



## Clinical trial results:

### Monitoring immunogenicity of SARS-Cov-2 vaccination in Dutch middle-aged and older individuals (participating in the Doetinchem Cohort Study)

#### Summary

EudraCT number	2021-001976-40
Trial protocol	NL
Global end of trial date	12 October 2024

#### Results information

Result version number	v1 (current)
This version publication date	08 November 2025
First version publication date	08 November 2025

#### Trial information

##### Trial identification

Sponsor protocol code	IIV-479
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	ABR number: NL76551.041.21

Notes:

#### Sponsors

Sponsor organisation name	RIVM
Sponsor organisation address	PO Box 1, Bilthoven, Netherlands, 3720BA
Public contact	Clinical Expertise Centre, RIVM , National Institute for Public Health and the Environment , mensgebonden-onderzoek@rivm.nl
Scientific contact	Clinical Expertise Centre, RIVM , National Institute for Public Health and the Environment , mensgebonden-onderzoek@rivm.nl

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	12 October 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 October 2024
Global end of trial reached?	Yes
Global end of trial date	12 October 2024
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The overall aim is to address the magnitude, quality and persistence of the antibody responses to SARS-CoV-2-vaccinations in the Dutch population of above 50 years of age.

- Assess the SARS-CoV-2 vaccine systemic antibody responses in 52+ years old male and female persons in the DC after SARS-CoV-2 (booster) vaccinations.
- Determine the kinetics and longevity of SARS-CoV-2 antibody responses based on the data at all timepoints related to frailty in 52-90 years old male and female persons in the DC.
- Assess the relation of age, frailty and specific co-morbidities in 52-90 years old male and female persons with antibody responses to SARS-CoV-2 and identifying subgroups of individuals more at risk for lower vaccine responsiveness

Protection of trial subjects:

SARS-COV-2 vaccines have been granted a conditional marketing authorization. The products are routinely used in several countries in the same age groups and considered safe. It is therefore unlikely that serious side effects will occur that can lead to premature termination of the study. These vaccines are given by the participants' own GP or the GGD as part of the routine immunization program for this age group, not as part of this study. Furthermore, the burden and risk of blood sampling is considered low. Collection of finger prick blood is regarded an adequate and safe alternative for full venous blood puncture. The applied lancet is easy to use, sterile and with a pricking needle which is designed to prevent exposure and re-use. Risk of infecting someone via the lancet is therefore very unlikely

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 March 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 1273
Worldwide total number of subjects	1273
EEA total number of subjects	1273

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)	580
From 65 to 84 years	669
85 years and over	24

## Subject disposition

### Recruitment

Recruitment details:

DCS participants: All persons still participating in the DCS who have participated in round 6 of the DCS (n=3200) were invited for participation in the current study. Recruitment was done by a personal letter inviting the subjects to participate.

### Pre-assignment

Screening details:

Inclusion:

- participated in DCS round 6
- receive SARS-CoV-2 vaccine
- Sign informed consent

Exclusion:

- received 2nd SARS-CoV-2 vaccine dose 1 months before signing ICF
- Incapacitated

### Period 1

Period 1 title	SARS-CoV-2 primary immunization
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

No blinding

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	SARS-CoV-2 primary immunization comirnaty

Arm description:

Participants that received their SARS-CoV-2 primary immunization with comirnaty, and participants that only received a single dose comirnaty as SARS-CoV-2 primary immunization.

Arm type	Experimental
Investigational medicinal product name	Comirnaty
Investigational medicinal product code	EU/1/20/1528 - J07BN01 - Covid-19, RNA-based vacci
Other name	
Pharmaceutical forms	Concentrate for dispersion for injection
Routes of administration	Intramuscular use

Dosage and administration details:

"Comirnaty is administered intramuscularly after dilution as a single dose of 0.3 mL for individuals 12 years of age and older regardless of prior COVID-19 vaccination status. For individuals who have previously been vaccinated with a COVID-19 vaccine, Comirnaty should be administered at least 3 months after the most recent dose of a COVID-19 vaccine.

Comirnaty 30 micrograms/dose concentrate for dispersion for injection should be administered intramuscularly after dilution. The preferred site is the deltoid muscle of the upper arm."

<b>Arm title</b>	SARS-CoV-2 primary immunization spikevax
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Arm description: -

Arm type	Experimental
Investigational medicinal product name	Spikevax
Investigational medicinal product code	EU/1/20/1507 - J07BN01 - Covid-19, RNA-based vacc
Other name	
Pharmaceutical forms	Dispersion for injection
Routes of administration	Intramuscular use

**Dosage and administration details:**

The primary series consists of 2 doses (0.5 ml each, containing 100 micrograms mRNA). It is recommended to administer the second dose 28 days after the first dose. Spikevax may be used to boost individuals 12 years of age and older who have received a primary series with Spikevax or a primary series comprised of another mRNA vaccine or adenoviral vector vaccine at least 3 months after completion of the primary series. The booster dose consists of 1 dose of 0.25 ml, containing 50 micrograms mRNA. The vaccine should be administered intramuscularly. The preferred site is the deltoid muscle of the upper arm or in infants and young children, the anterolateral aspect of the thigh.

<b>Arm title</b>	SARS-CoV-2 primary immunization Vaxzevria
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**Arm description:**

Participants that received their SARS-CoV-2 primary immunization with Vaxzevria, and participants that received a single dose of Vaxzevria and a single dose of comirnaty as SARS-CoV-2 primary immunization.

Arm type	Experimental
Investigational medicinal product name	Vaxzevria
Investigational medicinal product code	EU/1/21/1529 - J07BN02 - Covid-19, viral vector, n
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

**Dosage and administration details:**

The Vaxzevria primary vaccination course consists of two separate doses of 0.5 ml each. The second dose should be administered between 4 and 12 weeks (28 to 84 days) after the first dose. Vaxzevria is for intramuscular injection only, preferably in the deltoid muscle of the upper arm.

<b>Arm title</b>	SARS-CoV-2 primary immunization JCOVDEN
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**Arm description: -**

Arm type	Experimental
Investigational medicinal product name	JCOVDEN
Investigational medicinal product code	EU/1/20/1525 - J07BN02 - Covid-19, viral vector, n
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

**Dosage and administration details:**

"JCOVDEN is administered as a single-dose of 0.5 mL by intramuscular injection only. A booster dose (second dose) of 0.5 mL of JCOVDEN may be administered intramuscularly at least 2 months after the primary vaccination in individuals 18 years of age and older. JCOVDEN is for intramuscular injection only, preferably in the deltoid muscle of the upper arm."

<b>Arm title</b>	Vaccination unknown
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**Arm description:**

It is unknown what product this participant has received since the participant has not informed the study team about this.

Arm type	Experimental
Investigational medicinal product name	Comirnaty
Investigational medicinal product code	EU/1/20/1528 - J07BN01 - Covid-19, RNA-based vac
Other name	
Pharmaceutical forms	Concentrate for dispersion for injection
Routes of administration	Intramuscular use

**Dosage and administration details:**

"Comirnaty is administered intramuscularly after dilution as a single dose of 0.3 mL for individuals 12 years of age and older regardless of prior COVID-19 vaccination status. For individuals who have previously been vaccinated with a COVID-19 vaccine, Comirnaty should be administered at least 3 months after the most recent dose of a COVID-19 vaccine. Comirnaty 30 micrograms/dose concentrate for dispersion for injection should be administered intramuscularly after dilution. The preferred site is the deltoid muscle of the upper arm."

Investigational medicinal product name	Spikevax
Investigational medicinal product code	EU/1/20/1507 - J07BN01 - Covid-19, RNA-based vacc
Other name	
Pharmaceutical forms	Dispersion for injection
Routes of administration	Intramuscular use

Dosage and administration details:

The primary series consists of 2 doses (0.5 ml each, containing 100 micrograms mRNA). It is recommended to administer the second dose 28 days after the first dose. Spikevax may be used to boost individuals 12 years of age and older who have received a primary series with Spikevax or a primary series comprised of another mRNA vaccine or adenoviral vector vaccine at least 3 months after completion of the primary series. The booster dose consists of 1 dose of 0.25 ml, containing 50 micrograms mRNA. The vaccine should be administered intramuscularly. The preferred site is the deltoid muscle of the upper arm or in infants and young children, the anterolateral aspect of the thigh.

Investigational medicinal product name	Vaxzevria
Investigational medicinal product code	EU/1/21/1529 - J07BN02 - Covid-19, viral vector, n
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

The Vaxzevria primary vaccination course consists of two separate doses of 0.5 ml each. The second dose should be administered between 4 and 12 weeks (28 to 84 days) after the first dose. Vaxzevria is for intramuscular injection only, preferably in the deltoid muscle of the upper arm.

Investigational medicinal product name	JCOVDEN
Investigational medicinal product code	EU/1/20/1525 - J07BN02 - Covid-19, viral vector, n
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

"JCOVDEN is administered as a single-dose of 0.5 mL by intramuscular injection only. A booster dose (second dose) of 0.5 mL of JCOVDEN may be administered intramuscularly at least 2 months after the primary vaccination in individuals 18 years of age and older. JCOVDEN is for intramuscular injection only, preferably in the deltoid muscle of the upper arm."

Number of subjects in period 1	SARS-CoV-2 primary immunization comirnaty	SARS-CoV-2 primary immunization spikevax	SARS-CoV-2 primary immunization Vaxzevria
Started	880	20	333
Pre 1st primary SARS-CoV-2 immunization	878	20	332
1 month post 1st primary SARS-CoV-2 immu	869	20	325
1 month post 2nd primary SARS-CoV-2 immu	850	20	312
3 months post 2nd primary SARS-CoV-2 imm	828	20	297
6 months post 2nd primary SARS-CoV-2 imm	806	20	289
9 months post 2nd primary SARS-CoV-2 imm	762	19	273
1 year post 2nd primary SARS-CoV-2 immun	748	18	270
Completed	748	18	270
Not completed	132	2	63

Deceased	6	-	-
unknown	1	-	2
emigration	2	-	1
Participant decided to end participation	57	2	26
Lost to follow-up	66	-	34

Number of subjects in period 1	SARS-CoV-2 primary immunization JCOVDEN	Vaccination unknown
Started	37	3
Pre 1st primary SARS-CoV-2 immunization	37	3
1 month post 1st primary SARS-CoV-2 immu	35	2
1 month post 2nd primary SARS-CoV-2 immu	35	2
3 months post 2nd primary SARS-CoV-2 imm	35	2
6 months post 2nd primary SARS-CoV-2 imm	35	0
9 months post 2nd primary SARS-CoV-2 imm	34	0
1 year post 2nd primary SARS-CoV-2 immun	34	0
Completed	34	0
Not completed	3	3
Deceased	-	-
unknown	-	-
emigration	-	-
Participant decided to end participation	1	-
Lost to follow-up	2	3

## Period 2

Period 2 title	SARS-CoV-2 1st booster immunization
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

No blinding

## Arms

Are arms mutually exclusive?	Yes
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<b>Arm title</b>	SARS-CoV-2 1st booster immunization comirnaty
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Comirnaty
Investigational medicinal product code	EU/1/20/1528 - J07BN01 - Covid-19, RNA-based vacci
Other name	
Pharmaceutical forms	Concentrate for dispersion for injection
Routes of administration	Intramuscular use

**Dosage and administration details:**

"Comirnaty is administered intramuscularly after dilution as a single dose of 0.3 mL for individuals 12 years of age and older regardless of prior COVID-19 vaccination status. For individuals who have previously been vaccinated with a COVID-19 vaccine, Comirnaty should be administered at least 3 months after the most recent dose of a COVID-19 vaccine.

Comirnaty 30 micrograms/dose concentrate for dispersion for injection should be administered intramuscularly after dilution. The preferred site is the deltoid muscle of the upper arm."

<b>Arm title</b>	SARS-CoV-2 1st booster immunization spikevax
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Spikevax
Investigational medicinal product code	EU/1/20/1507 - J07BN01 - Covid-19, RNA-based vacc
Other name	
Pharmaceutical forms	Dispersion for injection
Routes of administration	Intramuscular use

**Dosage and administration details:**

The primary series consists of 2 doses (0.5 ml each, containing 100 micrograms mRNA). It is recommended to administer the second dose 28 days after the first dose. Spikevax may be used to boost individuals 12 years of age and older who have received a primary series with Spikevax or a primary series comprised of another mRNA vaccine or adenoviral vector vaccine at least 3 months after completion of the primary series. The booster dose consists of 1 dose of 0.25 ml, containing 50 micrograms mRNA. The vaccine should be administered intramuscularly. The preferred site is the deltoid muscle of the upper arm or in infants and young children, the anterolateral aspect of the thigh.

<b>Arm title</b>	Vaccination unknown
Arm description:	
It is unknown what product this participant has received since the participant has not informed the study team about this.	
Arm type	Experimental
Investigational medicinal product name	Comirnaty
Investigational medicinal product code	EU/1/20/1528 - J07BN01 - Covid-19, RNA-based vacci
Other name	
Pharmaceutical forms	Concentrate for dispersion for injection
Routes of administration	Intramuscular use

**Dosage and administration details:**

"Comirnaty is administered intramuscularly after dilution as a single dose of 0.3 mL for individuals 12 years of age and older regardless of prior COVID-19 vaccination status. For individuals who have previously been vaccinated with a COVID-19 vaccine, Comirnaty should be administered at least 3 months after the most recent dose of a COVID-19 vaccine.

Comirnaty 30 micrograms/dose concentrate for dispersion for injection should be administered intramuscularly after dilution. The preferred site is the deltoid muscle of the upper arm."

Investigational medicinal product name	Spikevax
Investigational medicinal product code	EU/1/20/1507 - J07BN01 - Covid-19, RNA-based vacc
Other name	
Pharmaceutical forms	Dispersion for injection
Routes of administration	Intramuscular use



**Dosage and administration details:**

The primary series consists of 2 doses (0.5 ml each, containing 100 micrograms mRNA). It is recommended to administer the second dose 28 days after the first dose. Spikevax may be used to boost individuals 12 years of age and older who have received a primary series with Spikevax or a primary series comprised of another mRNA vaccine or adenoviral vector vaccine at least 3 months after completion of the primary series. The booster dose consists of 1 dose of 0.25 ml, containing 50 micrograms mRNA. The vaccine should be administered intramuscularly. The preferred site is the deltoid muscle of the upper arm or in infants and young children, the anterolateral aspect of the thigh.

Number of subjects in period 2 <sup>[1]</sup>	SARS-CoV-2 1st booster immunization comirnaty	SARS-CoV-2 1st booster immunization spikevax	Vaccination unknown
Started	239	791	1
pre 1st SARS-CoV-2 booster immunization	238	773	1
1 month post 1st SARS-CoV-2 booster immunization	238	769	1
6 months post 1st SARS-CoV-2 booster immunization	227	732	0
1 year post 1st SARS-CoV-2 booster immunization	223	712	0
Completed	223	712	0
Not completed	16	79	1
Deceased	1	1	-
unknown	-	1	-
Participant decided to end participation	9	41	1
Lost to follow-up	6	36	-

**Notes:**

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Not all subjects received the 1st booster immunization. Then they completed period 1 (primary immunization) but did not start period 2 (1st booster) because they did not have the 1st booster immunization.

**Period 3**

Period 3 title	SARS-CoV-2 2nd booster immunization
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

**Blinding implementation details:**

No blinding

**Arms**

Are arms mutually exclusive?	Yes
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<b>Arm title</b>	SARS-CoV-2 2nd booster immunization comirnaty
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Comirnaty
Investigational medicinal product code	EU/1/20/1528 - J07BN01 - Covid-19, RNA-based vacci
Other name	
Pharmaceutical forms	Concentrate for dispersion for injection
Routes of administration	Intramuscular use

**Dosage and administration details:**

"Comirnaty is administered intramuscularly after dilution as a single dose of 0.3 mL for individuals 12 years of age and older regardless of prior COVID-19 vaccination status. For individuals who have previously been vaccinated with a COVID-19 vaccine, Comirnaty should be administered at least 3 months after the most recent dose of a COVID-19 vaccine.

Comirnaty 30 micrograms/dose concentrate for dispersion for injection should be administered intramuscularly after dilution. The preferred site is the deltoid muscle of the upper arm."

<b>Arm title</b>	SARS-CoV-2 2nd booster immunization spikevax
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Spikevax
Investigational medicinal product code	EU/1/20/1507 - J07BN01 - Covid-19, RNA-based vacc
Other name	
Pharmaceutical forms	Dispersion for injection
Routes of administration	Intramuscular use

**Dosage and administration details:**

The primary series consists of 2 doses (0.5 ml each, containing 100 micrograms mRNA). It is recommended to administer the second dose 28 days after the first dose. Spikevax may be used to boost individuals 12 years of age and older who have received a primary series with Spikevax or a primary series comprised of another mRNA vaccine or adenoviral vector vaccine at least 3 months after completion of the primary series. The booster dose consists of 1 dose of 0.25 ml, containing 50 micrograms mRNA. The vaccine should be administered intramuscularly. The preferred site is the deltoid muscle of the upper arm or in infants and young children, the anterolateral aspect of the thigh.

<b>Arm title</b>	SARS-CoV-2 2nd booster immunization unknown vaccine
Arm description:	
It is unknown what product this participant has received since the participant has not informed the study team about this.	
Arm type	Experimental
Investigational medicinal product name	Comirnaty
Investigational medicinal product code	EU/1/20/1528 - J07BN01 - Covid-19, RNA-based vacci
Other name	
Pharmaceutical forms	Concentrate for dispersion for injection
Routes of administration	Intramuscular use

**Dosage and administration details:**

"Comirnaty is administered intramuscularly after dilution as a single dose of 0.3 mL for individuals 12 years of age and older regardless of prior COVID-19 vaccination status. For individuals who have previously been vaccinated with a COVID-19 vaccine, Comirnaty should be administered at least 3 months after the most recent dose of a COVID-19 vaccine.

Comirnaty 30 micrograms/dose concentrate for dispersion for injection should be administered intramuscularly after dilution. The preferred site is the deltoid muscle of the upper arm."

Investigational medicinal product name	Spikevax
Investigational medicinal product code	EU/1/20/1507 - J07BN01 - Covid-19, RNA-based vacc
Other name	
Pharmaceutical forms	Dispersion for injection
Routes of administration	Intramuscular use

**Dosage and administration details:**

The primary series consists of 2 doses (0.5 ml each, containing 100 micrograms mRNA). It is recommended to administer the second dose 28 days after the first dose. Spikevax may be used to boost individuals 12 years of age and older who have received a primary series with Spikevax or a primary series comprised of another mRNA vaccine or adenoviral vector vaccine at least 3 months after completion of the primary series. The booster dose consists of 1 dose of 0.25 ml, containing 50 micrograms mRNA. The vaccine should be administered intramuscularly. The preferred site is the deltoid muscle of the upper arm or in infants and young children, the anterolateral aspect of the thigh.

<b>Number of subjects in period 3<sup>[2]</sup></b>	<b>SARS-CoV-2 2nd booster immunization comirnaty</b>	<b>SARS-CoV-2 2nd booster immunization spikevax</b>	<b>SARS-CoV-2 2nd booster immunization unknown vaccine</b>
Started	200	475	3
1 month post 2nd SARS-CoV-2 booster immunization	196	447	3
6 months post 2nd SARS-CoV-2 booster immunization	188	436	1
1 year post 2nd SARS-CoV-2 booster immunization	183	431	1
Completed	183	431	1
Not completed	17	44	2
Deceased	-	1	-
unknown	5	1	1
Participant decided to end participation	8	26	-
Lost to follow-up	4	16	1

**Notes:**

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Not all subjects received the 2nd booster immunization. Then they completed period 2 (primary immunization) but did not start period 3 (2nd booster) because they did not have the 2nd booster immunization.

**Period 4**

Period 4 title	SARS-CoV-2 3rd booster immunization
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

**Blinding implementation details:**

No blinding

**Arms**

Are arms mutually exclusive?	Yes
<b>Arm title</b>	SARS-CoV-2 3rd booster immunization comirnaty
Arm description: -	
Arm type	Experimental

Investigational medicinal product name	Comirnaty
Investigational medicinal product code	EU/1/20/1528 - J07BN01 - Covid-19, RNA-based vacci
Other name	
Pharmaceutical forms	Dispersion for injection
Routes of administration	Intramuscular use

**Dosage and administration details:**

Comirnaty Original/Omicron BA.1 is administered intramuscularly as a single dose of 0.3 mL for individuals 12 years of age and older who have previously received at least a primary vaccination course against COVID-19. It should be administered at least 3 months after the most recent dose of a COVID-19 vaccine. Comirnaty Original/Omicron BA.1 (15/15 micrograms)/dose dispersion for injection should be administered intramuscularly.

<b>Arm title</b>	SARS-CoV-2 3rd booster immunization spikevax
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**Arm description: -**

Arm type	Experimental
Investigational medicinal product name	Spikevax
Investigational medicinal product code	EU/1/20/1507 - J07BN01 - Covid-19, RNA-based vacc
Other name	
Pharmaceutical forms	Dispersion for injection
Routes of administration	Intramuscular use

**Dosage and administration details:**

The booster consists of 1 dose (0.5 ml, containing 125 micrograms of elasomeran and 25 micrograms of imelasomeran, a COVID-19 mRNA Vaccine (nucleoside modified) (embedded in lipid nanoparticles)). There should be an interval of at least 3 months between administration of Spikevax bivalent Original/Omicron BA.1 and the last prior dose of a COVID-19 vaccine. Spikevax bivalent Original/Omicron BA.1 is only indicated for individuals who have previously received at least a primary vaccination course against COVID-19. The vaccine should be administered intramuscularly. The preferred site is the deltoid muscle of the upper arm.

<b>Arm title</b>	SARS-CoV-2 3rd booster immunization unknown vaccine
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**Arm description:**

It is unknown what product this participant has received since the participant has not informed the study team about this.

Arm type	Experimental
Investigational medicinal product name	Comirnaty
Investigational medicinal product code	EU/1/20/1528 - J07BN01 - Covid-19, RNA-based vacci
Other name	
Pharmaceutical forms	Dispersion for injection
Routes of administration	Intramuscular use

**Dosage and administration details:**

Comirnaty Original/Omicron BA.1 is administered intramuscularly as a single dose of 0.3 mL for individuals 12 years of age and older who have previously received at least a primary vaccination course against COVID-19. It should be administered at least 3 months after the most recent dose of a COVID-19 vaccine. Comirnaty Original/Omicron BA.1 (15/15 micrograms)/dose dispersion for injection should be administered intramuscularly.

Investigational medicinal product name	Spikevax
Investigational medicinal product code	EU/1/20/1507 - J07BN01 - Covid-19, RNA-based vacc
Other name	
Pharmaceutical forms	Dispersion for injection
Routes of administration	Intramuscular use

**Dosage and administration details:**

The booster consists of 1 dose (0.5 ml, containing 125 micrograms of elasomeran and 25 micrograms of imelasomeran, a COVID-19 mRNA Vaccine (nucleoside modified) (embedded in lipid nanoparticles)). There should be an interval of at least 3 months between administration of Spikevax bivalent Original/Omicron BA.1 and the last prior dose of a COVID-19 vaccine. Spikevax bivalent Original/Omicron BA.1 is only indicated for individuals who have previously received at least a primary vaccination course against COVID-19. The vaccine should be administered intramuscularly. The preferred site is the deltoid muscle of the upper arm.

<b>Number of subjects in period 4<sup>[3]</sup></b>	<b>SARS-CoV-2 3rd booster immunization comirnaty</b>	<b>SARS-CoV-2 3rd booster immunization spikevax</b>	<b>SARS-CoV-2 3rd booster immunization unknown vaccine</b>
Started	33	529	1
pre 3rd SARS-CoV-2 booster immunization	44	607	5
1 month post 3rd SARS-CoV-2 booster immu	44	604	3
6 months post 3rd SARS-CoV-2 booster imm	44	592	3
1 year post 3rd SARS-CoV-2 booster immun	37	537	2
Completed	37	537	2
Not completed	7	70	3
Deceased	-	3	-
Participant decided to end participation	-	18	1
Withdrawn from study by PI	7	49	1
Lost to follow-up	-	-	1
Joined	11	78	4
Did not participate in 2nd booster immu	11	78	4

Notes:

[3] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Not all subjects participated in the 3rd period because they did not get a 2nd booster immunization. These participants skipped the timepoints for 2nd booster immunization and rejoined for the 3rd booster immunization. Therefore the number of participants at the end of period 3 (2nd booster) is lower than at the start of period 4 (3rd booster).

## Baseline characteristics

### Reporting groups

Reporting group title	SARS-CoV-2 primary immunization
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Reporting group description: -

Reporting group values	SARS-CoV-2 primary immunization	Total	
Number of subjects	1273	1273	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	580	580	
From 65-84 years	669	669	
85 years and over	24	24	
Gender categorical Units: Subjects			
Female	679	679	
Male	594	594	

### Subject analysis sets

Subject analysis set title	T0
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Subject analysis set type	Per protocol
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Subject analysis set description:

Pre 1st primary SARS-CoV-2 immunization

Subject analysis set title	T1
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Subject analysis set type	Per protocol
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Subject analysis set description:

1 month post 1st primary SARS-CoV-2 immunization

Subject analysis set title	T2
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Subject analysis set type	Per protocol
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Subject analysis set description:

1 month post 2nd primary SARS-CoV-2 immunization

Subject analysis set title	T3
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Subject analysis set type	Per protocol
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Subject analysis set description:

3 months post 2nd primary SARS-CoV-2 immunization

Subject analysis set title	T4
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Subject analysis set type	Per protocol
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Subject analysis set description:

6 months post 2nd primary SARS-CoV-2 immunization

Subject analysis set title	T5
Subject analysis set type	Per protocol

Subject analysis set description:

9 months post 2nd primary SARS-CoV-2 immunization

Subject analysis set title	T6
Subject analysis set type	Per protocol

Subject analysis set description:

1 year post 2nd primary SARS-CoV-2 immunization

Subject analysis set title	B0
Subject analysis set type	Per protocol

Subject analysis set description:

pre 1st SARS-CoV-2 booster immunization

Subject analysis set title	B1
Subject analysis set type	Per protocol

Subject analysis set description:

1 month post 1st SARS-CoV-2 booster immunization

Subject analysis set title	B2
Subject analysis set type	Per protocol

Subject analysis set description:

6 months post 1st SARS-CoV-2 booster immunization

Subject analysis set title	B3
Subject analysis set type	Per protocol

Subject analysis set description:

1 year post 1st SARS-CoV-2 booster immunization

Subject analysis set title	C1
Subject analysis set type	Per protocol

Subject analysis set description:

1 month post 2nd SARS-CoV-2 booster immunization

Subject analysis set title	C2
Subject analysis set type	Per protocol

Subject analysis set description:

6 months post 2nd SARS-CoV-2 booster immunization

Subject analysis set title	C3
Subject analysis set type	Per protocol

Subject analysis set description:

1 year post 2nd SARS-CoV-2 booster immunization

Subject analysis set title	D0
Subject analysis set type	Per protocol

Subject analysis set description:

pre 3rd SARS-CoV-2 booster immunization

Subject analysis set title	D1
Subject analysis set type	Per protocol

Subject analysis set description:

1 month post 3rd SARS-CoV-2 booster immunization

Subject analysis set title	D2
Subject analysis set type	Per protocol

Subject analysis set description:

6 months post 3rd SARS-CoV-2 booster immunization

Subject analysis set title	D3
Subject analysis set type	Per protocol

Subject analysis set description:

1 year post 3rd SARS-CoV-2 booster immunization

Reporting group values	T0	T1	T2
Number of subjects	1270	1251	1220
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)	580	562	535
From 65-84 years	667	666	660
85 years and over	23	23	25
Gender categorical Units: Subjects			
Female	478	669	658
Male	593	582	562

Reporting group values	T3	T4	T5
Number of subjects	1183	1150	1088
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)	508	471	439
From 65-84 years	648	651	625
85 years and over	27	28	24
Gender categorical Units: Subjects			
Female	641	628	592
Male	542	522	496



Reporting group values	T6	B0	B1
Number of subjects	1070	1011	1008
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)	412	417	403
From 65-84 years	634	572	583
85 years and over	24	22	22
Gender categorical			
Units: Subjects			
Female	586	548	548
Male	485	463	460

Reporting group values	B2	B3	C1
Number of subjects	959	936	646
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)	353	307	145
From 65-84 years	582	602	478
85 years and over	24	27	23
Gender categorical			
Units: Subjects			
Female	519	508	326
Male	440	428	320

Reporting group values	C2	C3	D0
Number of subjects	625	615	656
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)	127	105	141

From 65-84 years	476	486	494
85 years and over	22	24	21

Gender categorical Units: Subjects			
Female	318	313	339
Male	307	302	317

<b>Reporting group values</b>	D1	D2	D3
Number of subjects	651	639	576
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)	134	116	78
From 65-84 years	496	501	470
85 years and over	21	22	28
Gender categorical Units: Subjects			
Female	335	327	294
Male	316	312	282

## End points

### End points reporting groups

Reporting group title	SARS-CoV-2 primary immunization comirnaty
Reporting group description: Participants that received their SARS-CoV-2 primary immunization with comirnaty, and participants that only received a single dose comirnaty as SARS-CoV-2 primary immunization.	
Reporting group title	SARS-CoV-2 primary immunization spikevax
Reporting group description: -	
Reporting group title	SARS-CoV-2 primary immunization Vaxzevria
Reporting group description: Participants that received their SARS-CoV-2 primary immunization with Vaxzevria, and participants that received a single dose of Vaxzevria and a single dose of comirnaty as SARS-CoV-2 primary immunization.	
Reporting group title	SARS-CoV-2 primary immunization JCOVDEN
Reporting group description: -	
Reporting group title	Vaccination unknown
Reporting group description: It is unknown what product this participant has received since the participant has not informed the study team about this.	
Reporting group title	SARS-CoV-2 1st booster immunization comirnaty
Reporting group description: -	
Reporting group title	SARS-CoV-2 1st booster immunization spikevax
Reporting group description: -	
Reporting group title	Vaccination unknown
Reporting group description: It is unknown what product this participant has received since the participant has not informed the study team about this.	
Reporting group title	SARS-CoV-2 2nd booster immunization comirnaty
Reporting group description: -	
Reporting group title	SARS-CoV-2 2nd booster immunization spikevax
Reporting group description: -	
Reporting group title	SARS-CoV-2 2nd booster immunization unknown vaccine
Reporting group description: It is unknown what product this participant has received since the participant has not informed the study team about this.	
Reporting group title	SARS-CoV-2 3rd booster immunization comirnaty
Reporting group description: -	
Reporting group title	SARS-CoV-2 3rd booster immunization spikevax
Reporting group description: -	
Reporting group title	SARS-CoV-2 3rd booster immunization unknown vaccine
Reporting group description: It is unknown what product this participant has received since the participant has not informed the study team about this.	
Subject analysis set title	T0
Subject analysis set type	Per protocol
Subject analysis set description: Pre 1st primary SARS-CoV-2 immunization	
Subject analysis set title	T1
Subject analysis set type	Per protocol
Subject analysis set description: 1 month post 1st primary SARS-CoV-2 immunization	

Subject analysis set title	T2
Subject analysis set type	Per protocol
Subject analysis set description: 1 month post 2nd primary SARS-CoV-2 immunization	
Subject analysis set title	T3
Subject analysis set type	Per protocol
Subject analysis set description: 3 months post 2nd primary SARS-CoV-2 immunization	
Subject analysis set title	T4
Subject analysis set type	Per protocol
Subject analysis set description: 6 months post 2nd primary SARS-CoV-2 immunization	
Subject analysis set title	T5
Subject analysis set type	Per protocol
Subject analysis set description: 9 months post 2nd primary SARS-CoV-2 immunization	
Subject analysis set title	T6
Subject analysis set type	Per protocol
Subject analysis set description: 1 year post 2nd primary SARS-CoV-2 immunization	
Subject analysis set title	B0
Subject analysis set type	Per protocol
Subject analysis set description: pre 1st SARS-CoV-2 booster immunization	
Subject analysis set title	B1
Subject analysis set type	Per protocol
Subject analysis set description: 1 month post 1st SARS-CoV-2 booster immunization	
Subject analysis set title	B2
Subject analysis set type	Per protocol
Subject analysis set description: 6 months post 1st SARS-CoV-2 booster immunization	
Subject analysis set title	B3
Subject analysis set type	Per protocol
Subject analysis set description: 1 year post 1st SARS-CoV-2 booster immunization	
Subject analysis set title	C1
Subject analysis set type	Per protocol
Subject analysis set description: 1 month post 2nd SARS-CoV-2 booster immunization	
Subject analysis set title	C2
Subject analysis set type	Per protocol
Subject analysis set description: 6 months post 2nd SARS-CoV-2 booster immunization	

Subject analysis set title	C3
Subject analysis set type	Per protocol
Subject analysis set description: 1 year post 2nd SARS-CoV-2 booster immunization	
Subject analysis set title	D0
Subject analysis set type	Per protocol
Subject analysis set description: pre 3rd SARS-CoV-2 booster immunization	
Subject analysis set title	D1
Subject analysis set type	Per protocol
Subject analysis set description: 1 month post 3rd SARS-CoV-2 booster immunization	
Subject analysis set title	D2
Subject analysis set type	Per protocol
Subject analysis set description: 6 months post 3rd SARS-CoV-2 booster immunization	
Subject analysis set title	D3
Subject analysis set type	Per protocol
Subject analysis set description: 1 year post 3rd SARS-CoV-2 booster immunization	

#### **Primary: Circulating IgG antibodies concentrations for SARS-CoV-2 spike protein**

End point title	Circulating IgG antibodies concentrations for SARS-CoV-2 spike protein
End point description:	
End point type	Primary
End point timeframe: all timepoints after the second or last primary vaccination (T2-T6) and at all time points after the booster vaccination(s) (B1-E3)	

<b>End point values</b>	T2	T3	T4	T5
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	1151	1101	647	24
Units: BAU/ml				
geometric mean (confidence interval 95%)	936.6825152 (867.72113 to 1011.12455)	366.6477934 (340.67271 to 394.60338)	183.2185913 (163.10807 to 205.80865)	775.5095921 (284.88872 to 2111.05277)

<b>End point values</b>	T6	B1	B2	B3
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	841	313	119
Units: BAU/ml				

geometric mean (confidence interval 95%)	4828.52767 (2695.92256 to 8648.12655)	4607.030342 (4361.76712 to 4866.08477)	4110.210571 (3607.80893 to 4682.57363)	2806.339551 (2296.39836 to 3429.51894)
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End point values	C1	C2	C3	D0
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	505	138	36	550
Units: BAU/ml				
geometric mean (confidence interval 95%)	8633.215234 (7985.96131 to 9332.92842)	3967.120399 (3225.08525 to 4879.88474)	3643.358957 (2749.30249 to 4828.15716)	3544.112801 (3226.22004 to 3893.32885)

End point values	D1	D2	D3	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	600	481	360	
Units: BAU/ml				
geometric mean (confidence interval 95%)	9954.809062 (9351.14418 to 10597.44365)	4768.882863 (4339.66077 to 5240.55795)	3230.29749 (2884.64069 to 3617.37319)	

## Statistical analyses

Statistical analysis title	Vaccine-specific serum IgG at T2 until D3
Statistical analysis description:	
Circulating IgG antibodies concentrations for SARS-CoV-2 spike protein at all timepoints after the second or last primary vaccination (T2-T6) and at all time points after the booster vaccination(s) (B1-E3). Geometric mean IgG concentrations with 95% confidence interval.	
Comparison groups	T2 v T3 v T4 v T5 v T6 v B1 v B2 v B3 v C1 v C2 v C3 v D0 v D1 v D2 v D3
Number of subjects included in analysis	6877
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)

## Secondary: Circulating IgG antibodies concentrations for SARS-CoV-2 spike protein

End point title	Circulating IgG antibodies concentrations for SARS-CoV-2 spike protein
End point description:	
End point type	Secondary

End point timeframe:  
pre vaccination (T0) and at 1 month after the first vaccination (T1)

End point values	T0	T1		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	858	997		
Units: BAU/ml				
geometric mean (confidence interval 95%)	0.6664 (0.58246 to 0.76253)	104.1130489 (94.30589 to 114.94009)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Self-reported experiences with possible SARS-CoV-2 infection from answers to a short questionnaire.

End point title	Self-reported experiences with possible SARS-CoV-2 infection from answers to a short questionnaire.
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End point description:

End point type	Secondary
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End point timeframe:  
all timepoints (T0-D3)

End point values	T0	T1	T2	T3
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	858	997	1151	1101
Units: number of participants	68	4	6	1

End point values	T4	T5	T6	B0
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	647	24	11	596
Units: number of participants	39	19	4	0

End point values	B1	B2	B3	C1
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	841	313	119	505

Units: number of participants	29	192	49	26
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End point values	C2	C3	D0	D1
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	138	36	550	600
Units: number of participants	98	24	1	33

End point values	D2	D3		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	481	360		
Units: number of participants	107	17		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Virus-specific serum IgG antibody levels to SARS-CoV-2 Core N protein.

End point title	Virus-specific serum IgG antibody levels to SARS-CoV-2 Core N protein.
End point description:	
End point type	Secondary
End point timeframe:	
all timepoints (T0-D3)	

End point values	T0	T1	T2	T3
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	858	997	1151	1101
Units: BAU/ml				
geometric mean (confidence interval 95%)	1.78705821 (1.61448 to 1.97808)	1.865683561 (1.70904 to 2.03668)	4.365313604 (4.00216 to 4.76142)	1.79855 (1.67105 to 1.93579)

End point values	T4	T5	T6	B0
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	647	24	11	596
Units: BAU/ml				
geometric mean (confidence interval 95%)	2.527670365	11.47558387	52.57177896	2.232999312



95%)	(2.2879 to 2.79256)	(5.0749 to 25.94909)	(21.09453 to 131.01938)	(2.04067 to 2.44346)
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End point values	B1	B2	B3	C1
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	841	313	119	505
Units: BAU/ml				
geometric mean (confidence interval 95%)	3.250543742 (3.02299 to 3.49523)	12.42411729 (10.35664 to 14.90433)	21.85940877 (15.05957 to 31.72959)	6.009452832 (5.36653 to 6.7294)

End point values	C2	C3	D0	D1
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	138	36	550	600
Units: BAU/ml				
geometric mean (confidence interval 95%)	10.12417126 (7.52352 to 13.62378)	36.31566196 (21.03002 to 62.71164)	7.971602286 (6.95399 to 9.13812)	9.422161452 (8.31914 to 10.67142)

End point values	D2	D3		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	481	360		
Units: BAU/ml				
geometric mean (confidence interval 95%)	17.66520259 (14.86832 to 20.98821)	11.94481629 (9.92612 to 14.37406)		

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:  
within one week after blood sampling for every timepoint.

Adverse event reporting additional description:

The adverse events are reported by the subject.

Assessment type	Non-systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	28.0
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### Reporting groups

Reporting group title	SARS-CoV-2 primary immunization
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Reporting group description:

Participants that received their SARS-CoV-2 primary immunization

Serious adverse events	SARS-CoV-2 primary immunization		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 1270 (0.00%)		
number of deaths (all causes)	24		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 0.02 %

Non-serious adverse events	SARS-CoV-2 primary immunization		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 1270 (0.16%)		
Skin and subcutaneous tissue disorders			
Puncture site pain	Additional description: Meddra code: 10065599 participant had painful finger after the finger prick.		
subjects affected / exposed	1 / 1270 (0.08%)		
occurrences (all)	1		
Wound healing delayed	Additional description: Meddra code: 10048036 puncture site after finger prick healed slowly		
subjects affected / exposed	1 / 1270 (0.08%)		
occurrences (all)	1		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 August 2021	The submission of the trial as drug research.
12 August 2021	additional sample collection from nursing homes
29 October 2021	Follow the immune responses after SARS-CoV-2 booster vaccination
09 March 2022	Follow the immune responses after the second and following SARS-CoV-2 booster vaccination
16 May 2023	1) Changes in the primary and secondary outcome measures due to the relevance and feasibility 2) change in informed consent procedure 3) adding questions about post-COVID complaints to questionnaire D3, 4) addition of questionnaires, covering letters, newsletters, and result letters
19 September 2023	Follow the immune responses in the nursing home participants after the fourth SARS-CoV-2 booster vaccination given in the autumn of 2023, with 2 extra fingerprick samples (E1 and E3)
08 October 2024	Corrections to make the protocol fully accurate and up to date.

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Results on the secondary endpoint 'Integrated endpoint analysis of all antibody analysis with frailty data and data of specific co-morbidities (subgroups)' can be found in the pubmed article 39407293 and will not be added to this EudraCT report.

Notes:

### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/39407293>

<http://www.ncbi.nlm.nih.gov/pubmed/36146557>

<http://www.ncbi.nlm.nih.gov/pubmed/37880758>

<http://www.ncbi.nlm.nih.gov/pubmed/39748353>