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Universität zu Köln

TRIAL PROTOCOL

A MULTINATIONAL, PHASE 2, RANDOMISED, ADAPTIVE PROTOCOL TO EVALUATE IMMUNOGENICITY AND REACTOGENICITY OF DIFFERENT COVID-19 VACCINES ADMINISTRATION IN OLDER ADULTS (≥75) ALREADY VACCINATED AGAINST SARS-COV-2

(EU-COVAT-1_AGED)

Sponsor

University of Cologne

Albertus-Magnus-Platz

50923 Köln

Germany

Principal Coordinating Investigator:

Prof. Dr. Oliver A. Cornely

Department I of Internal Medicine

University Hospital Cologne

Kerpener Strasse 62

50937 Cologne

Germany

Trial protocol code: uni-koeln-4602

EudraCT number: 2021-004526-29

Version of July 27, 2022, Version V06_0

Please note: This trial (*"EU-COVAT-1_AGED"*) is a sub-protocol embedded within the *EU-COVAT* master protocol.

II. Synopsis

Sponsor	University of Cologne Represented by: Prof. Dr. med. Oliver Cornely (Principal Coordinating Investigator, PCI) Department for Internal Medicine I University Hospital Cologne Kerpener Strasse 62 50937 Cologne Germany
Principal Coordinating Investigator	See above National representatives are detailed in a separate list for this multinational trial.
Title of the clinical trial	**A Multinational, Phase 2, Randomised, Adaptive Protocol to Evaluate Immunogenicity and Reactogenicity of Different COVID-19 Vaccines Administration in Older Adults (≥75) already Vaccinated Against SARS-CoV-2 (EU-COVAT-1 AGED)**
Indication	COVID-19 vaccination
Phase	Phase ll clinical trial

Type of trial, trial design, methodology	**Please note: This trial (“*EU-COVAT-1_AGED“)* is a sub-protocol embedded within the *EU-COVAT* master protocol.** **PLEASE NOTE:** **This protocol refers to Part B of the clinical trial in which new accruals are randomized to a 4th vaccination (second booster) with either BNT162b2 or mRNA-1273.** **Part A of the present trial in which individuals received a 3rd vaccination (first booster) is closed to further recruitment as of January 13, 2022. With the massive roll-out of booster campaigns throughout Europe, Part A was abandoned because of a poor recruitment rate.** **Individuals in Part A are followed-up as specified in protocol version V04_0 and analyzed descriptively, the statistical analysis plan will be adapted accordingly.** This is a randomised controlled, adaptive, multicentre Phase II protocol evaluating different booster strategies in **individuals aged 75 years and older** already vaccinated against SARS-CoV-2. Part B of this trial foresees testing of different vaccines as a **4th vaccination dose** (second booster) for comparative assessment of their immunogenicity and safety against SARS-CoV-2 wild-type and variants in the elderly, a usually neglected population. Additional vaccines and extended follow-up visits can be added through amendments of this sub-protocol. As stated in the *EU-COVAT* master protocol, this trial, i.e., the *EU-COVAT-1_AGED study,* implements a specific safety monitoring strategy (see below). **Randomisation in Part B** Subjects who - **prior to study entry** - got a primary vaccination series and 3rd vaccination dose of either • BNT162b2 + BNT162b2 + BNT162b2 or • BNT162b2 + BNT162b2 + mRNA-1273 or • mRNA-1273 + mRNA-1273 + mRNA-1273 or • mRNA-1273 + mRNA-1273 + BNT162b2 or • ChAdOx-1-S + ChAdOx-1-S + BNT162b2 or • ChAdOx-1-S + ChAdOx-1-S + mRNA-1273 or will receive a **4th vaccination dose** with an allocation ratio of 1:1 to either BNT162b2 or mRNA-1273. Accordingly, there are **6 cohorts** (equalling 12 arms). All individuals who were randomized to BNT162b2 represent

	Group 1, all individuals who were randomized to mRNA-1273 represent **Group 2**. Cohorts and arms can be withdrawn or added as deemed necessary according to the criteria specified in this protocol. **Blinding** No blinding is foreseen in this trial.
Number of subjects	The number needed has been calculated at 550 for **Part B**. **Sample size calculation with multiplicity adjustment within each cohort** When the sample size is 250 per randomized group (Group 1, Group 2) in Part B (275 without dropouts, i.e., assuming 8-10% dropouts), two-sided simultaneous 95% confidence intervals (with Bonferroni adjustment for 2 simultaneous confidence intervals within a cohort) for a proportion using the large sample normal approximation will extend no more than ±7.1% (percentage points) from the observed proportion. E.g., if the observed proportion is 50% (where the confidence interval is widest), the confidence interval ranges from about 42.9% to 57.1%.
Primary trial objective **(Part B)**	• To compare the immune response between treatment arms **after a 4th vaccination dose** against SARS-CoV-2.
Safety objective (Part B)	• To assess the safety of a 4th vaccination dose against SARS-CoV-2 in the study population.

Secondary trial objectives **(Part B)**	• To compare the **humoral response** against wild-type SARS-CoV-2 between treatment arms **after a 4th vaccination dose** against SARS-CoV-2. • To evaluate descriptively the **humoral response** against SARS-CoV-2 **variants of concern** between treatment arms after a 4th vaccination dose against SARS-CoV-2. • To evaluate descriptively the long-term humoral immune response of 4th vaccination dose against SARS-CoV-2.
Exploratory objectives **(Part B)**	• To investigate the cellular immune response after a 4th vaccination dose, virus neutralizing capacity against newly emerging variants in bio-banked samples and correlates of interest.
Study endpoints **(Part B)**	**Primary endpoint:** • Rate of 2-fold antibody titre increase 14 days **after a 4th vaccination dose** measured by quantitative enzyme-linked immunosorbent assay (Anti-RBD-ELISA) against wildtype virus. (Part B) **Safety endpoints:** • Unsolicited AEs until the end of trial. • Solicited AEs for 7 days after a 4th vaccination dose. • Rate of serious adverse events (SAEs) Grade ≥3 according to the National Cancer Institute Common Toxicity Criteria up to three months after a 4th vaccination dose. **Secondary endpoints:** • Change in neutralizing antibody titre (Virus Neutralisation Assay) against wild-type 14 days after a 4th vaccination dose, to be determined in a subgroup only. • Change in neutralizing antibody titre (Virus Neutralisation Assay) **against variants of concern** 14 days after a 4th vaccination dose, to be determined in a subgroup only. • Antibody titre level **at 12 months** after a 4th vaccination dose measured by a quantitative enzyme-linked immunosorbent assay (anti-RBD-ELISA assay).

	• Neutralizing antibody titre (Virus Neutralisation Assay) against wild-type SARS-CoV-2 at 12 months after a 4th vaccination dose, to be determined in a subgroup only. • Neutralizing antibody titre (Virus Neutralisation Assay) **against variants of concern** at 12 months after a 4th vaccination dose, to be determined in a subgroup only. **Exploratory endpoints:** • Change in cellular immune response (CD4+ and CD8+ T cell response) measured by qPCR 14 days after 4th vaccination dose, to be determined in a subgroup only. • Neutralizing antibody titre (Virus Neutralisation Assay) against newly emerging variants in bio-banked samples after 4th vaccination dose, to be determined in a subgroup only. • Correlates of humoral immune response, cellular immune response and viral neutralising capacity against SARS-CoV-2 variants of concern (VOCs), to be determined in a subgroup only.
Diagnosis and Principal inclusion and exclusion criteria (Part B)	**Medical condition or disease to be investigated:** Prevention of COVID-19 infection. **Principal inclusion criteria:** • Subject is ≥75 years old. • Prior to study entry the subject was vaccinated with one of the following vaccination regimens (1st + 2nd + 3rd dose): o BNT162b2 + BNT162b2 + BNT162b2 o BNT162b2 + BNT162b2 + mRNA-1273 o mRNA-1273 + mRNA-1273 + mRNA-1273 o mRNA-1273 + mRNA-1273 + BNT162b2 o ChAdOx-1-S + ChAdOx-1-S + BNT162b2 o ChAdOx-1-S + ChAdOx-1-S + mRNA-1273 • The last dose of the above listed vaccinations must have been administered at least 1 month prior to study entry. Vaccination status should be documented in the source data and will be captured in the eCRF.

	• Written informed consent from subject has been obtained. **Principal exclusion criteria**: • Prior to study entry the subject got vaccinated with a regimen not included in the list given above. • Last anti-SARS-CoV-2 vaccine dose administered less than one month prior to study entry. • Vaccination against a disease other than COVID-19 within 2 weeks prior to study entry. Only exception: Influenza vaccination which is allowed at any time. • Subjects with any significant or uncontrolled disease posing a risk due to vaccination as judged by the investigator. • Current immunosuppressive therapy, for example continuous glucocorticosteroid treatment equivalent to >10 mg/day prednisolone. • Subject simultaneously participates in another clinical trials or has participated in the past 30 days. • Subjects unable to report solicited adverse events. • Subject with any contraindications to the vaccines in the trial. A list of contraindications as listed in the Summary of medicinal Product Characteristics (SmPC, the Fachinformation in Germany), if appropriate.
Name of investigational medicinal product (IMP)	• BNT162b2 (Comirnaty®) including any VOC-modified vaccine product • mRNA-1273 (Spikevax®) including any VOC-modified vaccine product

Investigational medicinal product – dosage and method of administration

Intervention in Part A: no longer active - for information only

Cohort	Vaccination prior to study entry	Arm	Study intervention: 3rd vaccination dose	Part A with Cohorts 1 to 3 closed to further recruitment as of January 13, 2022
Cohort 1	BNT162b2 + BNT162b2	1	BNT162b2	
		2	mRNA-1273	
Cohort 2	mRNA-1273 + mRNA-1273	3	BNT162b2	
		4	mRNA-1273	
Cohort 3	ChAdOx-1-S + ChAdOx-1-S	5	BNT162b2	
		6	mRNA-1273	
Control	Control arm of the EU-COVAT subprotocol EudraCT no. 2021-004889-35, a separate sub-protocol embedded within the EU-COVAT master protocol, will be used for a descriptive comparison.			

Intervention in Part B: 4th vaccination dose

Cohort	Vaccination prior to study entry	Arm	Study intervention: 4th vaccination dose*
Cohort 4	BNT162b2 + BNT162b2 + BNT162b2	7	BNT162b2
		8	mRNA-1273
Cohort 5	BNT162b2 + BNT162b2 + mRNA-1273	9	BNT162b2
		10	mRNA-1273
Cohort 6	mRNA-1273 + mRNA-1273 + mRNA-1273	11	BNT162b2
		12	mRNA-1273
Cohort 7	mRNA-1273 + mRNA-1273 + BNT162b2	13	BNT162b2
		14	mRNA-1273
Cohort 8	ChAdOx-1-S + ChAdOx-1-S + BNT162b2	15	BNT162b2
		16	mRNA-1273
Cohort 9	ChAdOx-1-S + ChAdOx-1-S + mRNA-1273	17	BNT162b2
		18	mRNA-1273

** administered at least 1 month after the 3nd pre-study vaccination.*

<table>
<tr><td>IMP or therapy used as a comparator – dosage and method of administration</td><td>No vaccination in the control group of the EU-COVAT subprotocol EudraCT no. 2021-004889-35, a separate sub-protocol embedded within the EU-COVAT master protocol (applies to Part A of the trial, in Part B this is an option only).</td></tr>
<tr><td>Duration of treatment
(Part B)</td><td>Treatment consists of a single 4th dose of each vaccine foreseen in this protocol. Follow up of subject included will last for 12 months.</td></tr>
<tr><td>Time plan
(Part A and B)</td><td><table>
<tr><td>First patient first visit (FPFV):</td><td>November 2021</td></tr>
<tr><td>Last patient first visit (LPFV):</td><td>September 2022</td></tr>
<tr><td>Last patient last visit (LPLV):</td><td>September 2023</td></tr>
<tr><td>Analysis</td><td>October 2022 (Primary endpoint analysis)</td></tr>
<tr><td>End of study definition</td><td>The end of study will be on the day of database lock.</td></tr>
<tr><td>End of trial</td><td>November 2023</td></tr>
<tr><td>Final study report:</td><td>December 2023</td></tr>
</table></td></tr>
<tr><td>Statistician</td><td>Assoc. Prof. Priv.-Doz. Dr. Franz König
Center for Medical Statistics, Informatics and Intelligent Systems
Medical University of Vienna
Spitalgasse 23
1090 Vienna
Austria</td></tr>
<tr><td>Statistical methods
(Part B)</td><td>Firstly, the rates of 2-fold increase in antibody titre with multiplicity adjusted 95% confidence intervals (adjusted for arms within each cohort) will be reported for both randomized groups 1 and 2 in Part B.

Secondly, Cohorts of study participants are defined by the different pre-vaccination series eligible for part B of this trial. We compare the 4th vaccination doses of BNT162b2 and mRNA-1273 and compute a two-sided confidence interval. Based on these, we test for equivalence of one of the 4th vaccination doses (based on the equivalence margin as outlined in the Reflection Paper of EMA).</td></tr>
</table>

	Thirdly, we compare groups 1 and 2 based on homologous boosting (pre-study 3rd vaccine and on-study 4th vaccine **identical**) vs. heterologous boosting (pre-study 3rd vaccine and on-study 4th vaccine **different**). Further exploratory analyses will be performed based on different pre-vaccination series. **The primary endpoint analysis** will be triggered as soon as for all patients the primary endpoint (14 days after the 4th vaccination dose) has been observed. **Safety analysis.** All clinical safety data will be listed by participant, time from vaccination dose and treatment arm. Continuous variables will be summarised using sample size (N), mean, standard deviation, median, minimum, and maximum. Frequency counts will be reported for categorical data. A Data and Safety Monitoring Committee (DSMC) will review data for decisions on arms incorporation and withdrawal and will ensure the appropriate oversight and monitoring in conducting the clinical trial. **Interim analysis** An interim analysis will be performed as soon as 50% of participants have been recruited within Part B.
GCP compliance	The present trial will be conducted in accordance with the valid versions of the trial protocol and the internationally recognised Good Clinical Practice Guidelines (ICH-GCP), including archiving of essential documents.
Financing	European Commission

III. Table of contents

III.a) List of tables

III.b) List of figures

Please note: This trial (“*EU-COVAT-1_AGED*“) is a sub-protocol embedded within the *EU-COVAT* master protocol.

IV. Abbreviations

Abbreviation	Meaning
AE	Adverse Event
CA	Competent authority (BfArM, PEI)
CRF	Case Report Form
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
EC	Ethics Committee
EMA	European Medicines Agency
ISF	Investigator Site File
IMP	Investigational Medicinal Product
PBMC	Peripheral blood mononuclear cells
PCI	Principal Coordinating Investigator (Leiter der klinischen Prüfung, LKP)
PI	Principal Investigator
PEI	Paul-Ehrlich-Institut
SAE	Serious Adverse Event
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
VOC(s)s	Variant(s) of concern

Please note: **This trial (“*EU-COVAT-1_AGED“)* is a sub-protocol embedded within the *EU-COVAT* master protocol.**

PLEASE NOTE:

This protocol refers to Part B of the clinical trial in which new accruals are randomized to a 4th vaccination (second booster) with either BNT162b2 or mRNA-1273.

Part A of the present trial in which individuals received a 3rd vaccination (first booster) is closed to further recruitment as of January 13, 2022. With the massive roll-out of booster campaigns throughout Europe, Part A was abandoned because of a poor recruitment rate.

Individuals in Part A are followed-up as specified in protocol version V04_0 and analyzed descriptively, the statistical analysis plan will be adapted accordingly.

1. Introduction

The novel SARS-2 Coronavirus (SARS-CoV-2) was identified in December 2019 as a cause of severe pneumonia, acute respiratory distress syndrome (ARDS) and potential multiorgan failure in humans. The disease known as COVID-19 has since turned into a pandemic affecting nearly all countries in the world where it has caused widespread mortality and morbidity.

A huge research effort on prevention and treatment of COVID-19 has been ongoing globally. As of February 16, 2021, almost 5,000 trials related with COVID-19 have been registered. Vaccination against COVID-19 started on December 27, 2020, across the European Union. So far, four vaccines have been granted conditional marketing authorisation by the European Commission: mRNA vaccine BNT162b2 (BioNTech and Pfizer - COMIRNATY), mRNA vaccine CX-024414 (Moderna - SPIKEVAX), adenovirus vaccine ChAdOx1-S (AstraZeneca - VAXZEVRIA) and adenovirus vaccine Ad26.Cov2.S (Janssen-Cilag International NV). These vaccines are indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 or 18 years of age and older.

Clinical trials performed for marketing authorisation have demonstrated high efficacy in terms of preventing moderate and severe cases of COVID-19. However, there is low evidence on the efficacy of COVID-19 vaccines in special populations. An effectiveness study from Israel showed that participants aged 60 and older who were vaccinated with two doses of the Pfizer/BioNTech vaccine had a lower number of cases and hospitalisations compared to younger individuals and no more severe side effects.[11,12,]

This trial aims to evaluate immune response against wild-type SARS-CoV-2 of further vaccine doses as booster strategy in individuals aged 75 or older already fully vaccinated against SARS-CoV-2. This investigation will likely provide useful information for vaccination programs in Europe and elsewhere.

2. Objectives of the clinical trial

2.1. Rationale for the clinical trial

Recent data suggest that immunisation with any of the currently approved vaccines may not provide long-term or life-long protection.[13, 14] Therefore, additional follow-up vaccination (booster) doses are indicated at some point in time after full vaccination, especially so in subjects of advanced age and with regard to emerging variants of concerns (VOCs) of SARS-CoV-2.

Booster immunizations will be critical to substantially improve the immune response against emerging VOCs especially the Omicron (B.1.1.529) variant. The Omicron variant is causing high infection incidences all over the globe. Current monoclonal antibodies tested in studies show a strongly reduced neutralizing activity against the predominating Omicron variant and will limit treatment options for Omicron-induced COVID-19 disease. However, a recent study has shown, that a single dose (3rd dose) of BNT162b2 induced a remarkable increase in neutralizing serum activity one month after vaccination in individuals after primary vaccination series and in convalescent individuals. Since titres were nearly similar to those observed against Wu01 after first vaccination series in this study, booster vaccinations with already available vaccines still seem to be the most effective step in the prevention of (re)infection. With regard to the Omicron variant vaccination schedules, vaccination intervals will be kept tight in future to keep immunity levels high.[18,19,21,16,17]

In the elderly, adaptive immune response is reduced and therefore shorter intervals between booster doses may be warranted for satisfactory protection against SARS-CoV-2 infection.[20] Right now, there are no data on the optimal timing of booster doses in elderly subjects after a full vaccination schedule. Also, in the age group above 75 years no robust clinical evidence exists on the immune response using heterologous strategies for such boosting. Therefore, this trial aims to assess the impact of different mRNA-based vaccines as booster doses in the elderly aged 75 years and older. This will likely provide useful information for vaccination programs in Europe (and elsewhere) for this high-risk population. Time points for booster (i.e., 3rd and 4th) vaccinations in Part A and B of this trial are based on current vaccination policies in the EU, i.e., there is a minimum interval of 1 month since the last (2nd or 3rd) vaccination, with longer intervals as per local regulation or practice.

For a detailed assessment of potential risks and benefits see section 4.3.

2.2. Primary objective (Part B)

- To compare the immune response between treatment arms **after a 4th vaccination dose** against SARS-CoV-2.

2.3. Safety objective (Part B)

- To assess the safety of a 4th vaccination dose against SARS-CoV-2 in the study population.

2.4. Secondary objectives (Part B)

- To compare the **humoral response** against wild-type SARS-CoV-2 between treatment arms **after a 4th vaccination dose** against SARS-CoV-2.

- To evaluate descriptively the **humoral response** against SARS-CoV-2 **variants of concern** between treatment arms after a 4th vaccination dose against SARS-CoV-2.

- To evaluate descriptively the long-term humoral immune response of a 4th vaccination dose against SARS-CoV-2.

2.5. Exploratory objectives (Part B)

- To investigate the cellular immune response after a 4th vaccination dose, virus neutralizing capacity against newly emerging variants in bio-banked samples and correlates of interest.

3. Organisational and administrative aspects of the trial

3.1. Sponsor

Sponsor:	University of Cologne
Represented by:	Prof. Dr. med. Oliver A. Cornely Dep. I for Internal Medicine University Hospital of Cologne Kerpener Strasse 62 50937 Cologne Germany

3.2. Principal Coordinating Investigator

Principal Coordinating Investigator (PCI):	Prof. Dr. med. Oliver A. Cornely see above

3.3. Statistics

Statistician:	Assoc. Prof. Priv.-Doz. Dr. Franz König Center for Medical Statistics, Informatics and Intelligent Systems Medical University of Vienna Spitalgasse 23 1090 Vienna Austria

3.4. Data Monitoring Committee

According to section 3.4 of the accompanying master protocol:
A Data Monitoring Committee of independent experts will be set up. It consists of two physicians and a statistician who are not involved in the conduct of the trial and who are independent from the sponsor. The task of the DMC is to monitor the safety of the trial subjects in the clinical trial by periodically assessing the safety and efficacy of the trial therapy, and to monitor the integrity and

validity of the data collected and the conduct of the clinical trial. Details with list of members will be described in the DMC charter.

Throughout this process of surveillance, the DMC provides the sponsor with recommendations on trial continuation (including termination, temporary suspension or modification) based on the data collected. The data necessary for the DMC to fulfil this function is provided by the sponsor as determined in the DMC charter. Amongst other datasets, these must include listings providing information on serious adverse events and further variables that the DMC considers necessary. The frequency of the committee data review meetings and other working procedures will be detailed in a separate charter. The independent Data Monitoring Committee is responsible for:

a) Reviewing unblinded interim results of trials according to the protocols under the master protocol.
b) Advising the Steering Committee if, in their view, the randomised data provide evidence that may warrant a change in the protocol (e.g., modification or cessation of one or more of the treatment arms).

The DMC will hold meetings at pre-defined times. Meetings of the DMC will be conducted through video conference, by phone, or in-person as deemed necessary by the DMC. If scheduling problems prevent a timely meeting, review and comment may alternatively be conducted by e-mail. One member will be appointed chair of the DMC and be responsible for summarising DMC meetings and informing the Principal Coordinating Investigator and sponsor about meetings and recommendations for adaptation and/or operational setting of the trial in writing.

3.5. Central Coordinating Office (CCO)

According to section 3.5 of the accompanying master protocol:

The CCO is responsible for the overall coordination of the study, including:

i. Study planning and organisation of Steering Committee meetings;

ii. Ensuring necessary regulatory and ethics committee approvals;

iii. Development of Standard Operating Procedures and computer systems;

iv. Monitoring overall progress of the study;

v. Provision of study materials to regional or local coordinating centres (RCCs/LCCs);

vi. Monitoring and reporting safety information in line with the protocol and regulatory requirements;

vii. Dealing with technical, medical, and administrative queries from LCCs.

3.6. Regional/Country specific Coordinating Centre (RCC)

Refer to section 3.6 of the accompanying master protocol for details:

The RCCs are responsible for:

i. Ensuring necessary regulatory and ethics committee approvals;

ii. Provision of study materials to LCCs;

Dealing with technical, medical, and administrative queries from LCCs.

3.7. Local Clinical Centres (LCC)

Refer to section 3.7 of the accompanying master protocol:

The LCC lead investigator and LCC clinic staff are responsible for:

i. Obtaining all relevant local permissions (assisted by the CCO);

ii. All trial activities at the LCC, including appropriate training and supervision for clinical staff;

iii. Conducting trial procedures at the LCC in line with all relevant local policies and procedures;

Dealing with enquiries from participants and others.

3.8. Steering Committee

According to section 3.8. of the accompanying master protocol:

A Steering Committee (SC) will be set up to continuously monitor the progress of the trial. The Trial Steering Committee is responsible for:

i. Agreement of the final protocol and protocols under the master protocol and the data analysis plans;

ii. Reviewing progress of the trials under the master protocol and ensuring that the appropriate oversight and monitoring in conducting the clinical trials under the master protocol;

iii. Deciding on incorporation of new trials to the master protocol and approval of the new protocols;

iv. Deciding on protocol changes of trials under the master protocol, which includes adding or removing arms as necessitated by the adaptive nature of the trials;

v. Review and approval of study publications and sub-study proposals.

A list of the members of the Steering Committee is given in a separate Steering Committee Manual and is constituted by the VACCELERATE Coordination Board.

3.9. Advisory Committee

According to section 3.9. of the accompanying master protocol:

An Advisory Committee will be set up to provide guidance and advice on the planning, the development of the trial and the evaluation of results. This committee will include external experts in the field and patient representatives.

A list of the members of the Advisory Committee is given in a separate Advisory Committee Manual and is constituted by the VACCELERATE Ethical and Scientific Advisory Board.

3.10. Study laboratories and other technical services

Anti-RBD, anti-N and neutralising antibody samples will be analysed in a central lab in Ireland (Europe):

UCD Centre for Experimental Pathogen Host Research (CEPHR)
University College
Belfield
Dublin 4
Ireland

Cellular immunity by qPCR will be analysed in a central lab in Spain (Europe):

Laboratorio de Referencia en Inmunologia
Modular 79, 1er piso
Instituto de Salud Carlos III

Cara Majadahonda-Pozuelo km2
Majadahonda, Madrid, 28220
Spain

Samples for biobanking will be stored at a facility in Belgium (Europe):

BIOBANK ANTWERP
with legal entity part of University Hospital Antwerp
Drie Eikenstraat 655
B-2650 Edegem
Belgium

A laboratory manual will specify preparation, handling, storage and shipment of samples.

3.11. Central organisation units

Project management:	Clinical Trials Centre Cologne (in conjunction with Division of Infectious Disease II, Department I of Internal Medicine, University Hospital Cologne)
Monitoring:	Clinical Trials Centre Cologne (Germany), ECRIN (other countries)
Data management:	Clinical Trials Centre Cologne
Safety management:	Clinical Trials Centre Cologne
Scientific advice:	VACCELERATE Consortium represented by its Coordination Office Herderstraße 52 D-50935 Cologne Germany Tel.: +49 221 478 85523 Fax: +49 221 478 32702 E-mail: info@vaccelerate.eu

3.12. Principal investigators and trial sites

According to section 3.12. of the accompanying master protocol:

VACCELERATE is a clinical research network for the coordination and conduct of COVID-19 vaccine trials. The network is comprised of academic institutions from all over Europe: The consortium is led by the University of Cologne, Germany, and currently includes 26 national partners in 16 EU-member states & 5 countries associated to the EU Horizon 2020 research programme.

VACCELERATE conducts capacity mapping of new clinical trial sites & laboratories with standardised methods and protocols, and provides standardised educational measures, training and quality management for harmonised vaccine trials. It already holds information more than 400 clinical trial sites in 32 European countries (EUVAP: https://euvap.eu/ as of 12th July 2021). Harmonisation of data acquisition across all network sites enables open data exchange for valid data analysis.

The network aims to address research questions of interest, such as vaccine efficacy in virus variants, trials in children, pregnant women, immuno-compromised patients, trials on combination of different vaccines etc.

Specific to this trial:

This clinical trial will be conducted as a multicentre trial in up to 24 sites in up to 8 countries in Europe (approx. 3 sites per country). A separate country and site listing will be provided. If necessary, further qualified sites may be recruited. A list of the trial sites with names of the principal investigators is given separately. The listing of trial sites, principal investigators and sub-investigators and further trial staff, will be kept and continuously updated in a separate list, independent from the trial protocol. The final version of this list will be attached to the final report of the clinical trial.

Time points for booster vaccinations in this trial (i.e., 3rd and 4th vaccination in Part A and B respectively) are based on current vaccination policies in the EU, i.e., there is a minimum interval of 1 month since the last (2nd or 3rd) vaccination, with longer intervals as per local regulation or practice.

3.13. Requirements for principal investigators and trial sites

According to section 3.13. of the accompanying master protocol:

For each clinical trial under the master protocol and depending on the prerequisites and needs of each protocol, the appropriate number of centres and countries will be selected.

All principal investigators and trial sites participating in the trials under the master protocol are required to have previous experience with the conduct of clinical trials with vaccines, to have experience in the regulatory process of their respective country, adequate facilities, sufficient dedicated and trained staff, access to target population and COVID-19 testing available on site. The documents for the qualification of the clinical trial team are filed in the sponsor´s Trial Master File (TMF) as well as in the Investigator Site File at the local site (ISF).

Centres selected will be validated by the VACCELERATE network according to approved standardised validation procedures.

Specific to this trial:

All principal investigators and trial sites participating in this trial are required to have previous experience with the conduct of clinical trials with vaccines, to have experience in the regulatory process of their respective country, adequate facilities, sufficient dedicated and trained staff, access to target population and COVID-19 testing available on site. The documents for the qualification of the clinical trial team are filed in the sponsor´s Trial Master File (TMF) as well as the local trial site´s Investigator Site File (ISF).

3.14. Financing

According to section 3.13. of the accompanying master protocol for further details:

A detailed financial plan does not form part of the trial protocol. The financial plan is archived separately; it may be needed to gain approvals or to accompany contracts or it may be requested for submission to the ethics committee. However, all sources of financing must be listed there.

This clinical trial receives full financial support through a grant from the European Commission.

4. Trial conduct

4.1. General aspects of trial design

According to section 4.1 of the accompanying master protocol:

This is a randomised, adaptive, multicentre, Phase II master protocol evaluating different booster strategies in individuals against SARS-CoV-2. This protocol allows testing of different booster strategies to assess their immunogenicity and safety against SARS-CoV-2 and its variants. Different trial populations, different vaccines, additional doses and vaccination time points, and extended follow-up visits can be added throughout amendments of the master protocol. The master protocol contains a common control group that does not receive a 3rd nor a 4th vaccination, i.e., no booster dose at all. This control group is used for exploratory comparison as applicable. The trial implements a specific safety monitoring strategy for this control group.

Specific to this trial:

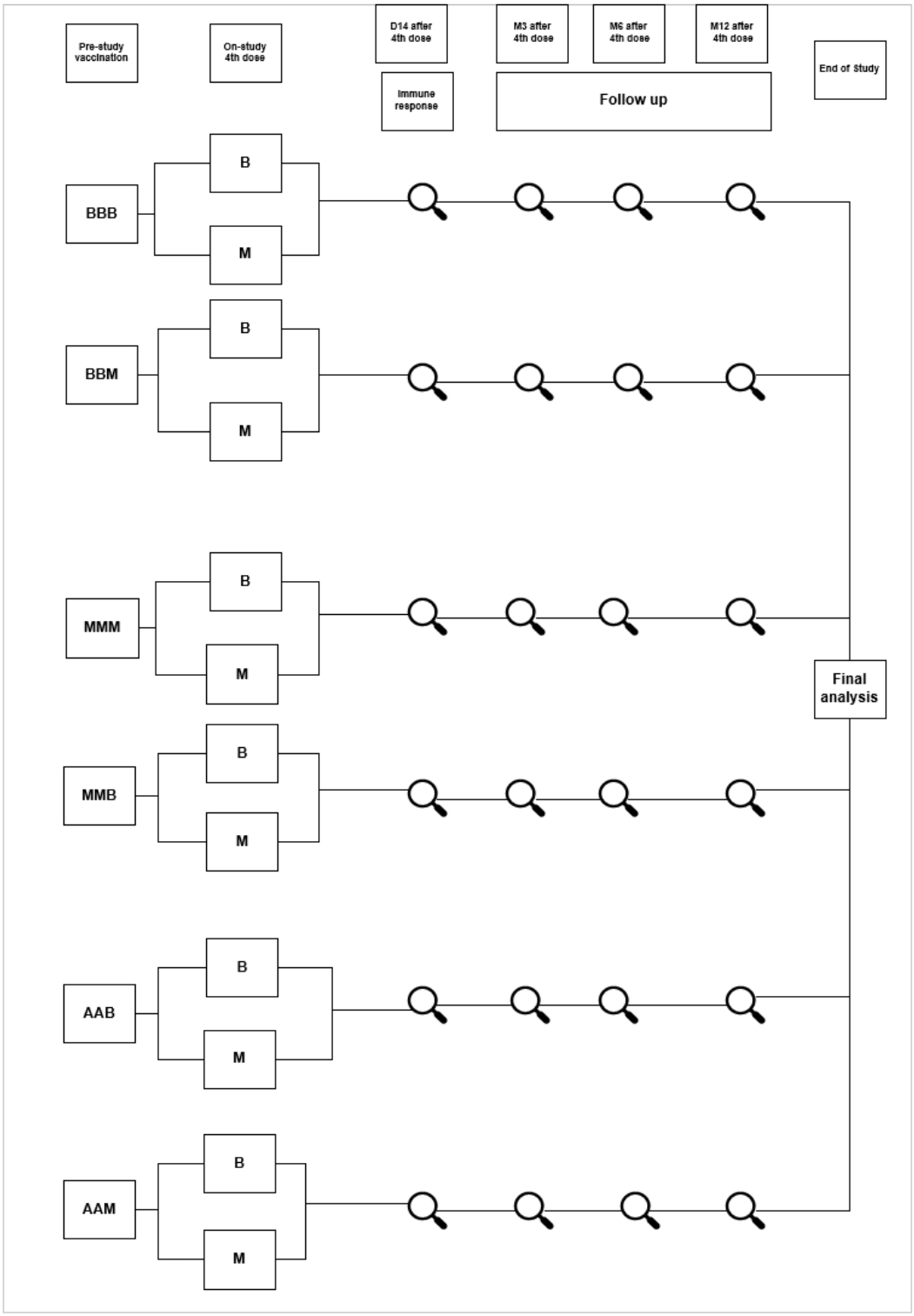
This is a randomised controlled, adaptive, multicentre Phase II protocol evaluating the immunogenicity and reactogenicity of different strategies of a 3rd (Part A) and 4th (Part B) vaccination dose ("boosters") in individuals ≥75 years after a primary vaccination series against SARS-CoV-2. This trial foresees testing of different vaccines as a 3rd or 4th vaccination dose (also referred to as booster vaccinations) for comparative assessment of their immunogenicity and safety against SARS-CoV-2 wild-type and variants in the elderly, a usually neglected population. Additional vaccines and extended follow-up visits can be added by means of amendments to this sub-protocol. As stated in the master protocol, this trial implements a specific safety monitoring strategy for the control group (see below).

Subjects in each cohort will be randomised to one of the arms planned in an equal allocation ratio. In each cohort, the number of arms foreseen at this moment is 2; therefore, the allocation ratio within in each cohort will be 1:1.

Arms can be withdrawn or added as deemed necessary according to the criteria specified in this protocol.

Figure 1 shows a schematic flow chart of the trial design.

Figure 1: Flow chart of the trial design, **4th vaccination dose in <u>Part B</u>**



A: AstraZeneca vaccine ChAdOx-1-S **B:** BioNTech vaccine Comirnaty® **M:** Moderna vaccine Spikevax®
D14: day 14
M3/6/12: month 3/6/12

4.1.1. Time schedule

The time schedule of this trial is detailed in table 1.

Table 1: Time schedule of the trial (Part A and Part B)

First patient first visit (FPFV):	November 2021
Last patient first visit (LPFV):	September 2022
Last patient last visit (LPLV):	September 2023
Analysis	October 2022 (Primary endpoint analysis)
End of study definition	The end of study will be on the day of database lock.
End of trial	November 2023
Final study report:	December 2023

End of study will be on the day of database lock, as planned 30 days after the last patient last visit.

4.2. Discussion of trial design

According to section 4.2 of the accompanying master protocol:

Trials under the master protocol allow testing of different booster strategies to assess their immunogenicity and safety against SARS-CoV-2 and its variants. Different trial populations, different vaccines, additional doses and vaccination time points, and extended follow-up visits can be added throughout amendments of the master protocol or trials under the master protocol.

Specific to this trial:

This trial is a sub-protocol embedded within the master protocol EU-COVAT: A Randomised, Controlled, Adaptive, Multicentre, Phase II Master Protocol Evaluating Different Booster Strategies in Individuals Already Vaccinated Against SARS-CoV-2.

This is a randomised controlled, adaptive, evaluator-blinded multicentre Phase II protocol evaluating immunogenicity and reactogenicity of different booster strategies in individuals 75 years and older after a primary vaccination series against SARS-CoV-2. This trial foresees testing of different vaccines as a 3rd (Part A) or 4th (Part B) vaccination dose (for details see Section 4.7.1, Tables 2.1 and 2.2) for comparative assessment of their immunogenicity and safety against SARS-CoV-2 wild-type and variants in the elderly, a usually neglected population. Different vaccines and extended follow-up visits can be added by means of amendments to this trial. As stated in the master protocol, this trial implements a specific safety monitoring strategy for a control group as implemented in the EU-COVAT subprotocol with the EudraCT no.: 2021-004889-35, a separate sub-protocol embedded

within the EU-COVAT master protocol (see below). This control group is used for exploratory comparison.

Vaccines used in this trial will be those already marketed and in their commercial presentation. In Part B the sample size planned is adequate for a precise enough estimation of the immune response after a 4th vaccination dose.

4.3. Risk-Benefit Assessment

4.3.1. Known Potential Risks

According to section 4.3.1 of the accompanying master protocol:

The risks will be based on the SmPC of each vaccine and any risk described in the literature.

Specific to this trial, Part B:

Side effects that have been reported with the Pfizer-BioNTech Comirnaty and Moderna Spikevax vaccine include:

- Headache, diarrhoea, nausea, vomiting, abdominal pain
- Arthralgia, myalgia
- Injection site pain, fatigue, chills, pyrexia
- injection site swelling, injection site redness
- Injection site pruritus
- Lymphadenopathy
- Hypersensitivity reactions (e.g. rash, pruritus, urticaria, angioedema), including anaphylaxis
- Decreased appetite, insomnia, lethargy, asthenia, malaise, dizziness
- Acute peripheral facial paralysis, paraesthesia, hypoaesthesia
- Myocarditis, pericarditis
- Hyperhidrosis, night sweats
- Erythema multiforme
- Pain in vaccinated extremity
- Extensive swelling of vaccinated limb, facial swelling

These may not be all of the possible side effects of Pfizer-BioNTech's BNT162b2 (Comirnaty®) and Moderna mRNA-1273 (Spikevax®) vaccines. Possible hitherto unknown side effects that cannot be

excluded when combinations of different vaccines are used, although there is a sufficient lag period between 2nd, 3rd and 4th vaccination doses as per enrolment criteria so that no overlap of acute side effects is expected. Serious and unexpected side effects may occur. Both vaccines are still being studied in clinical trials.

Respective potential risks will be described for other vaccines that may be included in the trial at a later stage.

4.3.2. Known Potential Benefits

According to section 4.3.2 of the accompanying master protocol, modified for Part B:

At present, the level and duration of protection against SARS-CoV-2 infection provided by the available vaccines and authorised vaccination schedules are not known, especially in the context of newly emerging VOCs. Therefore, 4th vaccine dose as an additional (i.e. second) booster may be needed to provide and/or maintain immunity against SARS-CoV-2 and, thus, may provide a benefit to subjects. Also, this protection may probably differ between age strata and the need for and the timing of administering a booster vaccination dose is unknown. Evaluation of the immune response to booster doses in different populations and at different timepoints after primary vaccination series will provide a rationale for further phase III trials and vaccination programs. Trial-specific benefits will be described in the respective sub-protocol.

Specific to this trial:

Older subjects are at very high risk of severe disease and death due to SARS-CoV-2 infection. Furthermore, the duration and grade of protection provided by the currently available vaccines, especially in the elderly above 75 years of age, is not known but immune response to vaccines of older subjects may indeed be low. We know that the vaccines presently available induce a strong immune response and there is evidence that this is related to the level of prevention of moderate and severe COVID-19. The use of booster doses may be needed to maintain immunity against SARS-CoV-2 and may therefore provide a benefit to subjects receiving booster vaccination doses.

4.3.3. Assessment of Potential Risks and Benefits

According to section 4.3.3 of the accompanying master protocol:

While the efficacy and safety profile of the approved COVID-19 vaccines are subject to investigation when used as homologous or heterologous boost regimen, it is not expected that risks associated to booster vaccination doses of a COVID-19 vaccine will increase compared to the standard, i.e.,

authorised, vaccine administration. Therefore, participants volunteering for this trial are not considered to be at additional risk related to the administration of the COVID-19 vaccines available. Any contraindication or precaution of use of any of the vaccines included in the trials under the master protocol will be considered and included in participant's selection criteria of each sub-protocol. A risk-benefit assessment will be performed in each protocol under the master protocol.

Participants in this study are exposed to some general risks. The participants may be subjected to additional blood sampling without representing any relevant harm or discomfort. Collection of other samples, like oropharyngeal or nasal swabs, or urine sampling, are considered not to cause any significant harm.

Participants' identities will be protected, and personal health information (PHI) held securely. No directly identifiable data will be stored in the clinical trial database, and the participant lists will be stored separately and secured at the local study sites. The risk of unauthorised persons accessing participant's PHI will be kept to a minimum, and measures will be taken to keep PHI confidential in accordance with legal requirements.

Specific to this trial:

Benefits and risks of COVID-19 vaccination are well known and are described in sections 4.3.1 and 4.3.2. Although there is only limited published information on the administration of booster doses after standard vaccination, it is expected that risks posed by subsequent doses are similar to those observed with the standard vaccination regimen. On the contrary, administration of booster doses may confer a higher and longer protection against COVID-19 in this vulnerable population and some protection against VOCs.

Potential benefit/risk balance will be assessed prior to the addition of other vaccines in the trial.

4.4. Selection of trial population

According to section 4.4 of the accompanying master protocol:

VACCELERATE has established a European volunteer registry for vaccine trials. A continuously growing number of interested individuals have expressed their interest in this registry. This will allow for fast and efficient recruitment of trial participants.

Subjects to be recruited in the trials under the master protocol will be those already fully vaccinated(all-comers) with no contra-indication against any of the vaccine products in the trial at the moment of inclusion and as specified in respective sub-protocol.

Within each trial, subjects will be stratified (as applicable and specified per sub-protocol) by:

- Gender (female/male).
- Vaccine product used for primary vaccination (BNT162b2; mRNA-1273; ChAdOx-1-S; other)
- Immune status (competent, immunocompromised).

Documented history of prior COVID-19 infection.

Reasons for gender distribution

Subjects included in this trial are expected to be similar to subjects that have been vaccinated within the vaccination programs in each country. Therefore, gender distribution in the present trial is expected to be similar to that of the general vaccinated population and no restrictions will be made with relation to biological sex, unless included in the selection criteria.

Specific to this trial, Part B:

Subjects included in this trial are expected to be similar to subjects that have been vaccinated within the vaccination programs in each country. Gender distribution will be therefore similar to that of the population vaccinated so far. Accordingly, Part B (for details see section 4.7.1, Tables 2.1 and 2.2) will include 550 subjects that are randomised 1:1 to either BNT162b2 or mRNA-1273. Recruitment of cohorts will be closed when the pre-planned number for each cohort is reached. Stratification is planned according to the pre-study vaccination series eligible for Part B (primary vaccination plus 3rd vaccine dose (= first booster), gender (female/male), documented history of prior COVID-19 infection (yes/no)), as applicable and defined also by enrolment criteria.

4.4.1. Inclusion criteria

- Subject is ≥75 years old.
- For study entry in **Part B** the subject was vaccinated with one of the following vaccination regimens (1st + 2nd + 3rd dose):
  - BNT162b2 + BNT162b2 + BNT162b2
  - BNT162b2 + BNT162b2 + mRNA-1273
  - mRNA-1273 + mRNA-1273 + mRNA-1273
  - mRNA-1273 + mRNA-1273 + BNT162b2
  - ChAdOx-1-S + ChAdOx-1-S + BNT162b2
  - ChAdOx-1-S + ChAdOx-1-S + mRNA-1273
- The last dose of the above vaccinations must have been administered at least 1 month prior to study entry. Vaccination status should be documented in the source data and will be captured in the eCRF.
- No contra-indication against any of the vaccine products in the trial.
- Written informed consent from subject has been obtained.

4.4.2. Exclusion criteria

- Prior to study entry the subject got vaccinated with a regimen not included in the above list.
- Last anti-SARS-CoV-2 vaccine dose administered less than one month prior to study entry.
- Vaccination against a disease other than COVID-19 within 2 weeks prior to study entry. Only exception: Influenza vaccination which is allowed at any time.
- Subjects with any significant or uncontrolled disease posing a risk due to vaccination as judged by the investigator.
- Current immunosuppressive therapy, for example continuous glucocorticosteroid treatment equivalent to >10 mg/day prednisolone.
- Subject simultaneously participates in another clinical trials or has participated in the past 30 days.
- Subjects unable to report solicited adverse events.
- Subject participates or participated in Part A of this trial.
- Subject with any contraindications to the vaccines in the trial. A list of contraindications as listed in the Summary of medicinal Product Characteristics (SmPC, the Fachinformation in Germany), if appropriate.

- Use of drugs with significant interaction with the investigational product according to the SmPC or similar documents.
- Diseases or findings that may have a significant effect on the target variables and which may therefore mask or inhibit the therapeutic effect under investigation.
- Subject had COVID-19 or tested positive for SARS-CoV-2 within the last 3 months.
- Persons with any kind of dependency on the principal investigator or employed by the sponsor or principal investigator.
- Legally incapacitated persons.
- Persons held in an institution by legal or official order.

4.5. Withdrawal of trial subjects after trial start

According to section 4.5. of the accompanying master protocol:
A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, or compliance/adherence reasons. This is expected to be uncommon. When a participant withdraws before study completion, the reason for withdrawal is to be documented in the eCRF and in the source document. If the reason for withdrawal from the study is withdrawal of consent, then no additional assessments are allowed. The participant will be permanently discontinued from the study intervention and the study at that time. If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent. If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the study site records.

4.6. Closure of trial sites/Premature termination of the clinical trial

4.6.1. Closure of trial sites

According to section 4.6.1 of the accompanying master protocol:
Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed. The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

4.6.2. Premature termination of trial

According to section 4.6.2. of the accompanying master protocol:

The sponsor has the right to terminate the trial prematurely if there are any relevant medical or ethical concerns, or if completing the trial is no longer practicable. If such action is taken, the reasons for terminating the trial must be documented in detail. All trial subjects at the time of termination shall undergo a final examination which must be documented, if deemed necessary for patient safety. The sponsor must be informed without delay if any principal investigator has ethical concerns about continuation of the trial.

Premature termination of the trial will be considered if:

- The risk-benefit assessment for trial subjects changes markedly.
- It is no longer ethical to continue treatment with the IMP.
- The sponsor considers that the trial must be discontinued for safety reasons (e.g., on the advice of the DMC).
- Results of other research show that one of the trial treatments is superior or inferior to another.
- It is no longer practicable to complete the trial.

The sponsor decides on whether to discontinue the trial in consultation with the PCI, DMC, SC, Advisory Board and trial statistician, as applicable.

4.7. Treatment

4.7.1. Treatments to be given

According to section 4.7.1. of the accompanying master protocol:
Vaccines to be evaluated in sub-protocols under the master protocol will be vaccines with marketing authorization at the time of each sub-protocol design and/or vaccines still in clinical development, i.e., pre-authorisation. Vaccines to be administered in the intervention and control arms will be defined in each sub-protocol depending on the hypothesis and the booster strategies tested. Subjects allocated to control arms could receive a 3rd vaccine dose or not receive a 3rd vaccine dose.

Specific to this trial, Part B:
Study vaccines will be given as a 4th dose in subjects already vaccinated with defined prior vaccination strategies (with BNT162b2, mRNA-1271 or ChAdOx-1-S) as per eligibility criteria. The

vaccines to be evaluated as 4th vaccination (second booster) dose will be BNT162b2 (Comirnaty®) and mRNA-1273 (Spikevax®). For a detailed overview of all cohorts and arms in this study please refer to Tables 2.1 and 2.2 below.

In Part B there is a <u>minimum interval of 1 month</u> between the on-study 4th vaccination dose and the 3rd pre-study vaccination, with longer intervals as per local regulation or practice.

Table 2.1: **Intervention in Part A** no longer active - for information only

Cohort	Vaccination prior to study entry	Arm	Study intervention: 3rd vaccination dose	Part A with Cohorts 1 to 3 closed to further recruitment as of January 13, 2022
Cohort 1	BNT162b2 + BNT162b2	1	BNT162b2	
		2	mRNA-1273	
Cohort 2	mRNA-1273 + mRNA-1273	3	BNT162b2	
		4	mRNA-1273	
Cohort 3	ChAdOx-1-S + ChAdOx-1-S	5	BNT162b2	
		6	mRNA-1273	
Control	Control arm of the EU-COVAT subprotocol EudraCT no. 2021-004889-35, a separate sub-protocol embedded within the EU-COVAT master protocol, will be used for a descriptive comparison.			

Table 2.2: **Intervention in Part B - 4th vaccination dose**

Cohort	Vaccination prior to study entry	Arm	Study intervention: 4th vaccination dose*
Cohort 4	BNT162b2 + BNT162b2 + BNT162b2	7	BNT162b2
		8	mRNA-1273
Cohort 5	BNT162b2 + BNT162b2 + mRNA-1273	9	BNT162b2
		10	mRNA-1273
Cohort 6	mRNA-1273 + mRNA-1273 + mRNA-1273	11	BNT162b2
		12	mRNA-1273
Cohort 7	mRNA-1273 + mRNA-1273 + BNT162b2	13	BNT162b2
		14	mRNA-1273
Cohort 8	ChAdOx-1-S + ChAdOx-1-S + BNT162b2	15	BNT162b2
		16	mRNA-1273
Cohort 9	ChAdOx-1-S + ChAdOx-1-S + mRNA-1273	17	BNT162b2
		18	mRNA-1273

** administered at least 1 month after the 3nd pre-study vaccination.*

4.7.2. Description of investigational medicinal product

Trade name: Comirnaty®

INN (International Nonproprietary Name)/active substance:

COVID-19 mRNA vaccine(nucleoside-modified).

ATC-Code: J07BX

Presentation: vaccine shot for intramuscular injection.

Dose: 30 µg (0.3 mL after dilution).

Manufacturer (or marketing authorisation holder if applicable): Pfizer-BioNTech.

Already approved for the following indication: Protection against COVID-19 infection.

Please note: Can be modified in composition to address emerging VOCs.

Trade Name: Spikevax®

ATC-code: J07BX03

Presentation: Dilution, vaccine shot for intramuscular injection.

Dose: 100 µg (0.5 mL after dilution); **please note that the 50 µg (0.25 mL) dose is not used in this trial - see dose justification further down below.**

Manufacturer: Moderna.

Already approved for the following indication: Protection against COVID-19 infection.

Please note: Can be modified in composition to address emerging VOCs.

4.7.2.1. Manufacture of the investigational medicinal product

Not applicable.

4.7.2.2. Labelling of investigational medicinal product

Vaccines to be administered in this trial are already marketed. Therefore, labelling is carried out as approved in each country. Preparation of the dose of each vaccine will be done according to the respective SmPC.

4.7.3. Storage of investigational medicinal product

All study vaccines must be stored in a secured location with no access for unauthorised personnel and at controlled temperatures as indicated on the commercial labels and manufacturer instructions.

If study vaccine is exposed to temperatures outside the specified temperature range according to SmPC as per market authorization, then the affected supplies will be destroyed in line with locally regulated procedures and replaced with new supplies.

Instructions for the preparation, handling and storage will be those described in the SmPC of COMIRNATY and SPIKEVAX approved by Regulatory Authorities. The investigator is responsible for ensuring that all study vaccines received at the site is inventoried and accounted for throughout the study. The study vaccine administered to the participant must be documented on the vaccine (drug) accountability form. All study vaccine will be stored and disposed of according to the manufacturer's instructions. Destruction of vaccines will be recorded on appropriate drug destruction logs.

4.7.4. Compliance with treatment/Dispensing and return of investigational medicinal product

This study will be conducted within hospitals and/or experienced commercial clinical trial sites. Treatment is administered at site and participants will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and captured in the eCRF. Deviation(s) from the trial-specific dosage regimen as given in section 4.7.2 are not permitted. Dates of intervention will also be recorded.

4.7.5. Assignment of trial subjects to treatment groups

According to section 4.7.5 of the accompanying master protocol:

Subject fulfilling selection criteria will be randomised to the different treatment arms in the trial through a central procedure. Randomisation will be stratified according to:

- Vaccine product used for primary vaccination (detailed in the concerned sub-protocol).
- Trial Site.
- Gender (female/male).
- Immune status (competent, immunocompromised as applicable in the concerned sub-protocol).

- Documented history of prior COVID-19 infection (none, asymptomatic, symptomatic/pre-vaccination or post-vaccination).

The participants are randomised into the study arms as defined in each sub-protocol. Randomisation will be implemented by a 24/7-Internet service (ALEA 17.1, FormsVision BV, Abcoude, NL) and prepared centrally by the Institute of Medical Statistics and Computational Biology (IMSB) at the University of Cologne.

Specific to this trial, Part B:

Subjects fulfilling selection criteria will be randomised to 4th dose through a central procedure. Subjects will be randomised in a 1:1 ratio to one of the two treatment groups:

- 4th vaccination with BTN162b2 (Comirnaty®), including modified vaccine product.
- 4th vaccination with mRNA-1273 (Spikevax®), including modified vaccine product.

Randomisation will be stratified as described below:

Stratification is planned according to the pre-study vaccination series eligible for Part B (primary vaccination plus 3rd vaccine dose (= first booster), gender (female/male), documented history of prior COVID-19 infection (yes/no), as applicable and defined also by enrolment criteria.

In this trial, there is <u>no</u> stratification in the randomisation

- according to the status of immune competency of the trial subject.
- according to trial site.

4.7.6. Selection of dosage of investigational medicinal product

Treatment will be given as a single shot using the approved dose and mode of administration of each vaccine included in this trial.

4.7.6.1. Justification of the 0.5 ml (100 µg) booster dose of Moderna's Spikevax COVID-19 vaccine (mRNA-1273*)*

In the present *EU-COVAT-1_AGED* study, subjects aged 75 years or older receive a booster dose of 0.5 ml (100 µg) mRNA-1273. This investigational booster dose of mRNA-1273 is identical with the first and second mRNA-1273 dose administered in the primary vaccination series. [22,23]

Under the jurisdictions of both FDA and EMA, mRNA-1273 is approved for a booster dose (3rd vaccination) of 0.25 ml (50 µg) six months after completion of the primary vaccination series in

individuals 18 years of age or older.[22,23] An mRNA-1273 dose of 0.5 ml (100 µg) one month after the primary vaccination series is approved in severely immunocompromised individuals, such as after organ transplantation or at an equivalent level of immunocompromise. [22,23]

The rationale for the lower booster dose of 0.25 ml (50 µg) was provided by Moderna, Inc. as follows:

"- *Goal was to use optimal effective dose for boosting.*

- *Lower booster doses than those used for primary series of other vaccines [was] shown to reactivate immune memory.*

- *Lower booster dose increases worldwide vaccine supply of mRNA-1273*." [24]

Safety, especially with regard to a potential myocarditis risk of the booster, was not a driver in choosing the 0.25 ml (50 µg) booster dose instead of 0.5 ml (100 µg). However, myocarditis/ pericarditis is indeed a concern in individuals of male sex aged under 30 years receiving either of the currently approved mRNA COVID-19 vaccines. Surveillance studies showed that myocarditis reporting rates were 40.6 cases per million second doses of mRNA COVID-19 vaccines administered to males aged 12−29 years and 2.4 per million second doses administered to males aged ≥30 years; reporting rates among females in these age groups were 4.2 and 1.0 per million second doses, respectively.[25,26] In comparison to the Pfizer/BioNTech BNT162b2 mRNA vaccine, there are 21.5 excess cases of myocarditis (including pericarditis) per million doses of the Moderna vaccine in males aged 18 to 39 years 0 to 7 days after the second dose[25]. Accordingly, the FDA Fact Sheet provides the following information for mRNA-1273: "*Postmarketing data demonstrate increased risks of myocarditis and pericarditis, particularly within 7 days following the second dose. The observed risk is higher among males under 40 years of age than among females and older males. The observed risk is highest in males 18 through 24 years of age.*"[22]

As outlined above, the target population of the present *EUCOVAT-1_AGED* study (75 years or older) does not fall into the at-risk group for an increased level of myocarditis/pericarditis after vaccination with mRNA-1273. Besides, there is further reassuring information available regarding the potential myocarditis/pericarditis risk of a booster dose (3rd dose) as compared to the second dose of an mRNA vaccine: "*Extrapolation from [Israeli surveillance] data obtained with the Pfizer-BioNTech COVID-19 vaccine […] suggests that the risk of myocarditis for the Moderna COVID-19 Vaccine following a third dose several months following the primary vaccination series is not associated with an unacceptable risk of myocarditis/pericarditis. […] … the risk of myocarditis/pericarditis appears to be more similar after the administration of the third dose to the*

risk observed after the first dose." [27] Of note, vaccinees with the Pfizer/BioNTech vaccine BNT162b2 receive identical doses for the booster as for the first and second administrations[28].

With a booster dose of mRNA-1273 identical to the doses of the primary vaccination series very old individuals (> 75 years) with assumed immunosenescence[29] may thus benefit from increased immunogenicity while not being exposed to a currently detectable increased risk of myocarditis/pericarditis.

Meanwhile, Moderna Tx. has communicated data that demonstrate markedly increased levels of Omicron neutralizing antibodies after the 100 µg mRNA-1271 booster (3rd) dose as compared to the 50 µg dose[30].

A full booster (3rd) dose (0.5 ml, 100 µg) of mRNA-1273 was administered in two subgroups of the COV-BOOST trial, either following primary vaccination series with twice ChAdOx1-S or twice BNT162b2. The median age in the ChAdOx1-S subgroup (n=112) was 70.2 years and 65.0 years in the BNT162b2 group (n=111)[31]. Data on a full dose mRNA-1273 booster in the very old above 75 years of age is thus still missing.

4.7.7. Time of administration and adjustments to dosage of the investigational medicinal product in the individual trial subject

Not applicable.

4.7.8. Blinding

No blinding is foreseen in this trial.

4.7.8.1. Unblinding

Not applicable.

4.7.9. Previous and concomitant medication

According to section 4.7.8. of the accompanying master protocol:

There are no previous or concomitant medication prohibited in this protocol. Any medication at the time of enrolment or received during the study must be recorded along with:

- Reason for use.

- Date of administration including start and end dates.
- Dosage information including dose and frequency.

4.7.9.1. Rescue therapy for emergencies

For any adverse drug reaction that is deemed an emergency (e. g. severe allergic reactions), rescue therapy according to standard of care will be applied and the trial subject be followed up until full resolution of the adverse drug reaction.

4.7.10. Continuation of treatment after the end of the clinical trial

Not applicable.

4.8. Efficacy and safety endpoints

According to section 4.8 of the accompanying master protocol:

Main overarching immunogenicity variables to be included in the sub-protocols are those standard tests showing the immune response to SARS-CoV-2 vaccines, as described below.

Overarching safety variables of interest include unsolicited and solicited adverse events day 14, as applicable, after a 4th vaccination dose administration and severe adverse events for the duration of the trial.

Specific to Part B of this clinical trial:
This trial aims to evaluate immunogenicity and safety of a 4th vaccination dose of COVID-19 vaccines in older (≥75) subjects having received a primary vaccination series plus a 3rd vaccine dose > 1month ago at the time of enrolment.

4.8.1. Measurement of efficacy and safety endpoints in Part B

4.8.1.1. Primary endpoints

According to section 4.8.1.1 of the accompanying master protocol:

- Rate of 2-fold antibody titre increase 14 days **after the 4th vaccination dose** measured by quantitative enzyme-linked immunosorbent assay (Anti-RBD-ELISA) against wild-type virus.

4.8.1.2. Safety endpoints

- Unsolicited AEs until the end of trial.

- Solicited AEs for 7 days after a 4th vaccination dose.
- Rate of severe adverse events (AEs) Grade ≥3 according to the National Cancer Institute Common Toxicity Criteria up to three months after a 4th vaccination dose (Note: Adverse events Grade ≥3 must be reported as SAE by using study specific SAE reporting process, see section 7.3).

4.8.1.3. Secondary endpoints

- Change in neutralizing antibody titre (Virus Neutralisation Assay) **against wild-type** 14 days after a 4th vaccination dose, to be determined in a subgroup only.

- Change in neutralizing antibody titre (Virus Neutralisation Assay) **against variants of concern** 14 days after a 4th vaccination dose, to be determined in a subgroup only.

- Antibody titre level **12 months** after a 4th vaccination dose measured by a quantitative enzyme-linked immunosorbent assay (anti-RBD-ELISA assay).

- Neutralizing antibody titre (Virus Neutralisation Assay) **against wild-type SARS-CoV-2** at 12 months after a 4th vaccination dose, to be determined in a subgroup only.

- Neutralizing antibody titre (Virus Neutralisation Assay) **against variants of concern** at 12 months after a 4th vaccination dose, to be determined in a subgroup only.

4.8.1.4. Exploratory endpoints

- Change in cellular immune response measured by qPCR 14 days after 4th booster dose, to be determined in a subgroup only.
- Neutralising capacity measured by neutralising activity against newly emerging variants in bio-banked samples after a 4th vaccination dose, to be determined in a subgroup only.
- Correlates of humoral immune response, cellular immune responses and viral neutralising capacity against SARS-CoV-2 variants of concern (VOCs), to be determined in a subgroup only.

Please note that the size of the above-mentioned subgroups (sections 4.8.1.3 and 4.8.1.4) is targeted to be 200 subjects each. Analysis will be performed in all samples if additional funding becomes available.

4.8.1.5. Safety data in Part B

- Solicited AEs (as defined in section 7.1.7) for 7 days after an on-trial 4th vaccination dose will be collected by using a diary (electronic or paper-based). Information collected will be entered into the eCRF by designated study site personnel.

- Unsolicited adverse events will be collected during visits up to the end of trial upon an open question by the investigator to the participant. Those unsolicited AEs graded as severe by the subject will be evaluated by the investigator to define the relationship with administered vaccines. Only those considered related will be accounted for and reported. Serious adverse events (SAEs) will be collected through an open question.
- SADRs will be collected and reported during the visits 3 to 5, reported spontaneously by the subject or elicited after an open question about any event of interest since the previous visit.

4.9. Description of visits

Patient visits are carried out at the following timepoints (see table 3.1). Subjects will be followed for 1 year after on-study vaccine administration.

Table 3.1: Visit schedule in Part B

Visit number	**1**	**2**	**3**	**4**	**5**
Procedure	Screening, enrolment, baseline 4th dose	Immune response evaluation	Follow up	Follow up	End of study
Day ± window	0	14 ±2 days after 4th dose	3 months ± 3 days after 4th dose	6 months ± 3 days after 4th dose	12 months ± 3 days after 4th dose
Screening for eligibility					
Informed consent [a]	X				
Demographics and medical history[f]	X				
Eligibility check	X				
Baseline procedures					
Concomitant medication review	X	X			
Physical exam	X	X[b]			
Vital signs	X	X[b]			
Immunogenicity					
Anti-RBD & anti-N IgG (ELISA)	X	X			X
Neutralising activity (wildtype) [c]	X	X			X
Neutralising activity (VOC) [c]	X	X			X
Cellular response (qPCR assay) [c]	X	X			
Biobanking [d]	X	X	X	X	X
IMP administration					
Vaccination[§]	X				
Safety					
AE/SAE [e]	X	X	X	X	X

AE, adverse events; SAE, serious adverse event
a: Informed consent must be obtained before obtaining consent for biobanking and secondary data use, and any other procedure to be undertaken.
b: will be performed at visit 2 only upon SAE
c: samples taken from all subjects, analysis performed in a subgroup only. Analysis will be performed in all samples if additional funding becomes available.
d: for secondary use defined in informed consent; also optional at visit 1 and visit 2: at trial site and upon agreement of trial participant additional blood collection for biobanking of peripheral blood mononuclear cells (PBMC) as per informed consent
e: solicited AEs are recorded by trial participant till Day 7 and records will be collected at visit 2 (Day 14) by trial staff and captured in eCRF; unsolicited AEs are recorded by trial investigator until the end of trial as described in this protocol.
f: medical history includes information on prior SARS-CoV-2 infection and COVID-19 disease if applicable; name of SARS-CoV-2 variant should be documented if known.
§Administration of 4th vaccination dose after blood sampling for immunogenicity and cellular immunity during visit 1. Trial participant is observed for any adverse reaction for at least 15 min or according to standard of care upon vaccination.

4.9.1. Rationale for assessment procedures

Monitoring of immunogenicity at 14 days has been a standard time-point for COVID-19 vaccines and the immunogenicity test performed at 3, 6 and 12 months are considered adequate for evaluating the duration of immunity in this population vaccinated against COVID-19.

Subjects will be evaluated for reactogenicity events during the first 14 days after 4th dose administration (solicited AEs until Day 7; unsolicited AEs up to Day 14 and until the end of trial) and thereafter every 3 months after 4th vaccination dose according to visit schedule (see Table 3) for SAEs reported. This is considered sufficient for safety monitoring of already marketed vaccines.

4.9.2. Pharmacokinetics/Determination of drug levels

Not applicable.

4.9.3. Biobanking

Serum, plasma, immune cell activation and optional isolation of peripheral blood mononuclear cells (PBMCs) will be prepared from whole blood collection. Samples will be used for determining the primary and secondary endpoints. Samples will be centrally collected and stored at the determined biobank – see section 3.10. The biobank will distribute samples to determined central laboratories (section 3.10) and store the samples for additional research. Trial subjects are informed in detail about the use of bio-banked samples in the informed consent form. The preparation, storage conditions and logistics of the samples for biobanking are described in a separate laboratory manual.

4.9.4. Ethics for accessing and using biobank samples

Scientists wishing to access biobank samples collected from this trial must obtain a positive vote from their concerned ethical committee in accordance with the Declaration of Helsinki (2013) prior to undertaking an intended research project. This positive vote must be provided to the sponsor and/or their representative before release of the samples for the intended research projects by the sponsor. The final decision about releasing biobank sample request lies with the sponsor and/or their representative. Further details about request, access and usage of biobank samples are provided in a separate biobanking concept.

4.10. Data quality assurance

4.10.1. Monitoring

According to section 4.10.1 of the accompanying master protocol:

The trial sites will be monitored to ensure the quality of the data collected. The objectives of the monitoring procedures are to ensure that the trial subject's safety and rights as a study participant are respected, that accurate, valid and complete data are collected, and that the trial is conducted in accordance with the trial protocol, the principles of GCP and local legislation.

The exact extent of the monitoring procedures is described in a separate monitoring manual. Monitoring will follow a risk-adapted on-site monitoring strategy (Brosteanu et al).

All principal investigators agree that the monitor regularly visits the trial site and assure that the monitor will receive appropriate support in their activities at the trial site, as agreed in separate contracts with each trial site. The declaration of informed consent (see section 5.5) includes a statement allowing the monitor to compare the case report forms (CRFs) with the trial subject's medical records (doctor's notes, ECGs, laboratory printouts etc.).

The principal investigator will secure access for the monitor to all necessary documentation for trial-related monitoring. The aims of the monitoring visits are as follows:

- To check the declarations of informed consent.
- To monitor trial subject safety (occurrence and documentation/reporting of AEs and SAEs).
- To check the completeness and accuracy of entries on the CRFs.
- To validate the entries on the CRFs against those in the source documents (source data verification, SDV).
- To perform drug accountability checks.
- To evaluate the progress of the trial.
- To evaluate compliance with the trial protocol.
- To assess whether the trial is being performed according to GCP at the trial site.
- To discuss with the principal investigator aspects of trial conduct and any deficiencies found.

A monitoring visit report is prepared for each visit describing the progress of the clinical trial and any problems. The principal investigator will reasonably consider the corrective and preventive measures suggested by the monitor. All participant data relating to the study will be recorded on electronic CRFs. The investigator is responsible for verifying that data entries are accurate and correct by

electronically signing the CRF. Guidance on completion of eCRFs will be provided in the Trial Master File. The investigator must permit study-related monitoring, audits, REC/NCA review, and regulatory agency inspections and provide direct access to source data documents.

Monitoring details describing strategy, including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan. The sponsor or designee is responsible for the data management of this study, including quality checking of the data. The sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organisations).

Specific details for this trial are outlined in a separate monitoring plan.

4.10.2. Audits/Inspections

According to section 4.10.2. of the accompanying master protocol:

As part of quality assurance, the sponsor has the right to audit the trial sites and any other institutions involved in the trial. The aim of an audit is to verify the validity, accuracy and completeness of data, to establish the credibility of the clinical trial, and to check whether the trial subject's rights and trial subject safety are being maintained. The sponsor may assign these activities to persons otherwise not involved in the trial (auditors). These persons are allowed access to all trial documentation (especially the trial protocol, case report forms, trial subjects' medical records, drug accountability documentation, and trial-related correspondence).

The sponsor and all trial sites involved undertake to support auditors and inspections by the competent authorities at all times and to allow the persons charged with these duties access to the necessary original documentation.

All persons conducting audits will keep all trial subject data and other trial data confidential.

4.11. Documentation

According to section 4.11. of the accompanying master protocol:

Principal Investigators will oversee and coordinate data collection, entry, and protection.
Trial-specific data will be collected by the clinical trial staff using designated source documents. Standard GCP practices will be followed to ensure accurate, reliable, and consistent data collection. Any correction to source documentation needs to ensure a valid correction trail, including leaving original entries legible and signed or initialled dated corrections. If source documents involve electronic patient files, then an audit trail of changes to documentation must be available.

All trial data must be verifiable to the source documentation. All source documents will be kept in a locked facility at the clinical site. Source documents include but are not limited to:

- Informed Consent Forms;
- Reported laboratory results;
- Lists of adverse events;
- Lists of concomitant medication;
- Documentations of existing conditions.

Medical records will be archived by the trial site as per local regulations.

All data relevant to the trial are documented by the Principal Investigators (PI) or designees in corresponding electronic case report forms (eCRFs). All eCRFs and laboratory reports will be reviewed by the clinical team to ensure that they are accurate and complete.

The Principal Investigators may authorise trial staff members to sign the eCRFs to confirm accuracy of the data. At the completion of the follow-up visits, final sign-off must be performed by the Principal Investigators.

4.11.1. Data management

According to section 4.11.1. in the accompanying master protocol:

Data management activities will be conducted by CTCC (Clinical Trials Centre Cologne).

The IT infrastructure and data management staff will be provided by the CTCC. The trial database will be developed and validated before data entry based on standard operating procedures at the CTCC. The data management system is based on commercial trial software and stores the data in a database. All changes made to the data are documented in an audit trail. The trial software has a user and role concept that can be adjusted on a trial-specific basis. The database is integrated into a general IT infrastructure and safety concept with a firewall and backup system. The data are backed

up daily. After completion and cleaning of data, the database is locked and the data are exported for statistical analysis.

The data will be entered online at the trial sites via the Internet. Plausibility checks are run during data entry, thereby detecting many discrepancies immediately. The CTCC Data Management will conduct further checks for completeness and plausibility and will clarify any questions with the trial sites electronically via the trial software. These electronic queries have to be answered by the trial site without unreasonable delay. Further details will be specified in the data management manual. A guidance document and web-based training for data entry in the eCRF will be provided.

All participant data relating to the study will be recorded on electronic CRFs unless transmitted to the sponsor or designee electronically (e.g., laboratory data) via secure platform transfer or encrypted e-mail. The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the CRF.

4.11.2. Archiving

According to section 4.11.2. in the accompanying master protocol:

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 10 years after study completion unless local regulations or institutional policies require a longer retention period, this applies to both the investigator and sponsor part of the TMF. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

Digitisation of paper-based documentation must meet regulatory requirements, especially concerning quality assurance, completeness and correctness. Paper-based documentation must not be destroyed after digitisation and must be archived according to applicable regulations.

5. Ethical and regulatory aspects

5.1. Ethics committee

The clinical trial will not be started before favourable opinion of the competent ethics committee.

This study will be conducted in accordance with the protocol and with the following:

- Consensus on ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines.
- Applicable ICH Good Clinical Practice (GCP) guidelines dated July 1996 and its Addendum E6(R2) of June 2017.

5.2. Applicable laws and regulations and ethical considerations

The protocol, protocol amendments, ICF, SmPCs and other relevant documents (e.g., advertisements) must be submitted to a Research Ethics Committee (REC) and National Competent Authority (NCA) by the sponsor and reviewed and approved by the REC and NCA before the study is initiated. The present trial protocol and any amendments were and will be prepared in accordance with the principles of the Declaration of Helsinki.

Protocols and any substantial amendments to the protocol will require National Competent Authority (NCA) approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The sponsor will be responsible for the following:

- Providing written summaries of the status of the study to the REC/NCA annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
- Notifying the REC/NCA of SAEs or other significant safety findings as required by REC/NCA procedures.

Providing oversight of the conduct of the study at the sites and adherence to requirements of ICH guidelines, the REC/NCA, European Directive 2001/20/EC and European Regulation 536/2014 for clinical trials on medicinal products, and all other applicable local regulations.

5.3. Legislation and guidelines

The present clinical trial will be conducted in accordance with the principles of the guidelines for Good Clinical Practice (ICH-GCP) and applicable legislation. All principal investigators and other staff involved in the trial will be informed that local and national competent authorities as well as competent authorities from foreign countries and authorised representatives of the sponsor have the right to review trial documentation and the trials subject´s medical records at any time under confidentiality (see also section 4.10.2).

5.4. Notification of the authorities, approval and registration

According to section 5.4. in the accompanying master protocol:

Before the start of the clinical trial, all necessary documentation will be submitted to the responsible national competent authority for approval. Local authorities will be notified according to applicable regulations.

Before the trial is started, it will be registered under a register approved by the World Health Organisation (WHO) (http://www.who.int/ictrp/en/).

In addition, trials conducted at the University Hospital and the University of Cologne have to be registered at “Site Management System” (https://clinicalsite.org/).

5.5. Obtaining informed consent from trial subjects

The investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant in a comprehensible language and answer all questions regarding the study. This includes consent to data access by representatives of the sponsors (e.g., monitors, auditors) and by the competent authorities.

Participants must be informed that their participation is voluntary. Participants will be required to give a statement of informed consent that meets the requirements of local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and those of the ethics committee. Trial subjects will be informed that withdrawal of consent is possible at any time without giving reasons and without jeopardising the subject´s well-being. Subjects must not be enrolled into the trial unless they have given their informed consent in writing to participate in the study.

The medical record must include a statement that written informed consent was obtained, before the participant was enrolled in the study, and the date on which the consent was obtained. The authorised person (investigator or sub-investigator) obtaining the informed consent must also sign the ICF.

Participants must be reconsented to the most current version of the ICF(s) during their participation in the study if relevant. A copy of the ICF(s) must be provided to the participant.

The ICF will contain a separate section that addresses the secondary use of data and of remaining samples for optional exploratory research.

The investigator or authorised designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. The participant can opt to document their agreement to allow any data and remaining specimens to be used for secondary exploratory research. Participants who decline to participate in this optional research will not provide this separate signature.

5.6. Insurance of trial subjects

All trial subjects enrolled are insured in accordance with regulatory requirements. The insurer's name, contact details, and policy number will be provided in the participant’s information sheet.

5.7. Data protection

The provisions of data protection legislation will be observed. It is assured by the sponsor that all investigational materials and data will be pseudonymised in accordance with data protection legislation.

Trial subjects will be informed that their pseudonymised data will be handled in accordance with applicable law. Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred. Sponsor staff that require access to personal data will agree to keep confidentiality. Data relevant to fulfil the objectives of the study will be collected only.

The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent. The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor and by inspectors from regulatory authorities. Study participants have the right to request access to their personal data and the right to request rectification of incorrect or incomplete data.

Exploratory research data will not be returned to participants or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

Subjects who do not agree to data handling as described in the informed consent form will not be enrolled into the trial.

The sponsor of each sub-protocol is responsible for data protection. Contact details for the sponsor's data protection officer are described respectively in each sub-protocol and in the trial specific ICF. Data processing will be performed by the Clinical Trials Center Cologne at the University of Cologne (CTCC, Gleueler Str. 269, 50935 Cologne).

6. Statistical methods and sample size calculation (Part B)

Below, the statistical analyses are outlined for the present trial. More details will be provided in the statistical analysis plan (SAP), which will be finalised before the first interim analysis.

6.1. Statistical and analytical plan

6.1.1. Analysis populations

According to section 6.1.1 in the accompanying master protocol:

The primary dataset for analysis is derived from the intention-to-treat (ITT; Full Analysis Set, FAS) population. This dataset includes all trial subjects enrolled into the trial and randomised.

The evaluation is carried out strictly in accordance with the allocation by randomisation.

The secondary dataset for analysis is derived from the per-protocol (PP) population. This dataset includes all trial subjects who were treated according to protocol and reached a defined endpoint in the trial.

The tertiary dataset for analysis is the safety population. This population includes all trial subjects who received any IMP or other trial treatment.

Details about analysis population are specified in the respective section of the concerned sub-protocol.

Specific to this trial:

Primary Analysis Population

The primary analysis population is a modified intention-to-treat population (mITT), consisting of all randomised subjects whose primary endpoint measurement is available.

Safety Population

The population for the safety analysis will be all randomised subjects that received the study vaccine.

6.1.2. Description of trial subject groups

For Part B, all statistical analyses described below will be performed separately from Part A of the trial. A full Statistical Analysis Plan (SAP) will be finalised for Part A and Part B separately before any analysis is performed.

Subjects are randomised to one of the two intervention groups BNT162b2 (Comirnaty) and mRNA-1273 (Spikevax).

Patient demographics and baseline characteristics will be summarised on the modified ITT (mITT) set, overall and by treatment cohort and randomised treatment arms, by means of summary descriptive statistics.

For qualitative variables (e.g., gender (biological sex)), absolute and relative frequencies will be calculated per treatment group. Data will be visualised by bar plots. For quantitative data (e.g., age), the number of valid observations, mean, standard deviation, standard error, median, minimum and maximum will be calculated for each treatment group and each time point separately. Data will be visualised by waterfall, boxplots and histograms.

6.1.3. Primary analysis

All primary analyses will be on the mITT set. The primary endpoint is the rate π of 2-fold antibody titre increase following the 4th vaccine dose measured by quantitative enzyme-linked immunosorbent assay (Anti-RBD-ELISA) against wildtype virus at 14 days after the 4th vaccine dose (versus immediately before vaccination).

For the binary primary endpoint absolute and frequencies in percent will be calculated for each study part (Part A, Part B) and treatment group. For each study part and treatment group the corresponding rate together with simultaneous 95% confidence intervals will be calculated. Exact Clopper Pearson confidence intervals at Bonferroni adjusted level of (1-0.05/2) *100% will be provided.

In additional supportive analysis, the primary endpoint will be performed in the same way for each cohort separately, i.e., further exploratory analyses will be performed based on different pre-vaccination series. Especially, within each cohort the multiplicity adjustment will be implemented.

The data will be visualised with bar charts.

6.1.3.1. Analysis time point for primary endpoint

For the second Part B (4th vaccination, cohorts 4-9), the primary endpoint analysis will be triggered as soon as for all patients the primary endpoint data (14 days after study vaccination) has been captured.

Analysis time (planned): October 2022 (primary endpoint analysis).

6.1.4. Secondary analyses

The geometric mean titres (GMT) following and the 4th dose vaccination measured by quantitative enzyme-linked immunosorbent assay (Anti-RBD-ELISA) against wildtype virus at 14 days after the 4th dose will be compared between the boosters BNT162b2 and mRNA-1273 computing two-sided 95% confidence intervals for the GMR or differences of GMC on log scale (base 10). Based on the confidence intervals, an equivalence test will be performed. The equivalence margins are the 1.5 to 0.67-fold change between the GMT in the two boost arms corresponding to a margin for the differences of GMC on log scale (base 10) which results in a margin ±0.174. This is suggested in Section 2.3.1 of the EMA/117973/2021 Reflection paper on the regulatory requirements for vaccines intended to provide protection against variant strain(s) of SARS-CoV-2.[11] Because GMT are expected to have a skewed distribution, the log10 scaled GMT values will be compared using a linear model with factors booster (BNT162b2/mRNA-1273) as well as the stratification variables used in the randomisation. As this is a secondary analysis, no adjustment for multiplicity will be made. For Part B in further secondary analyses, it will be explored whether switching or keeping the same vaccination for the 4th vaccination (study intervention in B) compared to the 3rd vaccination will have an effect. In this model the interaction between cohort and study drug will be included as well.

6.1.5. Exploratory analyses

Different combinations of vaccines (1st, 2nd, 3rd and the on-study 4th vaccine dose) will be assessed for equivalence in terms of humoral and/or cellular immune response against VOC compared to approved homologous COVID-19 vaccination. The analysis strategy will be as described in 6.1.3 and 6.1.4. Furthermore, exploratory comparisons of the primary endpoint as well as the humoral and/or cellular immune response against VOC will be performed between cohorts as well as between the treatment groups within cohorts. As an option only in Part B, it is planned to run comparisons with the control group from EU-COVAT subprotocol with the EudraCT no.: 2021-004889-35. The control group of EU-COVAT subprotocol EudraCT no. 2021-004889-35 will be only utilised if the sample size

in the age group of interest is sufficiently large. Otherwise, the data of the control group will be reported only descriptively. These analyses will be performed similar to the analysis described in 6.1.4.

6.1.6. Multiplicity adjustment

The different pre-study vaccine combinations are considered as inferentially independent, as the prior vaccination strategy cannot be influenced and there will be no extrapolation from one cohort to another one for the primary analysis. Therefore, the multiplicity adjustment concerning the primary endpoint will be applied within each cohort, but there will be no further adjustment for having several cohorts within the accompanying master protocol.

6.1.7. Subgroup analyses

Subgroup analyses will be performed by gender and documented history of prior COVID-19 infection (yes/no), respectively.

6.1.8. Interim Analysis

An interim analysis will be performed as soon as 50% of participants have been recruited within Part B. In the interim analysis, Haybittle–Peto boundaries of 0.0001 will be used to calculate the confidence intervals for the primary analysis in each cohort. There will be no stopping because of differences in the primary endpoint analysis at interim analysis.

If a treatment arm is dropped due to safety concerns, a sample size re-allocation to the remaining arms might be considered. However, in this case the overall sample is still fixed as initially planned, i.e., the total sample size over all cohorts in Part B is bounded by 550 patients in total.

The interim analysis will allow for a sample size reassessment in the interim analysis, e.g., to re-estimate the standard deviation. If a sample size reassessment is performed, the conditional error principle is implemented to control the FWER for the primary endpoint.

Note: In case enrolment is impacted by the dynamics of the pandemic and/or by public vaccination policies, the interim analysis may be omitted.

6.2. Safety Analysis

Summaries and analysis of safety data will be presented for the Safety Analysis Population.

An adverse event (AE) is any untoward medical occurrence in a trial subject administered an IMP. There does not necessarily have to be a causal relationship with this treatment. The adverse event may be, but is not restricted to: a new illness, worsening of a sign or symptom following trial-specific treatment (here 4th vaccination dose), the clinically significant abnormal results of an examination (e.g., laboratory findings, electrocardiogram) or deterioration of a pre-existing medical condition, or a combination of two or more of these factors, as applicable.

AEs will be documented starting from baseline visit and until the last scheduled visit after the 4th vaccine dose unless otherwise defined in the sub-protocol specific visit schedule.

The safety endpoints includes

- Unsolicited AEs until the end of trial.
- Solicited AEs for 7 days after a 4th vaccination dose.
- Rate of serious adverse events (SAEs) Grade ≥3 according to the National Cancer Institute Common Toxicity Criteria up to three months after a 4th vaccination dose.

Listing will be provided on a subject level reporting the severity and relationship to study vaccination (related / unrelated). Absolute and numbers in percent will be given per intervention group. Different types of AEs will be grouped. Additionally, the safety data will be reported descriptively for each intervention and cohort separately.

6.3. Sample size calculation

The number needed has been calculated at 550 for Part B (i.e., 600 overall for Part A and B, and including a potential dropout rate of 8-10% for Part B).

Sample size calculation with multiplicity adjustment:

Sample size calculation has been carried out for the primary endpoint for the rate π of 2-fold antibody titre increase following 4th dose vaccination. As two-sided simultaneous 95% confidence intervals for this rate should be calculated separately for each randomized group in Part B a Bonferroni adjustment was used in the sample size calculation accordingly.

When the sample size is 250 per randomized group, two-sided simultaneous 95% confidence intervals (with Bonferroni adjustment for 2 simultaneous confidence intervals in a cohort) for a proportion using the large sample normal approximation will extend no more than ±7.1% (percentage points) from the observed proportion. E.g., if the observed proportion is 50% (where the confidence interval is widest), the confidence interval ranges from about 42.9% to 57.1%.

To adjust for potential dropouts in Part B of about 8-10%, the total sample size for Part B (=4th vaccination and Cohorts 4-9) was set to 550.

In the table below the precision for the simultaneous two-sided 95%-confidence intervals (with the same assumptions as described above) is shown for varying sample sizes. This shows which precision could be achieved in the different cohorts based on the previous vaccination strategy (see also inclusion criteria for Part B).

Sample Size, n	250	200	150	125	90	50	40
Expected Proportion, π	0.500	0.500	0.500	0.500	0.5	0.500	0,5
Distance from Proportion to Limit, ω	0.071	0.079	0.092	0.100	0.118	0.158	0.177

Software program(s):

All statistical analyses will be conducted with statistical software like SAS 9.4. (or higher) and R 3.6.3. (or higher).

7. Safety

7.1. Definitions of adverse events and adverse drug reactions

7.1.1. Adverse event

According to section 7.1.1. in the accompanying master protocol:

An adverse event (AE) is any untoward medical occurrence in a trial subject administered an IMP. There does not necessarily have to be a causal relationship with this treatment. The adverse event may be, but is not restricted to: a new illness, worsening of a sign or symptom following trial-specific treatment (here 4th vaccination dose), the clinically significant abnormal results of an examination (e.g., laboratory findings, electrocardiogram) or deterioration of a pre-existing medical condition, or a combination of two or more of these factors, as applicable.

AEs will be documented starting from baseline visit and until the last scheduled visit after the 4th vaccine dose unless otherwise defined in the sub-protocol specific visit schedule.

7.1.1.1. Pregnancy

Since in this trial only adults ≥75 years of age are enrolled, pregnancies are excluded as female participants are considered post-menopausal.

7.1.2. Adverse drug reaction

According to section 7.1.2. in the accompanying master protocol:

All adverse events judged by either the investigator or the sponsor as having a reasonable suspected causal relationship to an investigational medicinal product qualify as adverse drug reactions (ADR).

7.1.3. Serious adverse events and serious adverse reactions

According to section 7.1.3. in the accompanying master protocol:

A serious AE (SAE) or serious ADR (SAR) is any untoward medical occurrence that at any dose:

1. Results in death;
2. Is life-threatening at the time of the event;
3. Requires inpatient hospitalisation or prolongation of existing hospitalisation;

4. Results in persistent or significant disability/incapacity;
5. Is a congenital anomaly or birth defect;
6. Is any other medical important event in the opinion of the investigator.

Additionally, those adverse events Grade ≥3 which are assessed as related to IMP by the investigator, will be reported as SAE by indicating "other medical important event" as seriousness criterion on the SAE report form and eCRF, if no other seriousness criteria apply.

Inpatient hospitalisation is defined as any stay in hospital that includes at least one night (midnight to 06:00). Admission to hospital as an inpatient planned before the first admission of the IMP is not considered as SAE but must be documented in a proper manner in the trial subject's medical records and CRF (see Section 7.1.1).

EXCEPTIONS: the following events are not considered as SAE requiring immediate reporting to the sponsor:

- The participant is formally admitted to a hospital for medical reasons with no seriousness criterion and does not require overnight hospitalisation.
- Elective or previously scheduled surgery or medical treatment; hospitalisation for social or administrative reasons.
- Pre-existing diseases or present conditions detected prior to start of study drug administration and which do not worsen.

7.1.4. Unexpected adverse drug reaction

According to section 7.1.4. in the accompanying master protocol:

An unexpected ADR is an ADR of which the nature or severity, outcome or frequency is not consistent with the applicable product information available for the IMP. ADRs listed in the Investigator's Brochure or Summary of Product Characteristics (SmPC, Information Sheet for Health Professionals) are not regarded as unexpected.

7.1.5. Suspected unexpected serious adverse reactions

According to section 7.1.5. in the accompanying master protocol:

A suspected unexpected serious adverse reaction (SUSAR) is an adverse event the nature or severity of which is not consistent with the product information available for the IMP (e.g., SmPC), is regarded as serious, and has at least a possible causal relationship with the IMP.

7.1.6. Adverse events of special interest

According to section 7.1.6. in the accompanying master protocol:

An adverse event of special interest (AESI) is an adverse event that may not be serious but has special meaning or importance for the clinical trial. AESI will be recorded if considered described specifically in a sub-protocol under the master protocol.

Specific to this trial:

No AESI are considered in this trial, besides solicited adverse events.

7.1.7. Solicited Adverse Events

According to section 7.1.7. in the accompanying master protocol:

Solicited adverse events are a list of events/symptoms that participants are specifically asked to record. Injectable drugs (i.e., vaccines) are associated with a number of well-characterised reactions referred to as 'solicited adverse events', including local and systemic manifestations. Solicited adverse events will be collected by the participants in an (electronic or paper-based) diary.

Table 1: Solicited Adverse Events

TYPE	EVENT
Local AEs (injection or infusion site)	Injection site redness Injection site swelling Injections site pruritus Injection site urticaria Injection site pain

Systemic Clinical AEs following injections / infusions	Chills, hyperhidrosis, night sweats, pyrexia Asthenia, malaise, fatigue Myalgia, Arthralgia Pain in vaccinated extremity Paraesthesia, hypoaesthesia Extensive swelling of vaccinated limb, facial swelling Generalized rash Nausea, vomiting, diarrhoea, abdominal pain Generalized pruritus Headache Dizziness Insomnia Decreased appetite

Intensity of solicited AEs will be graded by the trial participant as mild, moderate and severe according to CTCAE grading 1 to 3. When a solicited AE is reported by the participant in the diary, then the subject will contact the investigator as per instructions.

7.2. Documentation and follow-up of adverse events

According to section 7.2. in the accompanying master protocol:

The sponsor ensures that all persons involved in the treatment of trial subjects are adequately informed of the responsibilities and actions required when AEs occur. Trial subjects will be asked at each visit whether they have experienced AEs or SAEs. AEs will be documented in the trial subject's medical records and in the eCRF.

For the procedure of SAE-reporting see section 7.2.2. and section 4.8.1.5 for safety data.

7.2.1. Documentation of adverse events and adverse drug reactions

According to section 7.2.1. in the accompanying master protocol:

All AEs will be documented in the eCRF including all information listed below.

AEs occurring within the following time frame will be documented:

- between baseline visit and the last visit of the individual subject.

The AE is documented in the eCRF including the following information:

- AE verbatim;
- Date and time of onset and resolution;
- Severity;
- Causal relationship with IMP/study treatment;
- Seriousness;
- Action taken;
- Outcome.

If a causal relationship between the AE and the IMP is suspected, trial subjects who develop adverse events must be monitored until all symptoms have been subsided, pathological laboratory values have returned to pre-event levels, a plausible explanation is found for the AE, the trial subject has died, or the study has been terminated for the trial subject concerned, as applicable. AEs are followed up for up to 30 days after last visit of the trial subject, if applicable.

7.2.1.1. Exceptions from AE documentation

According to section 7.2.1.1. in the accompanying master protocol:

Pre-existing diseases (before administration of the IMP) are not documented as adverse events but as concomitant diseases. New diseases and pre-existing diseases that worsen during the trial are documented as AEs.

7.2.2. Severity of the adverse event

According to section 7.2.2. in the accompanying master protocol:

The CTCAE (Common Terminology Criteria for Adverse Events) grading table (v5.0) will be used by trial investigators to classify adverse events. It comprises the following categories:

- Grade 1: Mild.
  Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2: Moderate.
  Minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living* (ADL).
- Grade 3: Severe or medically significant but not immediately life-threatening.

Hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.

- Grade 4: Life-threatening consequences.
  Urgent intervention indicated.
- Grade 5: Death related to AE.
  (Apart from grading methods each death is to be assessed as grade 5).

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money etc.

**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

7.2.3. Causal relationship between adverse event and investigational medicinal product

According to section 7.2.3 in the accompanying master protocol:

The investigator will assess therefore every AE whether a causal relationship with the IMP and/or study procedure can be assumed or not. The assessment includes consideration of the nature and type of reaction, the temporal relationship with the IMP, the clinical status of the trial subject, concomitant medication and other relevant clinical factors. If the event is considered as a symptom or sign of an underlying disorder, no causal relationship will be assumed.

Every AE will be assessed (eCRF/SAE-Report) according to the causality determinations of CIOMS VI-Group (Council for International Organizations of Medical Sciences) as follows:

- Related: There is a reasonable possibility that the AE may be related to the IMP.
- Not related: There is not a reasonable possibility that the AE may be related to the IMP.

A report on an event which cannot be judged because information is insufficient or contradictory or has not been judged will be regarded as related.

Specific to this trial:

The investigator will assess therefore every AE whether a causal relationship with the following IMPs and/or study procedure can be assumed or not.

IMP:

- BTN162b2 (Comirnaty).
- mRNA-1273 (Spikevax).

Vaccines can be modified in composition to address emerging VOCs.

Please follow the below clarifications from the master protocol for the assessment of relatedness.

7.2.3.1. Related

- A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.
- A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfil this definition.
- A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
- A clinical event, including laboratory test abnormality, reported as an adverse reaction, about which more data is essential for a proper assessment or the additional data are under examination.
- A report suggesting an adverse reaction which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified.

7.2.3.2. Unrelated

- A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.

7.3. Reporting of serious adverse events, adverse events of special interest, pregnancy and changes in risk-benefit assessment

According to section 7.3. in the accompanying master protocol:

Every SAE that occurs from the time of IMP administration until up to the last visit, also as specified in the respective sub-protocol, must be documented in the appropriate part of the CRF and reported on an SAE form to the sponsor.

Instructions in case of pregnancy do not apply in this trial since female participants eligible for this trial are post-menopausal.

7.3.1. Reports from the investigator to the sponsor

According to section 7.3.1 in the accompanying master protocol:

The investigator will inform the sponsor of the occurrence or receipt of knowledge of the occurrence of an SAE without delay, at the latest within 24 hours of being made aware of the event.

The study specific SAE report forms must be completed and submitted by fax or e-mail to the Clinical Trials Center Cologne (CTCC, ZKS Köln) to which the sponsor has delegated the SAE management procedures:

SAE Dedicated Fax: +49 221 478 7984

SAE Reporting E-Mail: ZKS-Safety@uk-koeln.de

In the interest of participants' safety, follow-up for up to 30 days after the individual participant's study termination (individual study termination is defined as last visit) is required for SAEs that are not sufficiently resolved at the participant's final trial visit, if applicable.

7.3.2. Assessment of SAEs by the sponsor

According to section 7.3.2. in the accompanying master protocol:

All cases of suspected SAEs are assessed by the sponsor with regard to seriousness (see Section 7.1.3), causality (see Section 7.2.3) and expectedness (see Section 7.1.4), regardless of the investigator's assessments.

7.3.3. Unblinding for SUSAR when treatment is blinded

In contrast to section 7.3.3. in the accompanying master protocol, no blinding is foreseen in this trial. Therefore, unblinding processes do not apply.

7.3.4. Notification of ethics committee and competent authority

According to section 7.3.4. in the accompanying master protocol:

Every SUSAR that becomes known in a clinical trial will be reported by the sponsor to the competent authority and the ethics committee.

All reporting requirements are regulated in the appropriate document (manual or SOP).

Further, according to the corresponding section in the accompanying master protocol.

7.3.4.1. Fatal and life-threatening SUSARs

The competent authority and the responsible ethics committee must be informed by the sponsor of all fatal or life-threatening SUSARs. This must be done without delay, at the latest 7 calendar days after becoming aware of the minimum criteria for reporting. In all cases, attempts will be made to obtain further relevant information which will be supplied to the competent authority and the ethics committee within a further 8 days.

7.3.4.2. SUSARs that are not fatal or life-threatening

The competent authority and the responsible ethics committee will be informed without delay by the sponsor of all SUSARs, at the latest within 15 calendar days of becoming aware of the minimum criteria for reporting. Further relevant details will be passed on as soon as possible.

If the information at the time of reporting is incomplete, further information to enable adequate assessment of the case will be requested from the reporter or other available sources.

7.3.5. Review and reporting of changes in the risk-benefit ratio

According to section 7.3.5. in the accompanying master protocol:

The sponsor will inform the competent authority, the responsible ethics committee and the competent authorities of all other member states of the EU or EEA where the trial is being conducted, of any events or factors that mean that the risk-benefit ratio of the IMP has to be reviewed. This will be done without delay, at the latest within 15 days. This includes, but is not restricted to:

- Individual reports of expected SARs with an unexpected outcome;
- A clinically relevant increase in the rate of occurrence of expected SARs;

- SUSARs in trial subjects who have already completed the follow-up period of the clinical trial (”end-of-trial visit”);
- Events in connection with the conduct of the study or the development of the investigational medicinal product which may affect the safety of the trial subjects.

7.3.6. Informing the Data Monitoring Committee

According to section 7.3.6. in the accompanying master protocol:

The DMC will be informed of all safety-relevant events by the sponsor.

An independent data monitoring committee (DMC) consisting of independent scientists not otherwise involved in the trial will be appointed and will review the data regularly during the study for safety and scientific integrity and will make recommendations to the sponsor regarding the stopping of an intervention for harm or for futility. The frequency of the committee data review meetings and other aspects such as stopping rules will be detailed in a separate charter. There will only be one DMC overseeing all trial arms, and this committee will communicate with the DMCs of other corresponding platform trials to exchange information. The level of monitoring will depend on the safety profile of the intervention.

7.3.7. Informing the investigators

According to section 7.3.7. in the accompanying master protocol:

The sponsor will inform investigators of all SUSARs including all relevant further information within the periods set by the competent authority.

The sponsor will inform all investigators on any change of information concerning the scientific documents of the trial (SmPC, Investigator’s Brochure, risk-benefit-ratio).

7.3.8. Informing the marketing authorisation holder

According to section 7.3.8. in the accompanying master protocol:

The sponsor will also inform the marketing authorisation holder about all SUSARs including information reported to the competent authority and ethics committee in accordance with contractual agreements, if applicable.

Specific to this trial: not applicable.

7.4. Annual safety report (DSUR)

According to section 7.4. in the accompanying master protocol:

The sponsor will supply annually a report on the safety of trial subjects with all available relevant information concerning patient safety during the reference period to the competent authorities of all concerned member states of the EU or EEA. This report will also be supplied to the responsible ethics committee.

The annual safety report will be compiled according to the corresponding ICH guideline E2F „Development Safety Update Report – DSUR“.

The sponsor will supply the report within 60 days after the reference date (data-lock point) defined as one year from the first authorisation to conduct the clinical trial by the sponsor (the “Development International Birth Date” (DIBD) of the study drug. The start of the annual period for the DSUR is the month and date of the DIBD. The data lock point of the DSUR should be the last day of the one-year reporting period.

8. Trial results and publication

8.1. Reports

8.1.1. Interim reports

Section 7.4 describes the requirements for annual reports on the safety of trial subjects. Interim reports about the clinical trial progress will be provided upon requirements of the public funder of this trial.

8.1.2. Final report

According to section 8.1.2. in the accompanying master protocol:

The competent authority and ethics committee will be informed within 90 days after the end of the trial.

Within one year after the end of the trial, the competent authority and the ethics committee will be supplied with the full final study report (competent authority) or the summary of the final study report (ethics committee).

8.2. Publication

According to section 8.2. in the accompanying master protocol:

Trials under the master protocol will be registered in a public register, in which trial results will be posted. The results of this study will be published in a suitable publication irrespective of findings. Results will also be presented at scientific meetings.

The sponsor will comply with the requirements for publication of trials results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicentre studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship for each will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Conflicts of interests will be disclosed. The contribution of e.g., CTCC, ECRIN, national partners and others will be fairly described in the acknowledgement section or as co-author, depending on the contribution in the trial design, planning and publication.

In line with the EU data sharing policy, individual patient-level data will be shared with the scientific community (either as anonymised or pseudonymised data sets), while maintaining the integrity and privacy of the trial participants and in compliance with the EU General Data Protection Regulation and national or local rules.

Data and other trial documents should be made available through an appropriate data repository, helping to ensure that the data objects are properly prepared, are available in the longer term, are stored securely and are subject to rigorous governance. It is planned to use the COVID-19 repository for individual participant data from clinical trials developed within the EU-project EOSC-Life. The terms and conditions of data transfers to a repository and the data sharing process shall be subject to specific data processing agreements to be established between the concerned parties as well as to a specific data sharing plan, where the details are specified.

9. Amendments to the trial protocol

According to section 9. of the accompanying master protocol:

Changes to the master trial protocol and/or sub-protocols under the master protocol may only be implemented if agreed by the sponsor, sponsor's representative, the PCI and statistician. Any changes to the trial procedures must be made in writing and must be documented with reasons and signed by the sponsor's representative (i.e., the PCI) and the statistician.

Significant changes will be implemented after approval by the competent authority and favourable opinion of the ethics committee, only. Exceptions to this are amendments made to avoid immediate dangers.

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