Clinical trial results:
Reducing health care workers absenteeism in SARS-CoV-2 pandemic by enhanced trained immune responses through Bacillus Calmette-Guérin vaccination, a randomized controlled trial (COVID-19).

Summary

EudraCT number	2020-000919-69
Trial protocol	NL
Global end of trial date	17 May 2021

Results information

Result version number	v1 (current)
This version publication date	18 June 2022
First version publication date	18 June 2022

Trial information

Trial identification

Sponsor protocol code	73249

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04328441
WHO universal trial number (UTN)	U1111-1249-1107

Notes:

Sponsors

Sponsor organisation name	University Medical Center Utrecht
Sponsor organisation address	Heidelberglaan 100, Utrecht, Netherlands,
Public contact	Marc J. M. Bonten, University Medical Center Utrecht, 0031 8875 503 50 , M.J.M.Bonten@umcutrecht.nl
Scientific contact	Marc J. M. Bonten, University Medical Center Utrecht, 0031 8875 503 50 , M.J.M.Bonten@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	17 May 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 May 2021
Global end of trial reached?	Yes
Global end of trial date	17 May 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To reduce absenteeism among HCW with direct patient contacts during the epidemic phase of SARS-CoV-2.

Protection of trial subjects:

Participants were instructed throughout to contact the study team in case of (serious) adverse events, . Participants that reported a hospital admission in the mobile phone application were contacted by the research team. Known systemic and local injection site side effects of BCG vaccination were solicited during the first 7 days after injection, and local side effects again at the end of the trial.

Statistical analysis

The primary endpoint was analyzed as total counts (i.e. one total count per participant) using a Bayesian negative binomial regression and corrected for participant baseline characteristics. Secondary count endpoints (e.g. number of days reporting symptoms) were analyzed using maximum likelihood estimation (frequentist model) and are reported as RR with 95% confidence interval (CI), and secondary time-to-event endpoints (e.g. incidence of COVID-19) using Cox-proportional hazard models reporting hazard rations (HR) and 95% CIs, with adjustment for the same baseline participant characteristics as the primary analysis. COVID-19 related absenteeism was analyzed using the same method as the primary endpoint.

Interim analyses were performed as described for the primary outcome and were performed biweekly from weeks 4 to 26 and monthly from week 26 to study end (March 2021). Unblinded results of the interim analysis and incidence of (serious) adverse events were reported to the data safety monitoring board, once per month from week 4 to 26 and once per two months from week 26 to study end.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 May 2020
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Scientific research
Long term follow-up duration	1 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 1511
Worldwide total number of subjects	1511
EEA total number of subjects	1511

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)	1511
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were adult (≥18 years) healthcare workers (HCWs) working in the participating hospitals or their affiliated ambulance services, with expected exposure to COVID-19 patients as part of their clinical duties. Primary exclusion criteria were known allergy to BCG, active or latent Mycobacterium tuberculosis infection, any other active infec

Pre-assignment

Screening details:

Participants were recruited with advertisements on the hospital website or bij email. All participants provided written informed consent.

Period 1

Period 1 title	Inclusion period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Data analyst, Carer

Blinding implementation details:

Participants and study personnel conducting participant follow-up were blinded to treatment allocation. Study personnel preparing and administering the study vaccines were not blinded but could not influence treatment allocations or data collection. The trial statistician that conducted the interim and final analyses was not blinded throughout the trial but was not otherwise involved in trial conduct.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Placebo, normal saline solution as an intradermal injection in the left upper arm

Arm type	Placebo
Investigational medicinal product name	Not Applicable
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intradermal use

Dosage and administration details:

Normal saline solution 0.1 mL as an intradermal injection in the left upper arm.

Arm title	Bacillus Calmette-Guérin

Arm description:

0.1 mL of the Danish strain 1331, SSI, Denmark, equivalent to 0.075 mg attenuated Mycobacterium bovis

Arm type	Experimental
Investigational medicinal product name	Bacillus Calmette-Guérin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intradermal use

Dosage and administration details:

0.1 mL of the Danish strain 1331, SSI, Denmark, equivalent to 0.075 mg attenuated Mycobacterium bovis

Number of subjects in period 1	Placebo	Bacillus Calmette-Guérin
Started	758	753
Completed	706	722
Not completed	52	31
Lost to follow-up	52	31

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Placebo, normal saline solution as an intradermal injection in the left upper arm	
Reporting group title	Bacillus Calmette-Guérin
Reporting group description:	
0.1 mL of the Danish strain 1331, SSI, Denmark, equivalent to 0.075 mg attenuated Mycobacterium bovis	

Reporting group values	Placebo	Bacillus Calmette-Guérin	Total
Number of subjects	758	753	1511
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)	758	753	1511
From 65-84 years	0	0	0
85 years and over	0	0	0
Adults	0	0	0
Age continuous Units: years			
arithmetic mean	42.8	41.3	
standard deviation	± 12.7	± 12.6	-
Gender categorical Units: Subjects			
Female	550	572	1122
Male	208	181	389

Subject analysis sets	
Subject analysis set title	Intention to treat
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Data from all enrolled participants were included for analysis. If participants did not complete the follow-up period, the available data untill that time were included.	

Reporting group values	Intention to treat		
Number of subjects	1511		
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)	1511		
From 65-84 years	0		
85 years and over	0		
Adults	1511		
Age continuous			
Units: years			
arithmetic mean	42.1		
standard deviation	± 12.7		
Gender categorical			
Units: Subjects			
Female	1122		
Male	389		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Placebo, normal saline solution as an intradermal injection in the left upper arm	
Reporting group title	Bacillus Calmette-Guérin
Reporting group description:	
0.1 mL of the Danish strain 1331, SSI, Denmark, equivalent to 0.075 mg attenuated Mycobacterium bovis	
Subject analysis set title	Intention to treat
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Data from all enrolled participants were included for analysis. If participants did not complete the follow-up period, the available data untill that time were included.	

Primary: Unplanned absenteeism for any reason

End point title	Unplanned absenteeism for any reason
End point description:	
The primary endpoint was the number of days of unplanned absenteeism for any reason, reported as the average proportion of sick-days out of planned work days.	
End point type	Primary
End point timeframe:	
Within 12 months	

End point values	Placebo	Bacillus Calmette-Guérin	Intention to treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	758	753	1511	
Units: Percentage of days				
number (not applicable)	2.7	2.8	2.8	

Statistical analyses

Statistical analysis title	Primary endpoint analysis
Statistical analysis description:	
The primary endpoint was analyzed as total counts (i.e. one total count per participant) using a Bayesian negative binomial regression and corrected for participant baseline characteristics.	
Comparison groups	Bacillus Calmette-Guérin v Placebo v Intention to treat
Number of subjects included in analysis	3022
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05 [1]
Method	Bayesian negative binomial regression
Parameter estimate	95% Credible interval

Confidence interval	
level	95 %
sides	1-sided

Notes:

[1] - The primary endpoint was analyzed as total counts (i.e. one total count per participant) using a Bayesian negative binomial regression and corrected for participant baseline characteristics. These were defined on a 95% Credible interval.

Secondary: Documented COVID19

End point title	Documented COVID19

End point description:

Documented COVID-19 required self-reporting of any respiratory tract symptom (cough, dyspnea, nasal cold, sore throat or loss of smell or taste of any reported severity) or fever (body temperature >= 38.0 degrees Celsius) within 7 days before or up to 14 days after a positive SARS-CoV-2 PCR or rapid antigen test.

End point type	Secondary

End point timeframe:

Within 12 months

End point values	Placebo	Bacillus Calmette-Guérin	Intention to treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	758	753	1511	
Units: Patients with documented Covid-19	108	102	210	

Statistical analyses

Statistical analysis title	Secondary endpoint

Statistical analysis description:

Secondary count endpoints (e.g. number of days reporting symptoms) were analyzed using maximum likelihood estimation (frequentist model) and are reported as RR with 95% confidence interval (CI), and secondary time-to-event endpoints (e.g. incidence of COVID-19) using Cox-proportional hazard models reporting hazard rations (HR) and 95% CIs, with adjustment for the same baseline participant characteristics as the primary analysis.

Comparison groups	Placebo v Bacillus Calmette-Guérin v Intention to treat
Number of subjects included in analysis	3022
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	maximum likelihood estimation
Parameter estimate	Risk ratio (RR)
Confidence interval	
level	95 %

Secondary: COVID19 related hospitalization

End point title	COVID19 related hospitalization

End point description:

Participants that reported a hospital admission in the mobile phone application were contacted by the research team.

End point type	Secondary

End point timeframe:

Within 12 months

End point values	Placebo	Bacillus Calmette-Guérin	Intention to treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	758	753	1511	
Units: Number of participants	2	1	1511	

Statistical analyses

No statistical analyses for this end point

Secondary: Acute respiratory symptoms and/or fever

End point title	Acute respiratory symptoms and/or fever

End point description:

Presence of fever required a self-measured body temperature of ≥ 38.0 and respiratory symptoms required the presence of cough or dyspnea with a severity score of ≥ 2 (mild symptoms), or the presence of nasal congestion or sore throat with a severity score of ≥ 3 (moderate symptoms).

End point type	Secondary

End point timeframe:

Within 12 months

End point values	Placebo	Bacillus Calmette-Guérin	Intention to treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	758	753	1511	
Units: Number of participants	443	490	933	

Statistical analyses

No statistical analyses for this end point

Secondary: COVID19 related absenteeism

End point title	COVID19 related absenteeism

End point description:

COVID-19 related absenteeism was analyzed using the same method as the primary endpoint.

End point type	Secondary

End point timeframe:

Within 12 months

End point values	Placebo	Bacillus Calmette-Guérin	Intention to treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	758	753	1511	
Units: Percentage				
number (not applicable)	0.7	0.7	0.7	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Within 12 months

Adverse event reporting additional description:

Participants were instructed throughout to contact the study team in case of (serious) adverse events. Participants that reported a hospital admission in the mobile phone application were contacted by the research team. Known systemic and local injection site side effects of BCG vaccination were solicited during the first 7 days after injection, an

Assessment type	Non-systematic

Dictionary used

Dictionary name	List linings
Dictionary version	NA

Reporting groups

Reporting group title	Placebo

Reporting group description:

Placebo, normal saline solution as an intradermal injection in the left upper arm

Reporting group title	Bacillus Calmette-Guérin

Reporting group description:

0.1 mL of the Danish strain 1331, SSI, Denmark, equivalent to 0.075 mg attenuated Mycobacterium bovis

Serious adverse events	Placebo	Bacillus Calmette-Guérin	
Total subjects affected by serious adverse events			
subjects affected / exposed	18 / 758 (2.37%)	13 / 753 (1.73%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	1	
Cardiac disorders			
Cardiac disorders			
subjects affected / exposed	2 / 758 (0.26%)	2 / 753 (0.27%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nervous system disorders			
Nervous system disorders			
subjects affected / exposed	2 / 758 (0.26%)	2 / 753 (0.27%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Blood and lymphatic system disorders			

subjects affected / exposed	0 / 758 (0.00%)	1 / 753 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal disorders			
subjects affected / exposed	3 / 758 (0.40%)	2 / 753 (0.27%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory, thoracic and mediastinal disorders			
subjects affected / exposed	1 / 758 (0.13%)	0 / 753 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal and urinary disorders			
subjects affected / exposed	2 / 758 (0.26%)	4 / 753 (0.53%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal and connective tissue disorders			
subjects affected / exposed	5 / 758 (0.66%)	0 / 753 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infections and infestations			
subjects affected / exposed	1 / 758 (0.13%)	1 / 753 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	Bacillus Calmette-Guérin	
Total subjects affected by non-serious adverse events subjects affected / exposed	25 / 758 (3.30%)	82 / 753 (10.89%)	
Cardiac disorders Cardiac disorders subjects affected / exposed occurrences (all)	1 / 758 (0.13%) 1	0 / 753 (0.00%) 0	
Nervous system disorders Nervous system disorders subjects affected / exposed occurrences (all)	4 / 758 (0.53%) 4	5 / 753 (0.66%) 5	
General disorders and administration site conditions General disorders and administration site conditions alternative assessment type: Systematic subjects affected / exposed occurrences (all)	3 / 758 (0.40%) 3	59 / 753 (7.84%) 59	
Gastrointestinal disorders Gastrointestinal disorders subjects affected / exposed occurrences (all)	5 / 758 (0.66%) 5	3 / 753 (0.40%) 3	
Respiratory, thoracic and mediastinal disorders Respiratory disorders subjects affected / exposed occurrences (all)	4 / 758 (0.53%) 4	2 / 753 (0.27%) 2	
Renal and urinary disorders Urologic and gynecological disorders subjects affected / exposed occurrences (all)	7 / 758 (0.92%) 7	1 / 753 (0.13%) 1	
Endocrine disorders Endocrine disorders subjects affected / exposed occurrences (all)	1 / 758 (0.13%) 1	1 / 753 (0.13%) 1	
Musculoskeletal and connective tissue disorders Musculoskeletal and connective tissue disorders subjects affected / exposed occurrences (all)	0 / 758 (0.00%) 0	11 / 753 (1.46%) 11	

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