



Clinical trial results:

Vaccination of older persons against Sars-Cov-2 and cellular immunogenicity for long term protection (participating in the Doetinchem Cohort Study)

Summary

EudraCT number	2021-002363-22
Trial protocol	NL
Global end of trial date	05 December 2024

Results information

Result version number	v1 (current)
This version publication date	18 December 2025
First version publication date	18 December 2025

Trial information

Trial identification

Sponsor protocol code	IIV-482
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	ABR number: NL76719.041.21

Notes:

Sponsors

Sponsor organisation name	RIVM
Sponsor organisation address	Antonie van Leeuwenhoeklaan 9, Bilthoven, Netherlands, 3721 MA
Public contact	Clinical expertise centre, National Institute for Public Health and the Environment, mensgebonden-onderzoek@rivm.nl
Scientific contact	Clinical expertise centre, 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	05 December 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 December 2024
Global end of trial reached?	Yes
Global end of trial date	05 December 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The overall aim is to monitor and evaluate the magnitude, quality and persistence of immune responses induced by SARS-CoV-2 vaccination in the general older Dutch population 64-90 years of age. Furthermore, in older individuals inter-individual differences in the presence of frailty will be related to vaccine responsiveness.

- Assess the magnitude of systemic antibody responses to the SARS-CoV-2 vaccine in 64-90 years old male and female persons at a month after completion of SARS-CoV-2 vaccination.
- To address the magnitude and quality of T-cell and B-cell immune responses induced by the current new SARS-CoV-2 vaccines at a month after completion of SARS-CoV-2 vaccination in older male and female persons (64-90 years of age).

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	11 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: 101
Worldwide total number of subjects	101
EEA total number of subjects	101

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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	96
85 years and over	5

Subject disposition

Recruitment

Recruitment details:

All persons still participating in the DCS who have participated in the ISA substudy of the DCS (n=270) will be invited for participation in the current study. Recruitment was done by a personal letter inviting the subjects to participate.

First inclusion: 27-03-2021, Last inclusion: 30-07-2021

Pre-assignment

Screening details:

Inclusion:

- participated in ISA study
- receive SARS-CoV-2 vaccine
- Sign informed consent

Exclusion:

- Received 2nd SARS-CoV-2 vaccine dose more than 1 months before signing ICF

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
Arm title	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.

Arm title	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.

Arm title	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, viral vector, non-replicat
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.

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	95	1	5
Pre 1st primary SARS-CoV-2 immunization	95	1	5
1 month post 1st primary SARS-CoV-2 immu	94	1	5
1 month post 2nd primary SARS-CoV-2 immu	94	1	5
6 months post 2nd primary SARS-CoV-2 imm	90	1	4
1 year post 2nd primary SARS-CoV-2 immun	87	1	4
Completed	87	1	4
Not completed	8	0	1
Participant decided to end participation	8	-	1

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
Arm title	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.

Arm title	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.

Number of subjects in period 2^[1]	SARS-CoV-2 1st booster immunization comirnaty	SARS-CoV-2 1st booster immunization spikevax
Started	11	78
pre 1st SARS-CoV-2 booster immunization	11	78
1 month post 1st SARS-CoV-2 booster immu	11	77

6 months post 1st SARS-CoV-2 booster im	11	73
1 year post 1st SARS-CoV-2 booster immun	11	73
Completed	11	73
Not completed	0	5
Participant decided to end participation	-	5

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: Several subjects completing the 1st period (primary immunization) did not receive a booster vaccination and therefore did not participate in the 2nd period (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
Arm title	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.

Arm title	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.

Number of subjects in period 3^[2]	SARS-CoV-2 2nd booster immunization comirnaty	SARS-CoV-2 2nd booster immunization spikevax
Started	24	51
1 month post 2nd SARS-CoV-2 booster immu	24	51
6 months post 2nd SARS-CoV-2 booster imm	23	49
1 year post 2nd SARS-CoV-2 booster immun	21	49
Completed	21	49
Not completed	3	2
Participant decided to end participation	3	2

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: Several subjects completing the 2nd period (1st booster immunization) did not receive a 2nd booster vaccination and therefore did not participate in the 3rd period (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
Arm title	SARS-CoV-2 3rd booster immunization comirnaty
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Comirnaty Original/Omicron BA.1
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.

Arm title	SARS-CoV-2 3rd booster immunization spikevax
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Spikevax bivalent origineel/omicron BA.1
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 elasomeron and 25 micrograms of imelasomeron, 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."

Arm title	SARS-CoV-2 3rd booster immunization unknown vaccine
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Vaccine unknown
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Dispersion for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Vaccine used is either Comirnaty Original/Omicron BA.1 or Spikevax bivalent origineel/omicron BA.1

Number of subjects in period 4^[3]	SARS-CoV-2 3rd booster immunization comirnaty	SARS-CoV-2 3rd booster immunization spikevax	SARS-CoV-2 3rd booster immunization unknown vaccine
Started	1	64	1
pre 3rd SARS-CoV-2 booster immunization	1	64	1
1 month post 3rd SARS-CoV-2 booster immu	1	64	1
6 months post 3rd SARS-CoV-2 booster imm	1	63	0
1 year post 3rd SARS-CoV-2 booster immun	1	62	0
Completed	1	62	0
Not completed	0	2	1
Participant decided to end participation	-	2	1

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: Several subjects completing the 3rd period (2nd booster immunization) did not receive a 3rd booster vaccination and therefore did not participate in the 4th period (3rd booster immunization)

Period 5

Period 5 title	SARS-CoV-2 4th booster immunization
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

No blinding

Arms

Arm title	SARS-CoV-2 4th booster immunization comirnaty
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Comirnaty JN.1
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 JN.1 is administered intramuscularly as a single dose of 0.3 mL for individuals 12 years of age and older independent of prior vaccination against COVID-19. It should be administered at least 3 months after the most recent dose of a COVID-19 vaccine. Comirnaty JN.1 (30 micrograms)/dose dispersion for injection should be administered intramuscularly.

Number of subjects in period 5^[4]	SARS-CoV-2 4th booster immunization comirnaty
Started	53
1 month post 4th SARS-CoV-2 booster immu	53
1 year post 4th SARS-CoV-2 booster immun	53
Completed	53

Notes:

[4] - 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: Several subjects completing the 4th period (3rd booster immunization) did not receive a 4th booster vaccination and therefore did not participate in the 5th period (4th booster immunization)

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	101	101	
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)	0	0	
From 65-84 years	96	96	
85 years and over	5	5	
Gender categorical Units: Subjects			
Female	50	50	
Male	51	51	

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:

6 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:

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

Subject analysis set title	E1
Subject analysis set type	Per protocol

Subject analysis set description:

1 month post 4th SARS-CoV-2 booster immunization

Subject analysis set title	E3
Subject analysis set type	Per protocol

Subject analysis set description:

1 year post 4th SARS-CoV-2 booster immunization

Reporting group values	T0	T1	T2
Number of subjects	101	100	100
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	96	95	95
85 years and over	5	5	5
Gender categorical			
Units: Subjects			
Female	50	50	50
Male	51	50	50

Reporting group values	T3	T4	B0
Number of subjects	95	92	89
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	91	88	86
85 years and over	4	4	3
Gender categorical			
Units: Subjects			
Female	47	47	44
Male	48	45	45

Reporting group values	B1	B2	B3
Number of subjects	88	84	84
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	85	82	82
85 years and over	3	2	2
Gender categorical			
Units: Subjects			
Female	44	42	42
Male	44	42	42

Reporting group values	C1	C2	C3
Number of subjects	75	72	70
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	74	71	69
85 years and over	1	1	1
Gender categorical			
Units: Subjects			
Female	38	37	35
Male	37	35	35

Reporting group values	D0	D1	D2
Number of subjects	66	66	64
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0

From 65-84 years	65	65	63
85 years and over	1	1	1

Gender categorical Units: Subjects			
Female	34	34	33
Male	32	32	31

Reporting group values	D3	E1	E3
Number of subjects	63	53	53
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	62	52	52
85 years and over	1	1	1
Gender categorical Units: Subjects			
Female	33	26	26
Male	30	27	27

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 1st booster immunization comirnaty
Reporting group description: -	
Reporting group title	SARS-CoV-2 1st booster immunization spikevax
Reporting group description: -	
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 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: -	
Reporting group title	SARS-CoV-2 4th booster immunization comirnaty
Reporting group description: -	
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: 6 months post 2nd primary SARS-CoV-2 immunization	
Subject analysis set title	T4

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	
Subject analysis set title	E1
Subject analysis set type	Per protocol
Subject analysis set description: 1 month post 4th SARS-CoV-2 booster immunization	
Subject analysis set title	E3
Subject analysis set type	Per protocol
Subject analysis set description: 1 year post 4th SARS-CoV-2 booster immunization	

Primary: Specific serum IgG antibody concentrations at one month after the second vaccination

End point title	Specific serum IgG antibody concentrations at one month after the second vaccination ^[1]
End point description: Serum IgG levels voor SARS-CoV-2 S1 protein	
End point type	Primary
End point timeframe: One month after second primary vaccination (T2)	
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: Since participants did not have antibodies to SARSCoV2 at T0, in this observational study just induction of antibody responses at T2, post vaccination, have been analysed. Therefore, no statistical analyses can be specified.

End point values	T2			
Subject group type	Subject analysis set			
Number of subjects analysed	97			
Units: BAU/ml				
geometric mean (confidence interval 95%)	1273.285 (1031.586 to 1571.614)			

Statistical analyses

No statistical analyses for this end point

Primary: Frequencies of B-cells at one month after the second SARS-CoV-2 vaccination

End point title	Frequencies of B-cells at one month after the second SARS-CoV-2 vaccination ^[2]
End point description: Percentage of B-cells, memory B-cells or plasmablasts in comparison to total amount of PBMCs	
End point type	Primary
End point timeframe: One month after second primary vaccination (T2)	

Notes:

[2] - 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: Since participants did not have memory B-cell responses to SARSCoV2 at T0, in this observational study just induction of B-cell responses at T2, post vaccination, have been analysed. Therefore, no statistical analyses can be specified.

End point values	T2			
Subject group type	Subject analysis set			
Number of subjects analysed	40			
Units: Percentage cells				
geometric mean (standard deviation)				
B-cells	5.51 (± 1.91)			
Memory B-cells	0.26 (± 0.16)			
Plasmablasts	0.02 (± 0.01)			

Statistical analyses

No statistical analyses for this end point

Primary: Frequencies of the adaptive memory B-cell responses at one month after the second SARS-CoV-2 vaccination

End point title	Frequencies of the adaptive memory B-cell responses at one month after the second SARS-CoV-2 vaccination ^[3]
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End point description:

polyclonal stimulation of PBMCs in vitro followed by virus-protein specific ELISpot assay for spike protein S1

End point type	Primary
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End point timeframe:

At one month after primary vaccination (T2)

Notes:

[3] - 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: Since participants did not have memory B-cell responses to SARSCoV2 at T0, in this observational study just induction of B-cell responses at T2, post vaccination, have been analysed. Therefore, no statistical analyses can be specified.

End point values	T2			
Subject group type	Subject analysis set			
Number of subjects analysed	42			
Units: spots/100.000 PBMCs				
geometric mean (confidence interval 95%)	1.096 (0.262 to 4.589)			

Statistical analyses

No statistical analyses for this end point

Primary: Frequencies of functional T-cell responses at one month after the second

SARS-CoV-2 vaccination

End point title	Frequencies of functional T-cell responses at one month after the second SARS-CoV-2 vaccination ^[4]
End point description:	in vitro stimulation with viral proteins followed by INF-g ELISpot assay for spike protein S1 and S2
End point type	Primary
End point timeframe:	At one month after primary vaccination (T2)

Notes:

[4] - 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: Since participants did not have T-cell responses to SARSCoV2 at T0, in this observational study just induction of T-cell responses at T2, post vaccination, have been analysed. Therefore, no statistical analyses can be specified.

End point values	T2			
Subject group type	Subject analysis set			
Number of subjects analysed	63			
Units: spots/100.000 PBMCs				
geometric mean (confidence interval 95%)	2.894 (0.937 to 8.941)			

Statistical analyses

No statistical analyses for this end point

Secondary: Longevity of antibody levels at 1 year post (booster)vaccination

End point title	Longevity of antibody levels at 1 year post (booster)vaccination
End point description:	Serum IgG levels voor SARS-CoV-2 S1 protein
End point type	Secondary
End point timeframe:	At 1 year post primary vaccination (T4), and 1 year post booster vaccinations (B3, C3, D3, E3)

End point values	T4	B3	C3	D3
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	0 ^[5]	6	3	63
Units: BAU/ml				
geometric mean (confidence interval 95%)	(to)	5046.666 (1493.554 to 17052.505)	6968.184 (3773.825 to 12866.413)	2736.649 (2112.550 to 3545.122)

Notes:

[5] - All subject received booster vaccination within one year after primary vacc so T4 was not applicable

End point values	E3			
Subject group type	Subject analysis set			
Number of subjects analysed	52			

Units: BAU/ml				
geometric mean (confidence interval 95%)	4132.644 (3146.233 to 5428.316)			

Statistical analyses

No statistical analyses for this end point

Secondary: Longevity of cellular response (B-cells) at 1 year post (booster)vaccination

End point title	Longevity of cellular response (B-cells) at 1 year post (booster)vaccination
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End point description:

polyclonal stimulation of PBMCs in vitro followed by virus-protein specific ELISpot assay for spike protein S1

End point type	Secondary
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End point timeframe:

At 1 year post primary vaccination (T4), and 1 year post booster vaccinations (B3, C3, D3, E3)

End point values	T4	B3	C3	D3
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	0 ^[6]	6	0 ^[7]	0 ^[8]
Units: Spots/100.000 PBMCs				
geometric mean (confidence interval 95%)	(to)	43.647 (36.585 to 52.073)	(to)	(to)

Notes:

[6] - All subject received booster vaccination within one year after primary vacc so T4 was not applicable

[7] - Analysis was not performed

[8] - Analysis was not performed

End point values	E3			
Subject group type	Subject analysis set			
Number of subjects analysed	0 ^[9]			
Units: Spots/100.000 PBMCs				
geometric mean (confidence interval 95%)	(to)			

Notes:

[9] - Analysis was not performed

Statistical analyses

No statistical analyses for this end point

Secondary: Mucosal IgA and IgG antibodies will be determined in nose fluids at T2, T4 and pre and post booster vaccinations

End point title	Mucosal IgA and IgG antibodies will be determined in nose fluids at T2, T4 and pre and post booster vaccinations
End point description:	Mucosal IgA and IgG concentrations specific for SARS-CoV-2 S1 protein
End point type	Secondary
End point timeframe:	At one month and one year post primary vaccination (T2 and T4), and pre and post booster vaccinations (B0, B1, B3, C1, D0, D1)

End point values	T2	T4	B0	B1
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	3	3	76	85
Units: BAUM/ml				
geometric mean (confidence interval 95%)				
IgA	0.100 (0.056 to 0.179)	0.610 (0.072 to 5.158)	0.158 (0.111 to 0.225)	0.370 (0.279 to 0.491)
IgG	0.682 (0.082 to 5.655)	3.949 (0.139 to 112.345)	0.704 (0.511 to 0.969)	20.302 (15.356 to 26.842)

End point values	B3	C1	D0	D1
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	9	68	65	66
Units: BAUM/ml				
geometric mean (confidence interval 95%)				
IgA	2.361 (0.729 to 7.642)	0.870 (0.555 to 1.365)	1.194 (0.754 to 1.893)	1.276 (0.854 to 1.905)
IgG	27.614 (6.024 to 126.574)	39.435 (27.737 to 56.066)	17.475 (11.664 to 26.183)	36.075 (27.092 to 48.035)

Statistical analyses

No statistical analyses for this end point

Secondary: IgG antibodies to the SARS-CoV-2 core N protein indicating contact with the virus

End point title	IgG antibodies to the SARS-CoV-2 core N protein indicating contact with the virus
End point description:	
End point type	Secondary
End point timeframe:	At all timepoints

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	56	74	97	81
Units: BAU/ml				
geometric mean (confidence interval 95%)	1.419 (0.953 to 2.113)	2.111 (1.476 to 3.021)	2.560 (1.937 to 3.382)	2.417 (1.751 to 3.337)

End point values	B0	B1	B2	B3
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	80	74	8	6
Units: BAU/ml				
geometric mean (confidence interval 95%)	2.670 (1.914 to 3.725)	3.021 (2.259 to 4.040)	18.547 (8.226 to 41.817)	13.440 (3.695 to 48.889)

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	66	21	3	62
Units: BAU/ml				
geometric mean (confidence interval 95%)	6.902 (4.504 to 10.578)	11.038 (5.537 to 22.002)	157.299 (12.406 to 1994.372)	11.042 (7.108 to 17.154)

End point values	D1	D2	D3	E1
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	63	65	63	52
Units: BAU/ml				
geometric mean (confidence interval 95%)	13.167 (8.658 to 20.023)	34.146 (20.134 to 57.909)	19.319 (11.744 to 31.781)	16.571 (9.655 to 28.441)

End point values	E3			
Subject group type	Subject analysis set			
Number of subjects analysed	52			
Units: BAU/ml				
geometric mean (confidence interval 95%)	41.189 (22.654 to 74.886)			

Statistical analyses

No statistical analyses for this end point

Secondary: Self-reported experiences possible SARS-CoV-2 infection from answers to short questionnaires at the several timepoints.

End point title	Self-reported experiences possible SARS-CoV-2 infection from answers to short questionnaires at the several timepoints.
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End point description:

End point type	Secondary
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End point timeframe:

At all timepoints

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	56	74	97	81
Units: number of participants	5	0	0	2

End point values	T4	B0	B1	B2
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	0 ^[10]	80	74	8
Units: number of participants		0	1	15

Notes:

[10] - All subject received booster vaccination within one year after primary vacc so T4 was not applicable

End point values	B3	C1	C2	C3
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6	66	21	3
Units: number of participants	1	6	9	1

End point values	D0	D1	D2	D3
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	62	63	65	63
Units: number of participants	0	3	14	1

End point values	E1	E3		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	52	52		
Units: number of participants	0	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Longevity of cellular response (T-cells) at 1 year post (booster)vaccination

End point title	Longevity of cellular response (T-cells) at 1 year post (booster)vaccination
End point description:	in vitro stimulation with viral proteins followed by INF-g ELISpot assay for spike protein S1 and S2
End point type	Secondary
End point timeframe:	At 1 year post primary vaccination (T4), and 1 year post booster vaccinations (B3, C3, D3, E3)

End point values	T4	B3	C3	D3
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	0 ^[11]	6	0 ^[12]	25
Units: Spots/100.000 PBMCs				
geometric mean (confidence interval 95%)	(to)	1.268 (0.005 to 316.495)	(to)	23.562 (14.735 to 37.678)

Notes:

[11] - All subject received booster vaccination within one year after primary vacc so T4 was not applicable

[12] - Analysis was not performed

End point values	E3			
Subject group type	Subject analysis set			
Number of subjects analysed	0 ^[13]			
Units: Spots/100.000 PBMCs				
geometric mean (confidence interval 95%)	(to)			

Notes:

[13] - Analysis was not performed

Statistical analyses

No statistical analyses for this end point

Secondary: Antibody virus neutralization for SARS-CoV-2 positive serum samples at 1 month (T2), 6 months (T3) 1 year (T4) post vaccination and pre and post booster vaccination

End point title	Antibody virus neutralization for SARS-CoV-2 positive serum samples at 1 month (T2), 6 months (T3) 1 year (T4) post vaccination and pre and post booster vaccination
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End point description:

Selected SARS-CoV-2 positive serum samples will be tested for virus neutralization, providing a functional measure of immune protection

End point type	Secondary
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End point timeframe:

At 1 month post primary immunization (T2) and pre and post booster vaccinations (B0, B1, B3, C1, C2, D0, D1).

Timepoints T3 and T4 (6 months and 12 months post primary immunization) have not been included in this assay.

End point values	T2	B0	B1	B3
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	95	66	71	8
Units: titre				
geometric mean (confidence interval 95%)	42.838 (32.975 to 55.652)	9.611 (7.253 to 12.734)	429.507 (320.707 to 575.218)	442.007 (123.519 to 1581.698)

End point values	C1	C2	D0	D1
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	62	2	55	65
Units: titre				
geometric mean (confidence interval 95%)	470.756 (350.617 to 632.062)	1226.490 (532.111 to 2827.000)	424.498 (291.418 to 618.351)	1009.385 (775.295 to 1314.156)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:

only adverse events spontaneously reported by the subject related to and occurring within one week after blood sampling were reported

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	28
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Reporting groups

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

Participants that received SARS-CoV-2 primary immunization

Serious adverse events	SARS-CoV-2 primary immunization		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 101 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	SARS-CoV-2 primary immunization		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 101 (0.00%)		

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: only adverse events spontaneously reported by the subject related to and occurring within one week after blood sampling were reported

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 August 2021	Submission of the VOCAAL study as drug research at the request of the METC
29 October 2021	Follow the immune responses after SARS-CoV-2 booster vaccination and administration of 3th SARS-CoV-2 vaccination
09 March 2022	Follow the immune responses after the second and following SARS-CoV-2 booster vaccination
19 May 2023	changes secondary endpoint and changes in informed consent procedure
30 August 2023	Follow the immune responses after the fourth SARS-CoV-2 booster vaccination given in the autumn of 2023
18 October 2024	Extra blood sample at the end of the study for measuring the status of total SARS-CoV2 antibody responses after multiple vaccinations and possible infections as an endpoint state of the study in relation to the actual status of the immune cell characterization and inflammation markers in the plasma present per person.

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.

For T-cells cytokine analysis, frequencies and activation analysis has not been performed in this study, but has been performed in a different cohort (2019-000836-24). Furthermore, the avidity of serum antibodies has not been measured.

Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/37515012>

<http://www.ncbi.nlm.nih.gov/pubmed/38774878>

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

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

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