Clinical trial results:
COVID-19: A Phase 3, Randomized, Observer-Blinded, Placebo-Controlled Clinical Study Evaluating the Safety and Immunogenicity of Investigational SARS-CoV-2 mRNA Vaccine CVnCoV in Adult Health Care Workers in Mainz (Germany)

Summary

EudraCT number	2020-004066-19
Trial protocol	DE
Global end of trial date	08 June 2022

Results information

Result version number	v1 (current)
This version publication date	21 December 2022
First version publication date	21 December 2022

Trial information

Trial identification

Sponsor protocol code	CV-NCOV-005

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04674189
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	CureVac SE
Sponsor organisation address	Schumannstrasse 27, Frankfurt, Germany, 60325
Public contact	Clinical Trial Information, CureVac SE, 0049 6976805870, clinicaltrials@curevac.com
Scientific contact	Clinical Trial Information, CureVac SE, 0049 6976805870, clinicaltrials@curevac.com

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	08 June 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 June 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The trial aimed to:
- Evaluate the safety (in all participants) and reactogenicity (in a subset of participants) of CVnCoV administered as a 2-dose schedule to adult participants 18 years of age or older.
- Assess antibody responses to the receptor-binding domain (RBD) of spike protein of SARS-CoV-2 after 1 and 2 doses of CVnCoV in adult participants 18 years of age or older included in a subset of participants.

Protection of trial subjects:

This trial was conducted with the highest respect for the individual participants in compliance with the requirements of this clinical trial protocol (and amendments), and also in compliance with the following:
- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use E6 (R2) Good Clinical Practice: Revised and consolidated guidelines.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 December 2020
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	Germany: 2357
Worldwide total number of subjects	2357
EEA total number of subjects	2357

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0

Adolescents (12-17 years)	0
Adults (18-64 years)	2215
From 65 to 84 years	142
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This trial was performed in Germany between 23 December 2020 and 08 June 2022.

Pre-assignment

Screening details:

Of the 2357 participants who were randomized, 2351 participants were treated.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	CVnCoV: Group 1, Lot 1

Arm description:

Participants in Group 1 were vaccinated with CVnCoV 12 µg Lot 1 as an intramuscular injection by needle in the deltoid area on Day 1 and Day 29.

Arm type	Experimental
Investigational medicinal product name	CVnCoV Vaccine
Investigational medicinal product code	CV07050101
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Intramuscular injection.

Arm title	CVnCoV: Group 2, Lot 2

Arm description:

Participants in Group 2 were vaccinated with CVnCoV 12 µg Lot 2 as an intramuscular injection by needle in the deltoid area on Day 1 and Day 29.

Arm type	Experimental
Investigational medicinal product name	CVnCoV Vaccine
Investigational medicinal product code	CV07050101
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Intramuscular injection.

Arm title	Placebo

Arm description:

Participants received a placebo as an intramuscular injection by needle in the deltoid area on Day 1 and Day 29.

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Intramuscular injection.

Number of subjects in period 1	CVnCoV: Group 1, Lot 1	CVnCoV: Group 2, Lot 2	Placebo
Started	786	786	785
Safety Analysis Set	783	785	783
Completed	617	637	372
Not completed	169	149	413
Withdrawal by Participant	83	71	142
Physician Decision	1	-	-
Adverse event, non-fatal	-	-	1
Miscellaneous	27	23	207
Received Alternative Authorized Vaccine	-	1	17
Lost to follow-up	55	53	44
Did Not Receive Treatment	3	1	2

Baseline characteristics

Reporting groups	
Reporting group title	CVnCoV: Group 1, Lot 1
Reporting group description:	
Participants in Group 1 were vaccinated with CVnCoV 12 µg Lot 1 as an intramuscular injection by needle in the deltoid area on Day 1 and Day 29.	
Reporting group title	CVnCoV: Group 2, Lot 2
Reporting group description:	
Participants in Group 2 were vaccinated with CVnCoV 12 µg Lot 2 as an intramuscular injection by needle in the deltoid area on Day 1 and Day 29.	
Reporting group title	Placebo
Reporting group description:	
Participants received a placebo as an intramuscular injection by needle in the deltoid area on Day 1 and Day 29.	

Reporting group values	CVnCoV: Group 1, Lot 1	CVnCoV: Group 2, Lot 2	Placebo
Number of subjects	786	786	785
Age categorical			
Units: Subjects			
Age continuous			
Data were recorded for the Safety Analysis Set only. This included all participants randomized in the trial who received at least one dose of any lot of CVnCoV or placebo vaccine.			
Units: years			
arithmetic mean	42.2	43.4	42.7
standard deviation	± 14.88	± 14.80	± 14.52
Gender categorical			
Data were recorded for the Safety Analysis Set only. This included all participants randomized in the trial who received at least one dose of any lot of CVnCoV or placebo vaccine.			
Units: Subjects			
Female	527	539	521
Male	256	246	262
Not Recorded	3	1	2
Ethnicity			
Data were recorded for the Safety Analysis Set only. This included all participants randomized in the trial who received at least one dose of any lot of CVnCoV or placebo vaccine.			
Units: Subjects			
Hispanic or Latino	5	5	4
Not Hispanic or Latino	764	759	758
Unknown or Not Reported	14	21	21
Not Recorded	3	1	2
Race			
Data were recorded for the Safety Analysis Set only. This included all participants randomized in the trial who received at least one dose of any lot of CVnCoV or placebo vaccine.			
Units: Subjects			
White	755	765	760
Black or African American	2	1	0
Asian	13	9	14
American Indian or Alaska Native	0	1	0

Native Hawaiian or Other Pacific Islander	2	0	0
Other	4	3	5
Unknown or Not Reported	7	6	4
Not Recorded	3	1	2

Reporting group values	Total		
Number of subjects	2357		
Age categorical			
Units: Subjects			

Age continuous			
Data were recorded for the Safety Analysis Set only. This included all participants randomized in the trial who received at least one dose of any lot of CVnCoV or placebo vaccine.			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Data were recorded for the Safety Analysis Set only. This included all participants randomized in the trial who received at least one dose of any lot of CVnCoV or placebo vaccine.			
Units: Subjects			
Female	1587		
Male	764		
Not Recorded	6		
Ethnicity			
Data were recorded for the Safety Analysis Set only. This included all participants randomized in the trial who received at least one dose of any lot of CVnCoV or placebo vaccine.			
Units: Subjects			
Hispanic or Latino	14		
Not Hispanic or Latino	2281		
Unknown or Not Reported	56		
Not Recorded	6		
Race			
Data were recorded for the Safety Analysis Set only. This included all participants randomized in the trial who received at least one dose of any lot of CVnCoV or placebo vaccine.			
Units: Subjects			
White	2280		
Black or African American	3		
Asian	36		
American Indian or Alaska Native	1		
Native Hawaiian or Other Pacific Islander	2		
Other	12		
Unknown or Not Reported	17		
Not Recorded	6		

End points

End points reporting groups

Reporting group title	CVnCoV: Group 1, Lot 1
Reporting group description:	
Participants in Group 1 were vaccinated with CVnCoV 12 µg Lot 1 as an intramuscular injection by needle in the deltoid area on Day 1 and Day 29.	
Reporting group title	CVnCoV: Group 2, Lot 2
Reporting group description:	
Participants in Group 2 were vaccinated with CVnCoV 12 µg Lot 2 as an intramuscular injection by needle in the deltoid area on Day 1 and Day 29.	
Reporting group title	Placebo
Reporting group description:	
Participants received a placebo as an intramuscular injection by needle in the deltoid area on Day 1 and Day 29.	
Subject analysis set title	CVnCoV: Pooled Lots 1 and 2
Subject analysis set type	Per protocol
Subject analysis set description:	
Participants in Group 1 and Group 2. Participants were vaccinated with either CVnCoV 12 µg Lot 1 or CVnCoV 12 µg Lot 2 as an intramuscular injection by needle in the deltoid area on Day 1 and Day 29.	

Primary: Number of Participants Who Experienced a Medically Attended Adverse Event (AE) Occurring in the Following 6 Months After Dose 2

End point title	Number of Participants Who Experienced a Medically Attended Adverse Event (AE) Occurring in the Following 6 Months After Dose 2[1]
End point description:	
Medically attended AEs were defined as AEs with medically attended visits that are not routine visits for physical examination or vaccination, such as visits for hospitalization, an emergency room visit, or an otherwise unscheduled visit to or from medical personnel (medical doctor) for any reason. The Investigator assessed the relationship between trial vaccine and occurrence of each AE. Safety Analysis Set: All participants randomized in the trial who received at least one dose of any lot of CVnCoV or placebo vaccine.	
End point type	Primary
End point timeframe:	
Up to 6 months after Dose 2 (Days 29 to 211)	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No additional statistical analysis was pre-specified for this endpoint.

End point values	CVnCoV: Group 1, Lot 1	CVnCoV: Group 2, Lot 2	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	783	785	783	
Units: participants				
Any medically attended AEs	95	133	58	
Any related medically attended AEs	34	32	13	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants Who Experienced a Serious Adverse Event (SAE)

End point title	Number of Participants Who Experienced a Serious Adverse Event (SAE)[2]

End point description:

An SAE was defined as any untoward medical occurrence that, at any dose:
- Resulted in death.
- Was life-threatening.
- Required inpatient hospitalization or prolongation of existing hospitalization.
- Resulted in persistent disability/incapacity.
- Was a congenital anomaly/birth defect in the offspring of the participant.
- Was an important medical event.

The Investigator assessed the relationship between trial vaccine and occurrence of each AE.
Safety Analysis Set: All participants randomized in the trial who received at least one dose of any lot of CVnCoV or placebo vaccine.

End point type	Primary

End point timeframe:

Day 1 to Day 393

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No additional statistical analysis was pre-specified for this endpoint.

End point values	CVnCoV: Group 1, Lot 1	CVnCoV: Group 2, Lot 2	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	783	785	783	
Units: participants				
Any SAEs	8	10	6	
Any related SAEs	1	1	0	

Statistical analyses

No statistical analyses for this end point

Primary: Intensity of SAEs Per the Investigator's Assessment

End point title	Intensity of SAEs Per the Investigator's Assessment[3]

End point description:

An SAE was defined as any untoward medical occurrence that, at any dose:
- Resulted in death.
- Was life-threatening.
- Required inpatient hospitalization or prolongation of existing hospitalization.
- Resulted in persistent disability/incapacity.
- Was a congenital anomaly/birth defect in the offspring of the participant.
- Was an important medical event.

The Investigator made an assessment of intensity for each AE reported during the trial and assigned it to one of the following categories:
- Mild: an event that was easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: an event that caused sufficient discomfort to interfere with normal everyday activities.
- Severe: an event that prevented normal everyday activities.

Safety Analysis Set: All participants randomized in the trial who received at least one dose of any lot of CVnCoV or placebo vaccine.

End point type	Primary

End point timeframe:

Day 1 to Day 393

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No additional statistical analysis was pre-specified for this endpoint.

End point values	CVnCoV: Group 1, Lot 1	CVnCoV: Group 2, Lot 2	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	783	785	783	
Units: participants				
Any mild SAEs	0	0	0	
Any moderate SAEs	2	5	1	
Any severe SAEs	6	5	5	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants Who Experienced an Adverse Event of Special Interest (AESI) Occurring in the Following 1 Year After Dose 2

End point title	Number of Participants Who Experienced an Adverse Event of Special Interest (AESI) Occurring in the Following 1 Year After Dose 2[4]

End point description:

The following events were considered and collected as AESI throughout the trial:
- AEs with a suspected immune-mediated etiology.
- Other AEs relevant to SARS-CoV-2 vaccine development or the target disease.
- COVID-19.
The Investigator assessed the relationship between trial vaccine and occurrence of each AE.
Safety Analysis Set: All participants randomized in the trial who received at least one dose of any lot of CVnCoV or placebo vaccine.

End point type	Primary

End point timeframe:

Up to 1 year after Dose 2 (Days 29 to 393)

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No additional statistical analysis was pre-specified for this endpoint.

End point values	CVnCoV: Group 1, Lot 1	CVnCoV: Group 2, Lot 2	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	783	785	783	
Units: participants				
Any AESIs	14	14	5	
Any related AESIs	7	5	0	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants Who Experienced Death Due to SAE

End point title	Number of Participants Who Experienced Death Due to SAE[5]

End point description:

An SAE was defined as any untoward medical occurrence that, at any dose:
- Resulted in death.
- Was life-threatening.
- Required inpatient hospitalization or prolongation of existing hospitalization.
- Resulted in persistent disability/incapacity.
- Was a congenital anomaly/birth defect in the offspring of the participant.
- Was an important medical event.

Safety Analysis Set: All participants randomized in the trial who received at least one dose of any lot of CVnCoV or placebo vaccine.

End point type	Primary

End point timeframe:

Day 1 to Day 393

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No additional statistical analysis was pre-specified for this endpoint.

End point values	CVnCoV: Group 1, Lot 1	CVnCoV: Group 2, Lot 2	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	783	785	783	
Units: participants	0	0	0	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants Who Experienced an AE Leading to Vaccine Withdrawal Occurring in the Following 1 Year After Dose 2

End point title	Number of Participants Who Experienced an AE Leading to Vaccine Withdrawal Occurring in the Following 1 Year After Dose 2[6]

End point description:

Safety Analysis Set: All participants randomized in the trial who received at least one dose of any lot of CVnCoV or placebo vaccine.

End point type	Primary

End point timeframe:

Up to 1 year after Dose 2 (Days 29 to 393)

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No additional statistical analysis was pre-specified for this endpoint.

End point values	CVnCoV: Group 1, Lot 1	CVnCoV: Group 2, Lot 2	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	783	785	783	
Units: participants	7	5	2	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants Who Experienced an AE Leading to Trial Discontinuation Occurring in the Following 1 Year After Dose 2

End point title	Number of Participants Who Experienced an AE Leading to Trial Discontinuation Occurring in the Following 1 Year After Dose 2[7]

End point description:

Safety Analysis Set: All participants randomized in the trial who received at least one dose of any lot of CVnCoV or placebo vaccine.

End point type	Primary

End point timeframe:

Up to 1 year after Dose 2 (Days 29 to 393)

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No additional statistical analysis was pre-specified for this endpoint.

End point values	CVnCoV: Group 1, Lot 1	CVnCoV: Group 2, Lot 2	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	783	785	783	
Units: participants	1	0	1	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants Who Experienced an Unsolicited AE Occurring on the Day of Vaccination and the Following 28 Days After Any Dose

End point title	Number of Participants Who Experienced an Unsolicited AE Occurring on the Day of Vaccination and the Following 28 Days After Any Dose[8]

End point description:

eDiaries were used for the collection of unsolicited AEs on each vaccination day and the following 28 days.
The Investigator assessed the relationship between trial vaccine and occurrence of each AE.
Safety Analysis Subset: The first 1289 participants enrolled who belong to the Safety Analysis Set.

End point type	Primary

End point timeframe:

Day 1 to 28 days after Dose 2 (Day 57)

Notes:

[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No additional statistical analysis was pre-specified for this endpoint.

End point values	CVnCoV: Group 1, Lot 1	CVnCoV: Group 2, Lot 2	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	430	429	430	
Units: participants				
Any unsolicited AEs	245	270	187	
Any related unsolicited AEs	183	186	88	

Statistical analyses

No statistical analyses for this end point

Primary: Intensity of Unsolicited AEs Per the Investigator's Assessment Occurring on the Day of Vaccination and the Following 28 Days After Any Dose

End point title	Intensity of Unsolicited AEs Per the Investigator's Assessment Occurring on the Day of Vaccination and the Following 28 Days After Any Dose[9]

End point description:

eDiaries were used for the collection of unsolicited AEs on each vaccination day and the following 28 days.
The Investigator made an assessment of intensity for each AE reported during the trial and assigned it to one of the following categories:
- Mild: an event that was easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: an event that caused sufficient discomfort to interfere with normal everyday activities.
- Severe: an event that prevented normal everyday activities.
Safety Analysis Subset: The first 1289 participants enrolled who belong to the Safety Analysis Set.

End point type	Primary

End point timeframe:

Day 1 to 28 days after Dose 2 (Day 57)

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No additional statistical analysis was pre-specified for this endpoint.

End point values	CVnCoV: Group 1, Lot 1	CVnCoV: Group 2, Lot 2	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	430	429	430	
Units: participants				
Any mild unsolicited AEs	133	149	114	
Any moderate unsolicited AEs	73	71	42	
Any severe unsolicited AEs	14	28	10	
Any unsolicited AEs without intensity assessment	25	22	21	

Statistical analyses

No statistical analyses for this end point

Primary: Occurrence of Seroconversion for SARS-CoV-2 RBD of Spike Protein Antibodies (IgG) on Day 29 and Day 43

End point title	Occurrence of Seroconversion for SARS-CoV-2 RBD of Spike Protein Antibodies (IgG) on Day 29 and Day 43[10]

End point description:

Titers of IgG antibodies directed against the SARS-CoV-2 RBD of Spike Protein antigen were measured by enzyme-linked immunosorbent assay (ELISA). Percentage with 95% confidence interval (CI) of participants for whom a seroconversion was observed is presented by group. Seroconversion was defined as a fold increase above 1 in SARS-CoV-2 Spike Protein RBD IgG antibody levels in participants seronegative at Baseline. Participants who tested positive for COVID-19 had their data included up to the point of a positive test result. Participants who received a licensed/authorized vaccine were censored at the day after receiving the licensed/authorized vaccine. Per Protocol Immunogenicity Set: 250 participants who received both doses as randomized and within the windows defined in the protocol, had no major protocol deviations expected to impact the immunogenicity outcomes, and had not received medical treatments that may interfere with any of the immunogenicity measurements.

End point type	Primary

End point timeframe:

Baseline (Day 1), Day 29 and Day 43

Notes:

[10] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No additional statistical analysis was pre-specified for this endpoint.

End point values	CVnCoV: Group 1, Lot 1	CVnCoV: Group 2, Lot 2	Placebo	CVnCoV: Pooled Lots 1 and 2
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	99[11]	98[12]	48[13]	197[14]
Units: percentage of participants				
number (confidence interval 95%)				
Day 29	8.1 (3.6 to 15.3)	18.4 (11.3 to 27.5)	0.0 (0.0 to 7.4)	13.2 (8.8 to 18.7)
Day 43	95.5 (88.8 to 98.7)	94.2 (87.0 to 98.1)	0.0 (0.0 to 8.6)	94.8 (90.4 to 97.6)

Notes:

[11] - Day 43 N = 88.

[12] - Day 43 N = 86.

[13] - Day 43 N = 41.

[14] - Day 43 N = 174.

Statistical analyses

No statistical analyses for this end point

Primary: SARS-CoV-2 RBD of Spike Protein Antibody (IgG) Levels on Days 1, 29 and 43

End point title	SARS-CoV-2 RBD of Spike Protein Antibody (IgG) Levels on Days 1, 29 and 43[15]

End point description:

Titers of IgG antibodies directed against the SARS-CoV-2 RBD of Spike Protein antigen were measured by ELISA and expressed as geometric mean of titers (GMT) with 95% CI, by group. Individual values below the lower limit of quantification (LLOQ) were set to half of the LLOQ. Participants who tested positive for COVID-19 had their data included up to the point of a positive test result. Participants who received a licensed/authorized vaccine were censored at the day after receiving the licensed/authorized

vaccine. Per Protocol Immunogenicity Set: 250 participants who received both doses as randomized and within the windows defined in the protocol, had no major protocol deviations expected to impact the immunogenicity outcomes, and had not received medical treatments that may interfere with any of the immunogenicity measurements.

End point type	Primary

End point timeframe:

Baseline (Day 1), Day 29 and Day 43

Notes:

[15] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No additional statistical analysis was pre-specified for this endpoint.

End point values	CVnCoV: Group 1, Lot 1	CVnCoV: Group 2, Lot 2	Placebo	CVnCoV: Pooled Lots 1 and 2
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	99[16]	98[17]	48[18]	197[19]
Units: GMT				
geometric mean (confidence interval 95%)				
Day 1	50.000 (50.000 to 50.000)	50.000 (50.000 to 50.000)	50.000 (50.000 to 50.000)	50.000 (50.000 to 50.000)
Day 29	55.145 (51.403 to 59.160)	62.236 (56.437 to 68.631)	50.000 (50.000 to 50.000)	58.566 (55.144 to 62.199)
Day 43	1285.722 (1003.885 to 1646.683)	1151.416 (869.345 to 1525.008)	50.000 (50.000 to 50.000)	1217.489 (1011.594 to 1465.289)

Notes:

[16] - Day 43 N = 88.

[17] - Day 43 N = 86.

[18] - Day 43 N = 41.

[19] - Day 43 N = 174.

Statistical analyses

No statistical analyses for this end point

Secondary: Occurrence of Seroconversion for SARS-CoV-2 Neutralizing Antibodies on Day 29 and Day 43

End point title	Occurrence of Seroconversion for SARS-CoV-2 Neutralizing Antibodies on Day 29 and Day 43

End point description:

Neutralizing activity of induced antibodies was determined by an activity assay. Percentage with 95% CI of participants for whom a seroconversion was observed is presented by group. Seroconversion was defined as a fold increase above 1 in SARS-CoV-2 neutralizing antibody levels in participants seronegative at Baseline. Participants who tested positive for COVID-19 had their data included up to the point of a positive test result. Participants who received a licensed/authorized vaccine were censored at the day after receiving the licensed/authorized vaccine. Per Protocol Immunogenicity Set: 250 participants who received both doses as randomized and within the windows defined in the protocol, had no major protocol deviations expected to impact the immunogenicity outcomes, and had not received medical treatments that may interfere with any of the immunogenicity measurements.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Day 29 and Day 43

End point values	CVnCoV: Group 1, Lot 1	CVnCoV: Group 2, Lot 2	Placebo	CVnCoV: Pooled Lots 1 and 2
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	99[20]	98[21]	48[22]	197[23]
Units: percentage of participants				
number (confidence interval 95%)				
Day 29	2.0 (0.2 to 7.1)	2.0 (0.2 to 7.2)	0.0 (0.0 to 7.4)	2.0 (0.6 to 5.1)
Day 43	76.1 (65.9 to 84.6)	75.6 (65.1 to 84.2)	0.0 (0.0 to 8.6)	75.9 (68.8 to 82.0)

Notes:

[20] - Day 43 N = 88.

[21] - Day 43 N = 86.

[22] - Day 43 N = 41.

[23] - Day 43 N = 174.

Statistical analyses

No statistical analyses for this end point

Secondary: SARS-CoV-2 Neutralizing Antibody Levels on Days 1, 29 and 43

End point title	SARS-CoV-2 Neutralizing Antibody Levels on Days 1, 29 and 43

End point description:

Neutralizing activity of induced antibodies was determined by an activity assay. GMT with 95% CI of SARS-CoV-2 neutralizing antibody levels is presented by group. Individual values below the LLOQ were set to half of the LLOQ. Participants who tested positive for COVID-19 had their data included up to the point of a positive test result. Participants who received a licensed/authorized vaccine were censored at the day after receiving the licensed/authorized vaccine. Per Protocol Immunogenicity Set: 250 participants who received both doses as randomized and within the windows defined in the protocol, had no major protocol deviations expected to impact the immunogenicity outcomes, and had not received medical treatments that may interfere with any of the immunogenicity measurements.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Day 29 and Day 43

End point values	CVnCoV: Group 1, Lot 1	CVnCoV: Group 2, Lot 2	Placebo	CVnCoV: Pooled Lots 1 and 2
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	99[24]	98[25]	48[26]	197[27]
Units: GMT				
geometric mean (confidence interval 95%)				
Day 1	5.000 (5.000 to 5.000)	5.000 (5.000 to 5.000)	5.000 (5.000 to 5.000)	5.000 (5.000 to 5.000)
Day 29	5.160 (4.906 to 5.427)	5.071 (4.972 to 5.172)	5.000 (5.000 to 5.000)	5.116 (4.980 to 5.256)
Day 43	28.846 (21.716 to 38.318)	23.976 (18.394 to 31.252)	5.000 (5.000 to 5.000)	26.327 (21.707 to 31.929)

Notes:
[24] - Day 43 N = 88.
[25] - Day 43 N = 86.
[26] - Day 43 N = 41.
[27] - Day 43 N = 174.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Day 1 to Day 393	
Adverse event reporting additional description:	
Safety Analysis Set: All participants randomized in the trial who received at least one dose of any lot of CVnCoV or placebo vaccine.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups	
Reporting group title	CVnCoV: Group 1, Lot 1
Reporting group description:	
Participants in Group 1 were vaccinated with CVnCoV 12 µg Lot 1 as an intramuscular injection by needle in the deltoid area on Day 1 and Day 29.	
Reporting group title	CVnCoV: Group 2, Lot 2
Reporting group description:	
Participants in Group 2 were vaccinated with CVnCoV 12 µg Lot 2 as an intramuscular injection by needle in the deltoid area on Day 1 and Day 29.	
Reporting group title	Placebo
Reporting group description:	
Participants received a placebo as an intramuscular injection by needle in the deltoid area on Day 1 and Day 29.	

Serious adverse events	CVnCoV: Group 1, Lot 1	CVnCoV: Group 2, Lot 2	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 783 (1.02%)	10 / 785 (1.27%)	6 / 783 (0.77%)
number of deaths (all causes)	0	0	1
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	0 / 783 (0.00%)	0 / 785 (0.00%)	2 / 783 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic lymphocytic leukaemia			
subjects affected / exposed	1 / 783 (0.13%)	1 / 785 (0.13%)	0 / 783 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ganglioglioma			

subjects affected / exposed	0 / 783 (0.00%)	0 / 785 (0.00%)	1 / 783 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Invasive ductal breast carcinoma			
subjects affected / exposed	1 / 783 (0.13%)	0 / 785 (0.00%)	0 / 783 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Invasive lobular breast carcinoma			
subjects affected / exposed	1 / 783 (0.13%)	0 / 785 (0.00%)	0 / 783 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			
subjects affected / exposed	1 / 783 (0.13%)	0 / 785 (0.00%)	0 / 783 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Ligament rupture			
subjects affected / exposed	1 / 783 (0.13%)	0 / 785 (0.00%)	0 / 783 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ligament sprain			
subjects affected / exposed	0 / 783 (0.00%)	0 / 785 (0.00%)	1 / 783 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tendon rupture			
subjects affected / exposed	0 / 783 (0.00%)	1 / 785 (0.13%)	0 / 783 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	1 / 783 (0.13%)	0 / 785 (0.00%)	0 / 783 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 783 (0.00%)	1 / 785 (0.13%)	0 / 783 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	1 / 783 (0.13%)	0 / 785 (0.00%)	0 / 783 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 783 (0.00%)	1 / 785 (0.13%)	0 / 783 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Faecaloma			
subjects affected / exposed	0 / 783 (0.00%)	1 / 785 (0.13%)	0 / 783 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mechanical ileus			
subjects affected / exposed	0 / 783 (0.00%)	0 / 785 (0.00%)	1 / 783 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 783 (0.00%)	1 / 785 (0.13%)	0 / 783 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 783 (0.13%)	0 / 785 (0.00%)	1 / 783 (0.13%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthma			

subjects affected / exposed	1 / 783 (0.13%)	0 / 785 (0.00%)	0 / 783 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 783 (0.00%)	1 / 785 (0.13%)	0 / 783 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachypnoea			
subjects affected / exposed	1 / 783 (0.13%)	0 / 785 (0.00%)	0 / 783 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 783 (0.00%)	0 / 785 (0.00%)	1 / 783 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	0 / 783 (0.00%)	1 / 785 (0.13%)	0 / 783 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	0 / 783 (0.00%)	2 / 785 (0.25%)	0 / 783 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervical spinal stenosis			
subjects affected / exposed	0 / 783 (0.00%)	1 / 785 (0.13%)	0 / 783 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spondylolisthesis			
subjects affected / exposed	1 / 783 (0.13%)	0 / 785 (0.00%)	0 / 783 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 783 (0.00%)	1 / 785 (0.13%)	0 / 783 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestine gangrene			
subjects affected / exposed	0 / 783 (0.00%)	0 / 785 (0.00%)	1 / 783 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	CVnCoV: Group 1, Lot 1	CVnCoV: Group 2, Lot 2	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	542 / 783 (69.22%)	547 / 785 (69.68%)	475 / 783 (60.66%)
Nervous system disorders			
Headache			
subjects affected / exposed	428 / 783 (54.66%)	430 / 785 (54.78%)	293 / 783 (37.42%)
occurrences (all)	924	952	615
Dizziness			
subjects affected / exposed	37 / 783 (4.73%)	46 / 785 (5.86%)	34 / 783 (4.34%)
occurrences (all)	42	54	43
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	425 / 783 (54.28%)	427 / 785 (54.39%)	278 / 783 (35.50%)
occurrences (all)	835	852	530
Injection site pain			
subjects affected / exposed	387 / 783 (49.43%)	390 / 785 (49.68%)	160 / 783 (20.43%)
occurrences (all)	693	698	205
Chills			
subjects affected / exposed	276 / 783 (35.25%)	275 / 785 (35.03%)	81 / 783 (10.34%)
occurrences (all)	419	457	95
Pyrexia			
subjects affected / exposed	218 / 783 (27.84%)	221 / 785 (28.15%)	61 / 783 (7.79%)
occurrences (all)	309	330	64
Pain			

subjects affected / exposed	46 / 783 (5.87%)	62 / 785 (7.90%)	47 / 783 (6.00%)
occurrences (all)	53	68	52
Injection site pruritus			
subjects affected / exposed	27 / 783 (3.45%)	43 / 785 (5.48%)	18 / 783 (2.30%)
occurrences (all)	31	53	22
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	140 / 783 (17.88%)	132 / 785 (16.82%)	65 / 783 (8.30%)
occurrences (all)	197	195	82
Diarrhoea			
subjects affected / exposed	104 / 783 (13.28%)	113 / 785 (14.39%)	66 / 783 (8.43%)
occurrences (all)	146	144	78
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	106 / 783 (13.54%)	107 / 785 (13.63%)	99 / 783 (12.64%)
occurrences (all)	134	135	133
Nasal congestion			
subjects affected / exposed	98 / 783 (12.52%)	106 / 785 (13.50%)	95 / 783 (12.13%)
occurrences (all)	128	145	121
Cough			
subjects affected / exposed	70 / 783 (8.94%)	85 / 785 (10.83%)	62 / 783 (7.92%)
occurrences (all)	89	106	84
Rhinorrhoea			
subjects affected / exposed	32 / 783 (4.09%)	39 / 785 (4.97%)	41 / 783 (5.24%)
occurrences (all)	38	44	47
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	344 / 783 (43.93%)	341 / 785 (43.44%)	136 / 783 (17.37%)
occurrences (all)	569	565	183
Arthralgia			
subjects affected / exposed	250 / 783 (31.93%)	245 / 785 (31.21%)	75 / 783 (9.58%)
occurrences (all)	376	378	98
Infections and infestations			
COVID-19			
subjects affected / exposed	106 / 783 (13.54%)	99 / 785 (12.61%)	123 / 783 (15.71%)
occurrences (all)	111	103	131

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 March 2021	The protocol was updated to include: - Clarifications to protocol text "students in clinical years". - Clarifications that participants who reported to have COVID-19 symptoms were only followed-up if the Investigator considered the symptoms to potentially indicate a COVID-19 case. - Clarifications that participants who tested positive for SARS-CoV-2 outside of the trial context were considered for active surveillance for COVID-19. - Unblinding was allowed in the case a participant became eligible to receive an authorized/licensed vaccine. - Inclusion of information on authorized vaccine availability. - History of potential immune-mediated disease was separated from history of angioedema or anaphylactic reaction. - Instructions to state that viral ribonucleic acid (RNA) of SARS-CoV-2 should be sequenced at a Sponsor-designated laboratory to identify spike protein variants in participants with positive reverse transcriptase-polymerase chain reaction (RT-PCR) tests. - Guidance that participants may receive the second trial vaccine dose if they developed COVID-19 between Dose 1 and 2. - Inclusion of instructions that COVID-19 illness and its complications/sequelae were to be reported as an AESI. - Exclusion of the genitourinary system examination from the complete physical examination. Inclusion of O2 saturation measurement at the discretion of the Investigator. - Minor editorial and document formatting revisions.
23 July 2021	The protocol was updated to include: - The summary of CVnCoV final efficacy analysis of the HERALD trial. - The unblinding of all blinded participants and subsequent change on the schedules of activities to guarantee safety follow-up of all the participants exposed to CVnCoV. - Text that ensures access to information on the HERALD final analysis results for all the participants.
11 August 2021	The protocol was updated to include: - Clarification that the Trial Physician was responsible for providing trial results to participants. - Participants receiving authorized SARS-CoV-2 vaccines were not to be included in the antibody response. - Minor editorial and document formatting revisions.

22 December 2021	The protocol was updated to include: - New medical responsible person. - Added e-mail address for post-trial safety reporting. - Trial was to remain blinded until approval of trial protocol version 3.0. - Assessment of cell mediated immune response was cancelled. - Comparison of efficacy by pooling of results with trial COVID19-5-P-002 was cancelled. - Limitation of immunogenicity analyses to 100 CVnCoV participants per lot and 50 placebo participants and to the following time points: Baseline, Day 29 and Day 43. - Assessment of seroconversion to the N-protein of SARS-CoV-2 at Day 393 was cancelled. - Assessment of efficacy of CVnCoV in the prevention or reduction of asymptomatic infections was cancelled. - Measurement of antibody responses for all COVID-19 cases that occur in the trial was cancelled. - For positive RT-PCR tests, viral RNA of the SARS-CoV-2 sequencing to identify spike protein variants were no longer required. - Efficacy cases were no longer to be confirmed by adjudication. - AE recording was only to be done for criteria defined. - Withdrawal procedure for placebo participants added. - Option for remote source data verification included.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported