Clinical trial results:
A Phase 2, Comparative Randomised Trial to Evaluate the impact of reduced COVID-19 mRNA vaccination regimens on immunological responses and reactogenicity in paediatric subjects with and without prior SARS-CoV-2 infection (CoVacc)

Summary

EudraCT number	2021-005043-71
Trial protocol	NL NO DE SE GR
Global end of trial date	06 May 2024

Results information

Result version number	v1 (current)
This version publication date	22 November 2024
First version publication date	22 November 2024
Summary attachment (see zip file)	CoVacc Summary Clinical Study Report (CoVacc_Summary Clinical Study Report_V1.0_20241101.pdf)

Trial information

Trial identification

Sponsor protocol code	EU-COVPT-1

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University Medical Center Utrecht
Sponsor organisation address	Heidelberglaan 100, Utrecht, Netherlands, 3584 CX Utrecht
Public contact	Patricia Bruijning-Verhagen, University Medical Center Utrecht, p.bruijning@umcutrecht.nl
Scientific contact	Patricia Bruijning-Verhagen, University Medical Center Utrecht, p.bruijning@umcutrecht.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	15 August 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 May 2024
Global end of trial reached?	Yes
Global end of trial date	06 May 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine if the humoral immune response of a fractional compared to a full dose COVID19 vaccination is noninferior in paediatric subjects who are immunologically primed either by a first vaccine dose, or by natural infection.

Protection of trial subjects:

All legally authorized representatives provided extensive information about the trial in the subject information sheet and subsequently provided informed consent. In addition, in several countries an additional subject information sheet (and informed consent) was provided for certain age groups of the children.

In addition, as little visits as possible are implemented, with as little as possible blood sampling to reduce subject burden, while still being able to address the research objective. Furthermore, some study sites offered subjects the option of a numbing cream to lessen the feeling of the blood draw.

Background therapy:

N/a

Evidence for comparator: -

Actual start date of recruitment	31 May 2022
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 23
Country: Number of subjects enrolled	Norway: 5
Country: Number of subjects enrolled	Sweden: 3
Worldwide total number of subjects	31
EEA total number of subjects	31

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	0

months)	
Children (2-11 years)	31
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

From 31-May-2022 to 9-Jan-2024, a total of 31 subjects across 3 countries (NL, NO, SE) were enrolled and randomly assigned in the trial.

Pre-assignment

Screening details:

Subjects were screened using the eligibility criteria of the protocol.

Period 1

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

Blinding implementation details:

No blinding.

Arms

Are arms mutually exclusive?	Yes
Arm title	Two dose arm

Arm description:

Two doses of Comirnaty 10 µg or Comirnaty Original/Omicron BA.4-5 5/5 µg or Comirnaty Omicron XBB.1.5 10 µg, with an interval of 3-12 weeks (preferably 8 weeks) as per local standard practise.

Arm type	Control
Investigational medicinal product name	Comirnaty
Investigational medicinal product code	J07BN013
Other name	
Pharmaceutical forms	Concentrate for dispersion for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Comirnaty 10 µg or Comirnaty Original/Omicron BA.4-5 5/5 µg or Comirnaty Omicron XBB.1.5 10 µg first dose followed by a second Comirnaty 10 µg or Comirnaty Original/Omicron BA.4-5 5/5 µg or Comirnaty Omicron XBB.1.5 10 µg dose. The first and second dose of the vaccine should be the same.

Arm title	Single dose arm

Arm description:

A single Comirnaty 10µg dose or Comirnaty Original/Omicron BA.4-5 5/5 µg or Comirnaty Omicron XBB.1.5 10 µg dose

Arm type	Experimental
Investigational medicinal product name	Comirnaty
Investigational medicinal product code	J07BN013
Other name	
Pharmaceutical forms	Concentrate for dispersion for injection
Routes of administration	Intramuscular use

Dosage and administration details:

A single Comirnaty 10 µg or Comirnaty Original/Omicron BA.4-5 5/5 µg or Comirnaty Omicron XBB.1.5 10 µg dose.

Number of subjects in period 1	Two dose arm	Single dose arm
Started	15	16
Completed	15	16

Baseline characteristics

Reporting groups	
Reporting group title	Two dose arm
Reporting group description:	
Two doses of Comirnaty 10 µg or Comirnaty Original/Omicron BA.4-5 5/5 µg or Comirnaty Omicron XBB.1.5 10 µg, with an interval of 3-12 weeks (preferably 8 weeks) as per local standard practise.	
Reporting group title	Single dose arm
Reporting group description:	
A single Comirnaty 10µg dose or Comirnaty Original/Omicron BA.4-5 5/5 µg or Comirnaty Omicron XBB.1.5 10 µg dose	

Reporting group values	Two dose arm	Single dose arm	Total
Number of subjects	15	16	31
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	0	0	0
85 years and over	0	0	0
Children 5-11	15	16	31
Gender categorical Units: Subjects			
Female	6	9	15
Male	9	7	16

Subject analysis sets	
Subject analysis set title	PP - primary endpoint
Subject analysis set type	Per protocol
Subject analysis set description:	
All subjects who received a study vaccine and contributed both pre- and at least one post-vaccination blood sample for immunogenicity testing for which valid results were reported, but excluding subjects found to be ineligible at baseline, subjects who have had a confirmed new SARS infection between baseline and the visit concerned, subjects with major protocol deviations that are considered to affect the outcome, data from any visits that occurred substantially out of the foreseen time window.	
Subject analysis set title	mITT primary endpoint
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
All trial subjects who received a study vaccine and contributed both pre- and at least one post-vaccination blood sample for immunogenicity testing for which valid results were reported.	

Reporting group values	PP - primary endpoint	mITT primary endpoint	
Number of subjects	31	31	
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	0	0	
85 years and over	0	0	
Children 5-11	15	16	
Gender categorical Units: Subjects			
Female			
Male			

End points

End points reporting groups

Reporting group title	Two dose arm

Reporting group description:

Two doses of Comirnaty 10 µg or Comirnaty Original/Omicron BA.4-5 5/5 µg or Comirnaty Omicron XBB.1.5 10 µg, with an interval of 3-12 weeks (preferably 8 weeks) as per local standard practise.

Reporting group title	Single dose arm

Reporting group description:

A single Comirnaty 10µg dose or Comirnaty Original/Omicron BA.4-5 5/5 µg or Comirnaty Omicron XBB.1.5 10 µg dose

Subject analysis set title	PP - primary endpoint
Subject analysis set type	Per protocol

Subject analysis set description:

All subjects who received a study vaccine and contributed both pre- and at least one post-vaccination blood sample for immunogenicity testing for which valid results were reported, but excluding subjects found to be ineligible at baseline, subjects who have had a confirmed new SARS infection between baseline and the visit concerned, subjects with major protocol deviations that are considered to affect the outcome, data from any visits that occurred substantially out of the foreseen time window.

Subject analysis set title	mITT primary endpoint
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

All trial subjects who received a study vaccine and contributed both pre- and at least one post-vaccination blood sample for immunogenicity testing for which valid results were reported.

Primary: The geometric mean ratio of neutralising titers against wild type virus (Virus Neutralization Assay) at day 28 after completion of the control versus the intervention regimen of the vaccine

End point title	The geometric mean ratio of neutralising titers against wild type virus (Virus Neutralization Assay) at day 28 after completion of the control versus the intervention regimen of the vaccine

End point description:

The primary analysis of this study was the non-inferiority comparison of the primary endpoint between the control and intervention arm in the per protocol (PP) population. A linear model with the log10 transformed SARS-CoV-2 neutralizing titers as dependent variable and with independent variables treatment group, log10 transformed baseline titers and the variables used for stratification (sex) was planned to fit. Based on the linear model estimates for the factor treatment group, the null hypothesis that the intervention group is inferior to the standard two dose BNT162b2 vaccination regimen was tested. Non-inferiority was defined as a 1.5-fold difference for GMTs or 0.176 on the log scale (base 10). Based on the linear model 2-sided 95% confidence intervals for the fold difference in GMT were computed. If the 95% confidence interval for the difference excludes 0, inferiority / superiority was concluded. One sided p- values for the inferiority null hypothesis were reported.

End point type	Primary

End point timeframe:

28 days

End point values	Two dose arm	Single dose arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	16		
Units: geometric mean ratio				
geometric mean (confidence interval 95%)	1801.1 (1357.9 to	1715.5 (1064.2 to		

2388.9)	2765.4)

Statistical analyses

Statistical analysis title	Primary analysis
Comparison groups	Two dose arm v Single dose arm
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	GMT ratio
Point estimate	0.942
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.554
upper limit	1.601

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline to end of study visit

Adverse event reporting additional description:

All adverse events reported spontaneously by the subject or observed by the investigator or his staff were recorded.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups

Reporting group title	two dose arm

Reporting group description: -

Reporting group title	Single dose arm

Reporting group description: -

Serious adverse events	two dose arm	Single dose arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 15 (13.33%)	0 / 16 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 15 (6.67%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Bronchial hyperreactivity			
subjects affected / exposed	1 / 15 (6.67%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 15 (6.67%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	two dose arm	Single dose arm	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 15 (100.00%)	16 / 16 (100.00%)	
Surgical and medical procedures			
Tonsillectomy			
subjects affected / exposed	1 / 15 (6.67%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Headache			
subjects affected / exposed	10 / 15 (66.67%)	6 / 16 (37.50%)	
occurrences (all)	11	7	
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	2 / 15 (13.33%)	1 / 16 (6.25%)	
occurrences (all)	2	2	
General disorders and administration site conditions			
Chills			
subjects affected / exposed	6 / 15 (40.00%)	2 / 16 (12.50%)	
occurrences (all)	8	2	
Fatigue			
subjects affected / exposed	13 / 15 (86.67%)	6 / 16 (37.50%)	
occurrences (all)	23	8	
Influenza like illness			
subjects affected / exposed	1 / 15 (6.67%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Injection site erythema			
subjects affected / exposed	2 / 15 (13.33%)	1 / 16 (6.25%)	
occurrences (all)	2	1	
Injection site hypersensitivity			
subjects affected / exposed	13 / 15 (86.67%)	15 / 16 (93.75%)	
occurrences (all)	24	16	
Injection site pain			
subjects affected / exposed	14 / 15 (93.33%)	13 / 16 (81.25%)	
occurrences (all)	24	14	

Injection site swelling			
subjects affected / exposed	8 / 15 (53.33%)	4 / 16 (25.00%)	
occurrences (all)	11	4	
Pyrexia			
subjects affected / exposed	1 / 15 (6.67%)	1 / 16 (6.25%)	
occurrences (all)	1	1	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 15 (13.33%)	0 / 16 (0.00%)	
occurrences (all)	3	0	
Nausea			
subjects affected / exposed	4 / 15 (26.67%)	3 / 16 (18.75%)	
occurrences (all)	6	4	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 15 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Oropharyngeal pain			
subjects affected / exposed	2 / 15 (13.33%)	0 / 16 (0.00%)	
occurrences (all)	2	0	
Respiratory symptom			
subjects affected / exposed	5 / 15 (33.33%)	5 / 16 (31.25%)	
occurrences (all)	5	5	
Epiphysiodesis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 15 (20.00%)	3 / 16 (18.75%)	
occurrences (all)	4	4	
Myalgia			
subjects affected / exposed	8 / 15 (53.33%)	5 / 16 (31.25%)	
occurrences (all)	17	6	
Infections and infestations			
COVID-19			

subjects affected / exposed	1 / 15 (6.67%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Gastroenteritis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Pertussis			
subjects affected / exposed	1 / 15 (6.67%)	1 / 16 (6.25%)	
occurrences (all)	1	1	
Viral infection			
subjects affected / exposed	0 / 15 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 October 2021	Substantial amendment to address questions and comments from EC/CA review, regarding e.g. emergency unblinding, end of trial definition, and DMC process.
19 January 2022	Changes were made throughout the protocol, including protocol title, summary, section 1 Introduction and Rationale (including section 14 references to most recent clinical trials), section 2 Objectives and section 3 Study Design, to reflect updated study design and study population: • Replace Cohort A (SARS-CoV-2 naïve adolescents of 12 and 13 years) and Cohort B (adolescents of 12 and 13 years with documented evidence of prior SARS-CoV-2 infection) with a subject population of children 5 up to and including 11 years with documented evidence of prior SARS-CoV-2 infection; • Randomization into two arms: 1) a 10 µg BNT162b2 first dose followed by a second 10µg BNT162b2 dose, or 2) a single 10µg dose of BNT162b2 vaccine.
17 March 2022	Main changes included a clarification of the exclusion criteria, updated study timelines and updated visit schedule (incl removal of a visit in the single dose arm)
24 March 2023	The main changes included the addition of the Comirnaty bi-valent paediatric vaccine as study medication and removal of the inclusion criterion that required documented evidence of prior SARS-CoV-2 infection,.
22 September 2023	The main change included the addition of the Comirnaty Omicron XBB vaccine as study medication.

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.

Only 31 of the targeted 200 subjects were included by the end of the trial.

Notes: