Clinical trial results:
Using BCG vaccine to enhance non-specific protection of health care workers during the COVID-19 pandemic. A randomised controlled multi-center trial.

Summary

EudraCT number	2020-001888-90
Trial protocol	DK
Global end of trial date	31 July 2021

Results information

Result version number	v1
This version publication date	16 August 2022
First version publication date	16 August 2022

Trial information

Trial identification

Sponsor protocol code	20201504

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04373291
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Southern Denmark
Sponsor organisation address	Studiestraede 6, Copenhagen K, Denmark, 1455
Public contact	Clinical Institute, OPEN, University of Southern Denmark, open.adm@rsyd.dk
Scientific contact	Clinical Institute, OPEN, University of Southern Denmark, open.adm@rsyd.dk

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	01 July 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 July 2021
Global end of trial reached?	Yes
Global end of trial date	31 July 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To reduce absenteeism among health care workers during the COVID-19 pandemic.

Protection of trial subjects:

Participants were instructed to report (serious) adverse events in the weekly questionnaire but were also encouraged to contact study personnel these cases.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 May 2020
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	Denmark: 1221
Worldwide total number of subjects	1221
EEA total number of subjects	1221

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)	1181
From 65 to 84 years	40
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Healthcare workers (HCWs) recruited at nine Danish hospitals from 18-05-2020 to 21-01-2021. Participants were adults (>18 years) and working at the hospital at least 22 hours/week. Exclusion criteria were the known contraindications for BCG and previous confirmed SARS-CoV-2 infection.

Pre-assignment

Screening details:

1293 HCWs were screened for inclusion and 1233 were randomised. Three persons were randomised by mistake (1 BCG/2 placebo) as they did not fulfil inclusion criteria. They were not included and never received treatment. Nine participants never responded after enrolment (3 BCG/6 placebo). The final study population included 1221 participants.

Pre-assignment period milestones

Number of subjects started	1233[1]
Number of subjects completed	1221

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Lost to follow up: 9
Reason: Number of subjects	Mistakenly randomised: 3

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: In total 1233 persons were randomised. But three of these were randomised by mistake and were not included in the trial. Nine participants never responded after enrolment hence have no follow up data. All were alive at end of trial though. The true study population therefore consists of 1221 participants.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	BCG group

Arm description:

Standard dose intradermal BCG vaccination (Bacillus Calmette-Guérin), 0.1 ml (BCG strain 1331, AJ Vaccines, Denmark).

Arm type	Experimental
Investigational medicinal product name	BCG vaccine, AJ Vaccines, Denmark
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intradermal use

Dosage and administration details:

BCG was administered in the right upper arm, intradermally, 0.1 ml of the suspended vaccine.
After reconstitution one dose (0,1 ml) contains: Mycobacterium bovis BCG (Bacillus Calmette-Guerin), Danish strain 1331, live attenuated, 2-8 x 10_5 cfu.

Arm title	Placebo group

Arm description:

0.1 ml of sterile 0.9 % NaCl solution (saline).

Arm type	Placebo
Investigational medicinal product name	Sterile 0.9 % NaCl solution
Investigational medicinal product code	
Other name	Saline
Pharmaceutical forms	Solution for injection
Routes of administration	Intradermal use

Dosage and administration details:

Placebo was administered in the right upper arm, intradermally, 0.1 ml of sterile 0.9 % NaCl solution.

Number of subjects in period 1	BCG group	Placebo group
Started	610	611
Completed	610	611

Baseline characteristics

Reporting groups	
Reporting group title	BCG group
Reporting group description:	
Standard dose intradermal BCG vaccination (Bacillus Calmette-Guérin), 0.1 ml (BCG strain 1331, AJ Vaccines, Denmark).	
Reporting group title	Placebo group
Reporting group description:	
0.1 ml of sterile 0.9 % NaCl solution (saline).	

Reporting group values	BCG group	Placebo group	Total
Number of subjects	610	611	1221
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: years			
median	48	47	
inter-quartile range (Q1-Q3)	37 to 56	36 to 57	-
Gender categorical			
Units: Subjects			
Female	507	505	1012
Male	103	106	209
History of BCG vaccination			
Units: Subjects			
History of BCG vaccination	323	328	651
No history of BCG vaccination	287	283	570
BCG scar status			
BCG scar from previous vaccination present and inspected at inclusion.			
Units: Subjects			
BCG scar	285	311	596
No scar	325	300	625

End points

End points reporting groups

Reporting group title	BCG group
Reporting group description:	
Standard dose intradermal BCG vaccination (Bacillus Calmette-Guérin), 0.1 ml (BCG strain 1331, AJ Vaccines, Denmark).	
Reporting group title	Placebo group
Reporting group description:	
0.1 ml of sterile 0.9 % NaCl solution (saline).	
Subject analysis set title	Intention to treat
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Data from all enrolled participants. If participants did not complete the follow up period, the available data were included.	

Primary: Unplanned absenteeism

End point title	Unplanned absenteeism
End point description:	
Reported by randomisation group as mean number of days absent per 1000 workdays.	
End point type	Primary
End point timeframe:	
Within 6 months	

End point values	BCG group	Placebo group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	610	611		
Units: Mean days absent				
number (not applicable)	20	17		

Statistical analyses

Statistical analysis title	Primary endpoint analysis
Statistical analysis description:	
The primary endpoint was analysed as counts per week (multiple observations per subject) using Bayesian negative binomial regression and adjusted for hospital, gender and age.	
Comparison groups	Placebo group v BCG group
Number of subjects included in analysis	1221
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.05
Method	Bayesian negative binomial regression
Parameter estimate	95% Credible interval

Confidence interval	
level	95 %
sides	1-sided

Notes:

[1] - The effect was calculated as relative risk with 95% Credible interval.

Secondary: Verified COVID-19

End point title	Verified COVID-19

End point description:

Verified COVID-19 was defined as having a positive SARS-CoV-2 PCR (polymerase chain reaction) test, rapid antigen test or antibody test and was based on information from participants.

End point type	Secondary

End point timeframe:

Within 6 months

End point values	BCG group	Placebo group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	610	611		
Units: Subjects with verified COVID-19	43	33		

Statistical analyses

Statistical analysis title	Secondary endpoints

Statistical analysis description:

Secondary time-to-event outcomes (incidence outcomes) were analysed using Cox proportional hazards regression models. The effect was reported as a relative risk (RR) with 95% confidence interval. Incidence of death and hospitalisation were reported per 1000 follow-up days, using total days of follow-up since inclusion. Disease episodes and respiratory symptoms were reported per 1000 follow-up days counted among the completed questionnaires.

Comparison groups	BCG group v Placebo group
Number of subjects included in analysis	1221
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Regression, Cox
Parameter estimate	Risk ratio (RR)
Confidence interval	
level	95 %
sides	1-sided

Secondary: All-cause hospitalisation

End point title	All-cause hospitalisation

End point description:

All hospitalisations were explored by study personnel. Only acute admissions were taken into account. Planned operations and visits to outpatient clinics were not included in the analysis.

End point type	Secondary

End point timeframe:

Within 6 months

End point values	BCG group	Placebo group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	610	611		
Units: Number of cases	15	18		

Statistical analyses

No statistical analyses for this end point

Secondary: Self-reported infection episodes

End point title	Self-reported infection episodes

End point description:

Infectious disease episodes were defined by self-reported disease and symptoms of infection and were reported as total number of episodes per randomisation group. A new episode had to be separated from previous symptoms by 7 days or more. Each subject could contribute multible episodes.

End point type	Secondary

End point timeframe:

Within 6 months

End point values	BCG group	Placebo group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	610	611		
Units: Number of episodes	632	539		

Statistical analyses

No statistical analyses for this end point

Secondary: Absenteeism due to infections

End point title	Absenteeism due to infections

End point description:

Reported by randomisation group as mean number of days absent due to infectious disease per 1000 workdays.
Secondary absenteeism endpoints were analysed using the same method as the primary endpoint.

End point type	Secondary

End point timeframe:

Within 6 months

End point values	BCG group	Placebo group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	610	611		
Units: Mean days absent				
number (not applicable)	16	14		

Statistical analyses

No statistical analyses for this end point

Secondary: Absenteeism due to respiratory infection

End point title	Absenteeism due to respiratory infection

End point description:

Reported by randomisation group as mean number of days absent due to respiratory infection per 1000 workdays.

End point type	Secondary

End point timeframe:

Within 6 months

End point values	BCG group	Placebo group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	610	611		
Units: Mean days absent				
number (not applicable)	10	9		

Statistical analyses

No statistical analyses for this end point

Secondary: Absenteeism due to verified COVID-19

End point title	Absenteeism due to verified COVID-19

End point description:

Reported by randomisation group as mean number of days absent due to verified COVID-19 per 1000 workdays.

End point type	Secondary

End point timeframe:

Within 6 months

End point values	BCG group	Placebo group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	610	611		
Units: Mean days absent				
number (not applicable)	3	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Days of self-reported respiratory symptoms

End point title	Days of self-reported respiratory symptoms

End point description:

Number of days with symptoms per 1000 follow-up days. Respiratory symptoms were defined as one or more of the following symptoms: cough, sore throat, runny nose, loss of smell/taste or dyspnoea with or without general symptoms such as fever, muscle ache, headache, and fatigue (dyspnoea only if in combination with fever).

End point type	Secondary

End point timeframe:

Within 6 months

End point values	BCG group	Placebo group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	610	611		
Units: Days	13	13		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Within 6 months.

Adverse event reporting additional description:

Adverse events were registered within 7 days of randomisation. Serious adverse events until end of trial. Participants could report adverse events via the weekly electronic questionnaires or directly to the investigators at all times during the trial.

Assessment type	Systematic

Dictionary used

Dictionary name	None
Dictionary version	0

Reporting groups

Reporting group title	BCG group

Reporting group description:

Participants randomised to BCG vaccination.

Reporting group title	Placebo group

Reporting group description:

Participants randomised to placebo.

Serious adverse events	BCG group	Placebo group	
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 610 (2.30%)	8 / 611 (1.31%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm			
subjects affected / exposed	1 / 610 (0.16%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Injury			
subjects affected / exposed	2 / 610 (0.33%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Vascular			

subjects affected / exposed	1 / 610 (0.16%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac disorder			
subjects affected / exposed	1 / 610 (0.16%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Nervous system disorder			
subjects affected / exposed	1 / 610 (0.16%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Pregnancy	Additional description: Extrauterine pregnancy		
subjects affected / exposed	0 / 610 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Allergy	Additional description: Two allergic reactions unrelated to study medicine. One of unknown origin and one related to COVID-19 vaccine.		
subjects affected / exposed	2 / 610 (0.33%)	0 / 611 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache and lipotymia			
subjects affected / exposed	2 / 610 (0.33%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal disorder			
subjects affected / exposed	1 / 610 (0.16%)	2 / 611 (0.33%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			

Respiratory disorder			
subjects affected / exposed	0 / 610 (0.00%)	1 / 611 (0.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infection			
subjects affected / exposed	3 / 610 (0.49%)	2 / 611 (0.33%)	
occurrences causally related to treatment / all	0 / 5	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	BCG group	Placebo group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	79 / 610 (12.95%)	36 / 611 (5.89%)	
Nervous system disorders			
Neurological symptom			
subjects affected / exposed	1 / 610 (0.16%)	2 / 611 (0.33%)	
occurrences (all)	3	3	
General disorders and administration site conditions			
General symptom	Additional description: Headaches, fatigue and general malaise.		
subjects affected / exposed	42 / 610 (6.89%)	7 / 611 (1.15%)	
occurrences (all)	49	49	
Blood and lymphatic system disorders			
Lymph node pain	Additional description: Swollen lymph node after vaccination		
subjects affected / exposed	5 / 610 (0.82%)	0 / 611 (0.00%)	
occurrences (all)	5	5	
Eye disorders			
Eye disorder			
subjects affected / exposed	1 / 610 (0.16%)	0 / 611 (0.00%)	
occurrences (all)	1	1	
Gastrointestinal disorders			
Gastritis			
subjects affected / exposed	1 / 610 (0.16%)	0 / 611 (0.00%)	
occurrences (all)	1	1	
Musculoskeletal and connective tissue disorders			

Musculoskeletal disorder subjects affected / exposed occurrences (all)	2 / 610 (0.33%) 4	2 / 611 (0.33%) 4	
Infections and infestations Infection subjects affected / exposed occurrences (all)	27 / 610 (4.43%) 52	25 / 611 (4.09%) 52	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported