6.38%)		5 (5.56%)	6 (6.59%)	37 (5.56%)
	Injection site pruritus	1 (1.79%)	3 (3.09%)	1 (1.33%)	1 (1.61%)		31 (20.95%)	6 (6.67%)	6 (6.59%)	49 (7.36%)
	Injection site warmth		7 (7.22%)	2 (2.67%)	1 (1.61%)	1 (2.13%)	5 (3.38%)	6 (6.67%)	2 (2.20%)	24 (3.60%)
	Lymphadenopathy	1 (1.79%)	2 (2.06%)		2 (3.23%)	1 (2.13%)	2 (1.35%)	3 (3.33%)	1 (1.10%)	12 (1.80%)
	Oropharyngeal pain	2 (3.57%)	2 (2.06%)	1 (1.33%)	3 (4.84%)	1 (2.13%)	4 (2.70%)	3 (3.33%)	3 (3.30%)	19 (2.85%)
	Others	33 (58.93%)	45 (46.39%)	41 (54.67%)	33 (53.23%)	26 (55.32%)	64 (43.24%)	41 (45.56%)	46 (50.55%)	329 (49.40%)
Severity	1- Mild	41 (73.21%)	62 (63.92%)	51 (68.00%)	35 (56.45%)	30 (63.83%)	113 (76.35%)	61 (67.78%)	55 (60.44%)	448 (67.27%)
	2- Moderate	9 (16.07%)	32 (32.99%)	22 (29.33%)	24 (38.71%)	16 (34.04%)	34 (22.97%)	24 (26.67%)	34 (37.36%)	195 (29.28%)
	3- Severe	6 (10.71%)	3 (3.09%)	2 (2.67%)	3 (4.84%)	1 (2.13%)	1 (0.68%)	5 (5.56%)	2 (2.20%)	23 (3.45%)
Relationship treatment	Not related	18 (32.14%)	34 (35.05%)	19 (25.33%)	29 (46.77%)	22 (46.81%)	36 (24.32%)	21 (23.33%)	28 (30.77%)	207 (31.08%)

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	Related	38 (67.86%)	63 (64.95%)	56 (74.67%)	33 (53.23%)	25 (53.19%)	112 (75.68%)	69 (76.67%)	63 (69.23%)	459 (68.92%)
Medically attended event	No	46 (82.14%)	89 (91.75%)	69 (92.00%)	58 (93.55%)	42 (89.36%)	143 (96.62%)	82 (91.11%)	85 (93.41%)	614 (92.19%)
	yes	10 (17.86%)	8 (8.25%)	6 (8.00%)	4 (6.45%)	5 (10.64%)	5 (3.38%)	8 (8.89%)	6 (6.59%)	52 (7.81%)
AE of special interest	No	52 (92.86%)	97 (100.00%)	75 (100.00%)	62 (100.00%)	47 (100.00%)	148 (100.00%)	90 (100.00%)	91 (100.00%)	662 (99.40%)
	yes	4 (7.14%)								4 (0.60%)
Serious adverse event	No	55 (98.21%)	97 (100.00%)	75 (100.00%)	62 (100.00%)	47 (100.00%)	148 (100.00%)	90 (100.00%)	91 (100.00%)	665 (99.85%)
	yes	1 (1.79%)								1 (0.15%)

Confidential

Figure 31: Percentage of participants with a solicited local AEs reported within 14 days after 1st and 2nd vaccination, per study group and severity, mITT population

1a = 'Pfizer regular scheme'; 1b = 'Pfizer-Moderna scheme'; 1c ='Pfizer-AstraZeneca scheme'; 1d='Pfizer low dose scheme'; 1e = 'Pfizer long interval scheme'; 1f= 'Pfizer intradermal scheme'; 3a='Moderna regular scheme'; 3b='Moderna low dose scheme'

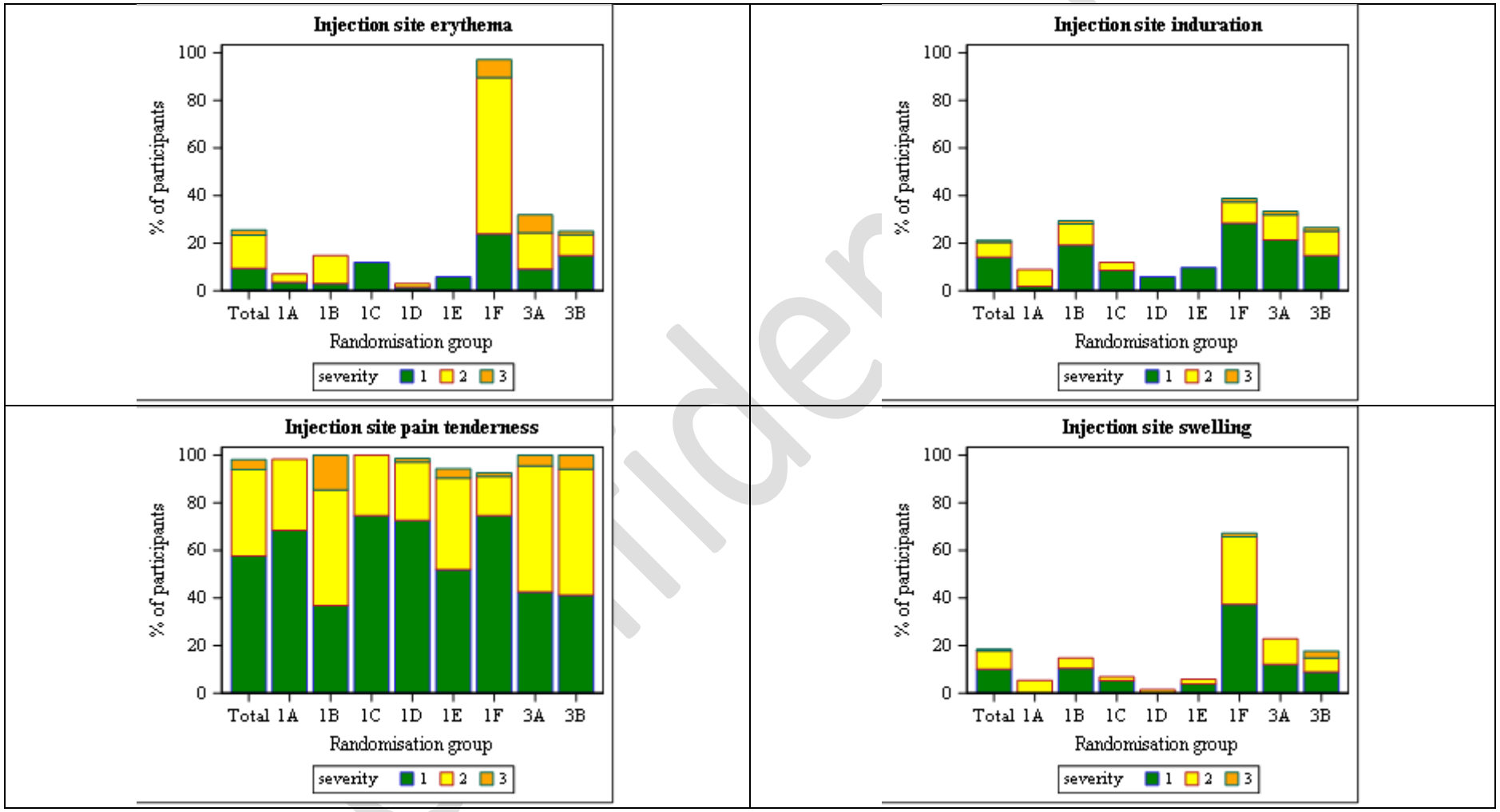
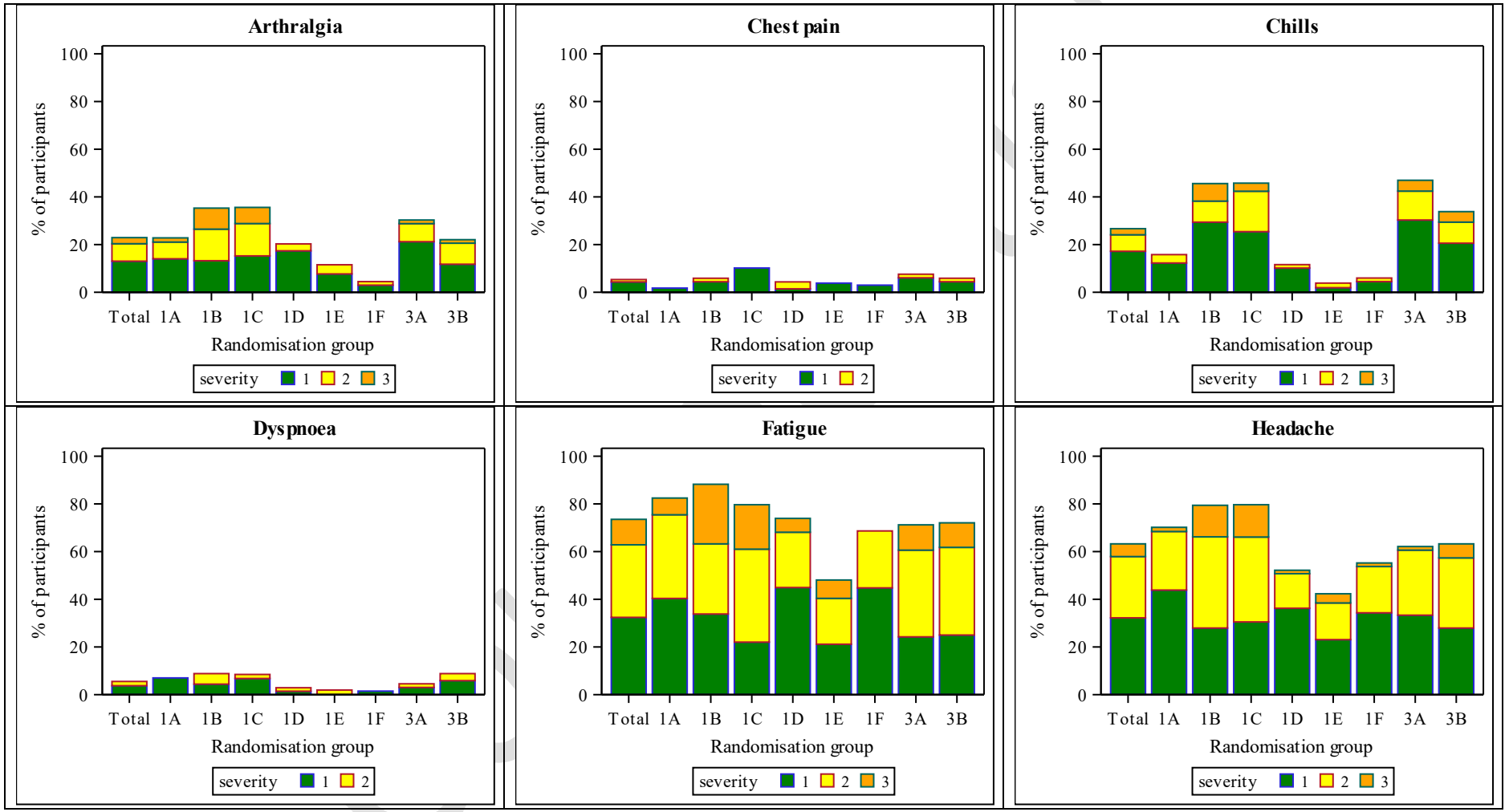
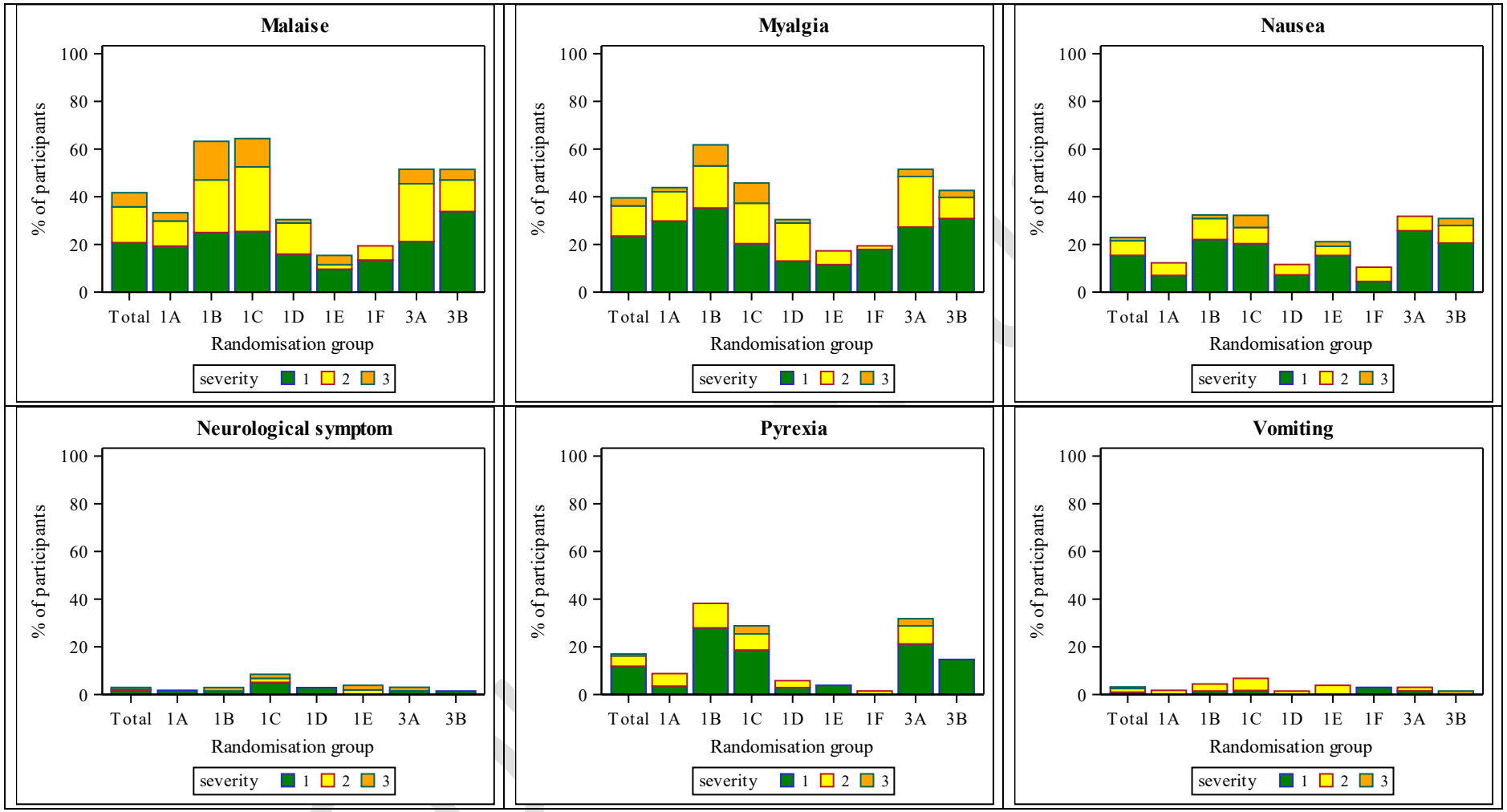


Figure 32: Percentage of participants with a solicited systemic AEs reported within 14 days after 1st and 2nd vaccination, per study group and severity, mITT population

1a = 'Pfizer regular scheme'; 1b = 'Pfizer-Moderna scheme'; 1c ='Pfizer-AstraZeneca scheme'; 1d='Pfizer low dose scheme'; 1e = 'Pfizer long interval scheme'; 1f= 'Pfizer intradermal scheme'; 3a='Moderna regular scheme'; 3b='Moderna low dose scheme'




Malaise
Myalgia
Nausea
Neurological symptom
Pyrexia
Vomiting
% of participants
0
20
40
60
80
100
Total 1A 1B 1C 1D 1E 1F 3A 3B
Randomisation group
severity 1 2 3

iv. Serious Adverse Event (SAEs)

An overview of all SAE's can be found in Table 62 presented as line listing and in table 63 presented as Cumulative Tabulation. No SAE was considered possible or probable related to IP. One life-threatening SAE was reported, this was a sepsis that started almost one year after study start, on 16/04/2022, and is rated as 'definitly not related to IP' (subj 89-123).

Table 62: line listing SAEs

SAE	Subject ID	Site	Age	Diagnosis	Date of SAE onset	Serious criteria	Severity	Relationship to ConMed	Relationship to IP	Expectedness	SUSAR	Outcome	Date of outcome	Action taken
1	89-53	UA-CEV	20	Arteria carotis interna occlusion left after dissection	8/07/2021	Disability	Severe	Unlikely	Unlikely	NA	NA	Permanent damage	8/07/2021	Medication given; diagnostic tests performed; medical procedure started
2	90-56	UZG-CEVAC	34	Abdominal pain	19/09/2021	Hospitalization	Severe	Definitely not	Unlikely	No	NA	Recovered	22/09/2021	Medical procedure started performed + medication given
3	90-88	UZG-CEVAC	21	Left Renal Stone	21/09/2021	Hospitalization	Severe	Definitely not	Definitely not	No	NA	Recovered	29/09/2021	Medication given and diagnostic test performed.
4	89-211	UA-CEV	47	Fracture left wrist	30/09/2021	Hospitalization	Severe	Definitely not	Definitely not	NA	NA	Recovered	1/10/2021	Diagnostic test + medical procedure
5	89-204	UA-CEV	49	Diverticulitis	11/10/2021	Hospitalization	Severe	Unlikely	Unlikely	NA	NA	Recovered	14/10/2021	Medication given
6	88-80	ITM	47	Chronic appendicitis with endoscopic appendectomy	23/08/2021	Hospitalization	Moderate	Definitely not	Definitely not	NA	NA	Recovered	26/08/2021	Diagnostic test + medical procedure + medication given
7	88-32	ITM	36	Gall bladder stones requering surgery and hospitalisation	15/10/2021	Hospitalization	Severe	Unlikely	Unlikely	NA	NA	Recovered	16/10/21	Medication given + medical procedure
8	90-56 - 002	UZG-CEVAC	34	Rotator cuff tear (left shoulder)	5/01/2022	Hospitalization	Moderate	Definitely not	Definitely not	NA	NA	Recovered	6/01/2022	medication given, diagnostic test

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														performed and medical procedure (surgery)
9	89-65	UA-CEV	40	Spontaneous pneumothorax	30/12/2021	Hospitalization	Moderate	Definitely not	Unlikely	NA	NA	Recovered	31/12/2021	medication given
10	89-198	UA-CEV	25	Appendicitis	24/01/2022	Hospitalization	Severe	Unlikely	Definitely not	NA	NA	Recovered	25/01/2022	medication given, diagnostic test performed, medical procedure started
11	88-54	ITM	39	Miscarriage	24/01/2022	Other	Moderate	Possibly	Definitely not	NA	NA	Not yet recovered		Diagnostic test performed
12	88-86	ITM	50	Worsening of degenerative discpathy requiring suergery	23/12/2021	Hospitalization	Severe	Definitely not	Definitely not	NA	NA	Recovered	26/12/2022	Medication given, medical procedure started
13	88-009	ITM	29	Bacterial tonsillitis	20/12/2021	Hospitalization	Severe	Definitely not	Definitely not	NA	NA	Recovered	1/01/2022	medication and diagnostic test
14	90-11	CEVAC	24	Clavicula fracture	30/12/2021	Hospitalization	Severe	Definitely not	Definitely not	NA	NA	Recovered	31/12/2021	Medication, medical procedure
15	88-129 (1)	ITM	47	Processus transversus fracture	1/01/2022	Hospitalization	Severe	Unlikely	Unlikely	NA	NA	Recovered	10/01/2022	Medication
16	88-129 (2)	ITM	47	Spleen rupture	1/01/2022	Hospitalization	Severe	Unlikely	Unlikely	NA	NA	Recovered	10/01/2022	Medication
17	89-123 (1)	UA-CEV	46	Bilateral pyelonephritis	16/04/2022	Hospitalization	Severe	Unlikely	Definitely not	NA	NA	Not yet recovered	02/05/2022	Medication
18	89-123 (2)	UA-CEV	46	Sepsis	16/04/2022	Hospitalization	Life-threatening	Unlikely	Definitely not	NA	NA	Recovered	01/05/2022	Medication given

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Table 63: Overview of all SAEs

1a = 'Pfizer regular scheme'; 1b = 'Pfizer-Moderna scheme'; 1c ='Pfizer-AstraZeneca scheme'; 1d='Pfizer low dose scheme'; 1e = 'Pfizer long interval scheme'; 1f= 'Pfizer intradermal scheme'; 3a='Moderna regular scheme'; 3b='Moderna low dose scheme'

	SAE number (cfr. Table 62)	Participants with a Reference Schedule	Participants with an adapted Schedule
SOC: Nervous System Disorders			
Carotid artery occlusion	1	1	0
SOC: Gastrointestinal disorders			
Abdominal pain	2	0	1
Appendicitis noninfective	6	1	0
SOC: Renal and Urinary disorders			
Nephrolithiasis	3	0	1
SOC: Injury, poisoning and procedural complications			
Wrist fracture	4	0	1
Clavicle fracture	14	0	1
Spinal fracture	15	0	1
Splenic rupture	16	0	1
SOC: hepatobiliary disorders			
Cholelithiasis	7	0	1
SOC: Musculoskeletal and connective tissue disorders			
Rotator cuff syndrome	8	0	1
Intervertebral disc degeneration	12	0	1
SOC: Respiratory, thoracic and mediastinal disorders			
Pneumothorax spontaneous	9	0	1
SOC: Infections and infestations			
Diverticulitis	5	0	1
Appendicitis	10	0	1
Tonsillitis bacterial	13	0	1
Pyelonephritis	17	0	1
Sepsis	18	0	1
SOC: Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous	11	0	1

Soc: System Organ Class

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v. Pregnancy

One pregnancy was reported. Subject had a history of 2 induced and 1 spontaneous abortion. On 05Jan2022 subject received her 3rd COVID-19 vaccine (0,25mg Spikevax), administered via the National vaccination campaign. An echo with heartbeat was performed on 11Jan2022. A COVID-19 test was positive on 17Jan2022. A spontaneous abortion was diagnosed on 27Jan2022. More details can be found in table 64 and in SAE 11, listed in table 62.

Table 64: Pregnancy listing

Pregnancy	Subject ID	Site	Age	First day of last merntual period	Date pregnancy was noted	Estimated date of delivery	Multiple fetuses/children	What was the pregnancy Outcome	Date of outcome	Relationship to IP	Relationship to ConMed	Infant information	SAE?
1	88-54	ITM	39	11/11/2021	12/12/2021	18/08/2022	No	Spontaneous abortion	27/01/2022	Definitely not	Possibly	NA	Yes

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10.9 Health Economics

Out of the 506 participants in the mITT population, 375 had a job and completed the questionnaire after receiving the first study vaccination, while 387 did so after the second study vaccination. For these participants, an indicator was constructed to determine whether they missed a day of work or would have missed one in the days following vaccination.

To evaluate the impact of different vaccination schedules on productivity, Table 65 presents the percentage of participants who missed at least one day of work for the eight study groups, Figure 33 provides a graphical representation of the same data.

There is no statistically significant difference observed in absenteeism rates among the eight study groups after the first vaccination ($p=0.5253$). However, after the second vaccination, the observed differences are statistically significant ($p<0.0001$). The groups with the highest absenteeism rates were 1b (Pfizer-Moderna scheme), 1c (Pfizer-AstraZeneca scheme), and 3a (Moderna reference scheme). These groups received a standard dose of mRNA-1273 vaccine or COVID-19 Vaccine AstraZeneca® as their second vaccine dose.

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Table 65: Observed absenteeism rates after first and second study vaccination

1a = 'Pfizer regular scheme'; 1b = 'Pfizer-Moderna scheme'; 1c ='Pfizer-AstraZeneca scheme'; 1d='Pfizer low dose scheme'; 1e = 'Pfizer long interval scheme'; 1f= 'Pfizer intradermal scheme'; 3a='Moderna regular scheme'; 3b='Moderna low dose

a) After first vaccination

	Absent from work after first vaccination				
	No		Yes, at least one day		Total
	N	%	N	%	N
Randomisation group					
Group 1a	41	97.62	1	2.38	42
Group 1b	50	96.15	2	3.85	52
Group 1c	50	98.04	1	1.96	51
Group 1d	45	97.83	1	2.17	46
Group 1e	35	94.59	2	5.41	37
Group 1f	48	100.00			48
Group 3a	42	87.50	6	12.50	48
Group 3b	50	98.04	1	1.96	51
Total	361	96.27	14	3.73	375

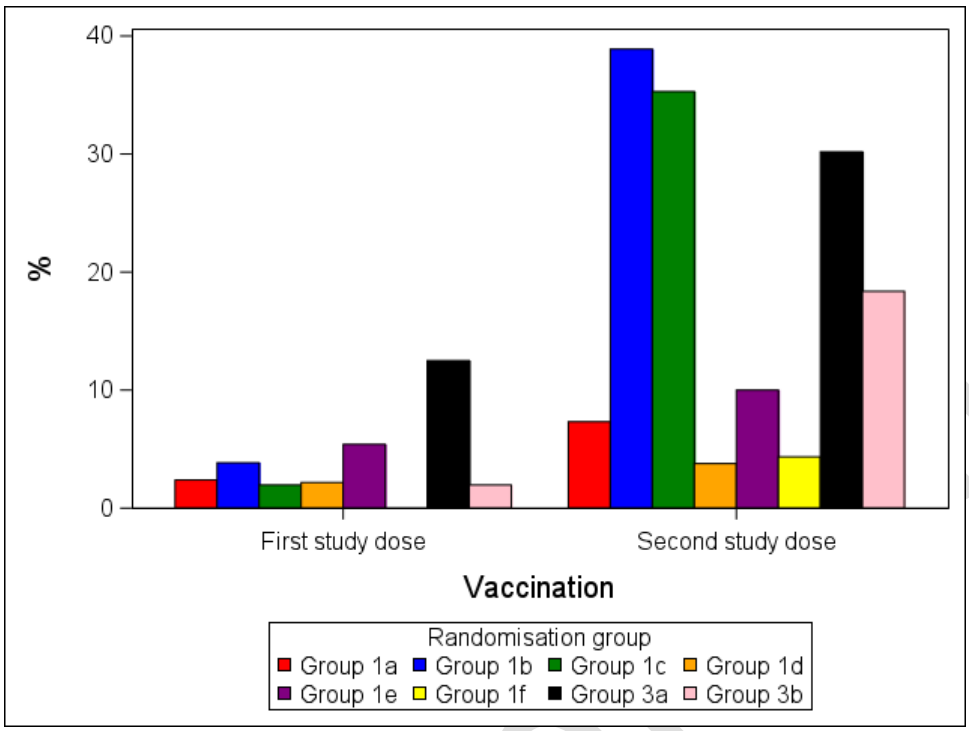
b)After second vaccination

	Absent from work after second vaccination				
	No		Yes, at least one day		Total
	N	%	N	%	N
Randomisation group					
Group 1a	38	92.68	3	7.32	41
Group 1b	33	61.11	21	38.89	54
Group 1c	33	64.71	18	35.29	51
Group 1d	51	96.23	2	3.77	53
Group 1e	36	90.00	4	10.00	40
Group 1f	44	95.65	2	4.35	46
Group 3a	37	69.81	16	30.19	53
Group 3b	40	81.63	9	18.37	49
Total	312	80.62	75	19.38	387

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Figure 33: Observed absenteeism rates after first and second study vaccination

1a = 'Pfizer regular scheme'; 1b = 'Pfizer-Moderna scheme'; 1c ='Pfizer-AstraZeneca scheme'; 1d='Pfizer low dose scheme'; 1e = 'Pfizer long interval scheme'; 1f= 'Pfizer intradermal scheme'; 3a='Moderna regular scheme'; 3b='Moderna low dose



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11 Trial conclusions

IMCOVAS is a prospective, post marketing, randomized, partially single blind, multicenter, interventional study in about 560 healthy adults (age range 18-55 years) with the aim to determine the immunogenicity and reactogenicity of adapted vaccine regimens against SARS-CoV-2.

The main objective of this trial was to demonstrate non-inferiority of the humoral immune response against SARS-Cov-2 virus of different vaccines against SARS-CoV-2 and adapted vaccine schedules in comparison with the reference schedule, at 28 days post second study vaccine dose administration, in COVID-19 naïve participants. To do so, antibodies binding to the Receptor Binding Domain of SARS-CoV-2 S protein (Wuhan SARS-CoV-2 strain) were measured by means of an ELISA.
Non-inferiority could be shown for the GMT of antibodies binding to the RBD of SARS-CoV-2 S protein in subjects receiving the second Pfizer dose after 12 weeks (group 1e), compared to subjects who received the standard Pfizer vaccine regime (group 1a). **Thus, prolonging the interval between subsequent vaccinations to 12 weeks does not hamper the development of an adequate immune response.**
The possibility of lowering the dose of mRNA in the Pfizer and Moderna vaccines was assessed. Non-inferiority of the immune response could not be demonstrated when lowering the Pfizer mRNA dose from 30 µg to 20 µg (group 1d) (result was not non-inferior). Lowering the mRNA dose in the Moderna vaccine to 50 µg – as opposed to the standard dose of 100 µg – (group 3b) resulted in a non-inferior antibody response. **Therefore, the mRNA dose of future Moderna vaccines might be decreased without jeopardizing the humoral immune response.**
The immune response after several heterologous vaccination schedules was quantified. The combination of a first vaccine dose with Pfizer followed by a second dose with AstraZeneca (group 1c) was inferior to the standard Pfizer schedule. In contrast, **it was found that a Pfizer-Moderna schedule (group 1b) resulted in a non-inferior antibody response, compared to the standard Pfizer schedule.**
Our data do not support the use of an intradermal administration of 6 µg of mRNA (Pfizer group 1f). Further research is necessary to evaluate whether this is due to the administration route itself, or due to the very low dose of mRNA.
Taken together, the anti-RBD antibody levels suggest that flexibility with regard to the vaccine schedules is – to a certain extent – possible. In particular, prolonging vaccine interval (Pfizer), lowering the vaccine dose (Moderna) and combining different brands of vaccines (Pfizer-Moderna) does not jeopardize the humoral immune response.

The evolution of the COVID-19 pandemic provided us with the opportunity to assess the humoral immune response after a third vaccination for SARS-CoV-2 in COVID-19 naïve participants. Vaccine was provided outside the trial and brand could be either Moderna of Pfizer. Non-inferiority of the IgG response could be demonstrated for all adapted schedules, compared to the reference schedules (Moderna-Moderna or Pfizer-Pfizer) at 28 days post third vaccination. Remarkably, the response was independent of the brand or dose of the third vaccination. **This suggests that, in order to boost immunity after one is fully vaccinated against SARS-CoV-2, it does not matter which COVID-19 vaccine is used.**

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As a secondary objective, the humoral immune response was further characterized by analyzing the titer of neutralizing antibodies against Wuhan, Delta and Omicron variants at 28 days post second study vaccine. It was found that i) replacing the second dose of Pfizer by the Moderna vaccine (group 1b), ii) lowering the dose of the Pfizer or Moderna vaccine (group 1d and 3b) and iii) prolonging the interval between subsequent Pfizer vaccines from 4 to 12 weeks (group 1e) resulted in a non-inferior development of neutralizing antibodies (both Wuhan NT50 and Delta NT50). **Not surprisingly, a good correlation was observed between the receptor binding antibodies and neutralizing antibodies in most treatment arms.** Surprisingly, neutralizing antibody levels were significantly higher when the interval between vaccinations was 12 weeks instead of 4 weeks. The clinical relevance of this observation requires further investigation.

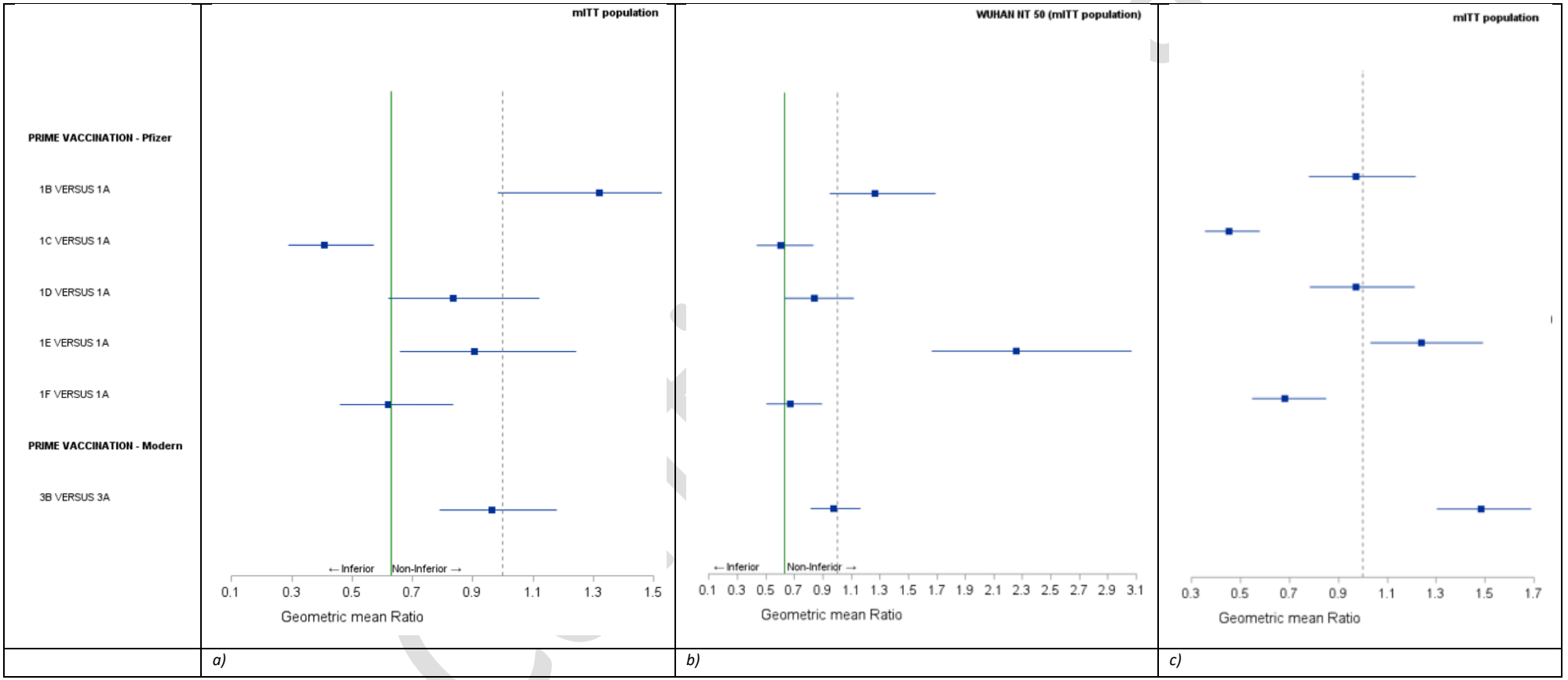
To further explore the immunogenicity of adapted vaccine schedules, avidity was assessed 4 weeks after the administration of the second vaccination in a subset of the study participants. In line with the antibody results, the immune response was lower – in terms of avidity – in subjects vaccinated with the Pfizer-AstraZeneca schedule (group 1c) and in subjects receiving their vaccines intradermally (group 1f). Notably, the avidity in subjects exposed to the long-interval Pfizer schedule was higher than those given the standard Pfizer schedule. The same was true for the subjects exposed to a lower dose of Moderna, but not for those given a lower dose of Pfizer. **Thus, we observe that there was no straightforward connection between the avidity of the antibody response and the antibody levels that were reached after 2 vaccinations (anti-RBD-IgG antibodies and neutralizing antibodies)**. This observation illustrates that the humoral immune response should be assessed in a broader way; not only quantitively (antibody levels), but also qualitatively (avidity).

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Figure 34 : Primary endpoint, comparison of the adapted schedules with the reference schedule

1a = 'Pfizer regular scheme'; 1b = 'Pfizer-Moderna scheme'; 1c ='Pfizer-AstraZeneca scheme'; 1d='Pfizer low dose scheme'; 1e = 'Pfizer long interval scheme'; 1f= 'Pfizer intradermal scheme'; 3a='Moderna regular scheme'; 3b='Moderna low dose scheme'

a) Anti-RBD IgG
b) nAb Wuhan NT50
c) Avidity

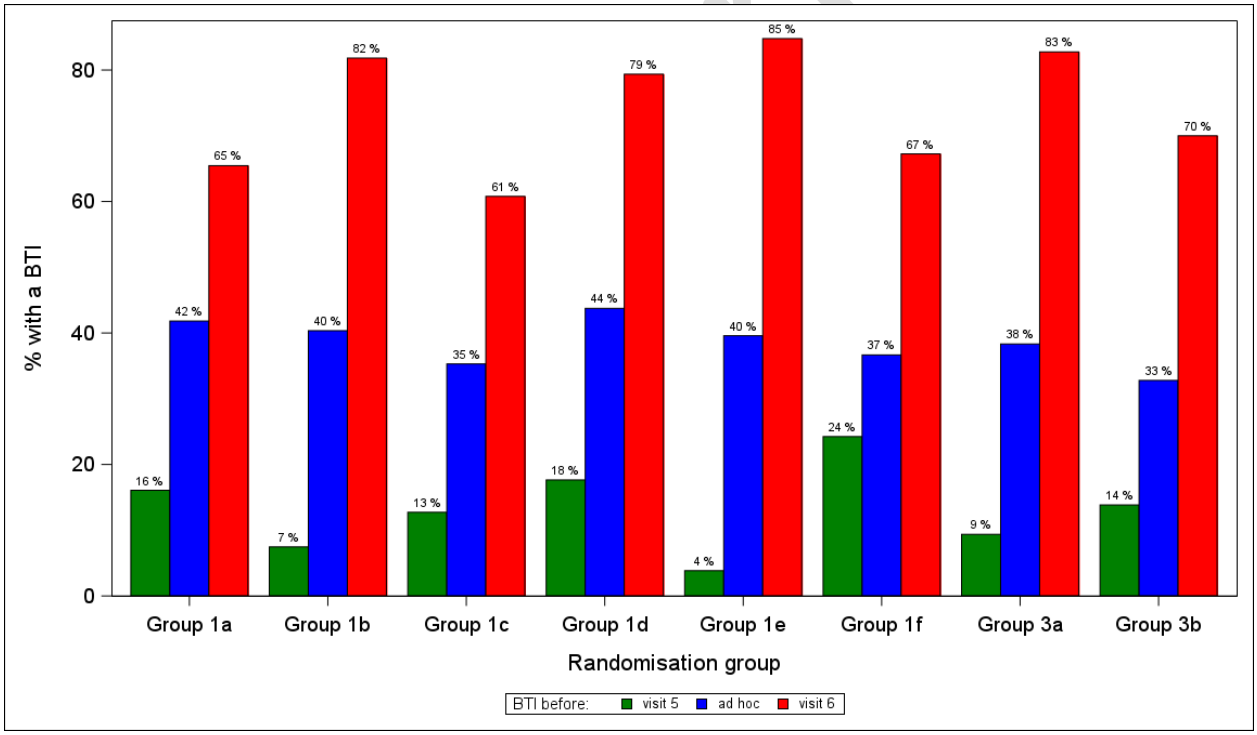


a) *b)* *c)*

Besides the evaluation of immunogenicity, the occurrence of COVID-19 break-through-infections was studied. Since this objective was added after the roll-out of the protocol of the study, our study was not powered to observe differences between the treatment arms and results were only be evaluated in an explorative manner. It was noted that, when looking at participants who remained in the trial until the end and who received 3 COVID-19 vaccines as prescribed by the protocol, the Pfizer-AstraZeneca treatment arm (group 1c) had the lowest breakthrough rate (61%), while the highest breakthrough rates were seen in the Pfizer long interval scheme (group 1e) (85%), the Moderna regular scheme (group 3a) (83%) and the Pfizer-Moderna scheme (group 1b) (82%). Although no definitive conclusions can be drawn, it is remarkable that the highest rate of breakthrough infection is present in the treatment arms with the highest antibody levels and vice versa. **This suggests that humoral immunity, as measures in this trial (anti-RBD IgG, nAb, avidity), do not correlate well with clinical protection against infection with SARS-CoV-2.**

Figure 35: Number of participants and visit timepoint influenced by BTIs after PE, per randomisation group, for subjects who remained in the study until the final visit (visit 6, D364) and received the third COVID-19 vaccine after September 2021, and no additional COVID-19 vaccines outside the study

1a = 'Pfizer regular scheme'; 1b = 'Pfizer-Moderna scheme'; 1c ='Pfizer-AstraZeneca scheme'; 1d='Pfizer low dose scheme'; 1e = 'Pfizer long interval scheme'; 1f= 'Pfizer intradermal scheme'; 3a='Moderna regular scheme'; 3b='Moderna low dose scheme'



In conclusion, from this unique study, conducted under pandemic conditions, we can conclude that COVID-19 vaccines lead to satisfying levels of humoral immunity in all intervention arms. As no correlation between markers of humoral immunity and breakthrough infections could be observed, the trial results reveal that more information is needed than what is observed in the humoral immunity assessment within this trial.

12 Appendix

Additional tables

Table 66 illustrate the percentage of participants who experience at least one adverse event, categorized by treatment group and severity, after **first** vaccination. If a participant experiences multiple adverse events of the same type, the most severe event is considered.

Table 66: Percentage of participants who experience at least one adverse event, categorized by treatment group and severity, after first vaccination

1a = 'Pfizer regular scheme'; 1b = 'Pfizer-Moderna scheme'; 1c ='Pfizer-AstraZeneca scheme'; 1d='Pfizer low dose scheme'; 1e = 'Pfizer long interval scheme'; 1f= 'Pfizer intradermal scheme'; 3a='Moderna regular scheme'; 3b='Moderna low dose scheme'

		RANDOMISATION GROUP								
		1A	**1B**	**1C**	**1D**	**1e**	**1F**	**3A**	**3B**	**Total**
Participants with at least one adverse event		54/57(94.74%)	64/68(94.12%)	56/59(94.92%)	63/69(91.30%)	50/52(96.15%)	66/67(98.51%)	66/66(100.00%)	68/68(100.00%)	487/506(96.25%)
Number of adverse events		148	208	147	177	127	322	241	221	1591
Number of solicited AE		81 (54.73%)	120 (57.69%)	64 (43.54%)	96 (54.24%)	71 (55.91%)	220 (68.32%)	129 (53.53%)	124 (56.11%)	905 (56.88%)
..... local AE		35 (23.65%)	45 (21.63%)	24 (16.33%)	34 (19.21%)	30 (23.62%)	149 (46.27%)	53 (21.99%)	47 (21.27%)	417 (26.21%)
..... systemic AE		46 (31.08%)	75 (36.06%)	40 (27.21%)	62 (35.03%)	41 (32.28%)	71 (22.05%)	76 (31.54%)	77 (34.84%)	488 (30.67%)
Number of un solicited AE		67 (45.27%)	88 (42.31%)	83 (56.46%)	81 (45.76%)	56 (44.09%)	102 (31.68%)	112 (46.47%)	97 (43.89%)	686 (43.12%)
Severity	1- Mild	113 (76.35%)	151 (72.60%)	118 (80.27%)	120 (67.80%)	84 (66.14%)	267 (82.92%)	157 (65.15%)	154 (69.68%)	1164 (73.16%)
	2- Moderate	33 (22.30%)	54 (25.96%)	26 (17.69%)	55 (31.07%)	38 (29.92%)	51 (15.84%)	79 (32.78%)	63 (28.51%)	399 (25.08%)
	3- Severe	2 (1.35%)	3 (1.44%)	3 (2.04%)	2 (1.13%)	5 (3.94%)	4 (1.24%)	5 (2.07%)	4 (1.81%)	28 (1.76%)
Relationship treatment	Not related	8 (5.41%)	27 (12.98%)	15 (10.20%)	23 (12.99%)	13 (10.24%)	18 (5.59%)	16 (6.64%)	18 (8.14%)	138 (8.67%)
	Related	140 (94.59%)	181 (87.02%)	132 (89.80%)	154 (87.01%)	114 (89.76%)	304 (94.41%)	225 (93.36%)	203 (91.86%)	1453 (91.33%)
Medically attended event	No	146 (98.65%)	204 (98.08%)	144 (97.96%)	175 (98.87%)	127 (100.00%)	321 (99.69%)	238 (98.76%)	217 (98.19%)	1572 (98.81%)
	yes	2 (1.35%)	4 (1.92%)	3 (2.04%)	2 (1.13%)		1 (0.31%)	3 (1.24%)	4 (1.81%)	19 (1.19%)
AE of special interest	No	148 (100.00%)	208 (100.00%)	147 (100.00%)	177 (100.00%)	127 (100.00%)	322 (100.00%)	241 (100.00%)	221 (100.00%)	1591 (100.00%)
Serious adverse event	No	148 (100.00%)	208 (100.00%)	147 (100.00%)	177 (100.00%)	127 (100.00%)	322 (100.00%)	241 (100.00%)	221 (100.00%)	1591 (100.00%)

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Table 67 illustrate the percentage of participants who experience at least one adverse event, categorized by treatment group and severity, after **second** vaccination. If a participant experiences multiple adverse events of the same type, the most severe event is considered.

Table 67: Percentage of participants who experience at least one adverse event, categorized by treatment group and severity, after second vaccination

1a = 'Pfizer regular scheme'; 1b = 'Pfizer-Moderna scheme'; 1c ='Pfizer-AstraZeneca scheme'; 1d='Pfizer low dose scheme'; 1e = 'Pfizer long interval scheme'; 1f= 'Pfizer intradermal scheme'; 3a='Moderna regular scheme'; 3b='Moderna low dose scheme'

		RANDOMISATION GROUP								
		1A	**1B**	**1C**	**1D**	**1e**	**1F**	**3A**	**3B**	**Total**
Participants with at least one adverse event		54/57(94.74%)	68/68(100.00%)	58/59(98.31%)	65/69(94.20%)	47/52(90.38%)	63/67(94.03%)	65/66(98.48%)	66/68(97.06%)	486/506(96.05%)
Number of adverse events		269	485	377	251	160	344	420	381	2687
Number of solicited AE		187 (69.52%)	363 (74.85%)	289 (76.66%)	174 (69.32%)	100 (62.50%)	232 (67.44%)	316 (75.24%)	273 (71.65%)	1934 (71.98%)
..... local AE		36 (13.38%)	62 (12.78%)	23 (6.10%)	33 (13.15%)	31 (19.38%)	150 (43.60%)	63 (15.00%)	54 (14.17%)	452 (16.82%)
..... systemic AE		151 (56.13%)	301 (62.06%)	266 (70.56%)	141 (56.18%)	69 (43.13%)	82 (23.84%)	253 (60.24%)	219 (57.48%)	1482 (55.15%)
Number of un solicited AE		82 (30.48%)	122 (25.15%)	88 (23.34%)	77 (30.68%)	60 (37.50%)	112 (32.56%)	104 (24.76%)	108 (28.35%)	753 (28.02%)
Severity	1- Mild	182 (67.66%)	247 (50.93%)	204 (54.11%)	177 (70.52%)	100 (62.50%)	217 (63.08%)	244 (58.10%)	222 (58.27%)	1593 (59.29%)
	2- Moderate	75 (27.88%)	168 (34.64%)	130 (34.48%)	64 (25.50%)	49 (30.63%)	120 (34.88%)	147 (35.00%)	131 (34.38%)	884 (32.90%)
	3- Severe	12 (4.46%)	70 (14.43%)	43 (11.41%)	10 (3.98%)	11 (6.88%)	7 (2.03%)	29 (6.90%)	28 (7.35%)	210 (7.82%)
Relationship treatment	Not related	14 (5.20%)	16 (3.30%)	7 (1.86%)	20 (7.97%)	15 (9.38%)	22 (6.40%)	13 (3.10%)	18 (4.72%)	125 (4.65%)
	Related	255 (94.80%)	469 (96.70%)	370 (98.14%)	231 (92.03%)	145 (90.63%)	322 (93.60%)	407 (96.90%)	363 (95.28%)	2562 (95.35%)
Medically attended event	No	261 (97.03%)	481 (99.18%)	372 (98.67%)	249 (99.20%)	155 (96.88%)	340 (98.84%)	413 (98.33%)	376 (98.69%)	2647 (98.51%)
	yes	8 (2.97%)	4 (0.82%)	5 (1.33%)	2 (0.80%)	5 (3.13%)	4 (1.16%)	7 (1.67%)	5 (1.31%)	40 (1.49%)
AE of special interest	No	265 (98.51%)	485 (100.00%)	377 (100.00%)	251 (100.00%)	160 (100.00%)	344 (100.00%)	420 (100.00%)	381 (100.00%)	2683 (99.85%)
	yes	4 (1.49%)								4 (0.15%)
Serious adverse event	No	268 (99.63%)	485 (100.00%)	377 (100.00%)	251 (100.00%)	160 (100.00%)	344 (100.00%)	420 (100.00%)	381 (100.00%)	2686 (99.96%)
	yes	1 (0.37%)								1 (0.04%)

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