Clinical trial results:
Reducing hospital admission of elderly in SARS-CoV-2 pandemic via the induction of trained immunity by bacillus Calmette-Guérin vaccination, a randomized controlled trial.

Summary

EudraCT number	2020-001591-15
Trial protocol	NL
Global end of trial date	22 September 2021

Results information

Result version number	v1 (current)
This version publication date	27 August 2022
First version publication date	27 August 2022

Trial information

Trial identification

Sponsor protocol code	NL73430.091.20

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04417335
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Radboudumc
Sponsor organisation address	Geert Grooteplein Zuid 10, Nijmegen, Netherlands,
Public contact	Jaap ten Oever, Radboudumc, 031 0243617257, jaap.tenoever@radboudumc.nl
Scientific contact	Jaap ten Oever, Radboudumc, 031 0243617257, jaap.tenoever@radboudumc.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 May 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 May 2021
Global end of trial reached?	Yes
Global end of trial date	22 September 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To reduce hospital admission of elderly people during the SARS-CoV-2 outbreak.

Protection of trial subjects:

Trial subjects received one injection with either placebo or the BCG vaccine. Potential discomfort includes only the side effects of the vaccine, of which localized skin reactions are most common, and is usually mild and self-limiting.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 April 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	Netherlands: 2014
Worldwide total number of subjects	2014
EEA total number of subjects	2014

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)	613
From 65 to 84 years	1372
85 years and over	29

Subject disposition

Recruitment

Recruitment details:

Recruitment of trial subjects took place from 09-04-2020 until 13-05-2020 and took place in two university medical hospitals in the Netherlands (Radboudumc and UMC Utrecht)

Pre-assignment

Screening details:

People aged 60 years or older, currently suffering from an acute illness, were able to contact us in case they were interested in participating in the study.

Period 1

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

Blinding implementation details:

Subjects were not told which injection they had received. Syringe was taken from one out of two unmarked boxes, both placebo and BCG injections looked the same and were administered intradermally.
During analysis the data analyst did not know what code matched what treatment,

Arms

Are arms mutually exclusive?	Yes
Arm title	BCG vaccination

Arm description: -

Arm type	Experimental
Investigational medicinal product name	BCG vaccine (SSI)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for injection
Routes of administration	Intradermal use

Dosage and administration details:

Dosage is 0.1 mL of dissolved product and is administered intradermally in the left upper arm around the distal insertion of the m. deltoideus

Arm title	Control

Arm description: -

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

Dosage and administration details:

0.1 mL intradermally in the left upper arm at the distal insertion of the m. deltoideus

Number of subjects in period 1	BCG vaccination	Control
Started	1008	1006
Completed	989	969
Not completed	19	37
Adverse event, serious fatal	2	3
Consent withdrawn by subject	14	24
Participation other trial same study intervention	-	1
Self-administered study product	-	2
Lost to follow-up	3	7

Baseline characteristics

Reporting groups	
Reporting group title	BCG vaccination
Reporting group description: -	
Reporting group title	Control
Reporting group description: -	

Reporting group values	BCG vaccination	Control	Total
Number of subjects	1008	1006	2014
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	67	67	
inter-quartile range (Q1-Q3)	64 to 72	64 to 72	-
Gender categorical Units: Subjects			
Female	492	464	956
Male	516	542	1058

End points

End points reporting groups

Reporting group title	BCG vaccination
Reporting group description: -	
Reporting group title	Control
Reporting group description: -	

Primary: Cumulative incidence respiratory tract infections requiring medical intervention

End point title	Cumulative incidence respiratory tract infections requiring medical intervention
End point description: Cumulative incidence: BCG - 0.029 Control - 0.024	
End point type	Primary
End point timeframe: Study period (1 year follow-up after injection)	

End point values	BCG vaccination	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1008	1006		
Units: Events	29	24		

Statistical analyses

Statistical analysis title	Primary
Comparison groups	BCG vaccination v Control
Number of subjects included in analysis	2014
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Fine-Gray competing risks
Parameter estimate	subdistribution hazard ratio
Point estimate	1.26
Confidence interval	
level	Other: 98.2 %
sides	2-sided
lower limit	0.65
upper limit	2.44

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Severe adverse events, full study period Adverse events, 14 days after injection	
Assessment type	Systematic

Dictionary used	
Dictionary name	CTCAE
Dictionary version	5

Reporting groups	
Reporting group title	BCG injection
Reporting group description:	
Solicited adverse events during the first 14 days and serious adverse events during the study period are reported here	
Reporting group title	Control
Reporting group description:	
Solicited adverse events during the first 14 days and serious adverse events during the study period are reported here	

Serious adverse events	BCG injection	Control	
Total subjects affected by serious adverse events			
subjects affected / exposed	28 / 1008 (2.78%)	19 / 1006 (1.89%)	
number of deaths (all causes)	2	3	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Cardiac disorder			
subjects affected / exposed	8 / 1008 (0.79%)	7 / 1006 (0.70%)	
occurrences causally related to treatment / all	0 / 8	0 / 7	
deaths causally related to treatment / all	0 / 1	0 / 2	
Nervous system disorders			
Nervous system disorders			
subjects affected / exposed	6 / 1008 (0.60%)	1 / 1006 (0.10%)	
occurrences causally related to treatment / all	0 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Blood or lymphatic disorder			
subjects affected / exposed	0 / 1008 (0.00%)	1 / 1006 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

General disorders and administration site conditions			
Unknown	Additional description: Participant did not disclose further details		
subjects affected / exposed	1 / 1008 (0.10%)	0 / 1006 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal disorders			
subjects affected / exposed	3 / 1008 (0.30%)	2 / 1006 (0.20%)	
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 disorder			
subjects affected / exposed	1 / 1008 (0.10%)	1 / 1006 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Urological and gynaecological disorders			
subjects affected / exposed	3 / 1008 (0.30%)	1 / 1006 (0.10%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal and connective tissue disorders			
subjects affected / exposed	4 / 1008 (0.40%)	2 / 1006 (0.20%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infection			
subjects affected / exposed	6 / 1008 (0.60%)	6 / 1006 (0.60%)	
occurrences causally related to treatment / all	0 / 6	0 / 6	
deaths causally related to treatment / all	0 / 1	0 / 0	

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	BCG injection	Control	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	758 / 1008 (75.20%)	134 / 1006 (13.32%)	
General disorders and administration site conditions			
Injection site reaction	Additional description: Within 7 days after injection		
subjects affected / exposed	758 / 1008 (75.20%)	55 / 1006 (5.47%)	
occurrences (all)	758	55	
Fever	Additional description: within 14 days after injection		
subjects affected / exposed	42 / 1008 (4.17%)	18 / 1006 (1.79%)	
occurrences (all)	42	18	
Myalgia	Additional description: Within 14 days after injection		
subjects affected / exposed	112 / 1008 (11.11%)	62 / 1006 (6.16%)	
occurrences (all)	112	62	
Chills	Additional description: Within 14 days after injection		
subjects affected / exposed	72 / 1008 (7.14%)	46 / 1006 (4.57%)	
occurrences (all)	72	46	
Fatigue	Additional description: Within 14 days after injection		
subjects affected / exposed	168 / 1008 (16.67%)	104 / 1006 (10.34%)	
occurrences (all)	168	104	
Headache	Additional description: Within 14 days after injection		
subjects affected / exposed	178 / 1008 (17.66%)	134 / 1006 (13.32%)	
occurrences (all)	178	134	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 April 2020	Placebo NaCl given to control group
06 May 2020	Increase amount of participants from 1600 to 2000, increase study period from 6 months to 12 months, venous blood collection at end of study in select group
08 July 2020	Reduced frequency questionnaire from daily to weekly after 6 months
16 September 2020	Change of primary endpoint due to unexpected decrease in Covid-19 cases and associated hospitalization, new primary endpoint includes previous primary endpoint
27 May 2021	Capillary blood collection at home

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/35247264