Clinical trial results:
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)

Summary

EudraCT number	2021-004526-29
Trial protocol	DE NO IE ES LT
Global end of trial date	30 November 2023
Results information	
Result version number	v1 (current)
This version publication date	14 December 2024
First version publication date	14 December 2024
Summary attachment (see zip file)	EU-COVAT-1_AGED (Neuhann et al_Trials 2022.pdf) EU-COVAT-1_AGED (Neuhann et al_Vaccine 2023.pdf) EU-COVAT-1_AGED (Kenny et al_Nature Comm 2023.pdf) EU-COVAT-1_AGED (Stemler et al_Int J Infect Dis 2024.pdf) EU-COVAT-1_AGED (CSR_Synopsis_V01_0.pdf)

Trial information

Trial identification	
Sponsor protocol code	uni-koeln-4602
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05160766
WHO universal trial number (UTN)	-

Notes:

Sponsors	
Sponsor organisation name	University of Cologne
Sponsor organisation address	Albertus-Magnus-Platz, Cologne, Germany, 50923
Public contact	Project Manager, University Hospital Cologne, +49 22147885523, eucovat-1-aged@vaccelerate.eu
Scientific contact	Sponsor Representative, University Hospital Cologne, +49 22147885523, oliver.cornely@uk-koeln.de

Notes:

Paediatric regulatory details	
Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 November 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 September 2023
Global end of trial reached?	Yes
Global end of trial date	30 November 2023
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To compare the immune response between treatment arms after a 3rd (Part A) or 4th (Part B) vaccination dose against SARS-CoV-2.

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. New COVID-19 vaccines targeting Omicron BA.1 and Omicron BA.4/BA.5 have been approved in September 2022 by the European Commission. Variant-adapted COVID-19 vaccines were rolled out in multiple countries as part of national booster campaigns. The EU-COVAT-1_AGED trial included BNT162b2 and mRNA-1273 as nonvariant adapated vaccines as IMP for booster vaccination. Recruitment was consequently prematurely terminated, thus all analyses should be considered as exploratory (pre-specified and post-hoc).

Protection of trial subjects:

Protection measures of the subjects are summarised in the following, subjects were healthy volunteers with regard to the condition against they were vaccinated:
a) An independent DMC was established to review efficacy and safety data, e.g. SAEs/SUSARs, and their impact on the benefit-risk assessment for the subjects. DMC gave recommendations on continuation, modification or early termination of the clinical trial considering particularly safety aspects, but also recruitment and potential superiority of specific treatment arms.
b) Continuous sponsor assessment of SAEs, assuring an ongoing evaluation and medical review of the SAEs and to evaluate SAEs regarding their seriousness, causality and expectedness.
c) An independent Medical Monitor was involved. Tasks of the Medical Monitor included periodic per subject and cumulative reviews of the accumulating safety data including a review of (S)AE, overdose and laboratory data (as applicable), medical review of specified clinical data to ensure completeness, consistency and medical sense, and review of medically related protocol deviations. The Medical Monitor war further involved in all correspondence addressed to the sponsor’s assessors in order to ensure a comprehensive medical surveillance by the Medical Monitor and immediate awareness of all SAEs including the SAE assessment and medical review information by the sponsor.
d) SAE tracking tables which documented all received and processed SAEs (initial and follow-up SAE reports) were transmitted to the sponsor assessors, the Medical Monitor and the DMC members by safety management on a monthly basis.

Background therapy:

Not applicable in a vaccination trial.

Evidence for comparator:

The present vaccination trial is a head-to-head comparison of two anti SARS-CoV-2 vaccines which had received marketing authorisation during the COVID-19 pandemic. There was no control arm without vaccination.

Actual start date of recruitment	02 November 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Norway: 50
Country: Number of subjects enrolled	Spain: 87
Country: Number of subjects enrolled	Germany: 132
Country: Number of subjects enrolled	Lithuania: 1
Worldwide total number of subjects	270
EEA total number of subjects	270

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	206
85 years and over	64

Subject disposition

Recruitment

Recruitment details:

Part A (3rd vaccination): n=53. First subject enrolled: 08 Nov 2021; last subject completed: 03 Jan 2023. One active trial site.
Part B (4th vaccination): n=270. First subject enrolled: 16 Feb 2022; last subject completed: 13 Sep 2023. 9 active trial sites (4 countries).

This report exclusively covers Part B. Part A results can be requested.

Pre-assignment

Screening details:

Not applicable in this trial.

Period 1

Period 1 title	Overall trial (Part B) (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	BNT162b2

Arm description:

BNT162b2 (Comirnaty®) was administered as 2nd COVID-19 booster dose (4th vaccination in total). It contains 30 µg of tozinameran (0.3 mL after dilution) as approved for individuals ≥12 years by the European Commission.

Arm type	Active comparator
Investigational medicinal product name	BNT162b2
Investigational medicinal product code	J07BX
Other name	Comirnaty®
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Dosage: 30 µg (0.3 mL after dilution)
Administration details: Intramuscular injection

Arm title	mRNA-1273

Arm description:

mRNA-1273 (Spikevax®) was administered as 2nd COVID-19 booster dose (4th vaccination in total). It contains 100 µg (0.5 mL after dilution).

Arm type	Active comparator
Investigational medicinal product name	mRNA-1273
Investigational medicinal product code	J07BX03
Other name	Spikevax®
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Dosage: 100 µg (0.5 mL after dilution)
Administration details: Intramuscular injection

Number of subjects in period 1	BNT162b2	mRNA-1273
Started	135	135
Completed	126	123
Not completed	9	12
Adverse event, serious fatal	2	5
Consent withdrawn by subject	3	2
Physician decision	-	1
Not showing up or showing up on the wrong date	1	1
Subject's decision	1	-
Lost to follow-up	1	2
Too time-consuming	-	1
Protocol deviation	1	-

Baseline characteristics

Reporting groups	
Reporting group title	BNT162b2
Reporting group description:	
BNT162b2 (Comirnaty®) was administered as 2nd COVID-19 booster dose (4th vaccination in total). It contains 30 µg of tozinameran (0.3 mL after dilution) as approved for individuals ≥12 years by the European Commission.	
Reporting group title	mRNA-1273
Reporting group description:	
mRNA-1273 (Spikevax®) was administered as 2nd COVID-19 booster dose (4th vaccination in total). It contains 100 µg (0.5 mL after dilution).	

Reporting group values	BNT162b2	mRNA-1273	Total
Number of subjects	135	135	270
Age categorical			
Units: Subjects			
>=75-<85	100	106	206
85+	35	29	64
Age continuous			
Units: years			
arithmetic mean	80.99	81.09	
standard deviation	± 5.49	± 5.88	-
Gender categorical			
Biological sex was differentiated by female and male.			
Units: Subjects			
Female	67	68	135
Male	68	67	135

End points

End points reporting groups

Reporting group title	BNT162b2

Reporting group description:

BNT162b2 (Comirnaty®) was administered as 2nd COVID-19 booster dose (4th vaccination in total). It contains 30 µg of tozinameran (0.3 mL after dilution) as approved for individuals ≥12 years by the European Commission.

Reporting group title	mRNA-1273

Reporting group description:

mRNA-1273 (Spikevax®) was administered as 2nd COVID-19 booster dose (4th vaccination in total). It contains 100 µg (0.5 mL after dilution).

Primary: Antibody Titre Increase 14 Days After 4th Vaccination Dose

End point title	Antibody Titre Increase 14 Days After 4th Vaccination Dose[1]

End point description:

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

Because the trial was terminated before the initial target sample size was reached, only confidence intervals for the rates per group are reported. All analyses should be considered as exploratory (pre-specified and post-hoc) due to the premature termination.

Descriptive analysis:
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. All primary analyses were performed on the mITT population set.

All trial data (Part A and B) will be shared upon request as per FAIR principles.

End point type	Primary

End point timeframe:

From Day 0 until Day 14

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Because the trial was terminated before the initial target sample size was reached, only confidence intervals for the rates per group are reported. All analyses should be considered as exploratory (pre-specified and post-hoc) due to the premature termination.

End point values	BNT162b2	mRNA-1273		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	130	133		
Units: Count of participants	102	116		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Neutralizing Antibody Titre Against Wild-type 14 Days After a 4th Vaccination Dose

End point title	Change in Neutralizing Antibody Titre Against Wild-type 14 Days After a 4th Vaccination Dose

End point description:

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.

Number of subjects for whom the difference of neutralizing activity (Day 14 minus Day 0) could be calculated.

For the descriptive statistics, only subjects with valid measurements at all timepoints have been considered.

End point type	Secondary

End point timeframe:

From Day 0 until Day 14

End point values	BNT162b2	mRNA-1273		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	122	120		
Units: Percentage				
arithmetic mean (standard deviation)	37.33 (± 22.93)	41.45 (± 24.09)		

Statistical analyses

Statistical analysis title	ANCOVA

Statistical analysis description:

For this analysis all subjects (n=262; BNT162b2 n= 129 and mRNA-1273 = 133) with valid values at baseline and Day 14 have been considered. No imputation of missing values.

Comparison groups	mRNA-1273 v BNT162b2
Number of subjects included in analysis	242
Analysis specification	Post-hoc
Analysis type	other
P-value	= 0.0101
Method	ANCOVA
Parameter estimate	Difference of means in percent
Point estimate	4.331
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.04
upper limit	7.621
Variability estimate	Standard error of the mean
Dispersion value	1.671

Secondary: Change in Neutralizing Antibody Titre Against Variants of Concern 14 Days After 4th Vaccination Dose

End point title	Change in Neutralizing Antibody Titre Against Variants of

	Concern 14 Days After 4th Vaccination Dose

End point description:

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.

The provided values refer to the variant "B.1.1.7 (alpha)". Besides for B.1.1.7 (alpha), all statistical tests described above were also conducted for the following variants of concern/interest: B.1.351 (beta), P.1 (gamma), P.2 (gamma), B.1.617, B.1.617.1 (kappa), AY.3 (delta), AY.4.2 (delta), B.1.617.3, B.1.526.1 (iota), BA.1 (omicron), BA.2 (omicron), BA.2+L452M (omicron), BA.2+L452R (omicron), BA.2.12.1 (omicron), BA.2.75 (omicron), BA.2.75.2 (omicron), BA.3 (omicron), BA.4 (omicron), BA.4.6 (omicron), BA.5 (omicron), BF.7 (omicron), BQ.1 (omicron), BQ.1.1 (omicron), and XBB.1 (omicron).

For the descriptive statistics, only subjects with valid measurements at all timepoints have been considered.

All trial results were published in an open-access journal. All trial data will be shared upon request.

End point type	Secondary

End point timeframe:

From Day 0 until Day 14

End point values	BNT162b2	mRNA-1273		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	122	120		
Units: difference of percentage (D14 minus D0)				
arithmetic mean (standard deviation)	38.17 (± 21.74)	44.04 (± 23.94)		

Statistical analyses

Statistical analysis title	ANCOVA

Statistical analysis description:

For this analysis all subjects (n=262; BNT162b2 n= 129 and mRNA-1273 = 133) with valid values at baseline and Day 14 have been considered. No imputation of missing values.

Comparison groups	mRNA-1273 v BNT162b2
Number of subjects included in analysis	242
Analysis specification	Post-hoc
Analysis type	other
P-value	= 0.00258
Method	ANCOVA
Parameter estimate	Difference of means in percent
Point estimate	6.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.41
upper limit	11.249
Variability estimate	Standard error of the mean
Dispersion value	2.244

Secondary: Antibody Titre Level at 12 Months After a 4th Vaccination Dose

End point title	Antibody Titre Level at 12 Months After a 4th Vaccination Dose

End point description:

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

Subjects in whom a blood sampling was performed at Month 12.

End point type	Secondary

End point timeframe:

From Day 0 until Month 12

End point values	BNT162b2	mRNA-1273		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	121		
Units: IU/ml				
geometric mean (standard deviation)	9961.92 (± 26292.23)	12024.3 (± 29129.18)		

Statistical analyses

No statistical analyses for this end point

Secondary: Neutralizing Antibody Titre Against Wild-type at 12 Months After a 4th Vaccination Dose

End point title	Neutralizing Antibody Titre Against Wild-type at 12 Months After a 4th Vaccination Dose

End point description:

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.

End point type	Secondary

End point timeframe:

Month 12

End point values	BNT162b2	mRNA-1273		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	123	121		
Units: Percentage				
arithmetic mean (standard deviation)	59.001 (± 30.67)	64.726 (± 31.205)		

Statistical analyses

No statistical analyses for this end point

Secondary: Neutralizing Antibody Titre Against Variants of Concern at 12 Months After a 4th Vaccination Dose

End point title	Neutralizing Antibody Titre Against Variants of Concern at 12 Months After a 4th Vaccination Dose

End point description:

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.

Titres of neutralizing antibodies were reported as change in neutralization capacity. Provided values refer to the variant "B.1.1.7 (alpha)". For all other variants of concern/interest, please see the open-access publication.

End point type	Secondary

End point timeframe:

Month 12

End point values	BNT162b2	mRNA-1273		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	122	121		
Units: Percentage				
arithmetic mean (standard deviation)	46.195 (± 31.1)	52.811 (± 33.279)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Unsolicited AEs

End point title	Unsolicited AEs

End point description:

Unsolicited AEs until the end of trial

End point type	Other pre-specified

End point timeframe:

From Day 0 until Month 12

End point values	BNT162b2	mRNA-1273		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	135	135		
Units: Participants	110	112		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Solicited AEs

End point title	Solicited AEs

End point description:

Solicited AEs for 7 days after a 4th vaccination dose.

End point type	Other pre-specified

End point timeframe:

From Day 0 until Day 7

End point values	BNT162b2	mRNA-1273		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	135	135		
Units: Participants	76	80		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Rate of SAEs Grade ≥3

End point title	Rate of SAEs Grade ≥3

End point description:

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.

Provided values refer to SAEs related to the IMP. All other trial data is available upon request.

End point type	Other pre-specified

End point timeframe:

From Day 0 until Month 3

End point values	BNT162b2	mRNA-1273		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	135	135		
Units: Participants	1	0		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change in Cellular Immune Response Measured by qPCR 14 Days After 4th Vaccination Dose

End point title	Change in Cellular Immune Response Measured by qPCR 14 Days After 4th Vaccination Dose

End point description:

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.

Inclusion required completed visits at Day 0 and Day 14 with a sufficient number of aliquots as per CTP. Provided results are absolute values of the cellular immune response on Day 14 of tubes stimulated with peptides from spike (tube A). Samples were also stimulated with peptides from a virus membrane nucleoprotein (tube B) and with peptides from the Omicron variant (tube C). All trial results will be provided upon request.

End point type	Other pre-specified

End point timeframe:

From Day 0 until Day 14

End point values	BNT162b2	mRNA-1273		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	92		
Units: CT actine				
arithmetic mean (standard deviation)	26.63 (± 1.58)	26.63 (± 1.59)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Neutralizing Antibody Titre Against Newly Emerging Variants in Bio-banked Samples After 4th Vaccination Dose

End point title	Neutralizing Antibody Titre Against Newly Emerging Variants in Bio-banked Samples After 4th Vaccination Dose

End point description:

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.

Provided values refer to the variant "XBB.1 (omicron)". For all other variants of interest, please see the open-access publication.

End point type	Other pre-specified

End point timeframe:

Month 12

End point values	BNT162b2	mRNA-1273		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	123	121		
Units: Percentage				
arithmetic mean (standard deviation)	30.663 (± 31.374)	35.018 (± 32.202)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From Day 0 until Month 12	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	26.1

Reporting groups	
Reporting group title	BNT162b2
Reporting group description: -	
Reporting group title	mRNA-1273
Reporting group description: -	

Serious adverse events	BNT162b2	mRNA-1273	
Total subjects affected by serious adverse events			
subjects affected / exposed	21 / 135 (15.56%)	22 / 135 (16.30%)	
number of deaths (all causes)	2	5	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	0 / 135 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			
subjects affected / exposed	1 / 135 (0.74%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial cancer			
subjects affected / exposed	1 / 135 (0.74%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningioma			
subjects affected / exposed	1 / 135 (0.74%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Plasmacytoma			
subjects affected / exposed	1 / 135 (0.74%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 135 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	1 / 135 (0.74%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Vertebroplasty			
subjects affected / exposed	1 / 135 (0.74%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 135 (0.74%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chills			
subjects affected / exposed	1 / 135 (0.74%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	1 / 135 (0.74%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			

subjects affected / exposed	1 / 135 (0.74%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 135 (0.74%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstructive sleep apnoea syndrome			
subjects affected / exposed	0 / 135 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 135 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 135 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	1 / 135 (0.74%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	1 / 135 (0.74%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	0 / 135 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Humerus fracture			
subjects affected / exposed	0 / 135 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 135 (0.74%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	1 / 135 (0.74%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	0 / 135 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 135 (0.74%)	3 / 135 (2.22%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block			
subjects affected / exposed	1 / 135 (0.74%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	1 / 135 (0.74%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 135 (0.00%)	2 / 135 (1.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure congestive			

subjects affected / exposed	1 / 135 (0.74%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	1 / 135 (0.74%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Sinus node dysfunction			
subjects affected / exposed	0 / 135 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Brain stem stroke			
subjects affected / exposed	0 / 135 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cerebral haemorrhage			
subjects affected / exposed	1 / 135 (0.74%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 135 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Dizziness			
subjects affected / exposed	1 / 135 (0.74%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysarthria			
subjects affected / exposed	0 / 135 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			

subjects affected / exposed	0 / 135 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 135 (0.00%)	3 / 135 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo positional			
subjects affected / exposed	1 / 135 (0.74%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Amaurosis fugax			
subjects affected / exposed	0 / 135 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glaucoma			
subjects affected / exposed	0 / 135 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Visual impairment			
subjects affected / exposed	0 / 135 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal disorder			
subjects affected / exposed	0 / 135 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia			
subjects affected / exposed	0 / 135 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 135 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 135 (0.74%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	1 / 135 (0.74%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			
subjects affected / exposed	1 / 135 (0.74%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	0 / 135 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic fracture			
subjects affected / exposed	0 / 135 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal sepsis			
subjects affected / exposed	0 / 135 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
COVID-19			

subjects affected / exposed	1 / 135 (0.74%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	0 / 135 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea infectious			
subjects affected / exposed	0 / 135 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	2 / 135 (1.48%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	3 / 135 (2.22%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 135 (0.74%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 135 (0.74%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	2 / 135 (1.48%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	BNT162b2	mRNA-1273	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	103 / 135 (76.30%)	110 / 135 (81.48%)	
Nervous system disorders			
Dizziness			
subjects affected / exposed	4 / 135 (2.96%)	7 / 135 (5.19%)	
occurrences (all)	5	7	
Headache			
subjects affected / exposed	14 / 135 (10.37%)	23 / 135 (17.04%)	
occurrences (all)	17	27	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	14 / 135 (10.37%)	16 / 135 (11.85%)	
occurrences (all)	14	19	
Chills			
subjects affected / exposed	6 / 135 (4.44%)	8 / 135 (5.93%)	
occurrences (all)	6	8	
Extensive swelling of vaccinated limb			
subjects affected / exposed	1 / 135 (0.74%)	4 / 135 (2.96%)	
occurrences (all)	1	4	
Fatigue			
subjects affected / exposed	31 / 135 (22.96%)	51 / 135 (37.78%)	
occurrences (all)	34	57	
Injection site erythema			
subjects affected / exposed	8 / 135 (5.93%)	20 / 135 (14.81%)	
occurrences (all)	8	22	
Injection site pain			
subjects affected / exposed	54 / 135 (40.00%)	59 / 135 (43.70%)	
occurrences (all)	55	62	
Injection site pruritus			
subjects affected / exposed	9 / 135 (6.67%)	9 / 135 (6.67%)	
occurrences (all)	9	9	
Injection site swelling			

subjects affected / exposed	10 / 135 (7.41%)	15 / 135 (11.11%)	
occurrences (all)	10	15	
Malaise			
subjects affected / exposed	11 / 135 (8.15%)	17 / 135 (12.59%)	
occurrences (all)	11	18	
Pyrexia			
subjects affected / exposed	0 / 135 (0.00%)	3 / 135 (2.22%)	
occurrences (all)	0	3	
Swelling face			
subjects affected / exposed	0 / 135 (0.00%)	3 / 135 (2.22%)	
occurrences (all)	0	3	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	4 / 135 (2.96%)	4 / 135 (2.96%)	
occurrences (all)	4	4	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 135 (1.48%)	6 / 135 (4.44%)	
occurrences (all)	2	6	
Nausea			
subjects affected / exposed	1 / 135 (0.74%)	8 / 135 (5.93%)	
occurrences (all)	1	9	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 135 (0.74%)	3 / 135 (2.22%)	
occurrences (all)	1	3	
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	3 / 135 (2.22%)	12 / 135 (8.89%)	
occurrences (all)	3	14	
Night sweats			
subjects affected / exposed	3 / 135 (2.22%)	12 / 135 (8.89%)	
occurrences (all)	4	13	
Pruritus			
subjects affected / exposed	3 / 135 (2.22%)	5 / 135 (3.70%)	
occurrences (all)	4	6	

Rash			
subjects affected / exposed	3 / 135 (2.22%)	0 / 135 (0.00%)	
occurrences (all)	4	0	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	7 / 135 (5.19%)	15 / 135 (11.11%)	
occurrences (all)	9	17	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	6 / 135 (4.44%)	8 / 135 (5.93%)	
occurrences (all)	6	8	
Myalgia			
subjects affected / exposed	7 / 135 (5.19%)	11 / 135 (8.15%)	
occurrences (all)	8	11	
Pain in extremity			
subjects affected / exposed	34 / 135 (25.19%)	40 / 135 (29.63%)	
occurrences (all)	35	42	
Infections and infestations			
COVID-19			
subjects affected / exposed	31 / 135 (22.96%)	31 / 135 (22.96%)	
occurrences (all)	33	33	
Nasopharyngitis			
subjects affected / exposed	6 / 135 (4.44%)	5 / 135 (3.70%)	
occurrences (all)	7	5	
Urinary tract infection			
subjects affected / exposed	3 / 135 (2.22%)	3 / 135 (2.22%)	
occurrences (all)	4	5	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	4 / 135 (2.96%)	7 / 135 (5.19%)	
occurrences (all)	5	8	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 December 2021	The main changes concerned the protocol (CTP V04) in which the visit schedule was simplified and the number of visits reduced. The revision of the visit schedule also included a designated process presentation for obtaining a GCP-compliant informed consent prior to the initiation of study-relevant measures.
21 January 2022	The main changes concerned the protocol (CTP V05) and the associated synopsis due to the introduction of a fourth instead of a third vaccination dose. In addition to changes to the content, the wording of the protocol was clarified in some passages. Editorial changes were also made.
17 August 2022	The main changes concerned the protocol (CTP V06) and the associated synopsis. In addition to a few content-related changes, the wording of the protocol has been the wording was clarified and editorial adjustments were made.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/36209129

http://www.ncbi.nlm.nih.gov/pubmed/37919141

http://www.ncbi.nlm.nih.gov/pubmed/38992789

http://www.ncbi.nlm.nih.gov/pubmed/37919289