Clinical trial results:
BCG vaccination to Reduce the impact of COVID-19 in healthcare workers (BRACE) Trial

Summary

EudraCT number	2020-002503-19
Trial protocol	NL GB
Global end of trial date	27 May 2022

Results information

Result version number	v1 (current)
This version publication date	30 August 2023
First version publication date	30 August 2023
Summary attachment (see zip file)	BRACE trial (Research summary.pdf)

Trial information

Trial identification

Sponsor protocol code	62586

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04327206
WHO universal trial number (UTN)	U1111-1256-4104

Notes:

Sponsors

Sponsor organisation name	UMC Utrecht
Sponsor organisation address	Department Julius Centrum of Health Sciences and Primary Care of Heidelberglaan 100, Utrecht, Netherlands, 3584 CX
Public contact	sponsor-Europe, UMC Utrecht, +31 88755 0350,
Scientific contact	sponsor-Europe, UMC Utrecht, +31 88755 0350,
Sponsor organisation name	Murdoch Children's Research Institute
Sponsor organisation address	Royal Children's Hospital, 50 Flemington Rd, Parkville, Australia, 3052
Public contact	Prof Nigel Curtis, Murdoch Children's Research Institute, brace@mcri.edu.au
Scientific contact	Prof Nigel Curtis, Murdoch Children's Research Institute, brace@mcri.edu.au

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	10 November 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 November 2021
Global end of trial reached?	Yes
Global end of trial date	27 May 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

1) To determine if BCG vaccination (Intervention) compared with placebo (Comparator) reduces the incidence of COVID-19 disease (Outcome) measured over the 6 months following randomisation (Time) in healthcare workers exposed to SARS-CoV-2 (Participants).

2) To determine if BCG vaccination (Intervention) compared with placebo (Comparator) reduces the incidence of severe COVID-19 disease (with COVID 19 related death, hospitalisation, or non-hospitalised severe disease (defined as Non-ambulant1 for ≥ 3 consecutive days OR Unable to work2 for ≥ 3 consecutive days) (Outcome) measured over the 6 months following randomisation (Time) in healthcare workers exposed to SARS-CoV-2 (Participants).

The trial has 2 stages. Stage 1 took place in Australia only and Stage 2 took place in Australia, the Netherlands, Spain, the United Kingdom, and Brazil. This result focuses only on stage 2 of the trial because there was negligible SARSCoV- 2 community transmission during stage 1.

Protection of trial subjects:

The study protocol has been designed to ensure that the anticipated benefits to the subjects justify the foreseeable risks and inconveniences, involve as little pain, discomfort, fear and any other foreseeable risk as possible for the subjects. The risk threshold and the degree of distress are specifically defined in the protocol and trial subjects health is constantly monitored by appropriately qualified medical doctor. The study protocol and any amendments must receive IRB approval before implementation at sites.

Consent must be obtained from trial subjects before any study procedures can begin. Trial subjects need to be informed of any changes to the study.

The rights of the subjects to the protection of the data concerning them in accordance with Directive 95/46/EC will be safeguarded.The scientific research making use of the data outside the protocol of the clinical trial will be conducted in accordance with the applicable law on data protection.

Background therapy: -
Evidence for comparator: -

Actual start date of recruitment	30 March 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	Australia: 3262
Country: Number of subjects enrolled	Netherlands: 596
Country: Number of subjects enrolled	United Kingdom: 175
Country: Number of subjects enrolled	Spain: 227
Country: Number of subjects enrolled	Brazil: 2568
Worldwide total number of subjects	6828
EEA total number of subjects	823

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)	6641
From 65 to 84 years	187
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Potential trial subjects will receive information via email, healthcare facilities notice boards, websites. Potential trial subjects can also evaluate their eligibility online via a REDCap public link and if they meet the eligibility criteria access the site-specific participant information and consent form.

Pre-assignment

Screening details:

Trial subjects will be asked a number of questions about their medical history and will not be able to participate in the study if trial subjects had received medical treatment that affects the immune response, have a serious medical condition, received a live vaccine in the past month, or the BCG vaccine in the past year.

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, Carer

Blinding implementation details:

Randomisation will be using a web-based randomisation procedure and service will be provided by an independent statistician. Randomisation will be in randomly permuted blocks of variable length (2, 4, or 6). Randomisation will be stratified by stage of the study (prior to or post the addition of the placebo vaccination), study site, by age (<40 years; 4040 to 59 years; >=60 years) and by presence of comorbidity (any of diabetes, chronic respiratory disease,cardiac condition, hypertension).

Arms

Are arms mutually exclusive?	Yes
Arm title	BCG vaccination group (Modified Intention-to-Treat Population)

Arm description:

Participants will receive a single dose of BCG vaccine (BCG-Denmark). The adult dose of BCG vaccine is 0.1 mL injected intradermally over the distal insertion of the deltoid muscle onto the humerus (approximately one third down the upper arm).
BCG Vaccine: Freeze-dried powder: Live attenuated strain of Mycobacterium bovis (BCG), Danish strain 1331.
Each 0.1 ml vaccine contains between 200000 to 800000 colony forming units. Adult dose is 0.1 ml given by intradermal injection

Arm type	Experimental
Investigational medicinal product name	BCG Vaccine AJV
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solution for suspension for injection
Routes of administration	Intradermal use

Dosage and administration details:

BCG Denmark, 0.1 mL injected intradermal over the distal insertion of the deltoid muscle onto the humerus.

Arm title	Control group (Modified Intention-to-Treat Population)

Arm description:

Participants will receive a single 0.1 mL dose of 0.9%NaCl injected intradermally over the distal insertion of the deltoid muscle onto the humerus (approximately one third down the upper arm).
0.9%NaCl: 0.9% Sodium Chloride Injection

Arm type	Placebo

Investigational medicinal product name	NaCl
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intradermal use

Dosage and administration details:

0.1 ml of 0.9% NaCl injected intradermal over the distal insertion of the deltoid muscle onto the humerus.

Number of subjects in period 1[1]	BCG vaccination group (Modified Intention-to-Treat Population)	Control group (Modified Intention-to-Treat Population)
Started	1703	1683
Completed	1703	1683

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The primary population for all efficacy analyses will be the modified intention-to-treat population (mITT) which will only include participants who had a negative SARS-CoV-2 test result at time of randomisation.

Baseline characteristics

Reporting groups

Reporting group title	BCG vaccination group (Modified Intention-to-Treat Population)

Reporting group description:

Participants will receive a single dose of BCG vaccine (BCG-Denmark). The adult dose of BCG vaccine is 0.1 mL injected intradermally over the distal insertion of the deltoid muscle onto the humerus (approximately one third down the upper arm).
BCG Vaccine: Freeze-dried powder: Live attenuated strain of Mycobacterium bovis (BCG), Danish strain 1331.
Each 0.1 ml vaccine contains between 200000 to 800000 colony forming units. Adult dose is 0.1 ml given by intradermal injection

Reporting group title	Control group (Modified Intention-to-Treat Population)

Reporting group description:

Participants will receive a single 0.1 mL dose of 0.9%NaCl injected intradermally over the distal insertion of the deltoid muscle onto the humerus (approximately one third down the upper arm).
0.9%NaCl: 0.9% Sodium Chloride Injection

Reporting group values	BCG vaccination group (Modified Intention-to-Treat Population)	Control group (Modified Intention-to-Treat Population)	Total
Number of subjects	1703	1683	3386
Age categorical Units: Subjects			
Adults (18 to 40 years old)	740	734	1474
Adults (40 to 59 years old)	811	802	1613
Adults (60 years old and above)	152	147	299
Age continuous			
Measure Description: Plus-minus values are means ±SD. The modified intention-to-treat population was restricted to participants with a negative test for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) at baseline. Percentages may not total 100 because of rounding. BCG denotes bacille Calmette-Guérin, and PCR polymerase chain reaction.			
Units: years			
median	42.8	42.8	
standard deviation	± 12.0	± 12.0	-
Gender categorical Units: Subjects			
Female	1245	1281	2526
Male	458	402	860
Coexisting condition — no. (%) Units: Subjects			
Any coexisting condition	356	333	689
Chronic respiratory disease	111	92	203
Cardiovascular disease or hypertension	233	214	447
Diabetes mellitus	52	67	119
No coexisiting condition	951	977	1928
Obesity: BMI ≥30			
For BCG Vaccine group: 1672 participants were analyzed for BMI For Placebo group:1638 participants were analyzed for BMI No. of participant BMI ≤ 30 includes participants that do not have BMI data provided.			
Units: Subjects			

No. of participant BMI ≥30	362	338	700
No. of participant BMI ≤30	1341	1345	2686
No. of Smoker Units: Subjects			
No. of smoker	176	184	360
No. of non-smoker	1527	1499	3026
Previous BCG vaccination Units: Subjects			
No. participants previously had BCG Vaccination	1262	1244	2506
No. of participant previously had no BCG	441	439	880
Positive SARS-CoV-2 serologic status at baseline Units: Subjects			
No. participant analysed	1703	1683	3386
Positive SARS-CoV-2 serologic status at baseline	0	0	0
Positive SARS-CoV-2 PCR assay at baseline Units: Subjects			
No. Positive SARS-CoV-2 PCR assay at baseline	0	0	0
No. participant analysed	1006	999	2005
No. participant not analysed	697	684	1381
Direct contact with patients Units: Subjects			
No. of participant Direct contact with patients	1363	1341	2704
No. of participant No direct contact with patients	340	342	682
Occupation Units: Subjects			
Nurse or Midwife	359	326	685
Medical doctor	197	187	384
Allied Health	329	339	668
Adminstrative or clerical	257	252	509
Patient service assistant or hospital maintenance	246	232	478
Other	315	347	662
Region of Enrollment			
Primary analyses involved the modified intention-to-treat population, which was restricted to participants with a negative test for severe acute respiratory syndrome coronavirus 2 at baseline			
Units: Subjects			
Netherlands	282	284	566
Brazil	1006	999	2005
United Kingdom	88	85	173
Australia	214	206	420
Spain	113	109	222

End points

End points reporting groups

Reporting group title	BCG vaccination group (Modified Intention-to-Treat Population)

Reporting group description:

Participants will receive a single dose of BCG vaccine (BCG-Denmark). The adult dose of BCG vaccine is 0.1 mL injected intradermally over the distal insertion of the deltoid muscle onto the humerus (approximately one third down the upper arm).
BCG Vaccine: Freeze-dried powder: Live attenuated strain of Mycobacterium bovis (BCG), Danish strain 1331.
Each 0.1 ml vaccine contains between 200000 to 800000 colony forming units. Adult dose is 0.1 ml given by intradermal injection

Reporting group title	Control group (Modified Intention-to-Treat Population)

Reporting group description:

Participants will receive a single 0.1 mL dose of 0.9%NaCl injected intradermally over the distal insertion of the deltoid muscle onto the humerus (approximately one third down the upper arm).
0.9%NaCl: 0.9% Sodium Chloride Injection

Primary: Symptomatic COVID-19 by 6 Months

End point title	Symptomatic COVID-19 by 6 Months

End point description:

Number of participants with Symptomatic COVID-19 defined as
- positive SARS-Cov-2 test (PCR, RAT or serology), plus
- fever (using self-reported questionnaire), or
- at least one sign or symptom of respiratory disease including cough, shortness of breath, respiratory distress/failure (using self-reported questionnaire).

End point type	Primary

End point timeframe:

Measured over the 6 months following randomisation

End point values	BCG vaccination group (Modified Intention-to-Treat Population)	Control group (Modified Intention-to-Treat Population)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	132	106		
Units: percent				
number (confidence interval 95%)				
Event rate per 100 person-yr (95% CI)	29.4 (24.8 to 34.9)	24.4 (20.1 to 29.5)		
Unadjusted estimated percent (95% CI)	11.9 (9.9 to 13.9)	9.8 (7.9 to 11.8)		
Adjusted estimated percent (95% CI)	14.7 (12.0 to 17.3)	12.3 (9.7 to 14.8)		

Statistical analyses

Statistical analysis title	Symptomatic COVID-19 by 6 Months Units:

Statistical analysis description:

Analyses were done using a modified intention-to-treat (mITT) population with participants analysed according to randomisation group, regardless of the intervention they received, restricted to participants who had a negative baseline SARS-CoV-2 test result. Symptomatic Covid-19 occurred in 132 participants in BCG Vaccine group (adjusted estimated risk, 14.7%) and in 106 participants in Placebo group (12.3%) (difference, 2.4 percentage points; 95% confidence interval [CI], −0.7 to 5.5; P = 0.13)

Comparison groups	Control group (Modified Intention-to-Treat Population) v BCG vaccination group (Modified Intention-to-Treat Population)
Number of subjects included in analysis	238
Analysis specification	Post-hoc
Analysis type	superiority[1]
P-value	= 0.13
Method	flexible parametric survival model
Parameter estimate	[Difference in probability (BCG-Placebo)
Point estimate	2.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	5.5

Notes:

[1] - The primary outcomes were compared between the groups using a difference in probability of event by 6 months (presented as absolute difference in percentage).

Primary: Severe COVID-19 Incidence Over 6 Months

End point title	Severe COVID-19 Incidence Over 6 Months

End point description:

Number of participants with severe COVID-19 defined as:
- positive SARS-CoV-2 test (PCR, RAT or serology), PLUS
- death as a consequence of COVID-19, OR
- Hospitalised as a consequence of COVID-19, OR
- Non-hospitalised severe disease as a consequence of COVID-19, defined as non- ambulant* for ≥ 3 consecutive days unable to work** for ≥ 3 consecutive days

(*) "pretty much confined to bed (meaning finding it very difficult to do any normal daily activities".
(**) "I do not feel physically well enough to go to work"

End point type	Primary

End point timeframe:

Measured over the 6 months following randomisation

End point values	BCG vaccination group (Modified Intention-to-Treat Population)	Control group (Modified Intention-to-Treat Population)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	61		
Units: percent				
number (confidence interval 95%)				

Event rate per 100 person-yr	16.3 (13.0 to 20.5)	13.8 (10.8 to 17.8)		
Unadjusted estimated percent (95% CI)	6.7 (5.2 to 8.3)	5.5 (4.0 to 7.0)		
Adjusted estimated percent (95% CI)	7.6 (5.8 to 9.5)	6.5 (4.7 to 8.2)		

Statistical analyses

Statistical analysis title	Severe COVID-19 Incidence Over 6 Months
Comparison groups	BCG vaccination group (Modified Intention-to-Treat Population) v Control group (Modified Intention-to-Treat Population)
Number of subjects included in analysis	136
Analysis specification	Post-hoc
Analysis type	superiority[2]
P-value	= 0.34
Method	flexible parametric survival model
Parameter estimate	Difference in probability (BCG-Placebo)
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	3.5

Notes:

[2] - Analyses were done using a modified intention-to-treat (mITT) population. In the BCG Vaccine group, 75 participants had severe COVID-19. In the Placebo group 61 participants had severe COVID-19

The primary outcomes were compared between the groups using a difference in probability of event by 6 months (presented as absolute difference in percentage).

Primary: Severe Covid-19 episode by 6 mo

End point title	Severe Covid-19 episode by 6 mo

End point description:

End point type	Primary

End point timeframe:

Measured over the 6 months following randomisation

End point values	BCG vaccination group (Modified Intention-to-Treat Population)	Control group (Modified Intention-to-Treat Population)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	61		
Units: Particpants				
Death	0	1		
Hospitalization	5	4		
Severe disease without hospitalization	70	56		

Too sick to get out of bed for ≥3 consecutive days	12	18		
Too sick to go to work but not in bed for ≥3 conse	58	38		

Statistical analyses

Statistical analysis title	Severe COVID-19 Incidence Over 6 Months

Statistical analysis description:

umber of participants with severe COVID-19 defined as:
positive SARS-CoV-2 test (PCR, RAT or serology), PLUS
death as a consequence of COVID-19, OR
Hospitalised as a consequence of COVID-19, OR
Non-hospitalised severe disease as a consequence of COVID-19, defined as non- ambulant* for ≥ 3 consecutive days unable to work** for ≥ 3 consecutive days
(*) "pretty much confined to bed (meaning finding it very difficult to do any normal daily activities".
(**) "I do not feel physically well enoug

Comparison groups	BCG vaccination group (Modified Intention-to-Treat Population) v Control group (Modified Intention-to-Treat Population)
Number of subjects included in analysis	136
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.34
Method	flexible parametric survival model
Parameter estimate	Difference in probability (BCG-Placebo)
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	3.5

Secondary: Time to First Symptom of COVID-19

End point title	Time to First Symptom of COVID-19

End point description:

Participants who had either a symptomatic or severe COVID-19 episode will have time to first symptom of COVID-19 calculated as: [Date of any symptom onset for the first symptomatic or severe COVID-19 episode - Date of randomisation]
Participants who have not had a symptomatic or severe COVID-19 episode will have time calculated as: [Earliest censoring date - date of randomisation]

End point type	Secondary

End point timeframe:

Measured over the 6 and 12 months following randomisation

End point values	BCG vaccination group (Modified Intention-to-Treat Population)	Control group (Modified Intention-to-Treat Population)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1703	1683		
Units: Participants				
Time to First Symptom of COVID-19	135	107		

Statistical analyses

Statistical analysis title	Time to First Symptom of COVID-19
Comparison groups	BCG vaccination group (Modified Intention-to-Treat Population) v Control group (Modified Intention-to-Treat Population)
Number of subjects included in analysis	3386
Analysis specification	Post-hoc
Analysis type	superiority[3]
Parameter estimate	Hazard ratio (HR)
Point estimate	1.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.96
upper limit	1.59

Notes:

[3] - Analysis is done using a modified intention-to-treat (mITT) population. The outcome measure analysed is up to 6 month only. The 12 month outcome is pending analysis.

Secondary: Number of Episodes of COVID-19

End point title	Number of Episodes of COVID-19
End point description:	
The total number of symptomatic or severe COVID-19 episodes	
End point type	Secondary
End point timeframe:	
Measured over the 6 and 12 months following randomisation	

End point values	BCG vaccination group (Modified Intention-to-Treat Population)	Control group (Modified Intention-to-Treat Population)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1703	1683		
Units: Median no. of episodes of COVID-19				

median (inter-quartile range (Q1-Q3))				
Median no. of episodes of Covid-19	1.0 (1.0 to 1.0)	1.0 (1.0 to 1.0)		

Statistical analyses

Statistical analysis title	Number of Episodes of COVID-19
Statistical analysis description:	
Analysis is done using a modified intention-to-treat (mITT) population. The outcome measure analysed is up to 6 month only. The 12 month outcome is still pending analysis.	
Comparison groups	BCG vaccination group (Modified Intention-to-Treat Population) v Control group (Modified Intention-to-Treat Population)
Number of subjects included in analysis	3386
Analysis specification	Post-hoc
Analysis type	superiority
Parameter estimate	incidence rate ratio
Point estimate	0.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.74
upper limit	1.22

Secondary: Asymptomatic SARS-CoV-2 Infection

End point title	Asymptomatic SARS-CoV-2 Infection
End point description:	
Number of participants with asymptomatic SARS-CoV-2 infection defined as - Evidence of SARS-CoV-2 infection (by seroconversion) - Absence of respiratory illness (defined by trigger or non-trigger symptoms)(using self- reported questionnaire) - No evidence of exposure prior to randomisation	
End point type	Secondary
End point timeframe:	
Measured over the 6 and 12 months following randomisation	

End point values	BCG vaccination group (Modified Intention-to-Treat Population)	Control group (Modified Intention-to-Treat Population)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1703	1683		
Units: Adjusted estimated percent				
number (confidence interval 95%)				
Adjusted estimated percent	1.1 (0.5 to 1.8)	1.5 (0.8 to 2.3)		

Statistical analyses

Statistical analysis title	Asymptomatic SARS-CoV-2 Infection

Statistical analysis description:

Number of participants analyzed are participants with data. For BCG group 12 participants presented with Asymptomatic COVID-19 and for Placebo group 15 participants presented with Asymptomatic COVID-19 The result is for 6Months only. 12 Month result is still pending.

Comparison groups	BCG vaccination group (Modified Intention-to-Treat Population) v Control group (Modified Intention-to-Treat Population)
Number of subjects included in analysis	3386
Analysis specification	Post-hoc
Analysis type	superiority
Parameter estimate	Risk Difference
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.4
upper limit	0.6

Secondary: Work Absenteeism Due to COVID-19

End point title	Work Absenteeism Due to COVID-19

End point description:

Number of days (using self-reported questionnaire) unable to work (excludes quarantine/workplace restrictions) due to COVID-19 defined as
- positive SARS-Cov-2 test (PCR, RAT or serology), plus
- fever (using self-reported questionnaire), or
- at least one sign or symptom of respiratory disease including cough, shortness of breath, respiratory distress/failure (using self-reported questionnaire)

End point type	Secondary

End point timeframe:

Measured within 6 and 12 months following randomisation

End point values	BCG vaccination group (Modified Intention-to-Treat Population)	Control group (Modified Intention-to-Treat Population)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1703	1683		
Units: no. of days unable to work due to COVID				

median (confidence interval 95%)				
Median no. of days unable to work due to COVID	3.0 (0.0 to 8.0)	4.0 (0.0 to 11.0)		

Statistical analyses

Statistical analysis title	Work Absenteeism Due to COVID-19

Statistical analysis description:

Analysis is done using a modified intention-to-treat (mITT) population. The outcome measure analysed is up to 6 month only. The 12 month outcome is still pending analysis.

Comparison groups	BCG vaccination group (Modified Intention-to-Treat Population) v Control group (Modified Intention-to-Treat Population)
Number of subjects included in analysis	3386
Analysis specification	Post-hoc
Analysis type	superiority
Parameter estimate	Incidence rate ratio
Point estimate	0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.61
upper limit	1.26

Secondary: Bed Confinement Due to COVID-19

End point title	Bed Confinement Due to COVID-19

End point description:

Number of days confined to bed (using self-reported questionnaire) due to COVID-19 disease defined as
- positive SARS-Cov-2 test (PCR, RAT or serology), plus
- fever (using self-reported questionnaire), or
- at least one sign or symptom of respiratory disease including cough, shortness of breath, respiratory distress/failure (using self-reported questionnaire)

End point type	Secondary

End point timeframe:

Measured over 6 and 12 months following randomisation

End point values	BCG vaccination group (Modified Intention-to-Treat Population)	Control group (Modified Intention-to-Treat Population)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1703	1683		
Units: No. of days confined to bed due to COVID				
median (inter-quartile range (Q1-Q3))				

Median no. of days confined to bed due to COVID-19	0.0 (0.0 to 1.0)	0.0 (0.0 to 3.0)		

Statistical analyses

Statistical analysis title	Bed Confinement Due to COVID-19
Statistical analysis description:	
Analysis is done using a modified intention-to-treat (mITT) population. The outcome measure analysed is up to 6 month only. The 12 month outcome is still pending analysis.	
Comparison groups	BCG vaccination group (Modified Intention-to-Treat Population) v Control group (Modified Intention-to-Treat Population)
Number of subjects included in analysis	3386
Analysis specification	Post-hoc
Analysis type	superiority
Parameter estimate	Incidence rate ratio
Point estimate	0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.38
upper limit	1.5

Secondary: Symptom Duration of COVID-19 (<40 yr)

End point title	Symptom Duration of COVID-19 (<40 yr)
End point description:	
Number of days with symptoms in any episode of illness that meets the case definition for COVID-19 disease: - positive SARS-Cov-2 test (PCR, RAT or serology), plus - fever (using self-reported questionnaire), or - at least one sign or symptom of respiratory disease including cough, shortness of breath, respiratory distress/failure (using self-reported questionnaire)	
End point type	Secondary
End point timeframe:	
Measured over 6 and12 months following randomisation	

End point values	BCG vaccination group (Modified Intention-to-Treat Population)	Control group (Modified Intention-to-Treat Population)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	740	734		
Units: No. of days with COVID-19 Symptoms				
median (full range (min-max))				

According to age group <40 yr. Median no. of days	15 (9 to 22)	15 (11 to 25.5)		

Statistical analyses

Statistical analysis title	Symptom Duration of COVID-19

Statistical analysis description:

The outcome measure analyzed was only for 6 months. The 12 month outcome measure is still pending analysis.

Comparison groups	BCG vaccination group (Modified Intention-to-Treat Population) v Control group (Modified Intention-to-Treat Population)
Number of subjects included in analysis	1474
Analysis specification	Post-hoc
Analysis type	superiority[4]
Parameter estimate	Adjusted Incidence Rate Ratio
Point estimate	0.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.61
upper limit	1.01

Notes:

[4] - Comparing no. of days with symptoms between the BCG and placebo, shows strong evidence of interaction between treatment arms and 2 randomisation strata (age group and presence of comorbidities), rendering an overall comparison between randomisation groups non-interpretable. Subgroup analyses show in the ≥60-year age group, the BCG group had fewer days with symptoms compared with placebo group. In the subgroup without comorbidities, the BCG group had fewer days with symptoms compared with placebo

Secondary: Symptom Duration of COVID-19 (40 to 59 yr)

End point title	Symptom Duration of COVID-19 (40 to 59 yr)

End point description:

Number of days with symptoms in any episode of illness that meets the case definition for COVID-19 disease:
- positive SARS-Cov-2 test (PCR, RAT or serology), plus
- fever (using self-reported questionnaire), or
- at least one sign or symptom of respiratory disease including cough, shortness of breath, respiratory distress/failure (using self-reported questionnaire)

End point type	Secondary

End point timeframe:

The outcome measure analyzed was only for 6 months. The 12 month outcome measure is still pending analysis.

End point values	BCG vaccination group (Modified Intention-to-Treat Population)	Control group (Modified Intention-to-Treat Population)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1703	1683		
Units: No. of days with COVID-19 Symptoms				
median (inter-quartile range (Q1-Q3))				
According to age group 40 to 59 yr. Median no. of	16 (10 to 23)	14 (9 to 27)		

Statistical analyses

Statistical analysis title	Symptom Duration of COVID-19

Statistical analysis description:

The outcome measure analyzed was only for 6 months. The 12 month outcome measure is still pending analysis.

Comparison groups	BCG vaccination group (Modified Intention-to-Treat Population) v Control group (Modified Intention-to-Treat Population)
Number of subjects included in analysis	3386
Analysis specification	Post-hoc
Analysis type	superiority[5]
Parameter estimate	Adjusted Incidence Rate Ratio
Point estimate	0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.64
upper limit	1.34

Notes:

[5] - Comparing no. of days with symptoms between the BCG and placebo, shows strong evidence of interaction between treatment arms and 2 randomisation strata (age group and presence of comorbidities), rendering an overall comparison between randomisation groups non-interpretable. Subgroup analyses show in the ≥60-year age group, the BCG group had fewer days with symptoms compared with placebo group. In the subgroup without comorbidities, the BCG group had fewer days with symptoms compared with placebo

Secondary: Symptom Duration of COVID-19 (≥60 yr)

End point title	Symptom Duration of COVID-19 (≥60 yr)

End point description:

Number of days with symptoms in any episode of illness that meets the case definition for COVID-19 disease:
- positive SARS-Cov-2 test (PCR, RAT or serology), plus
- fever (using self-reported questionnaire), or
- at least one sign or symptom of respiratory

End point type	Secondary

End point timeframe:

Measured over 6 and12 months following randomisation

End point values	BCG vaccination group (Modified Intention-to-Treat Population)	Control group (Modified Intention-to-Treat Population)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	152	147		
Units: No. of days with COVID-19 symptoms				
median (inter-quartile range (Q1-Q3))				
According to age group ≥60 yr. Median no. of days	16.5 (8 to 24)	38 (27 to 50)		

Statistical analyses

Statistical analysis title	Symptom Duration of COVID-19

Statistical analysis description:

The outcome measure analyzed was only for 6 months. The 12 month outcome measure is still pending analysis.

Comparison groups	BCG vaccination group (Modified Intention-to-Treat Population) v Control group (Modified Intention-to-Treat Population)
Number of subjects included in analysis	299
Analysis specification	Post-hoc
Analysis type	superiority[6]
Parameter estimate	Adjusted Incidence Rate Ratio
Point estimate	0.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.19
upper limit	0.53

Notes:

[6] - Comparing no. of days with symptoms between the BCG and placebo, shows strong evidence of interaction between treatment arms and 2 randomisation strata (age group and presence of comorbidities), rendering an overall comparison between randomisation groups non-interpretable. Subgroup analyses show in the ≥60-year age group, the BCG group had fewer days with symptoms compared with placebo group. In the subgroup without comorbidities, the BCG group had fewer days with symptoms compared with placebo

Secondary: Symptom Duration of COVID-19 (Presence of any coexsisting condition)

End point title	Symptom Duration of COVID-19 (Presence of any coexsisting condition)

End point description:

Number of days with symptoms in any episode of illness that meets the case definition for COVID-19 disease:
- positive SARS-Cov-2 test (PCR, RAT or serology), plus
- fever (using self-reported questionnaire), or
- at least one sign or symptom of respiratory disease including cough, shortness of breath, respiratory distress/failure (using self-reported questionnaire)

End point type	Secondary

End point timeframe:

Measured over 6 and12 months following randomisation

End point values	BCG vaccination group (Modified Intention-to-Treat Population)	Control group (Modified Intention-to-Treat Population)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	356	333		
Units: No. of days				
median (inter-quartile range (Q1-Q3))				
Any coexisting condition. Median no. of days	19.5 (15.5 to 31.5)	17 (12 to 22)		

Statistical analyses

Statistical analysis title	Symptom Duration of COVID-19

Statistical analysis description:

The outcome measure analyzed was only for 6 months. The 12 month outcome measure is still pending analysis.

Comparison groups	BCG vaccination group (Modified Intention-to-Treat Population) v Control group (Modified Intention-to-Treat Population)
Number of subjects included in analysis	689
Analysis specification	Post-hoc
Analysis type	superiority[7]
Parameter estimate	Adjusted Incidence Rate Ratio
Point estimate	1.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.88
upper limit	2.52

Notes:

[7] - Comparing no. of days with symptoms between the BCG and placebo, shows strong evidence of interaction between treatment arms and 2 randomisation strata (age group and presence of comorbidities), rendering an overall comparison between randomisation groups non-interpretable. Subgroup analyses show in the ≥60-year age group, the BCG group had fewer days with symptoms compared with placebo group. In the subgroup without comorbidities, the BCG group had fewer days with symptoms compared with placebo

Secondary: Symptom Duration of COVID-19 (Absence of any coexisting condition)

End point title	Symptom Duration of COVID-19 (Absence of any coexisting condition)

End point description:

Number of days with symptoms in any episode of illness that meets the case definition for COVID-19

disease:
- positive SARS-Cov-2 test (PCR, RAT or serology), plus
- fever (using self-reported questionnaire), or
- at least one sign or symptom of respiratory disease including cough, shortness of breath, respiratory distress/failure (using self-reported questionnaire)

End point type	Secondary

End point timeframe:

Measured over 6 and12 months following randomisation

End point values	BCG vaccination group (Modified Intention-to-Treat Population)	Control group (Modified Intention-to-Treat Population)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1347	1350		
Units: Median no. of day				
median (inter-quartile range (Q1-Q3))				
Absence of any coexisting condition Median no.days	13 (0.9 to 22)	15.5 (11 to 30)		

Statistical analyses

Statistical analysis title	Symptom Duration of COVID-19

Statistical analysis description:

The outcome measure analyzed was only for 6 months. The 12 month outcome measure is still pending analysis.

Comparison groups	BCG vaccination group (Modified Intention-to-Treat Population) v Control group (Modified Intention-to-Treat Population)
Number of subjects included in analysis	2697
Analysis specification	Post-hoc
Analysis type	superiority[8]
Parameter estimate	Adjusted Incidence Rate Ratio
Point estimate	0.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.58
upper limit	0.91

Notes:

[8] - Comparing no. of days with symptoms between the BCG and placebo, shows strong evidence of interaction between treatment arms and 2 randomisation strata (age group and presence of comorbidities), rendering an overall comparison between randomisation groups non-interpretable. Subgroup analyses show in the ≥60-year age group, the BCG group had fewer days with symptoms compared with placebo group. In the subgroup without comorbidities, the BCG group had fewer days with symptoms compared with placebo

Secondary: Pneumonia Due to COVID-19

End point title	Pneumonia Due to COVID-19

End point description:

Number of pneumonia cases (using self-reported questionnaire and/or medical/hospital records) due to COVID-19

End point type	Secondary

End point timeframe:

Measured over the 6 and 12 months following randomisation

End point values	BCG vaccination group (Modified Intention-to-Treat Population)	Control group (Modified Intention-to-Treat Population)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1703	1683		
Units: Participants				
No. of participants	7	7		

Statistical analyses

Statistical analysis title	Pneumonia Due to COVID-19

Statistical analysis description:

Analysis is done using a modified intention-to-treat (mITT) population. The outcome measure analysed is up to 6 month only. The 12 month outcome is pending analysis.

Comparison groups	BCG vaccination group (Modified Intention-to-Treat Population) v Control group (Modified Intention-to-Treat Population)
Number of subjects included in analysis	3386
Analysis specification	Post-hoc
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.32
upper limit	2.64

Secondary: Oxygen Therapy Due to COVID-19

End point title	Oxygen Therapy Due to COVID-19

End point description:

End point type	Secondary

End point timeframe:

Measured over the 6 and12 months following randomisation

End point values	BCG vaccination group (Modified Intention-to-Treat Population)	Control group (Modified Intention-to-Treat Population)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1703	1683		
Units: Participants				
No. of participants	3	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Critical Care Admissions Due to COVID-19

End point title	Critical Care Admissions Due to COVID-19

End point description:

Number of admission to critical care (using self-reported questionnaire and/or medical/hospital records) due to COVID-19

End point type	Secondary

End point timeframe:

Measured over the 6 and 12 months following randomisation

End point values	BCG vaccination group (Modified Intention-to-Treat Population)	Control group (Modified Intention-to-Treat Population)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1703	1683		
Units: Participants				
No. of participants	2	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Mechanical Ventilation Due to COVID-19

End point title	Mechanical Ventilation Due to COVID-19

End point description:

Number of participants needing mechanical ventilation (using self-reported questionnaire and/or medical/hospital records)

End point type	Secondary

End point timeframe:

Measured over the 12 months following randomisation

End point values	BCG vaccination group (Modified Intention-to-Treat Population)	Control group (Modified Intention-to-Treat Population)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1703	1683		
Units: Participants				
No. of participants	2	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Hospitalisation Duration With COVID-19

End point title	Hospitalisation Duration With COVID-19

End point description:

Number of days of hospitalisation due to COVID-19 (using self-reported questionnaire and/or medical/hospital records).

End point type	Secondary

End point timeframe:

Measured over the 6 and 12 months following randomisation

End point values	BCG vaccination group (Modified Intention-to-Treat Population)	Control group (Modified Intention-to-Treat Population)		

Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1703	1683		
Units: Participants				
No. of participants	5	5		

Statistical analyses

Statistical analysis title	Hospitalisation Duration With COVID-19

Statistical analysis description:

Analysis is done using a modified intention-to-treat (mITT) population. The outcome measure analysed is up to 6 month only. The 12 month outcome is still pending analysis.

Comparison groups	BCG vaccination group (Modified Intention-to-Treat Population) v Control group (Modified Intention-to-Treat Population)
Number of subjects included in analysis	3386
Analysis specification	Post-hoc
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.27
upper limit	3.21

Secondary: Mortality Due to COVID-19

End point title	Mortality Due to COVID-19

End point description:

Number of deaths due to COVID-19

End point type	Secondary

End point timeframe:

Measured over the 6 and 12 months following randomisation

End point values	BCG vaccination group (Modified Intention-to-Treat Population)	Control group (Modified Intention-to-Treat Population)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1703	1683		
Units: Participants				
No. of participants	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Work Absenteeism Due to Fever or Respiratory Illness

End point title	Work Absenteeism Due to Fever or Respiratory Illness

End point description:

Number of days (using self-reported questionnaire) unable to work (excludes quarantine/workplace restrictions) due to fever or respiratory illness defined as
- fever (using self-reported questionnaire), or
- at least one sign or symptom of respiratory disease including cough, shortness of breath, respiratory distress/failure, runny/blocked nose (using self-reported questionnaire)

End point type	Secondary

End point timeframe:

Measured over the 12 months following randomisation

End point values	BCG vaccination group (Modified Intention-to-Treat Population)	Control group (Modified Intention-to-Treat Population)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1703	1683		
Units: No. of days of unplanned absentee				
median (inter-quartile range (Q1-Q3))				
Median no. of days of unplanned absentee	6.0 (3.0 to 11.0)	6.0 (2.0 to 11.0)		

Statistical analyses

Statistical analysis title	Work Absenteeism Due to Fever or Respiratory Illne
Comparison groups	BCG vaccination group (Modified Intention-to-Treat Population) v Control group (Modified Intention-to-Treat Population)
Number of subjects included in analysis	3386
Analysis specification	Post-hoc
Analysis type	superiority[9]
Parameter estimate	Incidence rate ratio
Point estimate	1.12

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.99
upper limit	1.27

Notes:

[9] - Difference between BCG and placebo groups will be summarised as difference in the logs of expected number of episodes and its 95%CI estimated using Zero-Inflated Negative Binomial (ZINB) model adjusted for stratification factors used at randomisation

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
6 Months	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups	
Reporting group title	BCG vaccination group (Modified Intention-to-Treat Population)
Reporting group description: -	
Reporting group title	Control group (Modified Intention-to-Treat Population)
Reporting group description: -	

Serious adverse events	BCG vaccination group (Modified Intention-to-Treat Population)	Control group (Modified Intention-to-Treat Population)	
Total subjects affected by serious adverse events			
subjects affected / exposed	20 / 1703 (1.17%)	9 / 1683 (0.53%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	1 / 1703 (0.06%)	0 / 1683 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal procedural complication			
subjects affected / exposed	1 / 1703 (0.06%)	0 / 1683 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fracture of ankle			
subjects affected / exposed	0 / 1703 (0.00%)	1 / 1683 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hand repair operation			

subjects affected / exposed	0 / 1703 (0.00%)	1 / 1683 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leg fracture	Additional description: Hospitalisation for femur fracture secondary to skate fall.		
subjects affected / exposed	0 / 1703 (0.00%)	1 / 1683 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 1703 (0.00%)	1 / 1683 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hospitalisation	Additional description: Hospitalised for cardiac symptoms, related to underlying chronic disease.		
subjects affected / exposed	1 / 1703 (0.06%)	0 / 1683 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
COVID-19			
subjects affected / exposed	4 / 1703 (0.23%)	4 / 1683 (0.24%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Acute appendicitis			
subjects affected / exposed	2 / 1703 (0.12%)	0 / 1683 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Crohn's disease			
subjects affected / exposed	1 / 1703 (0.06%)	0 / 1683 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hospitalisation	Additional description: Hospitalisation for acute vomiting, diarrhoea and dehydration.		

subjects affected / exposed	1 / 1703 (0.06%)	0 / 1683 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain epigastric	Additional description: Hospitalisation for epigastric pain.		
subjects affected / exposed	1 / 1703 (0.06%)	0 / 1683 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Gallstones removal			
subjects affected / exposed	1 / 1703 (0.06%)	0 / 1683 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute dyspnoea			
subjects affected / exposed	1 / 1703 (0.06%)	0 / 1683 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Acute depression			
subjects affected / exposed	1 / 1703 (0.06%)	0 / 1683 (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			
Acute pyelonephritis			
subjects affected / exposed	1 / 1703 (0.06%)	0 / 1683 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haematuria			
subjects affected / exposed	2 / 1703 (0.12%)	0 / 1683 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscesses of skin	Additional description: Hospitalisation for injection site abscess with pus discharge (approx. 80ml) and systemic symptoms. Plastics team review on readmission and immunology assessment.		

subjects affected / exposed	1 / 1703 (0.06%)	0 / 1683 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 1703 (0.06%)	0 / 1683 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dengue			
subjects affected / exposed	0 / 1703 (0.00%)	1 / 1683 (0.06%)	
occurrences causally related to treatment / all	0 / 0	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	BCG vaccination group (Modified Intention-to-Treat Population)	Control group (Modified Intention-to-Treat Population)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 1703 (0.82%)	0 / 1683 (0.00%)	
Infections and infestations			
Abscesses of skin			
subjects affected / exposed	14 / 1703 (0.82%)	0 / 1683 (0.00%)	
occurrences (all)	14	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 April 2020	Modifications following HREC review of amendment · Addition of details around clinicaltrials.gov registration · Increase of planned number of participants to 10,078, including updated information on trial statistics · Addition of sites to enable recruitment of 10,078 participants · Change to timing of flu vaccine: can be given concurrently with BCG OR can have been given a minimum of 72 hours prior to randomisation · Change to Primary Outcome 2: - definition of severe COVID-19 disease: "COVID-19 positive test, AND hospitalised OR non-hospitalised severe disease" · Change to follow-up blood collection from 6m, to 3m & 12m · Change to follow-up surveys: increase from 6m to 12m · Change to outcome measures: "febrile respiratory illness" revised to "fever OR respiratory illness" · Minor changes for clarity and correction of typographical errors Updates to inclusion/exclusion criteria: flu vaccine timeframe changed in IC, BCG adverse reactions added as EC, influenza contraindications added to EC, breastfeeding removed from EC as not required, participation in other COVID-12 prevention trials added as EC.
30 April 2020	· Addition of placebo for those randomised to non-BCG arm · Removal of option of receiving influenza vaccine at same time as BCG vaccine. Participants will have obtained their flu vaccine prior to enrolment and randomisation.
29 May 2020	· Change to definition of healthcare worker for Australian sites – expand to match definition for European sites · Addition of information about data retention and Gates Foundation requirements · Correction of error in product stability information in protocol, to match product information · Addition of appendix describing stool sample collection, to take place at selected sites only · Updates for clarity

25 August 2020	· Trial name updated by removing 'following Coronavirus exposure' · Refining of objective language and definitions, as well as removal of secondary objective · Addition of additional blood samples at 6- and 9-month time points · Recruitment window for the BRACE trial extended to 2.5 years · In line with the window for blood samples extended to 42 days, the timeline for participant follow-up has been updated to 13.5 months from randomisation · Clarification of roles of Chief PI, Regional PI and Site PI, as well as addition of Brazil and UK collaborators · Update to the influenza vaccination eligibility criteria · Review of the Recruitment and Consent section to ensure practical application across all BRACE sites · Inclusion of detail pre-randomisation blood sample · Expansion of needle gauge size under Administration of trial drug · Update to the trial timeline and schedule of assessments · Update to the descriptions of procedures · Consolidated procedure discontinuation, withdrawals and losses to follow-up for clarity and include additional detail on processes in Brazil · Safety definitions and information have been consolidated for clarity and a toxicity grading scale has been included · Adjustments made to the data and information management section · Revisions to the description of the BRACE trial Governance structure · Removal of Appendix which outlines division of sponsor responsibilities between Chief PI · Site specific Appendices included
22 September 2020	· Update of Regional Principal Investigator for Rio de Janerio, Brazil, · A negative PCR test is not proposed as an inclusion criteria for participants in Brazil. Such a screening test was mooted as possible but has since been found to be logistically impossible. · A respiratory swab will be collected at baseline, following informed consent and randomisation. These swabs are being collected as the Brazilian investigators are keen to conduct a COVID prevalence sub-study. These samples cannot be rapidly analysed due to logistic limitations but will be batch analysed at a later date. Brazilian health authorities will be informed of the results after analysis. Results will be shared with participants approximately 3 months after randomisation. Participants will be specifically told that they won't be informed of the results for approximately 3 months. · Expansion of needle gauge size under Administration of trial drug to include Preference to use 25G or 26G accepted up to 30G to incorporate BCG administration practice in Europe, · Refinement of SUSAR definition of expectedness to align with WHO information sheet, · Update to Appendix 4 Brazil Specific Requirements; o To clarify safety reporting roles o Adjustment of approach to collection of respiratory swab at baseline with additional detail included outlining the strategy.

26 November 2020	AMENDMENT TO OUTCOMES: Administrative correction to the Objective 2 and 4 to ensure minor adjustment to correct language and ensure consistency of wording throughout the protocol. Secondary outcomes 5, 6 and 7 will analyze data over the 6 and 12 months following randomization. Inclusion in exploratory outcome 13 specific reference factors including COVID-19 vaccines that influence adult immune responses, infection and COVID-19 risk. Section 1.3: To reach recruitment target a longer recruitment period will be required. Recruitment will be extended until the end in March 2021. Section 1.4: Section removed. Section 4.1: Inclusion of some specific site details ie. site names in Brazil. Inclusion of electronic messaging as a form of follow-up as preferred by study teams and participants in Brazil. Section 4.3.2: Collaborators in Europe have reported a number of operational challenges in the access and availability of the influenza vaccine for healthcare workers in 2020. Influenza vaccination levels in Spain are significantly lower than other sites. After discussion and review of the impact on recruitment and the trial, proposing the adjustment of the inclusion criteria related to influenza vaccination will be relevant for Australian sites only. Section 4.3.3: Add exclusion criteria to ensure exclusion of people receiving antibiotics as a preventative treatment against TB, add detail on the definition of previous SARSCoV- 2 to include positive PCR and approved antigen testing and clarification on alternative site. Section 5.8: timeline for participants not taking part in any other COVID-19 preventative intervention clinical trial is revised to 6 months. Section 7.3: Inclusion of electronic messaging in Brazil. Added detail on questionnaires sent. Blood samples at 9 and 12 months collect for subset of participants. Adjust DBS timepoint. Section 8.5: Itch added to the toxicity grading scale in line with updated BRACE SAE/AE SOP. Section 11.3: Add sub group
10 December 2020	Section 4.3.3: Due to the rapid roll-out of COVID-19-specific vaccines in the United Kingdom, additional exclusion criteria proposed - Have previously received a COVID-19-specific vaccine Section 7.3: Proposal to retain ad hoc blood sample collection due to the changeable context and enable additional sample collection if required. Appendix 4: Adjustment to language around COVID-19 testing in Campo Grande and Rio.
08 February 2021	Appendix 8: With the availability of COVID-19-specific vaccines, healthcare workers are being prioritized to receive COVID-19-specific vaccines due to their high risk of SARS-CoV-2 exposure. As healthcare workers, participants in the BRACE trial will be prioritized to receive a COVID-19- specific vaccine.There is evidence that BCG can improve the immune responses to other vaccines, so it is possible that this will also apply to COVID-19-specific vaccines as well. The inclusion on Appendix 8 Optional sub-study: a collection of blood samples to measure immune responses to COVID 19-specific vaccines will enable us to determine if BCG vaccination can improve immunity to COVID-19- specific vaccines have important implications for the potential of BCG-vaccination to increase efficacy of COVID-19- specific vaccines, and may also impact our interpretation of the outcomes of the BRACE Trial. This is particularly important for the COVID-19-specific vaccines that have a lower efficacy (e.g. less than 90% efficacy). The changes in protocol v10.2 will only apply to sites that agree to Appendix 8. Site will need to submit protocol v10.2 and the site-specific PICF to their HREC/Governance for approval. Local COVID-19 safe plans will be utilized to ensure researcher/participant safety in relation to COVID-19
11 February 2021	Appendix 4: For Visit 1 – Blood can be collected up to 14 days before participant receive the first dose of a COVID-19 specific vaccine. In specific sites, an earlier time-point (<7 days) will enable the exploration of the initial gene expression responses to vaccination. For Visit 2 – Blood can be collected up to 28 days instead of 28 days only after the participant have received the first dose of COVID-19 specific vaccine. The changes implemented is to allow flexibility in collecting blood sample. For visit 2 with the increase of the number of days it has provided the study with an opportunity to explore the initial gene expression to vaccination but this will be site specific only.

04 June 2021	Section 4.1: Added Fundação de Medicina Tropical and Health State Office as the principal site for Manaus, Amazonas, Brazil. Section 10.1.2 and 11.1: Update information on interim analysis Section 11.4: The interim analysis will consider severe episodes of COVID-19 by 6 months now only in Stage 2 of the trial this is because Stage 1 includes only Australia, which has had negligible COVID-19. For the primary outcome of severe COVID-19, the strategy has been changed to split the alpha. The DSMB had recommended unbinding and dissemination of the interim analysis results if they determined they were of clinical or public health importance. A larger alpha spend on the interim analysis will provide the best chance of the interim analysis providing results that the DSMB can recommend be unblinded. Appendix 8: A larger number of participants will be recruited to the BCOS sub-study in Brazil to enable the identification of biomarkers predictive of vaccine efficacy against variants. This analysis is in line with exploratory outcome No 13. Manaus will provide more participants in a region with a high prevalence of the P.1 variant.
14 September 2021	Section 3.1.3: Addition of Planned Exploratory Analyses 14 (Brazil Specific) to identify biomarkers for diagnosing TB infection. Appendix 4: Updates to include the additional volume of blood to be collected for Planned Exploratory Analyses.
11 November 2021	Appendix 9: Addition of Appendix 9 (Brazil Specific) to examine the interplay between SARS-CoV-2 variants and the immune system (for example the immune responses to SARS-CoV-2 and vaccines). This is for testing the respiratory swabs previously collected for further analysis, or access variant results. No additional clinic visits or samples required from participants. An additional PICF will be provided to participants to optionally consent to this sub-study, to test the respirator
17 May 2022	All revisions made to the protocol are minor/administrative in nature and do not impact the safety or scientific value of the clinical study. Revision have also been done to align with the Statistical Analysis Plan. - "Symptomatic" word has been added to distinguish COVID 19 from Severe COVID19 - To specific RAT is the antigen test - "Number of participants with" is removed as the outcome is what Sponsor will be collecting from participant. For instance, "symptomatic COVID19 over 6 months" is collected from participants, whereas "Number of participants with symptomatic COVID-19" is what Sponsor's will analyse/compare between the groups. - Clarify the case definitions for asymptomatic COVID-19 is (e.g. ensure matching format for the outcomes) - Assessing of death registry will not be performed - Clarify the definition of what is severe fever or respiratory illness - Clarification of secondary outcomes related to febrile or respiratory illness - To clarify at which timepoints will objective be assessed and to match with information in objective 8 outcomes - To clarify that BRACE will look at the number of days of unplanned absenteeism due to acute illness or hospitalisation instead of any reason which can include carer' leave or annual leave. - Data linkage will not be conducted for the study - As Stage 1 recruitment is done in Australia for Victoria and Western Australia sites, where there is negligible COVID-19 exposure risk, there is a high probability that positive SARS-CoV-2 serology results are false positive. As a result Stage 1 data will not be included in Meta- Analysis. This update have been done to also align with the Statical Analysis Plan.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Availability of Covid-19 vaccines affected recruitment number. Definition of severe Covid-19 differed from that widely used in Covid-19 studies. Definition of symptomatic Covid-19 was limited to the original case definition. Blinding is a challenge.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/37099341