Clinical trial results:
Immune Responses Induced by Vaccination Against COVID-19 in Dutch healthy subjects

Summary

EudraCT number	2021-001357-31
Trial protocol	NL
Global end of trial date	12 February 2024

Results information

Result version number	v1 (current)
This version publication date	24 July 2024
First version publication date	24 July 2024

Trial information

Trial identification

Sponsor protocol code	IIV-478

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	ABR number: NL76440.041.21

Notes:

Sponsors

Sponsor organisation name	RIVM
Sponsor organisation address	PO box 1, Bilthoven, Netherlands, 3720BA
Public contact	Clinical Expertise Centre, National Institute of Health and the Environment, mensgebonden-onderzoek@rivm.nl
Scientific contact	Clinical Expertise Centre, National Institute of 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	Interim
Date of interim/final analysis	13 June 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 February 2024
Global end of trial reached?	Yes
Global end of trial date	12 February 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Monitoring & evaluation of immune responses induced by COVID-19 vaccines in the general population in the Netherlands, specifically vaccine (e.g. Spike protein)-specific serum IgG GMC at day 28 after completion of COVID-19 vaccination by multiplex immune assay (MIA).

Protection of trial subjects:

SARS-CoV-2 vaccines have been granted a conditional marketing authorization. These vaccines are given by the participants' own GP or the GGD as part of the immunization program provided by the Dutch government and are not part of this study. The products are considered safe, as the products are used in several countries in the same age groups.
Furthermore, the risk of sampling of blood via finger pricks and venipuncture, faeces and nasal mucosal fluid is considered low. Blood collection could result in a small bruise at the site of blood withdrawal, which will disappear within a few days. The amount of blood drawn within the study is maximum 269 mL and is well within the standard that is maintained by Sanquin Bloodbank. In case of a booster vaccination additional blood will be collected in up to four visits (three home visits in the subgroup with an additional max. total volume of 132 mL and one fingerprick at B2s of 800 µL) amounting in total to an additional max. volume of 133 mL for the booster amendment, over 1 year.
For the children the subset groups will be divided in 2 groups. Half of the children (innate group) will have a home visit at T0 and a home visit at T1 (with smaller amounts of blood volume than the adaptive group). The other half (adaptive group) will have a home visit at T0 and no T1 timepoint. This diminishes the burden for the children. Also the blood volume collected will be age dependent. For the booster vaccination study amendment, all subgroups in children will be considered one adaptive subgroup, with age dependent blood volume collected.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 May 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: 1459
Worldwide total number of subjects	1459
EEA total number of subjects	1459

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)	47
Adolescents (12-17 years)	143
Adults (18-64 years)	1269
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Adults aged 18-60 years and children aged 5-12 and 12-18 years were invited; via the VASCO study or other RIVM studies; by random sampling from the BRP; by spontaneous applications. First inclusion 29-05-2021, last inclusion 22-08-2022.
Arm assignment was based on age and vaccination type given in the immunization program by the Dutch Government.

Pre-assignment

Screening details:

Pre-screening was performed through an online questionnaire were in-/exclusion criteria were checked. The trial was looking for generally healthy participants, in order to generate a comparison group for trials with specific diseases.

Period 1

Period 1 title	COVID immunization primary series
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	5-11 years of age - primary vaccination - Pfizer-BioNTech

Arm description:

Participants 5-11 years of age - primary vaccination - Pfizer-BioNTech COVID-19 vaccine

Arm type	Experimental
Investigational medicinal product name	Comirnaty
Investigational medicinal product code	
Other name	Pfizer–BioNTech COVID-19 vaccine
Pharmaceutical forms	Dispersion for injection
Routes of administration	Intramuscular use

Dosage and administration details:

One dose (0.2 mL) contains 10 micrograms of tozinameran, a COVID-19 mRNA Vaccine (embedded in lipid nanoparticles). Usually, 2 dosages were given with a interval of 3-4 weeks. According to the national immunization program, there were reasons for receiving one instead of two dosages.

Arm title	12-17 years of age - primary vaccination - Pfizer-BioNTech

Arm description:

Participants 12 -17 years of age - primary vaccination - Pfizer-BioNTech COVID-19 vaccine

Arm type	Experimental
Investigational medicinal product name	Comirnaty
Investigational medicinal product code	
Other name	Pfizer–BioNTech COVID-19 vaccine
Pharmaceutical forms	Dispersion for injection
Routes of administration	Intramuscular use

Dosage and administration details:

One dose (0.3 mL) contains 30 micrograms of tozinameran, a COVID-19 mRNA Vaccine (embedded in lipid nanoparticles). Usually, 2 dosages were given with a interval of 3-4weeks. According to the national immunization program, there were reasons for receiving one instead of two dosages.

Arm title	18-30 years of age - primary vaccination - Pfizer-BioNTech

Arm description:

Participants 18-30 years of age - primary vaccination - Pfizer-BioNTech COVID-19 vaccine

Arm type	Experimental

Investigational medicinal product name	Comirnaty
Investigational medicinal product code	
Other name	Pfizer–BioNTech COVID-19 vaccine
Pharmaceutical forms	Dispersion for injection
Routes of administration	Intramuscular use

Dosage and administration details:

One dose (0.3 mL) contains 30 micrograms of tozinameran, a COVID-19 mRNA Vaccine (embedded in lipid nanoparticles). Usually, 2 dosages were given with a interval of 4-6 weeks. According to the national immunization program, there were reasons for receiving one instead of two dosages.

Arm title	31-45 years of age - primary vaccination - Pfizer-BioNTech

Arm description:

Participants 31-45 years of age - primary vaccination - Pfizer-BioNTech COVID-19 vaccine

Arm type	Experimental
Investigational medicinal product name	Comrinaty
Investigational medicinal product code	
Other name	Pfizer–BioNTech COVID-19 vaccine
Pharmaceutical forms	Dispersion for injection
Routes of administration	Intramuscular use

Dosage and administration details:

One dose (0.3 mL) contains 30 micrograms of tozinameran, a COVID-19 mRNA Vaccine (embedded in lipid nanoparticles). Usually, 2 dosages were given with a interval of 4-6 weeks. According to the national immunization program, there were reasons for receiving one instead of two dosages.

Arm title	46-60 years of age - primary vaccination - Pfizer-BioNTech

Arm description:

Participants 46-60 years of age - primary vaccination - Pfizer-BioNTech COVID-19 vaccine

Arm type	Experimental
Investigational medicinal product name	Comirnaty
Investigational medicinal product code	
Other name	Pfizer–BioNTech COVID-19 vaccine
Pharmaceutical forms	Dispersion for injection
Routes of administration	Intramuscular use

Dosage and administration details:

One dose (0.3 mL) contains 30 micrograms of tozinameran, a COVID-19 mRNA Vaccine (embedded in lipid nanoparticles). Usually, 2 dosages were given with a interval of 4-6 weeks. According to the national immunization program, there were reasons for receiving one instead of two dosages.

Arm title	18-30 years of age - primary vaccination - Moderna

Arm description:

Participants 18-30 years of age - primary vaccination - Moderna COVID-19 vaccine

Arm type	Experimental
Investigational medicinal product name	Moderna COVID-19 Vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Dispersion for injection
Routes of administration	Intramuscular use

Dosage and administration details:

One dose (0.50 mL) contains 100 micrograms of elasomeran, a COVID-19 mRNA Vaccine (embedded in SM-102 lipid nanoparticles). Usually, 2 dosages were given with a interval of 4-6 weeks. According to the national immunization program, there were reasons for receiving one instead of two dosages.

Arm title	31-45 years of age - primary vaccination - Moderna

Arm description:

Participants 31-45 years of age - primary vaccination - Moderna COVID-19 vaccine

Arm type	Experimental

Investigational medicinal product name	Moderna COVID-19 Vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Dispersion for injection
Routes of administration	Intramuscular use

Dosage and administration details:

One dose (0.50 mL) contains 100 micrograms of elasomeran, a COVID-19 mRNA Vaccine (embedded in SM-102 lipid nanoparticles). Usually, 2 dosages were given with a interval of 4-6 weeks. According to the national immunization program, there were reasons for receiving one instead of two dosages.

Arm title	46-60 years of age - primary vaccination - Moderna

Arm description:

Participants 46-60 years of age - primary vaccination - Moderna COVID-19 vaccine

Arm type	Experimental
Investigational medicinal product name	Moderna COVID-19 Vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Dispersion for injection
Routes of administration	Intramuscular use

Dosage and administration details:

One dose (0.50 mL) contains 100 micrograms of elasomeran, a COVID-19 mRNA Vaccine (embedded in SM-102 lipid nanoparticles). Usually, 2 dosages were given with a interval of 4-6 weeks. According to the national immunization program, there were reasons for receiving one instead of two dosages.

Arm title	18-30 years of age - primary vaccination - Jcovden

Arm description:

Participants 18-30 years of age - primary vaccination - Jcovden (previously COVID-19 Vaccine Janssen)

Arm type	Experimental
Investigational medicinal product name	Jcovden (previously COVID-19 Vaccine Janssen)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

One dose (0.5 mL) contains Adenovirus type 26 encoding the SARS-CoV-2 spike glycoprotein (Ad26.COV2-S), not less than 8.92 log10 infectious units (Inf.U).

Arm title	31-45 years of age - primary vaccination - Jcovden

Arm description:

Participants 31-45 years of age - primary vaccination - Jcovden (previously COVID-19 Vaccine Janssen)

Arm type	Experimental
Investigational medicinal product name	Jcovden (previously COVID-19 Vaccine Janssen)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

One dose (0.5 mL) contains Adenovirus type 26 encoding the SARS-CoV-2 spike glycoprotein (Ad26.COV2-S), not less than 8.92 log10 infectious units (Inf.U).

Arm title	46-60 years of age - primary vaccination - Jcovden

Arm description:

Participants 46-60 years of age - primary vaccination - Jcovden (previously COVID-19 Vaccine Janssen)

Arm type	Experimental

Investigational medicinal product name	Jcovden (previously COVID-19 Vaccine Janssen)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

One dose (0.5 mL) contains Adenovirus type 26 encoding the SARS-CoV-2 spike glycoprotein (Ad26.COV2-S), not less than 8.92 log10 infectious units (Inf.U).

Arm title	18-30 years of age unknown vaccine primary vaccination

Arm description:

Participants 18-30 years of age - primary unknown vaccination

Arm type	Experimental
Investigational medicinal product name	Unknown vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

These participants didn't communicate the vaccination they received. Therefore the COVID-19 vaccination is unknown.

Arm title	31-45 years of age unknown vaccine primary vaccination

Arm description:

Participants 31-45 years of age - primary unknown vaccination

Arm type	Experimental
Investigational medicinal product name	Unknown vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

These participants didn't communicate the vaccination they received. Therefore the COVID-19 vaccination is unknown.

Arm title	46-60 years of age unknown vaccine primary vaccination

Arm description:

Participants 46-60 years of age - primary unknown vaccination

Arm type	Experimental
Investigational medicinal product name	Unknown vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

These participants didn't communicate the vaccination they received. Therefore the COVID-19 vaccination is unknown.

Number of subjects in period 1	5-11 years of age - primary vaccination - Pfizer-BioNTech	12-17 years of age - primary vaccination - Pfizer-BioNTech	18-30 years of age - primary vaccination - Pfizer-BioNTech
Started	47	32	351
1-3 days post 1st COVID immunization(T1)	0 [1]	21	30 [2]
28 days post 1st COVID immunization (T2)	14 [3]	57	347
28 days post 2nd COVID immunization (T3)	37	137	361
6 months post 2nd COVID immunization(T4)	27	116	58 [4]
12 mnths post 2nd COVID immunization(T5)	27	81	181 [5]
Completed	27	91	292
Not completed	20	52	116
Physician decision	3	-	3
Logistic issues	1	4	2
Took a booster before end of study period 1	1	2	6
Participant discontinuation	-	17	25
Lost to follow-up	6	29	76
Participant discontuniation	9	-	-
Maximum number participants reached	-	-	-
(temporarily) emigrated	-	-	4
Joined	0	111	57
Late recruitment	-	111	57
Late recruitment reason		Included after vaccination	Included after vaccination

Number of subjects in period 1	31-45 years of age - primary vaccination - Pfizer-BioNTech	46-60 years of age - primary vaccination - Pfizer-BioNTech	18-30 years of age - primary vaccination - Moderna
Started	439	167	25
1-3 days post 1st COVID immunization(T1)	35 [6]	3 [7]	0 [8]
28 days post 1st COVID immunization (T2)	391	145 [9]	25
28 days post 2nd COVID immunization (T3)	420	174	22
6 months post 2nd COVID immunization(T4)	78 [10]	65 [11]	3 [12]
12 mnths post 2nd COVID immunization(T5)	280 [13]	136 [14]	15 [15]
Completed	391	166	20
Not completed	90	18	7
Physician decision	3	-	1
Logistic issues	-	-	-
Took a booster before end of study period 1	6	2	-
Participant discontinuation	9	2	1
Lost to follow-up	72	14	5

Participant discontuniation	-	-	-
Maximum number participants reached	-	-	-
(temporarily) emigrated	-	-	-
Joined	42	17	2
Late recruitment	42	17	2
Late recruitment reason	Included after vaccination	Included after vaccination	Included after vaccination

Number of subjects in period 1	31-45 years of age - primary vaccination - Moderna	46-60 years of age - primary vaccination - Moderna	18-30 years of age - primary vaccination - Jcovden
Started	48	22	34
1-3 days post 1st COVID immunization(T1)	2 [16]	1 [17]	3 [18]
28 days post 1st COVID immunization (T2)	42	17	0 [19]
28 days post 2nd COVID immunization (T3)	50	30	35
6 months post 2nd COVID immunization(T4)	15 [20]	16	28
12 mnths post 2nd COVID immunization(T5)	32 [21]	17	12 [22]
Completed	45	26	27
Not completed	8	6	14
Physician decision	-	-	1
Logistic issues	-	-	-
Took a booster before end of study period 1	-	1	-
Participant discontinuation	-	1	3
Lost to follow-up	8	4	9
Participant discontuniation	-	-	-
Maximum number participants reached	-	-	-
(temporarily) emigrated	-	-	1
Joined	5	10	7
Late recruitment	5	10	7
Late recruitment reason	Included after vaccination	Included after vaccination	Included after vaccination

Number of subjects in period 1	31-45 years of age - primary vaccination - Jcovden	46-60 years of age - primary vaccination - Jcovden	18-30 years of age unknown vaccine primary vaccination
Started	15	11	6
1-3 days post 1st COVID immunization(T1)	0 [23]	1 [24]	0
28 days post 1st COVID immunization (T2)	0 [25]	0 [26]	0
28 days post 2nd COVID immunization (T3)	15	12	0
6 months post 2nd COVID immunization(T4)	13 [27]	12	0
12 mnths post 2nd COVID immunization(T5)	7 [28]	9 [29]	0

Completed	16	12	0
Not completed	1	0	6
Physician decision	-	-	-
Logistic issues	-	-	-
Took a booster before end of study period 1	-	-	-
Participant discontinuation	-	-	1
Lost to follow-up	1	-	2
Participant discontuniation	-	-	-
Maximum number participants reached	-	-	3
(temporarily) emigrated	-	-	-
Joined	2	1	0
Late recruitment	2	1	-
Late recruitment reason	Included after vaccination	Included after vaccination	

Number of subjects in period 1	31-45 years of age unknown vaccine primary vaccination	46-60 years of age unknown vaccine primary vaccination
Started	5	3
1-3 days post 1st COVID immunization(T1)	0	0
28 days post 1st COVID immunization (T2)	0	0
28 days post 2nd COVID immunization (T3)	0	0
6 months post 2nd COVID immunization(T4)	0	0
12 mnths post 2nd COVID immunization(T5)	0	0
Completed	0	0
Not completed	5	3
Physician decision	-	-
Logistic issues	-	-
Took a booster before end of study period 1	-	-
Participant discontinuation	3	1
Lost to follow-up	1	2
Participant discontuniation	-	-
Maximum number participants reached	1	-
(temporarily) emigrated	-	-
Joined	0	0
Late recruitment	-	-
Late recruitment reason		

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: It is correct that it seems that the number of subjects in the milestones are inconsistent with the total number of subjects in the arm. Because not all participants were included in all of the

timepoints (milestones), due to missing data/blood samples for some timepoints.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: It is correct that it seems that the number of subjects in the milestones are inconsistent with the total number of subjects in the arm. Because not all participants were included in all of the timepoints (milestones), due to missing data/blood samples for some timepoints.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: It is correct that it seems that the number of subjects in the milestones are inconsistent with the total number of subjects in the arm. Because not all participants were included in all of the timepoints (milestones), due to missing data/blood samples for some timepoints.

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: It is correct that it seems that the number of subjects in the milestones are inconsistent with the total number of subjects in the arm. Because not all participants were included in all of the timepoints (milestones), due to missing data/blood samples for some timepoints.

[5] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: It is correct that it seems that the number of subjects in the milestones are inconsistent with the total number of subjects in the arm. Because not all participants were included in all of the timepoints (milestones), due to missing data/blood samples for some timepoints.

[6] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: It is correct that it seems that the number of subjects in the milestones are inconsistent with the total number of subjects in the arm. Because not all participants were included in all of the timepoints (milestones), due to missing data/blood samples for some timepoints.

[7] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: It is correct that it seems that the number of subjects in the milestones are inconsistent with the total number of subjects in the arm. Because not all participants were included in all of the timepoints (milestones), due to missing data/blood samples for some timepoints.

[8] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: It is correct that it seems that the number of subjects in the milestones are inconsistent with the total number of subjects in the arm. Because not all participants were included in all of the timepoints (milestones), due to missing data/blood samples for some timepoints.

[9] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: It is correct that it seems that the number of subjects in the milestones are inconsistent with the total number of subjects in the arm. Because not all participants were included in all of the timepoints (milestones), due to missing data/blood samples for some timepoints.

[10] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: It is correct that it seems that the number of subjects in the milestones are inconsistent with the total number of subjects in the arm. Because not all participants were included in all of the timepoints (milestones), due to missing data/blood samples for some timepoints.

[11] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: It is correct that it seems that the number of subjects in the milestones are inconsistent with the total number of subjects in the arm. Because not all participants were included in all of the timepoints (milestones), due to missing data/blood samples for some timepoints.

[12] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: It is correct that it seems that the number of subjects in the milestones are inconsistent with the total number of subjects in the arm. Because not all participants were included in all of the timepoints (milestones), due to missing data/blood samples for some timepoints.

[13] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: It is correct that it seems that the number of subjects in the milestones are inconsistent with the total number of subjects in the arm. Because not all participants were included in all of the timepoints (milestones), due to missing data/blood samples for some timepoints.
[14] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: It is correct that it seems that the number of subjects in the milestones are inconsistent with the total number of subjects in the arm. Because not all participants were included in all of the timepoints (milestones), due to missing data/blood samples for some timepoints.
[15] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: It is correct that it seems that the number of subjects in the milestones are inconsistent with the total number of subjects in the arm. Because not all participants were included in all of the timepoints (milestones), due to missing data/blood samples for some timepoints.
[16] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: It is correct that it seems that the number of subjects in the milestones are inconsistent with the total number of subjects in the arm. Because not all participants were included in all of the timepoints (milestones), due to missing data/blood samples for some timepoints.
[17] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: It is correct that it seems that the number of subjects in the milestones are inconsistent with the total number of subjects in the arm. Because not all participants were included in all of the timepoints (milestones), due to missing data/blood samples for some timepoints.
[18] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: It is correct that it seems that the number of subjects in the milestones are inconsistent with the total number of subjects in the arm. Because not all participants were included in all of the timepoints (milestones), due to missing data/blood samples for some timepoints.
[19] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: It is correct that it seems that the number of subjects in the milestones are inconsistent with the total number of subjects in the arm. Because not all participants were included in all of the timepoints (milestones), due to missing data/blood samples for some timepoints.
[20] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: It is correct that it seems that the number of subjects in the milestones are inconsistent with the total number of subjects in the arm. Because not all participants were included in all of the timepoints (milestones), due to missing data/blood samples for some timepoints.
[21] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: It is correct that it seems that the number of subjects in the milestones are inconsistent with the total number of subjects in the arm. Because not all participants were included in all of the timepoints (milestones), due to missing data/blood samples for some timepoints.
[22] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: It is correct that it seems that the number of subjects in the milestones are inconsistent with the total number of subjects in the arm. Because not all participants were included in all of the timepoints (milestones), due to missing data/blood samples for some timepoints.
[23] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: It is correct that it seems that the number of subjects in the milestones are inconsistent with the total number of subjects in the arm. Because not all participants were included in all of the timepoints (milestones), due to missing data/blood samples for some timepoints.
[24] - The number of subjects at this milestone seems inconsistent with the number of subjects in the

arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: It is correct that it seems that the number of subjects in the milestones are inconsistent with the total number of subjects in the arm. Because not all participants were included in all of the timepoints (milestones), due to missing data/blood samples for some timepoints.
[25] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: It is correct that it seems that the number of subjects in the milestones are inconsistent with the total number of subjects in the arm. Because not all participants were included in all of the timepoints (milestones), due to missing data/blood samples for some timepoints.
[26] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: It is correct that it seems that the number of subjects in the milestones are inconsistent with the total number of subjects in the arm. Because not all participants were included in all of the timepoints (milestones), due to missing data/blood samples for some timepoints.
[27] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: It is correct that it seems that the number of subjects in the milestones are inconsistent with the total number of subjects in the arm. Because not all participants were included in all of the timepoints (milestones), due to missing data/blood samples for some timepoints.
[28] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: It is correct that it seems that the number of subjects in the milestones are inconsistent with the total number of subjects in the arm. Because not all participants were included in all of the timepoints (milestones), due to missing data/blood samples for some timepoints.
[29] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: It is correct that it seems that the number of subjects in the milestones are inconsistent with the total number of subjects in the arm. Because not all participants were included in all of the timepoints (milestones), due to missing data/blood samples for some timepoints.

Period 2

Period 2 title	COVID immunization, first booster
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	12 -17 years of age - 1st Booster - Pfizer–BioNTech

Arm description:

Participants 12 -17 years of age - 1st Booster - Pfizer–BioNTech COVID-19 vaccine

Arm type	Experimental
Investigational medicinal product name	Comirnaty
Investigational medicinal product code	
Other name	Pfizer–BioNTech COVID-19 vaccine
Pharmaceutical forms	Dispersion for injection
Routes of administration	Intramuscular use

Dosage and administration details:

One dose (0.3 mL) contains 30 micrograms of tozinameran, a COVID-19 mRNA Vaccine (embedded in lipid nanoparticles).

Arm title	18-30 years of age - 1st booster - Pfizer–BioNTech

Arm description:

Participants 18 -30 years of age - 1st Booster - Pfizer–BioNTech COVID-19 vaccine

Arm type	Experimental

Investigational medicinal product name	Comirnaty
Investigational medicinal product code	
Other name	Pfizer–BioNTech COVID-19 vaccine
Pharmaceutical forms	Dispersion for injection
Routes of administration	Intramuscular use

Dosage and administration details:

One dose (0.3 mL) contains 30 micrograms of tozinameran, a COVID-19 mRNA Vaccine (embedded in lipid nanoparticles).

Arm title	31-45 years of age - 1st booster - Pfizer–BioNTech

Arm description:

Participants 31-45 years of age - 1st Booster - Pfizer–BioNTech COVID-19 vaccine

Arm type	Experimental
Investigational medicinal product name	Comirnaty
Investigational medicinal product code	
Other name	Pfizer–BioNTech COVID-19 vaccine
Pharmaceutical forms	Dispersion for injection
Routes of administration	Intramuscular use

Dosage and administration details:

One dose (0.3 mL) contains 30 micrograms of tozinameran, a COVID-19 mRNA Vaccine (embedded in lipid nanoparticles).

Arm title	46-60 years of age - 1st booster - Pfizer–BioNTech

Arm description:

Participants 46-60 years of age - 1st Booster - Pfizer–BioNTech COVID-19 vaccine

Arm type	Experimental
Investigational medicinal product name	Comirnaty
Investigational medicinal product code	
Other name	Pfizer–BioNTech COVID-19 vaccine
Pharmaceutical forms	Dispersion for injection
Routes of administration	Intramuscular use

Dosage and administration details:

One dose (0.3 mL) contains 30 micrograms of tozinameran, a COVID-19 mRNA Vaccine (embedded in lipid nanoparticles).

Arm title	18-30 years of age - 1st booster - Moderna

Arm description:

Participants 18-30 years of age - 1st Booster - Moderna COVID-19 Vaccine

Arm type	Experimental
Investigational medicinal product name	Moderna COVID-19 Vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Dispersion for injection
Routes of administration	Intramuscular use

Dosage and administration details:

One dose (0.25 mL) contains 50 micrograms of elasomeran, a COVID-19 mRNA Vaccine (embedded in SM-102 lipid nanoparticles).

Arm title	31-45 years of age - 1st booster - Moderna

Arm description:

Participants 31-45 years of age - 1st Booster - Moderna COVID-19 Vaccine

Arm type	Experimental

Investigational medicinal product name	Moderna COVID-19 Vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Dispersion for injection
Routes of administration	Intramuscular use

Dosage and administration details:

One dose (0.25 mL) contains 50 micrograms of elasomeran, a COVID-19 mRNA Vaccine (embedded in SM-102 lipid nanoparticles).

Arm title	46-60 years of age - 1st booster - Moderna

Arm description:

Participants 46-60 years of age - 1st Booster - Moderna COVID-19 Vaccine

Arm type	Experimental
Investigational medicinal product name	Moderna COVID-19 Vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Dispersion for injection
Routes of administration	Intramuscular use

Dosage and administration details:

One dose (0.25 mL) contains 50 micrograms of elasomeran, a COVID-19 mRNA Vaccine (embedded in SM-102 lipid nanoparticles).

Number of subjects in period 2[30][31]	12 -17 years of age - 1st Booster - Pfizer–BioNTech	18-30 years of age - 1st booster - Pfizer–BioNTech	31-45 years of age - 1st booster - Pfizer–BioNTech
Started	7	238	372
28 days post booster 1 (B1)	6	261	369
6 motnhs post booster 1 (B2)	9	207	340
12 motnhs post booster 1 (B3)	9	86	183
Completed	9	86	183
Not completed	1	215	219
Physician decision	-	2	-
Transferred to other arm/group	-	60	57
Crucial measurement missing	-	5	9
Took a booster before end of study period 1	-	31	56
Participant discontinuation	-	4	8
Lost to follow-up	1	110	89
(temporarily) emigrated	-	3	-
Joined	3	63	30
Late recruitment	3	63	30
Late recruitment reason	Included after booster vaccination	Included after booster vaccination	Included after booster vaccination

Number of subjects in period 2[30][31]	46-60 years of age - 1st booster - Pfizer–BioNTech	18-30 years of age - 1st booster - Moderna	31-45 years of age - 1st booster - Moderna
Started	43	3	18
28 days post booster 1 (B1)	45	2	18

6 motnhs post booster 1 (B2)	39	2	18
12 motnhs post booster 1 (B3)	21	1	7
Completed	21	1	7
Not completed	26	2	12
Physician decision	2	-	-
Transferred to other arm/group	-	-	2
Crucial measurement missing	-	-	-
Took a booster before end of study period 1	13	-	6
Participant discontinuation	1	1	-
Lost to follow-up	10	1	4
(temporarily) emigrated	-	-	-
Joined	4	0	1
Late recruitment	4	-	1
Late recruitment reason	Included after booster vaccination		Included after booster vaccination

Number of subjects in period 2[30][31]	46-60 years of age - 1st booster - Moderna
Started	137
28 days post booster 1 (B1)	138
6 motnhs post booster 1 (B2)	120
12 motnhs post booster 1 (B3)	46
Completed	46
Not completed	97
Physician decision	2
Transferred to other arm/group	40
Crucial measurement missing	4
Took a booster before end of study period 1	17
Participant discontinuation	7
Lost to follow-up	27
(temporarily) emigrated	-
Joined	6
Late recruitment	6
Late recruitment reason	Included after booster vaccination

Notes:

[30] - 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: The trial started with the primary series. Later on, booster vaccinations were available that not all participants took. Each period is a separate part of the trial. Participants could then choose to enroll in the second period and/or the third period. Group allocation in the other periods was based on the booster vaccination, irrespective of the vaccination in the primary series. The number of participants starting another period is thus not equal to the number completing a previous period.

[31] - The number of subjects transferring in and out of the arms in the period are not the same. It is expected the net number of transfers in and out of the arms in a period, will be zero.

Justification: The trial started with the primary series. Later on, booster vaccinations were available that

not all participants took. Each period is a separate part of the trial. Participants could then choose to enroll in the second period and/or the third period. Group allocation in the other periods was based on the booster vaccination, irrespective of the vaccination in the primary series. The number of participants starting another period is thus not equal to the number completing a previous period.

Period 3

Period 3 title	COVID immunization, repeat vaccination
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	12 -17 years of age - repeat vaccination - Pfizer bivalent

Arm description:

Participants 31-45 years of age - repeat vaccination - Pfizer bivalent COVID-19 vaccine

Arm type	Experimental
Investigational medicinal product name	Comirnaty Original/Omicron BA.1
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Dispersion for injection
Routes of administration	Intramuscular use

Dosage and administration details:

One dose (0.3 mL) contains 15 micrograms of tozinameran and 15 micrograms of riltozinameran, a COVID-19 mRNA Vaccine (embedded in lipid nanoparticles).

Arm title	18-30 years of age - repeat vaccination - Pfizer bivalent

Arm description:

Participants 18-30 years of age - repeat vaccination - Pfizer bivalent COVID-19 vaccine

Arm type	Experimental
Investigational medicinal product name	Comirnaty Original/Omicron BA.1
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Dispersion for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Not apOne dose (0.3 mL) contains 15 micrograms of tozinameran and 15 micrograms of riltozinameran, a COVID-19 mRNA Vaccine (embedded in lipid nanoparticles).

Arm title	31-45 years of age - repeat vaccination - Pfizer bivalent

Arm description:

Participants 31-45 years of age - repeat vaccination - Pfizer bivalent COVID-19 vaccine

Arm type	Experimental
Investigational medicinal product name	Comirnaty Original/Omicron BA.1
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Dispersion for injection
Routes of administration	Intramuscular use

Dosage and administration details:

One dose (0.3 mL) contains 15 micrograms of tozinameran and 15 micrograms of riltozinameran, a COVID-19 mRNA Vaccine (embedded in lipid nanoparticles).

Arm title	46-60 years of age - repeat vaccination - Pfizer bivalent

Arm description:	
Participants 46-60 years of age - repeat vaccination - Pfizer bivalent COVID-19 vaccine	
Arm type	Experimental
Investigational medicinal product name	Comirnaty Original/Omicron BA.1
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Dispersion for injection
Routes of administration	Intramuscular use
Dosage and administration details:	
One dose (0.3 mL) contains 15 micrograms of tozinameran and 15 micrograms of riltozinameran, a COVID-19 mRNA Vaccine (embedded in lipid nanoparticles).	

Arm title	31-45 years of age - repeat vaccination - Moderna bivalent
Arm description:	
Participants 31-45 years of age - repeat vaccination - Moderna bivalent COVID-19 vaccine	
Arm type	Experimental
Investigational medicinal product name	Spikevax bivalent Original/Omicron BA.1
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Dispersion for infusion
Routes of administration	Intramuscular use
Dosage and administration details:	
One dose (0.5 mL) contains 25 micrograms of elasomeran and 25 micrograms of imelasomeran, a COVID-19 mRNA Vaccine (nucleoside modified) (embedded in lipid nanoparticles).	
Arm title	46-60 years of age - repeat vaccination - Moderna bivalent
Arm description:	
Participants 46-60 years of age - repeat vaccination - Moderna bivalent COVID-19 vaccine	
Arm type	Experimental
Investigational medicinal product name	Spikevax bivalent Original/Omicron BA.1
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Dispersion for injection
Routes of administration	Intramuscular use
Dosage and administration details:	
One dose (0.5 mL) contains 25 micrograms of elasomeran and 25 micrograms of imelasomeran, a COVID-19 mRNA Vaccine (nucleoside modified) (embedded in lipid nanoparticles).	

Number of subjects in period 3[32]	12 -17 years of age - repeat vaccination - Pfizer bivalent	18-30 years of age - repeat vaccination - Pfizer bivalent	31-45 years of age - repeat vaccination - Pfizer bivalent
Started	13	56	56
28 days post repeat vaccination (D1)	14	53	47
6 months post repeat vaccination (D2)	11	45	42
12 months post repeat vaccination (D3)	12	47	40
Completed	12	47	40
Not completed	3	15	18
Physician decision	-	1	2
Crucial measurement missing	1	9	11

Participant discontinuation	2	2	1
Took a booster before end of study period 1	-	-	2
Lost to follow-up	-	3	2
Joined	2	6	2
Late recruitment	2	6	2
Late recruitment reason	Included after repeat vaccination	Included after repeat vaccination	Included after repeat vaccination

Number of subjects in period 3[32]	46-60 years of age - repeat vaccination - Pfizer bivalent	31-45 years of age - repeat vaccination - Moderna bivalent	46-60 years of age - repeat vaccination - Moderna bivalent
Started	4	6	35
28 days post repeat vaccination (D1)	3	4	27
6 months post repeat vaccination (D2)	3	4	24
12 months post repeat vaccination (D3)	2	4	24
Completed	2	4	24
Not completed	2	2	14
Physician decision	-	-	1
Crucial measurement missing	1	2	12
Participant discontinuation	-	-	-
Took a booster before end of study period 1	1	-	1
Lost to follow-up	-	-	-
Joined	0	0	3
Late recruitment	-	-	3
Late recruitment reason			Included after repeat vaccination

Notes:

[32] - 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: The trial started with the primary series. Later on, booster vaccinations were available that not all participants took. Each period is a separate part of the trial. Participants could then choose to enroll in the second period and/or the third period. Group allocation in the other periods was based on the booster vaccination, irrespective of the vaccination in the primary series. The number of participants starting another period is thus not equal to the number completing a previous period.

Baseline characteristics

Reporting groups	
Reporting group title	COVID immunization primary series

Reporting group description: -

Reporting group values	COVID immunization primary series	Total	
Number of subjects	1459	1459	
Age categorical Units: Subjects			
Children (2-11 years)	47	47	
Adolescents (12-17 years)	143	143	
Adults (18-64 years)	1269	1269	
Age continuous Units: years			
arithmetic mean	32.03		
full range (min-max)	5 to 60	-	
Gender categorical Units: Subjects			
Female	935	935	
Male	520	520	
Other	4	4	

End points

End points reporting groups

Reporting group title	5-11 years of age - primary vaccination - Pfizer-BioNTech
Reporting group description: Participants 5-11 years of age - primary vaccination - Pfizer-BioNTech COVID-19 vaccine	
Reporting group title	12-17 years of age - primary vaccination - Pfizer-BioNTech
Reporting group description: Participants 12 -17 years of age - primary vaccination - Pfizer-BioNTech COVID-19 vaccine	
Reporting group title	18-30 years of age - primary vaccination - Pfizer-BioNTech
Reporting group description: Participants 18-30 years of age - primary vaccination - Pfizer-BioNTech COVID-19 vaccine	
Reporting group title	31-45 years of age - primary vaccination - Pfizer-BioNTech
Reporting group description: Participants 31-45 years of age - primary vaccination - Pfizer-BioNTech COVID-19 vaccine	
Reporting group title	46-60 years of age - primary vaccination - Pfizer-BioNTech
Reporting group description: Participants 46-60 years of age - primary vaccination - Pfizer-BioNTech COVID-19 vaccine	
Reporting group title	18-30 years of age - primary vaccination - Moderna
Reporting group description: Participants 18-30 years of age - primary vaccination - Moderna COVID-19 vaccine	
Reporting group title	31-45 years of age - primary vaccination - Moderna
Reporting group description: Participants 31-45 years of age - primary vaccination - Moderna COVID-19 vaccine	
Reporting group title	46-60 years of age - primary vaccination - Moderna
Reporting group description: Participants 46-60 years of age - primary vaccination - Moderna COVID-19 vaccine	
Reporting group title	18-30 years of age - primary vaccination - Jcovden
Reporting group description: Participants 18-30 years of age - primary vaccination - Jcovden (previously COVID-19 Vaccine Janssen)	
Reporting group title	31-45 years of age - primary vaccination - Jcovden
Reporting group description: Participants 31-45 years of age - primary vaccination - Jcovden (previously COVID-19 Vaccine Janssen)	
Reporting group title	46-60 years of age - primary vaccination - Jcovden
Reporting group description: Participants 46-60 years of age - primary vaccination - Jcovden (previously COVID-19 Vaccine Janssen)	
Reporting group title	18-30 years of age unknown vaccine primary vaccination
Reporting group description: Participants 18-30 years of age - primary unknown vaccination	
Reporting group title	31-45 years of age unknown vaccine primary vaccination
Reporting group description: Participants 31-45 years of age - primary unknown vaccination	
Reporting group title	46-60 years of age unknown vaccine primary vaccination
Reporting group description: Participants 46-60 years of age - primary unknown vaccination	
Reporting group title	12 -17 years of age - 1st Booster - Pfizer–BioNTech
Reporting group description: Participants 12 -17 years of age - 1st Booster - Pfizer–BioNTech COVID-19 vaccine	
Reporting group title	18-30 years of age - 1st booster - Pfizer–BioNTech

Reporting group description:
Participants 18 -30 years of age - 1st Booster - Pfizer–BioNTech COVID-19 vaccine

Reporting group title	31-45 years of age - 1st booster - Pfizer–BioNTech

Reporting group description:
Participants 31-45 years of age - 1st Booster - Pfizer–BioNTech COVID-19 vaccine

Reporting group title	46-60 years of age - 1st booster - Pfizer–BioNTech

Reporting group description:
Participants 46-60 years of age - 1st Booster - Pfizer–BioNTech COVID-19 vaccine

Reporting group title	18-30 years of age - 1st booster - Moderna

Reporting group description:
Participants 18-30 years of age - 1st Booster - Moderna COVID-19 Vaccine

Reporting group title	31-45 years of age - 1st booster - Moderna

Reporting group description:
Participants 31-45 years of age - 1st Booster - Moderna COVID-19 Vaccine

Reporting group title	46-60 years of age - 1st booster - Moderna

Reporting group description:
Participants 46-60 years of age - 1st Booster - Moderna COVID-19 Vaccine

Reporting group title	12 -17 years of age - repeat vaccination - Pfizer bivalent

Reporting group description:
Participants 31-45 years of age - repeat vaccination - Pfizer bivalent COVID-19 vaccine

Reporting group title	18-30 years of age - repeat vaccination - Pfizer bivalent

Reporting group description:
Participants 18-30 years of age - repeat vaccination - Pfizer bivalent COVID-19 vaccine

Reporting group title	31-45 years of age - repeat vaccination - Pfizer bivalent

Reporting group description:
Participants 31-45 years of age - repeat vaccination - Pfizer bivalent COVID-19 vaccine

Reporting group title	46-60 years of age - repeat vaccination - Pfizer bivalent

Reporting group description:
Participants 46-60 years of age - repeat vaccination - Pfizer bivalent COVID-19 vaccine

Reporting group title	31-45 years of age - repeat vaccination - Moderna bivalent

Reporting group description:
Participants 31-45 years of age - repeat vaccination - Moderna bivalent COVID-19 vaccine

Reporting group title	46-60 years of age - repeat vaccination - Moderna bivalent

Reporting group description:
Participants 46-60 years of age - repeat vaccination - Moderna bivalent COVID-19 vaccine

Subject analysis set title	Pre- primary vaccination immune response in adults (T0)
Subject analysis set type	Full analysis

Subject analysis set description:
Pre- primary vaccination immune response in adults (T0)

Subject analysis set title	1-3 days post 1st primary vaccination response in adults (T1)
Subject analysis set type	Full analysis

Subject analysis set description:
1-3 days post 1st primary vaccination immune response in adults (T1)

Subject analysis set title	Pre- primary vaccination immune response in adolescents (T0)
Subject analysis set type	Full analysis

Subject analysis set description:
Pre- primary vaccination immune response in adolescents (T0)

Subject analysis set title	1-3 days post 1st primary vaccination response in adolescents
Subject analysis set type	Full analysis

Subject analysis set description:

1-3 days post 1st primary vaccination response in adolescents (T1)

Subject analysis set title	VNT 28 days post primary vaccination(s) (T3)
Subject analysis set type	Full analysis

Subject analysis set description:

Virus neutralizing capacity of antibodies at T3 (28 days post primary vaccination(s))

Subject analysis set title	VNT Pre-booster vaccination (B0)
Subject analysis set type	Full analysis

Subject analysis set description:

Virus neutralizing capacity of antibodies at B0 (pre first booster vaccination)

Subject analysis set title	VNT 28 days post booster vaccination (B1)
Subject analysis set type	Full analysis

Subject analysis set description:

Virus neutralizing capacity of antibodies at B1 (28 days post booster vaccination)

Subject analysis set title	VNT Pre-repeat vaccination (D0)
Subject analysis set type	Full analysis

Subject analysis set description:

Virus neutralizing capacity of antibodies at D0 (pre repeat vaccination)

Subject analysis set title	VNT 28 days post repeat vaccination (D1)
Subject analysis set type	Full analysis

Subject analysis set description:

Virus neutralizing capacity of antibodies at D1 (28 days post repeat vaccination)

Subject analysis set title	ADCD 28 days post 2nd vaccination (T3)
Subject analysis set type	Full analysis

Subject analysis set description:

Complement deposition capacity of antibodies in MFI at T3 (28 days post 2nd COVID-19 vaccination)

Subject analysis set title	ADCP 28 days post 2nd vaccination (T3)
Subject analysis set type	Full analysis

Subject analysis set description:

Phagocytosis mediating capacity of antibodies in iMFI at T3 (28 days post 2nd COVID-19 vaccination)

Subject analysis set title	ADCC 28 days post 2nd vaccination (T3)
Subject analysis set type	Full analysis

Subject analysis set description:

% NK cell activation in cell based (NK-92) assay as a measure for ADCC inducing capacity of antibodies in serum at T3 (28 days post 2nd COVID-19 vaccination)

Subject analysis set title	MLF pre-primary COVID immunization (T0)
Subject analysis set type	Full analysis

Subject analysis set description:

MLF pre-primary COVID immunization (T0)

Subject analysis set title	MLF 28 days post 2nd COVID immunization (T3)
Subject analysis set type	Full analysis

Subject analysis set description:

MLF 28 days post 2nd COVID immunization (T3)

Subject analysis set title	MLF 12 months post 2nd COVID immunization (T5)
Subject analysis set type	Full analysis

Subject analysis set description:

MLF 12 months post 2nd COVID immunization (T5)

Subject analysis set title	MLF pre- first booster (B0)

Subject analysis set type	Full analysis
Subject analysis set description:	
MLF pre- first booster (B0)	
Subject analysis set title	MLF 28 days post booster 1 (B1)
Subject analysis set type	Full analysis
Subject analysis set description:	
MLF 28 days post booster 1 (B1)	
Subject analysis set title	MLF 12 months post booster 1 (B3)
Subject analysis set type	Full analysis
Subject analysis set description:	
MLF 12 months post booster 1 (B3)	
Subject analysis set title	MLF pre- repeat vaccination (D0)
Subject analysis set type	Full analysis
Subject analysis set description:	
MLF pre- repeat vaccination (D0)	
Subject analysis set title	MLF 28 days post repeat vaccination (D1)
Subject analysis set type	Full analysis
Subject analysis set description:	
MLF 28 days post repeat vaccination (D1)	
Subject analysis set title	Tcel ELISpot: pre-primary COVID immunization (T0)
Subject analysis set type	Full analysis
Subject analysis set description:	
Tcel ELISpot: pre-primary COVID immunization (T0)	
Subject analysis set title	Tcel ELISpot: post 2nd COVID immunization (T3)
Subject analysis set type	Full analysis
Subject analysis set description:	
Tcel ELISpot: post 2nd COVID immunization (T3)	
Subject analysis set title	Tcel ELISpot: pre- first booster (B0)
Subject analysis set type	Full analysis
Subject analysis set description:	
Tcel ELISpot: pre- first booster (B0)	
Subject analysis set title	Tcel ELISpot: 28 days post first booster (B1)
Subject analysis set type	Full analysis
Subject analysis set description:	
Tcel ELISpot: 28 days post first booster (B1)	
Subject analysis set title	Tcel ELISpot: pre-repeat vaccination (D0)
Subject analysis set type	Full analysis
Subject analysis set description:	
Tcel ELISpot: pre-repeat vaccination (D0)	
Subject analysis set title	Tcel ELISpot: 28 days post repeat vaccination (D1)
Subject analysis set type	Full analysis
Subject analysis set description:	
Tcel ELISpot: 28 days post repeat vaccination (D1)	
Subject analysis set title	Tcel ELISpot: 12 months post repeat vaccination (D3)
Subject analysis set type	Full analysis
Subject analysis set description:	
Tcel ELISpot: 12 months post repeat vaccination (D3)	
Subject analysis set title	Bcel ELISpot: pre-primary COVID immunization (T0)
Subject analysis set type	Full analysis
Subject analysis set description:	
Bcel ELISpot: pre-primary COVID immunization (T0)	
Subject analysis set title	Bcel ELISpot: post 2nd COVID immunization (T3)

Subject analysis set type	Full analysis
Subject analysis set description:	
Bcel ELISpot: post 2nd COVID immunization (T3)	
Subject analysis set title	Bcel ELISpot: pre- first booster (B0)
Subject analysis set type	Full analysis
Subject analysis set description:	
Bcel ELISpot: pre- first booster (B0)	
Subject analysis set title	Bcel ELISpot: 28 days post first booster (B1)
Subject analysis set type	Full analysis
Subject analysis set description:	
Bcel ELISpot: 28 days post first booster (B1)	
Subject analysis set title	Reactogenicity: first 5 days post primary vaccination
Subject analysis set type	Full analysis
Subject analysis set description:	
Reactogenicity; AEs recorded the first 5 days after 1st COVID 19 vaccination or until symptoms subside	

Primary: Vaccine-specific IgG GMC at day 28 after completion of COVID-19 vaccination

End point title	Vaccine-specific IgG GMC at day 28 after completion of COVID-19 vaccination
End point description:	
Measuring vaccine (e.g. Spike protein)- specific serum IgG GMC in Dutch healthy subject at day 28 after completion of COVID-19 vaccination by bead-based multiplex immune assay (MIA).	
End point type	Primary
End point timeframe:	
Period 1 - period 3	

End point values	5-11 years of age - primary vaccination - Pfizer-BioNTech	12-17 years of age - primary vaccination - Pfizer-BioNTech	18-30 years of age - primary vaccination - Pfizer-BioNTech	31-45 years of age - primary vaccination - Pfizer-BioNTech
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	29	121[1]	313	347[2]
Units: BAU/ml				
geometric mean (confidence interval 95%)				
Conc_COV19S1	4427.8 (3222.1 to 5633.5)	5345.4 (4750.9 to 5939.9)	3588.9 (3345.9 to 3831.8)	2537.6 (2358 to 2717.1)
Conc_COV19N	173.5 (50.1 to 296.8)	9.3 (5.5 to 13.1)	9.9 (5 to 14.8)	7.1 (5.5 to 8.8)
Conc_COV19RBD	2599.5 (1809.5 to 3389.5)	3777.2 (3299.9 to 4254.5)	2475.5 (2304.5 to 2646.6)	1824.2 (1691.2 to 1957.2)

Notes:

[1] - 1 subject was excluded from the analysis due to illness

[2] - 3 subjects were excluded from the analysis due to illness.

End point values	46-60 years of age - primary vaccination - Pfizer-BioNTech	18-30 years of age - primary vaccination - Moderna	31-45 years of age - primary vaccination - Moderna	46-60 years of age - primary vaccination - Moderna

Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	136[3]	19	43	23[4]
Units: BAU/ml				
geometric mean (confidence interval 95%)				
Conc_COV19S1	2699.7 (2297.5 to 3101.8)	5696 (3964.6 to 7427.3)	3743.9 (3065.7 to 4422.2)	3654.1 (2653 to 4655.2)
Conc_COV19N	16 (9.5 to 22.5)	8.6 (5.8 to 14.4)	11 (2.1 to 20)	48 (-31.8 to 127.8)
Conc_COV19RBD	1918.8 (1646.4 to 2191.3)	3868.9 (2668.6 to 5069.1)	2814.8 (2301.5 to 3328)	2686.5 (1975.6 to 3397.4)

Notes:

[3] - 4 subjects were excluded, 1 due to use of medication and 3 due to illnesses

[4] - 1 subject was excluded due to medication

End point values	18-30 years of age - primary vaccination - Jcovden	31-45 years of age - primary vaccination - Jcovden	46-60 years of age - primary vaccination - Jcovden	18-30 years of age unknown vaccine primary vaccination
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	26	11	8[5]	0[6]
Units: BAU/ml				
geometric mean (confidence interval 95%)				
Conc_COV19S1	1127.5 (334.2 to 1920.8)	52.1 (40.7 to 63.5)	779.4 (-317.6 to 1876.4)	(to)
Conc_COV19N	8.6 (3.5 to 13.6)	2.2 (0.9 to 3.6)	63.4 (-68.9 to 195.6)	(to)
Conc_COV19RBD	871.2 (308.8 to 1433.5)	52.5 (35.6 to 69.4)	697.9 (24.2 to 1371.5)	(to)

Notes:

[5] - 1 subject was excluded due to illness

[6] - No MIA data obtained, participants dropped out and no samples were collected.

End point values	31-45 years of age unknown vaccine primary vaccination	46-60 years of age unknown vaccine primary vaccination	12 -17 years of age - 1st Booster - Pfizer–BioNTech	18-30 years of age - 1st booster - Pfizer–BioNTech
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[7]	0[8]	6	250[9]
Units: BAU/ml				
geometric mean (confidence interval 95%)				
Conc_COV19S1	(to)	(to)	20322.4 (5507.6 to 35137.2)	7479.4 (6552.9 to 8405.8)
Conc_COV19N	(to)	(to)	8.1 (1 to 15.3)	31.6 (13.6 to 49.7)
Conc_COV19RBD	(to)	(to)	10820.9 (4490.1 to 17151.7)	4680.1 (3948.4 to 5411.7)

Notes:

[7] - No MIA data obtained, participants dropped out and no samples were collected.

[8] - No MIA data obtained, participants dropped out and no samples were collected.

[9] - 1 subject was excluded due to medication

End point values	31-45 years of age - 1st booster - Pfizer–BioNTech	46-60 years of age - 1st booster - Pfizer–BioNTech	18-30 years of age - 1st booster - Moderna	31-45 years of age - 1st booster - Moderna
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	356[10]	40[11]	2	17
Units: BAU/ml				
geometric mean (confidence interval 95%)				
Conc_COV19S1	5962.8 (5398.3 to 6527.4)	6995.9 (5342.3 to 8649.5)	19969.5 (-1442056.2 to 181995.2)	8942.5 (3299.1 to 14586)
Conc_COV19N	21.2 (7.2 to 35.3)	76.1 (-27.1 to 179.3)	3.8 (-31.7 to 39.2)	5.9 (1.8 to 10.1)
Conc_COV19RBD	3608.2 (3224.8 to 3991.6)	4405.7 (3235 to 5576.3)	15429.9 (-130497.9 to 161357.8)	5558 (1919.3 to 9196.7)

Notes:

[10] - 1 subject was excluded due to illness

[11] - 3 subjects were excluded, 1 due to medication and 2 due to illnesses

End point values	46-60 years of age - 1st booster - Moderna	12 -17 years of age - repeat vaccination - Pfizer bivalent	18-30 years of age - repeat vaccination - Pfizer bivalent	31-45 years of age - repeat vaccination - Pfizer bivalent
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	127[12]	10	47	42
Units: BAU/ml				
geometric mean (confidence interval 95%)				
Conc_COV19S1	8935.8 (7839.4 to 10032.1)	9844.7 (6774 to 12915.3)	9845.2 (8082 to 11608.5)	9225.5 (7372.8 to 11078.2)
Conc_COV19N	18.1 (-1.7 to 37.8)	130.9 (-29.9 to 291.7)	43.2 (23.8 to 62.6)	27.4 (16.6 to 38.1)
Conc_COV19RBD	5654 (4872.5 to 6435.5)	5923.9 (3853.8 to 7994)	6297.1 (5206.9 to 7387.3)	5965 (4725 to 7205)

Notes:

[12] - 3 subjects were excluded, 1 due to medication, 2 due to illnesses

End point values	46-60 years of age - repeat vaccination - Pfizer bivalent	31-45 years of age - repeat vaccination - Moderna bivalent	46-60 years of age - repeat vaccination - Moderna bivalent	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2	4	24	
Units: BAU/ml				
geometric mean (confidence interval 95%)				
Conc_COV19S1	9591.6 (-11912.4 to 31095.6)	10448.8 (-1205 to 22102.5)	15705.9 (12050.7 to 19361.2)	

Conc_COV19N	136.4 (-1334.2 to 1607)	9.6 (-4.7 to 23.9)	37.7 (14.6 to 60.8)	
Conc_COV19RBD	7000.4 (-3488 to 17488.7)	7006.6 (758.2 to 13255)	11390.2 (8453.4 to 14327)	

Statistical analyses

Statistical analysis title	Vaccine-specific serum IgG pre- vs 28 days post

Statistical analysis description:

IgG antibody responses to the S1 protein prior to and after primary vaccine doses. Geometric mean IgG concentrations with 95% confidence interval. Differences in antibody levels between time points were analyzed with two-tailed Wilcoxon matched-pairs signed-rank test. Subjects in this analysis = 290, with each 2 timepoints for comparison within group 'Period 1 31-45 years with the Pfizer vaccine'

Comparison groups	31-45 years of age - primary vaccination - Pfizer-BioNTech v 5-11 years of age - primary vaccination - Pfizer-BioNTech v 12-17 years of age - primary vaccination - Pfizer-BioNTech v 18-30 years of age - primary vaccination - Pfizer-BioNTech v 46-60 years of age - primary vaccination - Pfizer-BioNTech v 18-30 years of age - primary vaccination - Moderna v 31-45 years of age - primary vaccination - Moderna v 46-60 years of age - primary vaccination - Moderna v 18-30 years of age - primary vaccination - Jcovden v 31-45 years of age - primary vaccination - Jcovden v 46-60 years of age - primary vaccination - Jcovden
Number of subjects included in analysis	1076
Analysis specification	Pre-specified
Analysis type	other[13]
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)

Notes:

[13] - Only participants with a pre sample (T0) and a 28 days post vaccination sample (T3) were included. Therefore; only 290 subjects were included in the analysis

Secondary: Humoral, cellular and innate COVID-19 vaccine-induced immune responses in adults

End point title	Humoral, cellular and innate COVID-19 vaccine-induced immune responses in adults

End point description:

Innate COVID-19 vaccine-induced immune responses in adults.
The following variables were included in the panel for this analysis:
IL-1b
IL-6
TNFa
IP10*
IFNL1
IL-8
IL-12p70
IFNa2
IFNL2_3
GMCSF
IFNb
IL-10
IFNy
IL-8
IP10 _2
Eotaxin
TARC
MCP1

RANTES
MIP1a
MIG
ENA78
MIP3a
GROa
ITAC
MIP1b
IL-5
IL-13
IL-2
IL-6_2
IL-9
IL-10_2
IFNy_2
TNFa_2
IL-17A
IL-17F
IL-4
IL-22
TSLP
IL-1a
IL-1b_2
GMCSF_2
IFNa2_2
IL-23
IL-12p40
IL-12p70 _2
IL-15
IL-18
IL-11
IL-27
IL-33
IL-1β
IL-6
TNF-α
IP-10*
IFN-λ1
IL-8
IL-12p70
IFN-α2
IFN-λ2/3
GM-CSF
IFN-β
IL-10
IFN-γ
IL-8
IP-10
Eotaxin
TARC
MCP-1
RANTES
MIP-1α
MIG
ENA-78
MIP-3α
GROα
I-TAC
MIP-1β

*IP10 tested twice (different kits)

However, not all variables showed differences between the two timepoints. Therefor, 5 variables are displayed for this end point: CXCL10 (IP10), IFNy, CXCL9 (MIG), CCL20 (Mip3a) and CXCL11 (ITAC).

End point type	Secondary
End point timeframe:	
Pre-primary vaccination - 1-3 days post 1st COVID primary vaccination	

End point values	Pre- primary vaccination immune response in adults (T0)	1-3 days post 1st primary vaccination response in adults (T1)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	39	58		
Units: pg/ml				
geometric mean (confidence interval 95%)				
CXCL10 (IP10)	46.9 (38.6 to 55.2)	157 (114 to 200)		
IFNy	9.8 (-8 to 27.7)	60.5 (-0.5 to 121.5)		
CXCL9 (MIG)	282.7 (-235 to 800.5)	296.7 (-73.8 to 667.1)		
CCL20 (Mip3a)	3.4 (1.4 to 5.4)	5.8 (3.8 to 7.9)		
CXCL11 (ITAC)	13.9 (10.3 to 17.6)	32 (22.5 to 41.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Virus neutralizing capacity of antibodies induced by COVID-19 vaccination

End point title	Virus neutralizing capacity of antibodies induced by COVID-19 vaccination

End point description:

Virus neutralizing capacity of antibodies induced by COVID-19 vaccination

End point type	Secondary

End point timeframe:

28 days post primary vaccination(s) (T3)
Pre-booster vaccination (B0)
28 days post booster vaccination (B1)
Pre- repeat vaccination (D0)
28 days post repeat vaccination (D1)

End point values	VNT 28 days post primary vaccination(s) (T3)	VNT Pre-booster vaccination (B0)	VNT 28 days post booster vaccination (B1)	VNT Pre-repeat vaccination (D0)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	57	23	39	11
Units: VNT50				
geometric mean (confidence interval 95%)	221.3 (135.5 to 307.2)	413.4 (124.5 to 702.3)	1454.3 (1117.5 to 1791)	439.5 (-33.1 to 912)

End point values	VNT 28 days post repeat vaccination (D1)			
Subject group type	Subject analysis set			
Number of subjects analysed	11			
Units: VNT50				
geometric mean (confidence interval 95%)	1109.1 (441.1 to 1777.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Fc functionality: Complement deposition capacity of antibodies in MFI

End point title	Fc functionality: Complement deposition capacity of antibodies in MFI

End point description:

Complement deposition capacity of antibodies in MFI

End point type	Secondary

End point timeframe:

28 days post 2nd COVID-19 vaccination (T3)

End point values	ADCD 28 days post 2nd vaccination (T3)			
Subject group type	Subject analysis set			
Number of subjects analysed	120			
Units: MFI				
geometric mean (confidence interval 95%)				
experiment AG_044	5841.9 (5168 to 6515.8)			
experiment AG_052	1834.8 (1025.1 to 2644.5)			
experiment AG_061	302.8 (270.1 to 335.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Fc functionality: Phagocytosis mediating capacity of antibodies in iMFI

End point title	Fc functionality: Phagocytosis mediating capacity of antibodies in iMFI

End point description:

Phagocytosis mediating capacity of antibodies in iMFI

End point type	Secondary

End point timeframe:

28 days post 2nd COVID-19 vaccination (T3)

End point values	ADCP 28 days post 2nd vaccination (T3)			
Subject group type	Subject analysis set			
Number of subjects analysed	120			
Units: iMFI				
geometric mean (confidence interval 95%)				
experiment AG_036	445.3 (333.4 to 557.2)			
experiment AG_046	1187.6 (1054.9 to 1320.3)			
experiment AG_059	1101.8 (946 to 1257.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Fc functionality: % NK cell activation in cell based (NK-92) assay as a measure for ADCC inducing capacity of antibodies in serum

End point title	Fc functionality: % NK cell activation in cell based (NK-92) assay as a measure for ADCC inducing capacity of antibodies in serum

End point description:

% NK cell activation in cell based (NK-92) assay as a measure for ADCC inducing capacity of antibodies in serum

End point type	Secondary

End point timeframe:

28 days post 2nd COVID-19 vaccination (T3)

End point values	ADCC 28 days post 2nd vaccination (T3)			
Subject group type	Subject analysis set			
Number of subjects analysed	120			
Units: %CD107a+				
geometric mean (confidence interval 95%)				
experiment AG_053	4 (3.7 to 4.4)			
experiment AG_058	13.3 (11.8 to 14.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: COVID-19 vaccine-induced antibodies in nasal mucosal lining fluid

End point title	COVID-19 vaccine-induced antibodies in nasal mucosal lining fluid

End point description:

Measuring vaccine (e.g. Spike protein)-specific nasasl IgG and IgA GMC in Dutch healthy subjects

End point type	Secondary

End point timeframe:

pre- primary COVID immunization (T0) - 28 days post repeat vaccination (D1)

End point values	MLF pre-primary COVID immunization (T0)	MLF 28 days post 2nd COVID immunization (T3)	MLF 12 months post 2nd COVID immunization (T5)	MLF pre- first booster (B0)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	76	237	30	65
Units: AU/ml				
geometric mean (confidence interval 95%)				
IgG_Conc_COV19S1	0.1 (0 to 0.2)	25.6 (20.6 to 30.5)	29.7 (18.6 to 40.7)	6.1 (3.3 to 8.9)
IgG_Conc_COV19N	0.6 (0.4 to 0.8)	2 (1.4 to 2.7)	33.4 (-8.3 to 75.1)	2 (1.2 to 2.8)
IgA_Conc_COV19S1	0.6 (0.3 to 0.8)	0.7 (0.5 to 0.9)	10.1 (5.6 to 14.6)	1 (0.2 to 1.8)
IgA_Conc_COV19N	1.9 (1.4 to 2.4)	1.8 (1.5 to 2.2)	3 (1.8 to 4.3)	1.1 (0.9 to 1.3)

End point values	MLF 28 days post booster 1 (B1)	MLF 12 months post booster 1 (B3)	MLF pre-repeat vaccination (D0)	MLF 28 days post repeat vaccination (D1)

Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	146	60	26	25
Units: AU/ml				
geometric mean (confidence interval 95%)				
IgG_Conc_COV19S1	56.3 (42.1 to 70.6)	34.9 (24.7 to 45)	59.3 (20.2 to 98.5)	108.4 (65.1 to 151.6)
IgG_Conc_COV19N	4.2 (1.9 to 6.5)	25.1 (8.5 to 41.8)	8 (2 to 14)	8.8 (1.1 to 16.5)
IgA_Conc_COV19S1	2.1 (1.3 to 3)	7.3 (3.4 to 11.2)	7.4 (2.3 to 12.4)	4.1 (2.5 to 5.6)
IgA_Conc_COV19N	2 (1.2 to 2.8)	2.7 (1.6 to 3.8)	2.1 (1.3 to 3)	2.3 (1.2 to 3.4)

Statistical analyses

No statistical analyses for this end point

Secondary: Measuring antibody-secreting IFN-gamma producing T cells by ELISPOT assays

End point title	Measuring antibody-secreting IFN-gamma producing T cells by ELISPOT assays
End point description: Measuring IFN-gamma producing T cells by ELISPOT assays	
End point type	Secondary
End point timeframe: pre primary COVID immunization (T0) - 12 months post repeat vaccination (D3)	

End point values	Tcel ELISpot: pre-primary COVID immunization (T0)	Tcel ELISpot: post 2nd COVID immunization (T3)	Tcel ELISpot: pre- first booster (B0)	Tcel ELISpot: 28 days post first booster (B1)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	60[14]	118[15]	20[16]	60
Units: IFNg spots per 2x10^5 PBMC				
geometric mean (confidence interval 95%)				
Original strain S1+S2 (per 2x10^5 PBMC) - BLANK	3 (1.7 to 4.3)	29.5 (23.8 to 35.1)	8.2 (2.9 to 13.6)	35.1 (21.3 to 48.9)

Notes:

[14] - 3 subjects were excluded from the analyses due to low PHA response and low recovery.

[15] - 2 subjects were excluded from the analyses due to low PHA response and low recovery.

[16] - 3 subjects were excluded. 1 due to low PHA response, 1 due to no cells, 1 due to high blank

End point values	Tcel ELISpot: pre-repeat vaccination (D0)	Tcel ELISpot: 28 days post repeat vaccination (D1)	Tcel ELISpot: 12 months post repeat vaccination (D3)	

Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	30	32	32	
Units: IFNg spots per 2x10^5 PBMC				
geometric mean (confidence interval 95%)				
Original strain S1+S2 (per 2x10^5 PBMC) - BLANK	26.6 (18.6 to 34.6)	40.7 (18.4 to 63.1)	28.9 (15.4 to 42.4)	

Statistical analyses

No statistical analyses for this end point

Secondary: Measuring antibody-secreting B cells by ELISPOT assays

End point title	Measuring antibody-secreting B cells by ELISPOT assays

End point description:

Measuring antibody-secreting B cells by EISPOT assays

End point type	Secondary

End point timeframe:

pre primary COVID immunization (T0) - 28 days post first booster (B1)

End point values	Bcel ELISpot: pre-primary COVID immunization (T0)	Bcel ELISpot: post 2nd COVID immunization (T3)	Bcel ELISpot: pre- first booster (B0)	Bcel ELISpot: 28 days post first booster (B1)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	8	40	8	19[17]
Units: IFNg spots per 2x10^5 PBMC				
geometric mean (confidence interval 95%)				
Original strain S1 (per 2x10^5 PBMC) - BLANK	1.8 (0 to 3.7)	9.4 (6.5 to 12.3)	12 (5.7 to 18.3)	80.7 (36.5 to 124.8)

Notes:

[17] - 1 subject was excluded from the analyses due medication taken at this timepoint

Statistical analyses

No statistical analyses for this end point

Secondary: Reactogenicity self-reported in questionnaires shortly after vaccination

End point title	Reactogenicity self-reported in questionnaires shortly after vaccination

End point description:

The standard symptoms asked via the diary were: pyrexia, vaccination site erythema, vaccination site swelling, vaccination site induration, vaccination site bruising, vaccination site pain, vaccination site movement impairment, headache, fatigue, myalgia, arthralgia, malaise.
Participants could also rapport other symptoms spontaneously by the diary.

End point type	Secondary

End point timeframe:

Local, AEs recorded the first 5 days after 1st COVID 19 vaccination or until symptoms subside

End point values	Reactogenicity: first 5 days post primary vaccination			
Subject group type	Subject analysis set			
Number of subjects analysed	169			
Units: NA				
Pyrexia	19			
Vaccination site erythema	35			
Vaccination site swelling	25			
Vaccination site induration	33			
Vaccination site bruising	17			
Vaccination site pain	151			
Vaccination site movement impairment	106			
Headache	70			
Fatigue	106			
Myalgia	132			
Arthralgia	21			
Malaise	64			
Angioedema	1			
Axillary pain	1			
Cough	1			
Diarrhoea	1			
Dizziness	8			
Hypoaesthesia	1			
Limb discomfort	1			
Mood swings	1			
Musculoskeletal stiffness	5			
Nasopharyngitis	2			
Nausea	8			
Night sweats	1			
Noninfective gingivitis	1			
Oligomenorrhoea	2			
Oropharyngeal pain	6			
Pain in extremity	2			
Paraesthesia	3			
Restlessness	1			
Therapeutic response decreased	1			
Tremor	1			
Vaccination site coldness	1			
Vaccination site hypoaesthesia	1			
Vaccination site pruritus	1			
Vaccination site warmth	2			
Vasoconstriction	1			
Poor quality sleep	2			
Migraine	1			

Hot flush	2			
Dyspnoea	1			
Heart rate increased	1			
Gingival pain	1			
Body temperature fluctuation	1			
Toothache	1			
Rhinorrhoea	1			
Gingival ulceration	1			
Eye pain	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Humoral, cellular and innate COVID-19 vaccine-induced immune responses in adolescents

End point title	Humoral, cellular and innate COVID-19 vaccine-induced immune responses in adolescents

End point description:

Innate COVID-19 vaccine-induced immune responses in adolescents.
The following variables were included in the panel for this analysis:
IL-1b
IL-6
TNFa
IP10*
IFNL1
IL-8
IL-12p70
IFNa2
IFNL2_3
GMCSF
IFNb
IL-10
IFNy
IL-8
IP10 _2
Eotaxin
TARC
MCP1
RANTES
MIP1a
MIG
ENA78
MIP3a
GROa
ITAC
MIP1b
IL-5
IL-13
IL-2
IL-6_2
IL-9
IL-10_2
IFNy_2
TNFa_2
IL-17A
IL-17F
IL-4
IL-22
TSLP
IL-1a

IL-1b_2
GMCSF_2
IFNa2_2
IL-23
IL-12p40
IL-12p70 _2
IL-15
IL-18
IL-11
IL-27
IL-33
IL-1β
IL-6
TNF-α
IP-10*
IFN-λ1
IL-8
IL-12p70
IFN-α2
IFN-λ2/3
GM-CSF
IFN-β
IL-10
IFN-γ
IL-8
IP-10
Eotaxin
TARC
MCP-1
RANTES
MIP-1α
MIG
ENA-78
MIP-3α
GROα
I-TAC
MIP-1β

*IP10 tested twice (different kits)

However, not all variables showed differences between the two timepoints. Therefor, 3 variables are displayed for this end point: CXCL10 (IP10), CXCL9 (MIG) and CXC11 (ITAC)

End point type	Secondary

End point timeframe:

Pre- primary vaccination - 1-3 days post 1st primary vaccination

End point values	Pre- primary vaccination immune response in adolescents (T0)	1-3 days post 1st primary vaccination response in adolescents		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19	19		
Units: pg/ml				
geometric mean (confidence interval 95%)				
CXCL10 (IP10)	65 (55.8 to 74.1)	191.6 (138 to 245.2)		
CXCL9 (CIG)	443.4 (341.1 to 545.6)	716.9 (581.7 to 852)		
CXC11 (ITAC)	90.6 (73.6 to 107.7)	192.3 (145.2 to 239.4)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Any adverse event spontaneously reported by the subject related to and occurring within one week after nasal fluid collection or blood sampling.

Adverse event reporting additional description:

There were no SAEs and SUSARs.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	27

Reporting groups

Reporting group title	COVID Immunization

Reporting group description:

237 participants were asked to fill in the diary to report adverse events.
The other participants of the whole study population could report AE's spontaneously to the study teams, what was done by 25 participants.

Serious adverse events	COVID Immunization		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 1459 (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	COVID Immunization		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	180 / 1459 (12.34%)		
General disorders and administration site conditions			
Vaccination site pain			
subjects affected / exposed	151 / 1459 (10.35%)		
occurrences (all)	151		
Vaccination site movement impairment			

subjects affected / exposed	106 / 1459 (7.27%)		
occurrences (all)	106		
Fatigue			
subjects affected / exposed	106 / 1459 (7.27%)		
occurrences (all)	106		
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	132 / 1459 (9.05%)		
occurrences (all)	132		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 May 2021	To increase the chance of including enough participants in the study. More and more persons are invited for the corona vaccination. In order to include enough currently unvaccinated persons in the trial we propose to add the following recruitment option: Also persons participating in other RIVM studies can be invited, provided they consented to be contacted for additional research and meet the inclusion criteria.
03 June 2021	To increase the chance of including enough participants in the study. More and more persons are invited for the corona vaccination. In order to include enough currently unvaccinated persons in the trial we propose to add the following recruitment option: Lastly, also spontaneous applications from interested citizens are allowed. This can occur if they read about this study on the website (which includes the PIF&IC) or in the news or hear from friends.
25 June 2021	Later inclusion until T3 or T3s (28 days after the last vaccination) where necessary. The IIVAC study follows the national COVID-19 immunization program. The current inclusion into the subgroup, where we look more deeply into the (cellular) immunity, is lower than anticipated. For the general group (5 fingerprick samples in 12 months), the number of inclusions is going well (recruitment was possible all over the Netherlands). As soon as participants are vaccinated we will know the exact distribution over the vaccine groups. For the subgroup, participation is only possible for habitants of the province of Utrecht (or places within one hour drive from the RIVM). Therefore the recruitment covers a smaller part of the population. Participation is currently lower then needed considering the pace of national vaccine roll out. The primary endpoint of the trial is at T3(s) (28 days after the last vaccination). At that timepoint the comparison over all RIVM trials is possible as well as the comparison between the IIVAC study and the risk group studies funded by ZonMW. In order to reach enough participants for the primary endpoint we will allow inclusion in the subgroup up until timepoint T3s. If necessary, we may allow participation in the general group up until timepoint T3 if specific vaccinated (age)segments are underrepresented.
15 July 2021	To monitor and evaluate immune responses after corona vaccination in children. In the IIVAC study we evaluate immune responses after COVID-19 immunization, following the national vaccination program. The immunization of children 12-18 years of age has started. In order to examine the immune response in these younger age groups we would like to add 2 age groups to the IIVAC study (12-18 years of age and 0-12 years of age). We will study the duration and quality of the immune response and compare these to the adult groups and risk groups. The 0-12 group will only start once vaccines are registered for this age group and vaccination is implemented in the Netherlands We aim to include the children for the general as well as for the subgroup part of the study. In the subset part we made some changes in order to reduce the burden. First, sampling volumes are lower (age dependent), limiting the possibility to fulfil all secondary objectives. At T0s and T1s we split the group in two subsets: the adaptive group with sampling at T0s, not T1s; and the innate group with sampling at T0s and T1s but with lower blood volumes per timepoint.

05 August 2021	Tto increase (by necessity) the blood volume sampled by venapuncture with 1 ml for children aged 8-18 years old at home visits T0s, T3s and T5s. Due to unforeseen production problems and the world-wide increase in demand of blood collection tubes, the 4 ml serum tubes that we intended to use for children aged 8-18 years are currently not available. Therefore, 5ml serum tubes will necessarily be used for blood collection in this age group. Effectively this means that at home visit T0s for the innate group, total collected blood volume will be 23 ml; for the adaptive group total collected blood volume will be 41 ml. At visit T3s and T5s, total collected blood volume will be 41 ml. This amount is still within the guidelines drafted by the Nederlandse Vereniging voor Klinische Chemie en Laboratoriumgeneeskunde and the Clinical and Labatory Standards institute and thus is unlikely to pose any additional risk in this age group.
18 November 2021	We intend to follow immune responses after the SARS-CoV-2 booster vaccination, in those participants that take the SARS-CoV-2 booster vaccination. This will result in the following follow up schedule based on the SARS-CoV-2 booster vaccination date: pre booster (B0) and at 28 days (B1), 6 months (B2) and 12 months (B3) post booster vaccination. This study schedule can be repeated in case of additional boosters of similar or other vaccines against COVID-19, e.g. multivalent vaccines against other variants of concern . The data collected will provide insight into vaccine-induced immunity pre and post SARS-CoV-2 booster vaccination. Currently around 150 participants aged 12-18 years have been enrolled in the study. The subjects have been recruited via random sampling from the Basisregistratie Personen (BRP). Inclusion of these subjects was closely monitored. Most subjects applied for participation after one or both vaccinations had been received as part of the Dutch national vaccination program. Inclusion of the subjects until T3(s) has been allowed as described in amendment 4 and a large number of participants already received one to two vaccinations. As a result the total number of T0 (baseline) samples is limited. In addition, the inclusion of subjects in the innate group is not yet completed. Therefore we want to allow the inclusion of additional unvaccinated participants aged 12-18 years to obtain a sufficient number of T0(s) samples. The additional unvaccinated participants can be 11 years of age at the time of enrolment (pre vaccination timepoint), and are 12 years of age at the time of vaccination. They will be asked to sign the 12 years of age IC form at enrolment. in addition, section 8.6 has been adjusted to allow the replacement of subjects (<18 years) in case samples cannot be used for the analysis. A broader window is considered to be acceptable for sample data analyses.
01 September 2022	Adding letters for the research packages of the timepoints; little adaptations in different used documents; textual adaptations in subject information letter; children 5-12 years of age were recruited for the venipuncture group
26 October 2022	To include follow-up after a repeat vaccination. Equal to the previous booster vaccination follow up: - Participants who don’t get the repeat vaccination: o Follow the current timepoints of the study o Afterwards, the study is ended - Participants who get the repeat vaccination, but don’t want to participate in the extended study: o The study will be ended. o When a timepoint was planned after the repeat vaccination, this timepoint will be cancelled. Unlike the previous booster vaccination follow-up we decided not to include everyone. The different vaccinations rounds resulted in several groups. Some of these groups are too small. Therefore we decided to make selections for the new follow-up. In making these selections we follow the distributions of the general population as much as possible. Furthermore, we look at the participants with the most complete follow-up/sampling time points. Related to this, some groups will be followed only with self-sampling finger pricks instead of a venepuncture by homevisits.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/35396570

http://www.ncbi.nlm.nih.gov/pubmed/36680141

http://www.ncbi.nlm.nih.gov/pubmed/35891550