Clinical Study Report

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)

EudraCT No.: 2021-004526-29

ClinicalTrials.gov: NCT05160766

Protocol No.: uni-koeln-4602

Sponsor	*University of Cologne, Germany*
Indication studied	*3rd COVID-19 vaccination (Part A)*
	4th COVID-19 vaccination (Part B)
Name of test drug/investigational product	*BNT162b2 and mRNA-1273*
Developmental phase of study	*Phase 2*
Date of first subject enrolled (Part A)	*08 November 2021*
Date of first subject enrolled (Part B)	*16 February 2022*
Date of premature recruitment termination	*06 December 2022*
Date of last subject completed (Part A)	*03 January 2023*
Date of last subject completed (Part B)	*13 September 2023*
End of study	*30 November 2023*
Date of report	*12 August 2024*
Sponsor signatory and Principal Coordinating Investigator	*Prof. Dr. med. Oliver A. Cornely* *University Hospital Cologne, Germany* *Phone: +49 (0) 221 478 85523* *Fax: +49 (0) 221 478 1421445*

Due to the extensive roll-out of COVID-19 booster campaigns throughout Europe and poor recruitment rate as a consequence, Part A of the trial (3rd COVID-19 vaccination) was closed to further enrolment as of 13 January 2022. Part B of the trial (4th COVID-19 vaccination) was introduced as of 21 January 2022.

This study was performed in compliance with ICH Good Clinical Practice (GCP) including the archiving of essential documents.

2 SYNOPSIS

Name of Sponsor: University of Cologne

Name of Finished Drug: Comirnaty®; Spikevax®

Name of Active Ingredients: Tozinameran (BNT162b2); elasomeran (mRNA-1273)

Title of Study: 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)

Phase of Development: Phase 2

Study Centres: One clinical site in Germany (Part A); 11 clinical sites in Germany, Ireland, Lithuania, Norway and Spain (Part B)

Number of subjects: 323 subjects were randomised (Part A: n=53; Part B: n=270), of which 160 received BNT162b2 (Part A: n=25; Part B: n=135) and 162 received mRNA-1273 (Part A: n=27; Part B: n=135).

Principal Coordinating Investigator: Prof. Dr. med. Oliver A. Cornely, University Hospital Cologne, Germany

Study Period:

Part A:	Part B:
First subject enrolled: 08 November 2021	First subject enrolled: 16 February 2022
Last subject completed: 03 January 2023	Last subject completed: 13 September 2023

Medical condition to be investigated: Prevention of COVID-19 infection.

Objectives:

	Part A	Part B
Primary objective	CTP V03_0 and V04_0: • To assess the immunogenicity response of elderly adults (≥75 years) to different mRNA-based vaccines as 3rd vaccination dose	CTP V05_0: • To compare the reactogenicity between treatment arms after a 4th vaccination dose against SARS-CoV-2 CTP V06_0: • To compare the immune response between treatment arms after a 4th vaccination dose against SARS-CoV-2.
Safety objective	CTP V03_0 and V04_0: • To assess the safety of different booster strategies in elderly individuals (≥ 75 years) fully vaccinated against SARS-CoV-2.	CTP V05_0 and V06_0: • To assess the safety of a 4th vaccination dose against SARS-CoV-2 in the study population.
Secondary objectives	CTP V03_0 and V04_0: • To determine whether the humoral immune response against wild-type SARS-CoV-2 following heterologous 3rd vaccination dose is equivalent to a homologous 3rd dose in elderly individuals (≥75 years) already vaccinated against SARS-CoV-2. • To compare the humoral immune response against wild-type SARS-CoV-2 between treatment arms within each cohort following 3rd vaccination dose in elderly	CTP V05_0: • To compare the immunogenicity against wild-type SARS-CoV-2 between treatment arms after a 4th vaccination dose against SARS-CoV-2. • To evaluate descriptively the immunogenicity against SARS-CoV-2 VOCs between treatment arms after a 4th vaccination dose against SARS-CoV-2.

	individuals (≥75 years) already vaccinated against SARS-CoV-2. • To compare the humoral immune response against wild-type SARS-CoV-2 between cohorts following 3rd vaccination dose in elderly individuals (≥75 years) already vaccinated against SARS-CoV-2. • To evaluate immune response against SARS-CoV-2 variants of concern (VOCs) of different booster strategies in elderly individuals (≥75 years) already fully vaccinated against SARS-CoV-2. • To assess the CD4+ and CD8+ T cell response of different booster strategies in elderly individuals (≥75 years) already vaccinated against SARS-CoV-2. • To evaluate the long-term humoral immune response of different booster strategies in individuals already fully vaccinated against SARS-CoV-2.	• To evaluate descriptively the long-term humoral immune response (reactogenicity and immunogenicity) of a 4th vaccination dose against SARS-CoV-2. CTP V06_0: • 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 VOCs 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.
Exploratory objective	CTP V03_0 and V04_0: • To assess the immune function in elderly individuals	CTP V05_0 and V06_0: • To investigate the cellular immune response after a 4th vaccination dose, virus neutralizing activity against newly emerging variants in bio-banked samples and correlates of interest.

Rationale:
Recent data suggested that immunisation with any of the currently approved vaccines may not provide long-term or life-long protection. Therefore, additional follow-up vaccination (booster) doses could be indicated after full vaccination, especially in subjects of advanced age. This population has a reduced adaptive immune response and therefore may need shorter intervals between booster doses to be protected against severe SARS-CoV-2 infection. At the time of the start of the trial conduct, there were no data on the optimal timing of booster doses in subjects of advanced age after a full vaccination schedule. Also, no evidence existed on the immune response using heterologous strategies for boosting. Therefore, this trial aimed to assess the impact of different mRNA-based vaccines as 3rd and 4th vaccination dose in individuals ≥75 years. This should provide useful information for vaccination programs in Europe (and elsewhere) for this high-risk population.

Methodology:
This was a randomised controlled, adaptive, multicentre Phase 2 protocol evaluating different booster strategies in individuals ≥75 years already vaccinated against SARS-CoV-2 for comparative assessment of their immunogenicity and safety against SARS-CoV-2 wild-type and variants.

In this trial, a 3rd vaccination (Part A) with either BNT162b2 or mRNA-1273 was tested in subjects having a prior vaccination regimen of homologous BNT162b2, mRNA-1273 or ChAdOx-1-S (AstraZeneca). Due to a diminishing population for recruitment due to a recommendation for a 3rd vaccination by national vaccination programs, the trial intervention was changed in January 2022 to a 4th vaccination with either BNT162b2 or mRNA-1273, referred to as Part B. IMP allocation ratio was 1:1.

Criteria for Selection

Inclusion Criteria – subjects were eligible for the study if they met all of the following criteria:	
Part A (CTP V03_0 and V04_0): • Already fully vaccinated adults with BioNTech, Moderna or Astra Zeneca vaccines (same vaccine product for 1st and 2nd dose)	Part B (CTP V05_0 and V06_0): • 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):

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9 ± 3 months since the second vaccine dose at time of enrolment for the planned 3rd vaccine dose in the trial. Vaccination status should be documented in the source data and captured in the electronic case report form (eCRF).
Elderly (≥75 years old).
Genders (female, male)
No contra-indication against any of the vaccine products in the trial.
Written informed consent from subject has been obtained.

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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 listed vaccinations must have been administered at least 1 month prior to study entry. Vaccination status should have been documented in the source data and was captured in the eCRF.
No contra-indication against any of the vaccine products in the trial.
Written informed consent from subject has been obtained.

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<td colspan="2">Exclusion Criteria – subjects meeting any of the following criteria were excluded from the study:</td>
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<u>Part A (CTP V03_0 and V04_0):</u>

Primary vaccination performed with different vaccine products as sole (e.g., COVID-19 Vaccine Janssen) or, 1st and 2nd vaccination doses (heterologous vaccination scheme).
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.
Participation in other interventional trials.
Subjects unable to report solicited adverse events (AE).
Subject with any contraindications to the vaccines in the trial at randomisation. 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.
Any current SARS-CoV-2 infection or proven in the preceding 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.

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<u>Part B (CTP V05_0 and V06_0):</u>

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 AEs.
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 SmPC, 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.

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Test Drug, Dose and Mode of Administration, Batch Number: Subjects randomised to BNT162b2 received 30µg tozinameran (Anatomical Therapeutic Chemical (ATC) code J07BX; 0.3 mL after dilution) (Part A: Intervention arms 1, 3, 5; Part B: Intervention arms 7, 9, 11, 13, 15, 17) as single dose. Subjects randomised to mRNA-1273 received 100µg elasomeran (ATC code J07BX03; 0.5 mL after dilution) (Part A: Intervention arms 2, 4, 6; Part B: Intervention arms 8, 10, 12, 14, 16, 18) as single dose. Both IMPs are vaccines for administration via intramuscular injection. IMPs were obtained from local pharmacies from national vaccination programmes, thus no study-specific batch numbers were used.

Duration of Treatment: Subjects were administered a single shot if the randomized IMP at Day 0, followed by four follow-up visits (incl. immune response evaluation) until 12 months after study vaccination.

Criteria for Evaluation:

Primary endpoint:

Part A (CTP V03_0 and V04_0):	Part B (CTP V05_0 and V06_0):
• Rate of 2-fold antibody titre increase following 3rd dose vaccination measured by quantitative enzyme-linked immunosorbent assay (Anti-RBD-ELISA) against wild-type virus 14 days after 3rd dose.	• 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.

Safety endpoints:

Part A (CTP V03_0 and V04_0):	Part B (CTP V05_0 and V06_0):
• Unsolicited AEs until the end of trial. • Solicited AEs for 7 days after 3rd dose. • Rate of serious adverse events (SAEs) Grade ≥3 according to the National Cancer Institute Common Toxicity Criteria up to three months after 3rd dose.	• Unsolicited AEs until the end of trial. • Solicited AEs for 7 days after a 4th vaccination dose. • Rate of SAEs Grade ≥3 according to the National Cancer Institute Common Toxicity Criteria up to three months after a 4th vaccination dose.

Secondary endpoints:

Part A (CTP V03_0 and V04_0):	Part B (CTP V05_0 and V06_0):
• Antibody titre increase following 3rd dose measured by neutralising activity against wild-type virus (Virus Neutralisation Assay) in a subgroup 14 days after 3rd dose. • Change in neutralising capacity measured by neutralising activity against VOCs (Virus Neutralisation Assay) in a subgroup 14 days after 3rd dose. • Antibody titre level following 3rd dose measured by a quantitative enzyme-linked immunosorbent assay (anti-RBD-ELISA assay) 12 months after 3rd dose. • Antibody titre level following 3rd dose measured by neutralising activity against wild-type virus (Virus Neutralisation Assay) in a subgroup 12 months after 3rd dose. • Change in neutralising capacity 12 months after 3rd dose measured by neutralising activity against VOCs (Virus Neutralisation Assay) in a subgroup of subjects.	• 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 VOCs 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; CTP V06_0: […] to be determined in a subgroup only. • Neutralizing antibody titre (Virus Neutralisation Assay) against VOCs at 12 months after a 4th vaccination dose; CTP V06_0: […] to be determined in a subgroup only.

Exploratory endpoints:

Part A (CTP V03_0 and V04_0):	Part B (CTP V05_0 and V06_0):
• Change in cellular immune response measured by qPCR 14 days after 3rd dose in a subgroup analysis. • Neutralising capacity measured by neutralising activity against newly emerging variants in bio-banked samples in a subgroup analysis. • Correlates of humoral immune response, cellular immune responses and viral neutralising capacity against SARS-CoV-2 VOCs.	• 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 VOCs; CTP V06_0: […] to be determined in a subgroup only.

Efficacy:

This trial did not evaluate efficacy of the IMPs. Primary endpoints consisted of immunogenicity parameters as listed above.

Primary endpoint:

Part A:	Part B:
In the BNT162b2 group, 25/25 (100%) (97.5%-CI: 83.9% - 100%) subjects and in the mRNA-1273 group, 25/25 (100%) (97.5%-CI: 83.9% - 100%) subjects, respectively, had a two-fold increase in anti-RBD IgG titres 14 day after the 3rd dose.	In the BNT162b2 group 102/130 (78.5%) [97.5% CI: 69.2% - 86%] subjects showed a two-fold increase in anti-RBD IgG titres at 14 days after 4th dose compared to 116/133 (87.2%) [97.5% CI: 79.3% - 93%] subjects in the mRNA-1273 group.

Secondary endpoints:

Part A:	Part B:
• Virus neutralisation capacity was lower for omicron variants compared to other variants 14 days after 3rd vaccination. • Virus neutralisation capacity was higher in the mRNA-1273 group with higher mean values compared to the BNT162b2 group and an overall higher virus neutralisation for wild-type, B.1.1.7 (alpha variant) and AY.4.2 (delta variant). • After 12 months of follow-up, the geometric mean titre (GMT) of anti-RBD IgG was 9,319.7 IU/mL (after 14 days 8,568.4 IU/mL) in the BNT162b2 group (n=21) and 14,163.8 IU/mL (day 14: 14,266.7 IU/mL) in the mRNA-127 group (n=21). • Virus neutralisation capacity 12 months after the 3rd mRNA vaccination was similar for Omicron variants, whereas the mRNA-1273 group showed markedly higher values for the Wuhan wild-type, B.1.1.7 (alpha), P.1 and P.2 (both gamma), B1.617 and B.1.617.1 (kappa) and AY.3 and AY.4.2 (both delta) and B.1.526.1 (iota).	• Virus neutralizing capacity 14 days after 2nd booster was lower for Omicron variants compared to other variants across both groups. • The mRNA-1273 group showed a consistent pattern of a higher SARS-CoV-2 antibody neutralisation capacity compared to the BNT162b2 group, especially against Wuhan wild-type, B.1.1.7 (alpha variant), and AY.4.2 (delta variant). • After 12 months of follow-up, the GMT of anti-RBD IgG was 9,962 IU/mL (after 14 days 15,248.2 IU/mL) in the BNT162b2 group and 12,024.3 IU/mL (day 14: 21325.6IU/mL) in the mRNA-127 group, respectively • Mean virus neutralisation capacity 12 months after 4th vaccination decreased in both groups for all tested variants including wild-type while the mRNA-1273 group presented with slightly higher mean neutralisation capacity values than the BNT162b2 group for all tested variants including wild-type.

Safety Evaluations: Safety was evaluated by the assessment of AEs, unsolicited AEs until the end of the trial, solicited AEs for 7 days after trial vaccination), SAE, serious adverse reactions (SAR), and suspected unexpected serious adverse reactions (SUSAR). Safety data was reviewed by the Data Monitoring Committee (DMC). In the course of the clinical trial, two DMC meetings took place. The DMC recommended to continue the study conduct while no safety concerns or study modification requests were reported.

The medical monitor reviewed safety information in a complete and timely fashion to identify trends that may be indicative of hazards associated with trial vaccination. No safety-related concerns were reported to the sponsor by the medical monitor.

Statistical Methods: For the primary endpoint (2-fold increase in antibody titre), the rates with corresponding multiplicity adjusted 95% confidence intervals (adjusted for treatment arms) were reported for each group randomized to BNT162B2 and mRNA-1273. The analyses were conducted separately for both, Part A and Part B.

Further supportive analyses have been performed including analysis within cohorts, Cochrane-Mantel-Haenszel tests, logistic regression models and GMT.

For secondary endpoints, linear models and also mixed model for repeated measurements have been applied.

Summary Conclusions:

Efficacy Results: The primary immunogenicity endpoint of a 2-fold anti-RBD-IgG antibody titre increase 14 days after 1st (Part A) or 2nd (Part B) booster vaccination, respectively was reached by 100% (97.5%-CI: 83.9% - 100%) of subjects in the BNT162b2 group, and 100% (97.5%-CI: 83.9% - 100%) of subjects in the mRNA-1273 group for Part A while for Part B the primary immunogenicity endpoint was reached by 78.5% (97.5%-CI: 69.2% - 86%) of subjects BNT162b2 group, compared to 87.2% (97.5%-CI: 79.3% - 93%) of subjects in the mRNA-1273 group. Efficacy endpoints regarding prevention of infection, hospitalization or death were not included in this study.

Safety Results: Reported AE and SAE in this trial did not change the overall benefit-risk assessment of BNT162B2 and mRNA-1273. No safety-related abnormalities in laboratory values were identified by the medical monitor. The DMC, had no safety concerns or study modification request, the number of SAEs were limited with regards to the advanced age of this population.

Others: Not applicable.

Conclusion: Summarizing primary endpoint analyses of Part A and Part B, both 3rd and 4th doses of either BNT162b2 or mRNA-1273 provided substantial circulating antibody increase 14 days after vaccination. Full-dose mRNA-1273 provided higher antibody levels with an overall similar safety profile for people ≥ 75 years.

Date of the Report: 12 August 2024